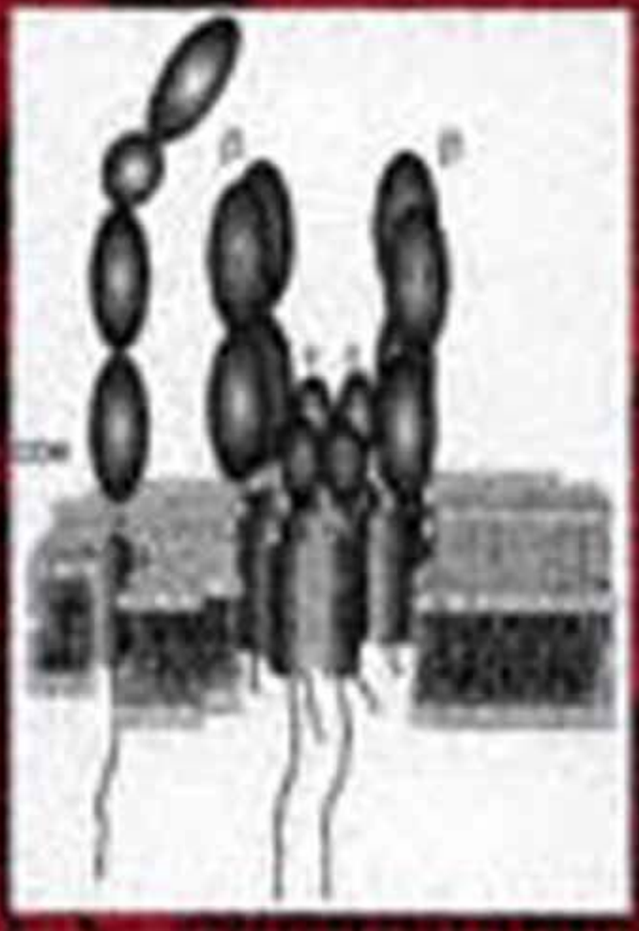
Handbook of Immune Response Genes



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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging-in-Publication Data

On file

ISBN 0-306-45647-8

A Division of Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

http://www.plenum.com

10 9 8 7 6 5 4 3 2 1

To my wife Jane for her courage, to Simon for his patience and enthusiasm, and especially to Jacob for his faith

— J. S.

Preface

The study of immunology encompasses a vast and ever-growing body of information that in some way or other incorporates most areas of medical biological research. As the body of information in the medical sciences continues to increase its rate of expansion, one of the greatest challenges to investigators will be to integrate this information in a manner that is intellectually fruitful and productive. Considering the intended scope of this text, we could not pretend to have gone too far toward achieving such an integration—and considering the pace of change, in its very best form a measured approximation of such lofty goals might be the most we could hope for. Nevertheless, in these pages we have sought to produce a collection of information that is at once concise and up-to-date regarding areas where important developments are impacting on the way we understand the vertebrate immune system. In addition, although the information is geared toward advanced study, we have discussed some basic elements and concepts that we hope make the text a useful resource for both the immunologist and the nonspecialist. The intention is to provide the researcher, clinician, or advanced undergraduate student with a brief overview of specific components of the immune system, and to provide a place from which to begin further detailed study if necessary. To this end, we made every effort to supply extensive referencing—although limitations in space prevented exhaustive or complete referencing in some cases.

In Chapter 1, the major histocompatibility complex is introduced with a basic overview of the region in mice and humans. The emphasis here is placed on the class I and class II molecules, describing the structural and functional features of these molecules. Peptide display is a cornerstone of adaptive immunity and is a central theme in the evolution of the MHC genes. As a consequence, peptide binding by class I and class II molecules is discussed as well in this chapter.

Antigen presentation and processing are two sides of the same coin. Indeed, important genes in the MHC region include those involved in antigen display, the class I and class II molecules, and those involved in processing and generating the peptides themselves, such as the LMP genes. In Chapter 2, we discuss the business of peptide production with a particular appreciation for the unique role of the genes involved in enhancing antigenic variability. The front-line role that IFNγ plays in immune response induction is underpinned by its important function in regulating expression of genes involved in antigen processing and presentation, and reference is made to this cytokine throughout the chapter.

In Chapters 3 and 4, we discuss the important genes and proteins expressed in T and B lymphocytes, respectively, that facilitate an adaptive immune response. Because T and B lymphocytes share a common mechanism for generating antigen receptor diversity, there is some redundancy in genes discussed in both chapters, i.e., the RAG genes. However, the depth of knowledge about the operation of such genes varies in the context of T or B lymphocytes, and there is little harm in dissecting out information that exists for such genes as is specifically known for either case. Moreover, because it is our intention to provide the reader with a quick reference, we sought to, within reason, create each chapter so that it was more or less self-contained. In the discussion about B-lymphocyte genes, we spent some time examining the biology of the immunoglobulins, as these entities play such an important and independent role as immune response molecules. An in-depth study of the development of T and B lymphocytes was deemed to be beyond the scope of this book; as a result, there is only a brief overview provided and the reader is directed elsewhere for excellent reviews on the subject.

There appears to be a fine line between an effective adaptive immune response and *horror autotoxicus,* or autoimmune disease. How the immune system achieves this balance is as intriguing a question as it is an important one. In Chapter 5, a synopsis of some of the more common diseases with autoimmune components is provided. Although the etiology of autoimmune disease in general remains to be well defined, there is considerable interest in and evidence of a crucial role for genetic factors. There are many data on the correlation between the expression of MHC genes and the susceptibility to disease. These and other genetic susceptibility factors are brought into context for the various diseases mentioned.

In addition to autoimmune disease, infidelity of an adaptive immune system poses risk at a more fundamental level. Faulty rearrangement of germline sequences, resulting from infidelity in the machinery and/or mechanisms involved in generating the functional antigen receptor genes, can and does frequently result in catastrophe. Errors in rearrangement, notably those that result in the translocation and juxtapositioning of antigen receptor genes with those of nonreceptor genes, can produce deregulated expression of genes that play critical roles in regulating cell growth and development. Such deregulation can result in malignant transformation, ultimately with lethal consequences. In Chapter 6, errant translocations between the T- and B-lymphocyte receptor genes and other loci are described.

In Chapter 7 some of the major cytokines involved in regulating the immune system are discussed. As there are over 60 known cytokines, it was necessary to make some tradeoffs between the depth of treatment for each cytokine and the breadth of those covered. The most commonly studied mediators are discussed, particularly the interleukins, in sufficient detail as to provide a meaningful and current overview of their function as immune response genes. A recurring theme in these sections (and perhaps in their biology) is the importance of these cytokines in directing Th1 versus Th2 responses. However, at the same time there was a conscious attempt to avoid generalizations or oversimplifications concerning the function of these mediators vis-à-vis current paradigms such as Th1- and Th2-type responses. Although this may at times result in some ambiguity in descriptions of cytokine function, this is a fair reflection of the current level of understanding of the complex role these cytokines play in regulating the immune system.

Finally, we believe this volume is appropriately concluded with a table summarizing the ever-growing list of CD antigens. Although such summaries are commonly found in introductory texts of immunology, it is rare to find a summary with sufficient detail that

offers some utility or convenience for a more advanced reader. Although providing such information in the limits of a table is a difficult task, this table at least goes toward achieving such a goal.

We would like to thank the following persons for contributing their thoughts and energies to improving this text: Stuart Berger, Neil Berinstein, Don Capra, Kirsten Fischer-Lindahl, John Girdlestone, Henrik Griesser, Hitoshi Kikutani, Michael S. Neuberger, Joseph Penninger, Chris Richardson, Mary Saunders, John Trowsdale, Judy A. Wade, Tania H. Watts, and Wen Chen Yeh. We would also like to thank Irene Ng for always being there when we needed her and Lilly Teng for her diligent assistance. Finally, we are indebted to our friends and colleagues at the Amgen Institute for creating the kind of environment that helps make our work enjoyable and rewarding.

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Contents

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Genes of the Major Histocompatibility Complex

Since the beginning of this century the curious nature of tissue rejection has intrigued investigators. It was no later than 1936 when Peter Gorer clearly articulated the existence of the MHC using transplanted tumors. Gorer's work was the culmination of efforts to show that the rejection of transplanted tumor cells in mice involved a set of linked genetic loci, or *histocompatibility* genes. The term *major histocompatibility complex,* or MHC, evolved from observations that rejection responses could be vigorous or mild, i.e., there were strong and weak histocompatibility loci, or, conversely, that there were major and minor histocompatibility antigens. As it is understood today, the MHC might simply be described as a collection of genes that encode immunologically relevant molecules, particularly those involved in cell-mediated T-lymphocyte immunity. The most fundamental elements of the MHC are a set of highly polymorphic genes that encode molecules involved in the presentation of antigenic peptides to $\alpha\beta$ and perhaps $\gamma\delta$ T lymphocytes. The extreme polymorphism of these so-called class I and class II genes facilitates display of myriad different antigenic peptides, a repertoire that must vary among different individuals in a population in order to protect from catastrophic disease. Genes encoding functionally diverse molecules such as TNF, LMP, and TAP (see Chapter 2) are also incorporated into the MHC gene cluster, suggesting perhaps a long evolutionary existence of the MHC in the vertebrate immune system. Although it is tempting to speculate that the MHC is a central feature in the evolution of vertebrate immunity, it must be remembered that only about 0.1% of vertebrate species have been investigated. Nonetheless, in all cases there exist MHC regions that share some degree of similarity. In this chapter we provide a brief overview of the MHC by way of discussing the genes and protein products of the class I and II regions. Immune response genes present in the class III region are discussed elsewhere (see chapters on antigen presentation and cytokines).

1.1. MHC OF THE LABORATORY MOUSE

The murine MHC, known as the histocompatibility complex-2 (H-2 complex), contains eight loci or groups of genes on chromosome 17. The regions are designated K, A, E, S, D(L), Q, T, and M and span in total more than 3×10^6 base pairs, encompassing dozens

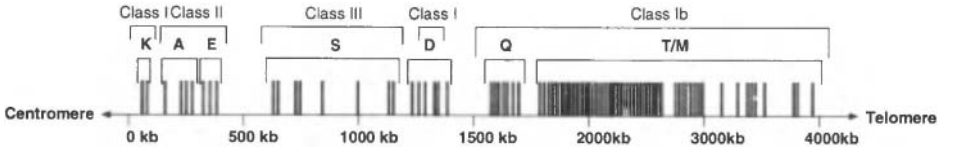

Figure 1.1. Regions of murine MHC complex.

of genes most of which remain to be characterized (Figure 1.1). Regions Q, T, and M encode genes for so-called nonclassical, or class Ib, molecules that comprise the majority of genes in the H-2 complex.

1.1.1. Class I (Class Ia or Classical Class I Molecules)

The polymorphic class I genes encode the transmembrane glycoproteins responsible for mediating peptide-antigen presentation to T lymphocytes. Class I genes are encoded in about 4.5 kb of DNA and contain six to eight exons, each roughly corresponding to discrete domains of the mature 40- to 45-kDa transmembrane glycoprotein (Figure 1.2). The three extracellular domains contain about 90 amino acid residues each and together provide several sites for glycosylation. Polymorphism is largely restricted to positions in $\alpha 1$ and $\alpha 2$ domains, each domain contributing α-helical and a β-pleated-sheet secondary structure, which form the sides and base of the peptide binding groove, respectively. Polymorphisms in these domains are responsible for producing the allelic differences in peptide specificity (1).

The class I genes that encode the heavy chain, or α chain, are located in K and D regions. The K region encodes a single functional gene, with both gene and protein product being designated K (H-2K). The D region contains one functional gene D and in some strains there may be a second functional gene L. There are also variable numbers of D pseudogenes designated D2, D3, D4, and so on. Thus, the D locus is expressed in most mouse strains whereas some strains also express an L gene product (Figure 1.3). As a consequence, the typical laboratory mouse expresses both K and D class I molecules, and possibly a third L heavy chain. Each of these gene products can form functional class I heavy chain molecules that associate noncovalently with β_2-microglobulin (β_2M) and have the potential to display peptides on the cell surface.

The non-MHC-encoded molecule, β_2M, was first identified as a serum globulin species isolated from urine. Although β_2M is not essential for expression of peptide–class I dimers (2,3), the class I trimer (β_2M + peptide + class I) has greater stability than either heavy chain or peptide–heavy chain complexes alone (4) (Figure 1.2). β_2M exhibits little demonstrable intraspecies polymorphism, although there is significant variation between β_2M of different species. Because of the stability afforded by β_2M, it appears to be important in facilitating the expression of antigenically relevant class I molecules on the cell surface (5).

Class I genes have their highest expression on leukocytes and on various cell types in lymphoid organs, but are also inducible or expressed to a lesser degree in most other cell types (Table 1.1) (6–9). In addition to overall variations in the total level of class I expression on different tissues, relative expression levels of the K, D, and L loci vary for different strains. For example, homozygous H-2^d mice express class I molecules from all

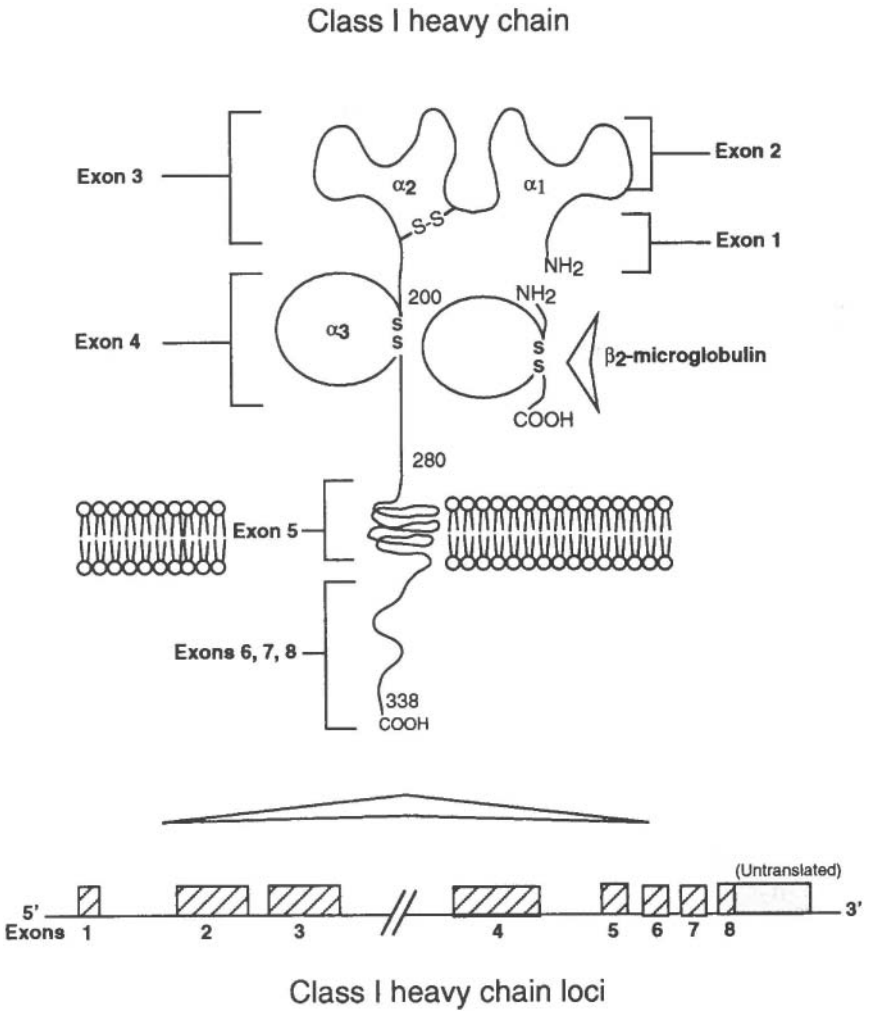

Figure 1.2. Exons of the class I loci correspond roughly to the various domains of the class I heavy chain molecule. Exon 1 encodes a leader sequence at the N-terminus of the heavy chain.

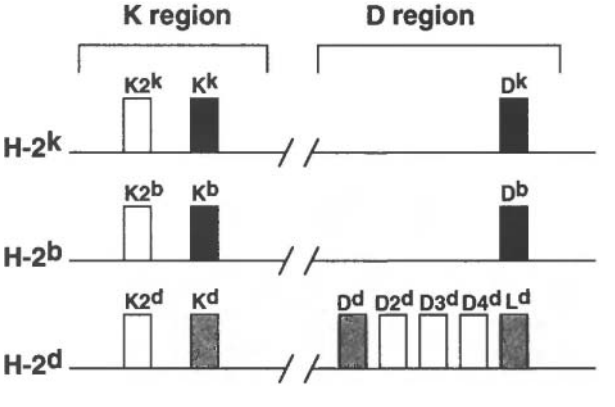

Figure 1.3. Examples of class I genes expressed by three different laboratory mouse strains. The shaded boxes represent those genes that are expressed. Open boxes represent class I genes or pseudogenes that do not produce functional proteins. K expression levels are generally lower than those for *D*.

Table 1.1
Tissue-Specific Expression of Class I Molecules[a]

Tissue (cell type)	Human	Mouse
Endocrine organs		
Thyroid	+	
Parathyroid	+	
Pancreatic islet cells	+	-
Adrenal	+ +	
Gastrointestinal		
Epithelial cells of		
Esophagus (basal layer)	+ +	Inducible
Stomach	+	-
Small intestine	+ +	+ +
Colon		+
Pancreas		
Acinar cells	−	−
Duct cells	+ +	+
Liver		
Kupffer cells	+ +	+
Sinusoids, biliary epithelium	+ / −	Inducible
Hepatocytes	+ / −	Inducible
Respiratory and cardiovascular		
Brochial and alveolar epithelium		
Intestitial cells	+ +	+
Bronchiolar epithelium		Inducible
Heart		
Myocardium	+	−
Endocardium		+
Pericardium		Inducible
Endothelium		
Capilliaries and large vessels in all organs		+
Nervous system		
Central		
Neurons	−	−
Astrocytes, microglia, and oliodendrocytes		Inducible
Peripheral	+ +	
Kidney		
Tubular epithelium	+ +	
Glomeruli	+ +	
Testis		
Spermatozoa	+	
Muscle		
Skeletal	+ / −	Inducible
Smooth	+	Inducible
Langerhans cells, interstitial dendritic cells (all organs)	+ +	Inducible
Keratinocytes	+	+ +
Placenta		
Villous trophoblast	−	
Spongioblast and labyrinthine zone		+

Table 1.1 (Continued)

Tissue (cell type)	Human	Mouse
Thymus		
Medullary lymphocytes and stromal structures	+	+
Cortical lymphocytes and epithelial reticular cells		Inducible
Lymph nodes (all cell types)	++	++
Spleen (all cell types)	++	++

[a] + and ++ indicate relative staining intensity on unstimulated cells. "Inducible" indicates that class I levels are nominal on unstimulated cells but are upregulated after treatment with IFNγ. Table adapted from *Immunology Today*, Vol. 11, No. 9, 1990. Used with permission.

three loci, L^d, D^d, and K^d. However, the number of L^d molecules (~20,000) detected on splenocytes is less than half that for either D^d or K^d. This appears to largely reflect differences in enhancer/promoter regulatory elements at the different loci (6, 10). Class I expression levels are also a function of gene dosage: F_1 mice from different homozygous parental strains express approximately 50% as much of each parentally derived class I molecule so that, for example, the total number of class molecules expressed from both K^d and K^k alleles in an H-2^d × H-2^k cross are about the same as that expressed from K loci of either parent. Small variations in class I expression levels are also observed depending on age and sex of the mice (11). Regulation of class I gene expression ultimately reflects a variety of factors including promoter heterogeneity (10), variations in the 3′ untranslated region (12), and differences in the coding sequences which affect the amino-terminus protein structure and in turn alter surface expression, oligosaccharide processing, and β_2M association (see below) (13).

1.1.2. Class Ib

Genes encoding the oligomorphic nonclassical class I molecules (class Ib) are products of the Q, T, and M genes, which include the majority of genes in the MHC (14, 15). The role of class Ib genes and protein products (where such exist) is the subject of diverse speculation and active study. Expression levels for the functional genes vary significantly according to loci and with respect to tissue specificity. Some class Ib molecules are secreted, others bound to the membrane via phosphatidylinositol anchors, and some are pseudogenes and are thus not expressed. Despite these differences from class I molecules, class Ib shares a high degree of primary sequence identity in extracellular domains, ranging from about 40 to 80%. However, the observation that mice missing most Q genes have no apparent immunological defect (16), together with the understanding that most T-region loci are pseudogenes (17), fueled speculation that class I genes outside regions K and D might not serve any functional role in the immune system and that the class Ib genes might merely be leftovers of an MHC region prone to expansions and contractions (i.e., to the gain and loss of genes through recombination events) over evolutionary periods.

At the same time, significant evidence has accumulated that supports a role for at least some class Ib molecules in antigen presentation to both αβ and γδ T cells (reviewed in Refs. 18–20). A class Ib molecule from the M-region locus, H-2M3, has been shown to have a specialized role in displaying peptides that are formylated at their N-terminus (21–

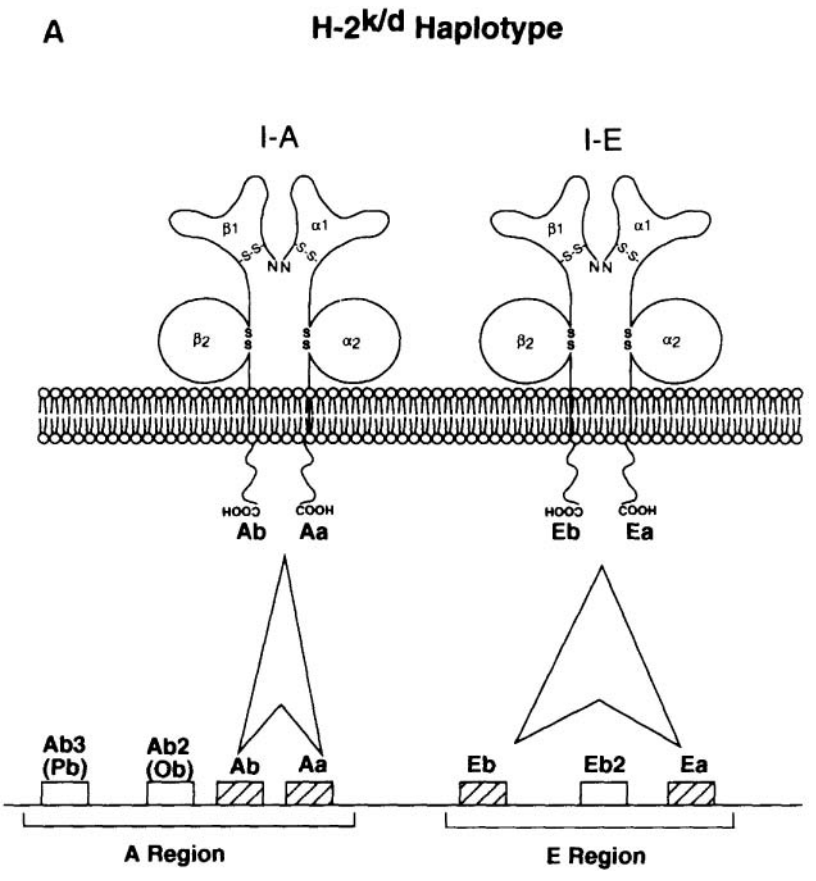

Figure 1.4. (A) Class II heterodimers are transcribed from pairs of genes in A and E regions of the MHC. The A and E regions also contain class II genes that produce no functional proteins. Slashed boxes indicate functional genes.

25). Such modifications are found in prokaryotic proteins. Thus, the H-2M3 molecule may function as a restriction element for cytotoxic T cells and in some cases mediate antigen presentation and host protection against pathogens (26,27). Class Ib products from T-region genes have also been shown to act as restriction elements (i.e., antigen-presenting molecules) for γδ T cells (28,29). Mice that transgenically express the class Ib thymus leukemia antigen H-2T18d have multiple immuno-irregularities, including elevated numbers of $CD4^+$ thymocytes and peripheral T cells, skewed TCR usage, and tissue rejection after autologous transplantation of transgenic tissue onto nontransgenic mice (30). Moreover, class Ib-restricted allograft rejection has recently been reported in γδ TCR transgenic mice (31,32).

1.1.3. Class II

Murine class II heterodimers are encoded in the 500-kb stretch of DNA that makes up the A and E regions of the MHC (Figure 1.1). Mature class II heterodimers are assembled from α and β subunits, each produced from separate genes located within the A or E

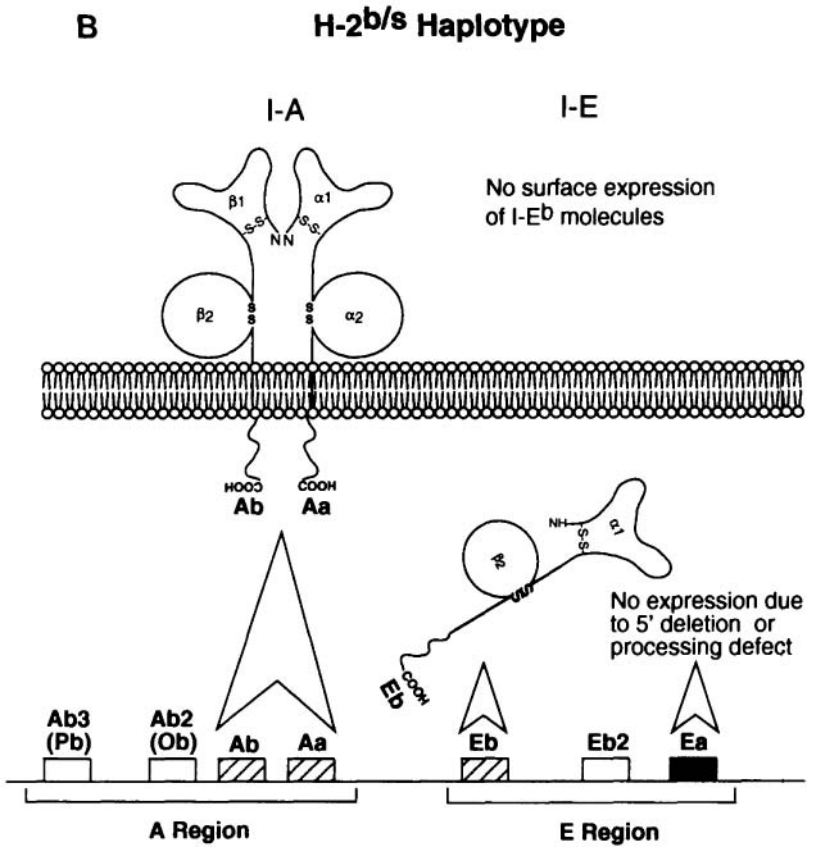

Figure 1.4. (B) Some strains of mice (i.e., H-2b and H-2s) have deletions in the 5′ promoter region of the E_a gene or other irregularities that prevent transcription of a functional E_a subunit. Transcription of E_b results in accumulation of E_b chain in the cytoplasm. In effect, therefore, the presence (or not) of a functional E_a chain regulates expression of the E_a:E_b heterodimer. Slashed boxes indicate functional expression.

regions. Thus, A-region genes encoding α and β chains are designated A_a and A_b, respectively. Additional class II genes in the same A region are named A_{a2}, A_{a3}, or A_{b2} (Ob), A_{b3} (Pb), and the same rule applies for E-region genes, designated E_a and E_b, E_{a2} and E_{b2} (Figure 1.4A). All mouse strains appear to express a heterodimeric class II molecule from two independent A-region loci. However, a number of strains (H-2^b, H-2^f, H-2^q, and H-2^s) have either deletions in the 5′ promoter region of E_a genes, or other irregularities regarding processing of transcripts, such that no functional E_a chain is produced (33–35). In these mice E_b genes are transcribed and translated, but E_b subunits do not form functional class II homodimers (which is the rule for all class II subunits) and probably remain trapped in intracellular compartments (Figure 1.4B) [as would E_a chains in the absence of E_b (36)]. Wild-type mice have also been identified with identical E_a deletions (33,37,38). Yet wild-type mice are expected to be almost invariably heterozygous at MHC loci (39). As E-region products expressed from different parental alleles can form functional heterodimers, a deficiency for class II I-E molecules requires homozygous defects, and thus wild-type mice lacking class II E molecules are likely to be rare. The implication is that both I-A and I-E expression in wild-type animals are probably

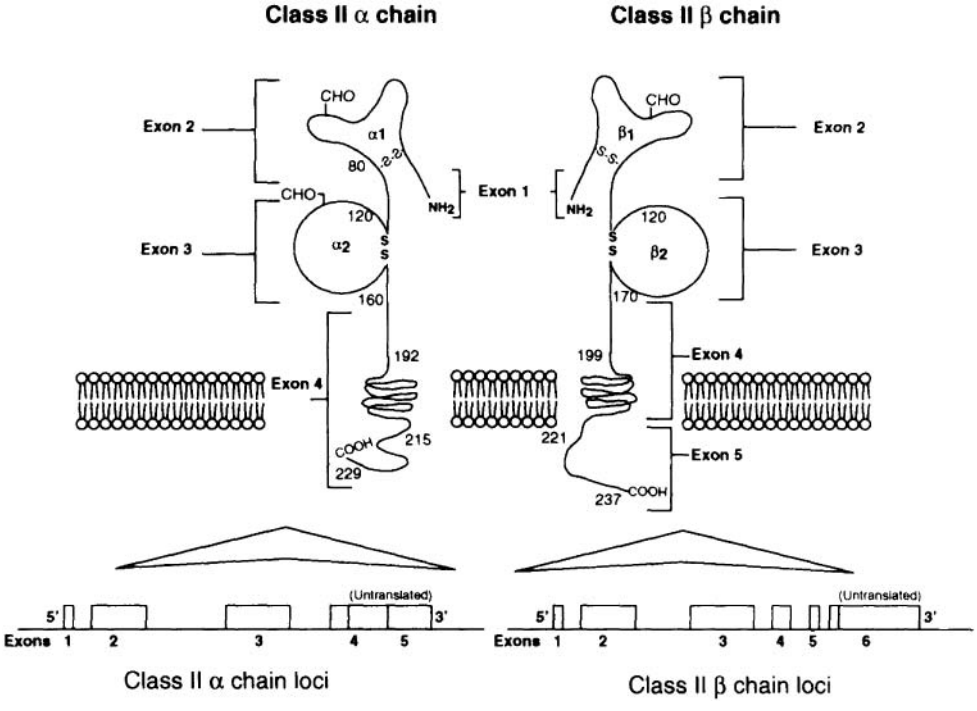

Figure 1.5. Individual genes with similar exon/intron arrangements produce the α and β chains. For both chains, exon 1 encodes the leader peptide and exons 2 and 3 encode the α1 and α2 or β1 and β2 domains, respectively. The genes differ, however, at exons 4, 5, and 6. Exon 4 of the α chain encodes all of the membrane proximal region, transmembrane, and cytoplasmic tail, in addition to a portion of the 3' untranslated sequences. β-chain transmembrane and cytoplasmic regions are encoded by exons 4 and 5, with an additional exon encoding the remainder of the cytoplasmic tail and the 3' untranslated region. Amino acid positions are indicated for a typical length of respective chains at A or E loci.

required for optimal function of the immune system. The importance of only a single functional E-region gene in laboratory mouse strains is thus open to interpretation.

Class II α and β chains each have two extracellular domains, including Ig-like membrane-proximal domains that contain an intrachain disulfide bond. The α and β chains have similar transmembrane regions, cytoplasmic tails, and similar total numbers of residues (Figure 1.5). Exon/intron structure for α- and β-chain genes are also similar. However, E_a chains lack significant polymorphism and thus E_a:E_b heterodimers depend on β-chain variations for establishing broad peptide binding profiles (40,41). Both A_a and A_b subunits are polymorphic at locations involved in forming the peptide binding groove. E_a subunits are generally compatible to form heterodimers with E_b subunits expressed from either parental loci, as are A_a and A_b molecules. Heterozygous individuals can therefore form a variety of class II αβ heterodimers by mixing and matching α and β subunits from respective E- and A-region alleles. In F_1 mice bred from homozygous parents, the result is a four-fold expansion in class II heterodimer diversity (Figure 1.6).

1.1.4. Class III Genes

The S region of the mouse MHC contains so-called class III genes that encode important immune response molecules, in addition to other products with no clear func-

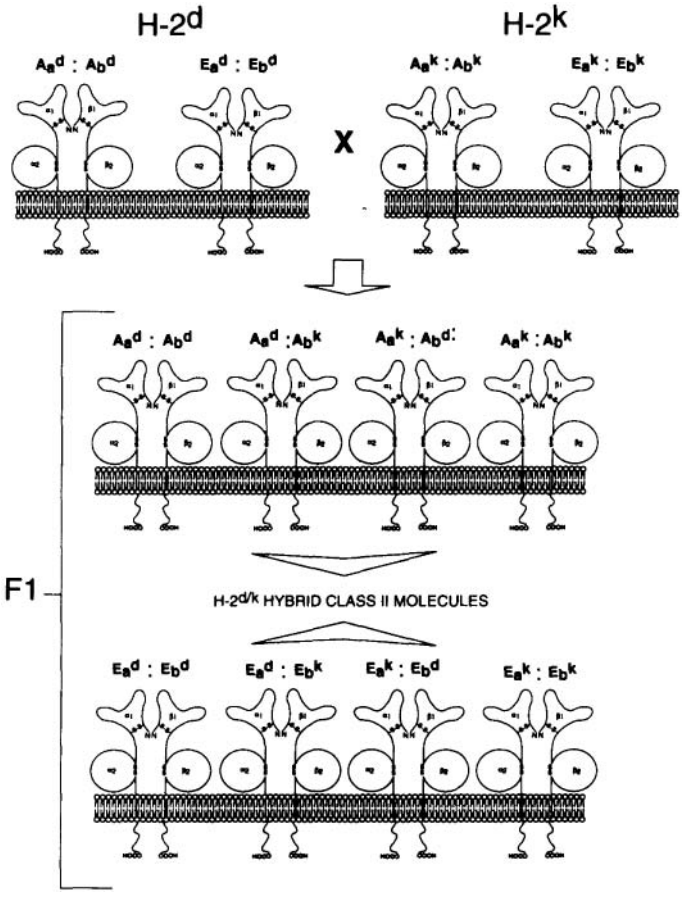

Figure 1.6. In heterozygous individuals, products of E_a and A_a genes heterodimerize with products with E_b and A_b genes, respectively. As a result, heterozygous progeny express class II heterodimers on the cell surface that represent the total number of possible combinations of heterodimers from E- and A-region loci. Gene dosage effects result in the same total number of class II molecules on the cell surface.

tion in the immune system. The S region derived its name after C4 complement, isolated from serum, was first located to the region. The C4b gene is flanked on either side by genes encoding 21-OH-A (21-hydroxylase) and nonfunctional 21-OH-B. Other genes in the region encode factor B (Bf) of the alternate complement fixation pathway and C2 of the classical pathway. Telomeric in the S region are genes encoding TNFα and β and heat shock protein HSP-70. The linear order of S-region genes beginning from the centromere-proximal end is: 21-OH-B, C4, 21-OH-A, Bf, C2, HSP, TNFα, and TNFβ. More genes in this region will become known (particularly telomeric to HSP) as more extensive maps are made.

1.2. THE HUMAN LEUKOCYTE ANTIGENS (HLA)

The HLA complex, the human equivalent of the mouse MHC, is located on the short arm of chromosome 6 encompassing a total of about 3500 kb of DNA. Centromere-

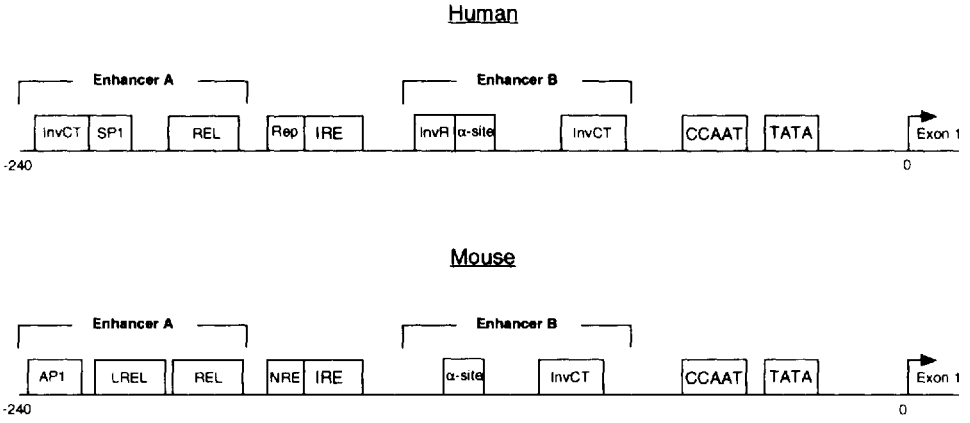

Figure 1.7. The *cis*-acting regulatory elements for class I genes. Elements depicted—with small variations—are found in most class I genes, including those of class Ib. InvCT, inverted CCAAT; Rep, repressor binding site; InvR, inverted repressor binding site; α-site, weakly binds AP-1 (FOS/JUN) and nuclear hormone (retinoic acid) receptor; LREL, low-affinity REL binding site.

proximal regions encode class II and class III genes, whereas a stretch of 2000 kb telomeric to the class III region contains class I and class Ib genes (Figure 1.8). Although there are differences in total numbers of genes, and in the linear order in which different regions occur, the MHC of mice and humans are highly analogous both genetically and in terms of proteins expressed (42). As with mice, gene density in the HLA region is greater than that expected for the genome as a whole (43). The HLA locus is divided into several major regions, which include A and B–C regions that contain genes for the functional class I molecules HLA-A, HLA-B, and HLA-C. Class Ib molecules are expressed from the HLA-E, F, and G genes, although a number of new genes have been identified in the HLA-A/F regions and their functions remain to be elucidated (44,45). The HLA-DP and DQ-DR subregions contain genes for class II molecules in addition to other functional and nonfunctional genes (46). In humans, class I and class II regions are separated by a 1000-kb stretch of DNA that encodes a variety of related and unrelated functional genes collectively referred to as the class III genes.

1.2.1. HLA Class I

Direct comparisons have been made between class I products from A, B, and C regions of human MHC with those expressed from murine K, D, and L, respectively (47). The A and B regions of the human MHC code for class I molecules with well-established roles in antigen presentation. Gene structure and function of A, B, and C loci are analogous to those of murine class I genes in K, D, and L regions. At present, more than 50 alleles have been identified for HLA-A, 98 for HLA-B, and at least 34 for HLA-C (Table 1.2) (48). As with murine class I, polymorphism in the HLA alleles predominates in exons encoding α_1 and α_2 extracellular domains, at positions involved in forming the peptide binding cleft. Intralocus versus interlocus comparisons for HLA-A, -B, and -C reveal locus-specific polymorphisms and suggest that A, B, and C loci might have diverged in order to produce class I alleles with unique peptide-binding characteristics (49,50).

Table 1.2
A List of Class I HLA Alleles

HLA alleles	HLA specificity	Previous names	Source	Accession number
A*0101	A1	—	LGL721, MOLT4	X55710, M24043
A*0102	A1	—	UAIJDI	UO7161
A*0201	A2	A2.1	LCI 721,JY, GM637, GRC138, T5-1	M32322, K02883, M84379
A*0202	A2	A2.2F	M7	M17566, M17588
A*0203	A203	A2.3	DK1	U03862, M17667, M19670
A*0204	A2	—	RML,AN	Xb/954, M86404
A*0205	A2	A2.2Y	WT40,AM	U03863
A*0206	A2	A2.4a	CLA,T7527	M24042
A*0207	A2	A2.4b	KNE	
A*0208	A2	A2.4c	KLO	
A*0209	A2	A2-UZB	OZB	
A*0210	A210	A2-LEE	XIJ-ND	Z23071
A*0211	A2	A2.5	KIME,GRC138	X60764, MB4377
A*0212	A2	—	KRC033	M84378
A*0213	A2	A2SLU	SLUGED	Z2/120
A*0301	A3	A3.1	JG	X00492, KO2057
A*0302	A3	A3.2	E1B2	—
A*1101	A11	A11E, A11.1	CJO-A, KUE, MMU, YMU	M16007, M16008, X13111, D16841
A*1102	A11	A11K, A11.2	KLIE,KOK, CTA	X13112, D16842
A*2301	A23(9)	—	SHJO, EL.ON	M64742
A*2401	A24(9)	—	JG	M15497
A*2402	A24(9)	—	SHJO, 32/37, KRC032	M64740, MB4376
A*2403	A2403	A9.3	APA,KPE	M64741
A*2501	A25(10)	—	BM92	M32321
A*2601	A26(10)	A26.1, A26.3	GM637, O2BN5, MGAR, N.M.	M24095, U03697, D16843
A*2602	A26(10)	A26.2, A26.1	KT14, Y.I., E.K.	M98453, D14350
A*2603	A26(10)	A26.4	T.M.,S.M.	U14351
A*2604	A26(10)	A108A	Y.S.	D14354
A*2901	A29(19)	—	JOE	M23780
A*2902	A29(19)	A29.2	LAM	X60108
A*3001	A30(19)	A30.3, A30RGH	LBF,RSH	M30576, M28414, UO7234
A*3002	A30(19)	A30.2	CR-8	X61702
A*3003	A30(19)	A30JS	JS,HT	M93657
A*31011	A31(12)	—	JHAF	M30578, M28416
A*31012	A31(19)	—	KRCO33, TB	M84375, M88405
A*3201	A32(19)	—	AM	P10314
A*3301	A33(19)	Aw33.1	JOE	M30580, M28415
A*3302	A33(19)	Aw33.2	IT	L06440
A*3401	A34(10)	—	ENA	X61704

(*continued*)

Table 1.2 (Continued)

HLA alleles	HLA specificity	Previous names	Source	Accession number
A*3402	A34(10)		WWAI	X61705
A*3601	A36	—	MASCH	X61700
A*4301	A43	—	CC	X61703
A*6601	A66(10)		25/1506, TEM	X61711
A*6602	A66(10)	—	CR-D, MAL8, HUT 102	X61712, X51745
A*68011	A68(28)	Aw68.1	LB	X03070, X03071
A*68012	A68(28)	Aw68.1	GRC187	LO5425
A*6802	A68(26)	Aw68.2	PA,TO	U03861
A*6901	A69(28)	—	IUE,ZM,BJ	X03158, X03159
A*7401	A74(10)	—	CC,PDAV, ATUR	X601701
A*8001	—	AX"BG," A-new	VII,35020, 35841, 32611, CODI, MIKA, LADA	M94880, L18898, L19403
B*0701	B7	B7.1	CF	—
B*0702	B7	B7.2	JY	M16102, M32317, M35444, P01889
B*0703	B703	BPOT	POT71	X64454
B*0704	B7	B7E	10243	U04245
B*0801	B8	—	LCL721, MF,CGM1	M59841, M24036, M28204
B*0802	B8	B8V	20015	U04244
B*1301	B13	B13,1	HE	M24075
B*1302	B13	B13,2	LBF,TO	M19757, M24041
B*1401	B64(14)	—	MRWC, 32387, W6106	M24040
B*1402	B65(14)	—	BB,CGM1	M59840, M24032
B*1501	B62(15)	—	MF,HA, BCK,OLGA (OLL),KT17	M28203, M83198, U03859
B*1502	B75(15)	—	APB,LW	M75138, M83192
B*1503	B72(70)	—	CC,25931, 31708	X61709
B*1504	B62(15)	Bw620G	GRC138, KG	M84382, M86402
B*1505	B62(15)	Bw62.1	VB	M83191
B*1506	B62(15)	Bw62.4	WI	M83194
B*1507	B62(15)	Bw62.5	SB	M83195
B*1508	B62(15)	B62 variant	KIIAGNI, LATIE, DAN723	L11666
B*1509	B70	B70.1	34863	L115/1
B*1510	B71(70)	B70.2	25514,19014, GU373	L11570
B*1511	B15	B15variant	LEE748	L11604
B*1512	B76(15)	B76	THA1742	L11603
B*1513	B77(15)	B77	RSA-ND, CAM020	L15005
B*1514	B76(15)	B76	SS713	L19937
B*1515	B62(15)	B62s	MLH727	L22027
B*1516	B63(15)	B63.1, 8W66	DOP-ND, 21909, 31133	L09735
B*1517	B63(15)	B63	JAP-NF	U01848
B*1518	—	B7901, B"X"-HS	HS	—
B*1519	B76(15)	B76	GEE018	UO3027
B*1520	B62(15)	—	OLBA (OLL)	U06862

Table 1.2 (Continued)

HLA alleles	HLA specificity	Previous names	Source	Accession number
B*1801	B18	—	SGAR,F24	M24039
B*1802	B18	R18PF	PETCH	D25275
B*2701	B27	271	LH	—
B*2702	B27	27e,27K, B27.2	BRUG	X03664, X03667
B*2703	B27	27d,27J	CH(CHI)	M54883, M27272
B*2704	B27	27b,27C, B27.3	WEWAK 1	
B*27051	B27	27a,27W, B27.1	BRUG	X03665, X03666
B*27052	B27	27a,27W, B27.1	CB,HC, MRWC, KCA,MVL,LG2.	X03945, M12967, 120088, M14013, M12678
B*2706	B27	27D,B27.4	LIE,PAR	X73578
B*2707	B27	B27-HS	HS	M62852
B*2708	—	B7Oul	19418, BCK	L19923
B*3501	B35	—	HS, KT17	M28109 12
B*3502	B35	—	DL	M63454
B*3503	B35	—	C1R, HMY2	M81798
B*3504	B35		AN	M86403
B*3505	B35	B35-G	GRC212, KRC032	M84385
B*3506	B35	B35-K	KRC103	M84381
B*3507	B35	—	#2073	L04605
B*3608	B35	B35TL	#22338,TL	L04696, Z22651
B*3701	B37	—	KAS011. MG	M32320
B*3801	B38(16)	B16.1	Z	M29864
B*3802	B38(15)		RSA-ND	L22028
B*39011	B3901	B39.1, B16.2	S.JC	M94052, M29865
B*39013	B3901	B39.1J	IT,#591	M94051
B*39021	B3902	B39.2	YAM	M84053
B*39022	B3902	B39.2	CL170	U04243
B*3903	B39(16)	—	AUCA#19	L20088
B*3904	B39(18)	B39N	TO	L22649
B*40011	B60(40)	—	LB.#W7079	P01890, U03698
B*40012	B60(40)	B60Ut	Ut-m	M95530
B*4002	B61(40)	B40	SWEIG, CALDGERO, YUKI, 10014	L09736, D14343
B*4003	B40	B40-G1	GRC138	M84383
B*4004	B40	B40-G2	GRC212	M84384
B*4005	B4005	BN21	00136	M841691
B*4006	B61(40)	B61	Ot-s	M95531
B*4101	B41	—	SGAR	M24035
B*4201	B42		BB	M211031
B*4402	B44(12)	B44.1, B44.2	FMB,BAU	M24038, M15470
B*4403	B44(12)	B44.1 New	PITOUT, F24	X64366

(continued)

Table 1.2 (Continued)

HLA alleles	HLA specificity	Previous names	Source	Accession number
B*4404	B44(12)	B44.4	TAN,BEB	X75953, X78426, X78427
B*4501	B45(12)	—	OMW	X61710
B*4601	B46	—	T7527, THA1742	M24033
B*4701	B47	—	PLH	M19756
B*4801	B48	—	KCR103, HS67	M84380
B*4802	B48	—	AUCA#18	L20089
B*4901	B49(21)	—	AM	M21037
B*5001	B50(21)	—	SH,JO	X61706
B*5101	B51(5)	—	LKT-2,TO,BM92,CD	M32319, M21035, M22786-8, M28207
B*5102	B5102	B6.36	UM,02627	M68961
B*5103	B5103	BTA	30-BY3	M80670
B*5104	B51(5)	—	KRC005, GRC187, GRC150	Z15148
B*5105	B61(6)	B61v	LK	U08697
B*52011	B52(3)	—	MT,LK707	M21038, M2283-9
B*52021	B52(5)	—	AUCA#2	L20090
B*5301	B53	—	AMAI,AM	M33574, M58636
B*5401	B54(22)	—	LKT-3,TTL	M77774
B*5501	B55(22)	—	VEN	M77778
B*5502	B55(22)	—	APA	M77777
B*5601	B56(22)	—	VOO	M77776
B*5602	B56(22)	—	ENA	M77775
B*5701	B57(17)	—	W1N,MOC, MOLT4	X55711, M32318
B*5702	B57(17)	Bw57.2	32/32	X61707
B*5801	B58(17)	—	WT49	M11799
B*5901	B59	—	AT,KY	L07743
B*0701	B07	—	11367, #591, #W7079	L17005
B*7301	B73	—	LK/O/, LE023, HL	UU4/8/, X7658, L24373
B*7801	B7801	B'SNA', Bx1	SNA,32/32	X61708, M33673
Cw*0101	Cw1	Cw1.1	BRUG	M16272
Cw*0102	Cw1	Cw1.2	T7527,AP	M84171
Cw*0201	Cw2	Cw2.1	BRUG	M16273
Cw*02021	Cw2	Cw2.2	MVL	M24030
Cw*02022	Cw2	Cw2.2	SWEIG	M26712
Cw*0301	Cw3	—	JG	K02058, X00495
Cw*0302	Cw3	—	AP	M81172
Cw*0303	Cw3	—	GRC150	M99390
Cw*0304	Cw3	—	KRC110	M99389
Cw*0401	Cw4	—	C1R, KRC103	M84386, X58536
Cw*0402	Cw4	BeWD C.1	BeWD	M26432
Cw*0501	Cw5	—	OBL,RC	M58630, M34290, L24491

Table 1.2 (Continued)

HLA alleles	HLA specificity	Previous names	Source	Accession number
Cw*0601	Cw6	—	JOE	M28160
Cw*0602	Cw6	Cw6(W)	MS,G088, DJS	M26208, X70857, Z22752-4
Cw*0701	Cw7	—	MF	M28205
Cw*0702	Cw7	JY328	JY	—
Cw*0703	Cw7	HLA-4	?	M11886
Cw*0801	Cw8	—	02627	M84174
Cw*0208	Cw8	—	CQM1, LWAGS, WT51	M59885, M84173
Cw*0803	Cw8	—	KRC103	Z15144
Cw*1201	—	Cx52	AKIBA	M21963, D12471-2
Cw*12021	—	Cb2	MT	M28172, M28174, M28176, M28178
Cw*12022	—	Cw1202 gyp	G085	X70856
Cw*1203	—	Cw12New	D0208915. WDV, YAR	U08895, U06698
Cw*1301	—	CwBL18	TCC	M58631, M34291
Cw*1401	—	Cb-1	LKT2	M20171, M28173, M28175, M28177
Cw*1402	—	V14New	LUY	U0648/
Cw*1501	—	CI.8	GM637	M24069
Cw*1502	—	C'X,Cw'6.2	AUCA#2, GO85, GO88	L20091, X67818
Cw*1503	—	—	GRC150	M99388
Cw*1504	—	Cw158p	C047	X73518
Cw*1601	—	CI.10	GM697	M24097
Cw*1602	—	Cw16v	C073	X76189
Cw*1701	—	Cw16New	RSH	U06835
E*0101	—	JTW15	JT,YN,HF	M20022
E*0102	—	HLA-6.2	LCL/21	M21533
E*0103	—	M32507	MT,MH.TK	M32507
E*0104	—	M23508	KS	M32508
G*01011	—	HLA6.0, G*1	LCL/21.144,ASR53, Mou, SP0010	J03027, X17273, L27836, L27836, L27837
G*01012	—	BeWb G7	BeWb	M32800
G*0102	—	Ice 8.23-5.4H	ICE 8	880807
G*0103	—	G*III	LWAGS	M99048

1.2.2. HLA Class Ib

The HLA class Ib gene products have a number of similarities with class Ia molecules and may function in antigen presentation. HLA-E surface levels vary according to the availability of appropriate HLA-E binding peptide which, similar to class Ia molecules, is necessary for optimum surface expression (51,52). HLA-F appears to exhibit a

significant degree of intraspecies conservation in various primate and nonprimate species, which is suggestive of an important functional role for the molecule (53,54), and both HLA-E and HLA-F have been proposed as restriction elements for γδ T cells (55). Recently, mutation in the HLA-H gene has been associated with the inherited disease hemochromatosis (56). HLA-G is expressed in placental extravillous cytotrophoblasts during specific stages of development, with its different isoforms being secreted or localized on the cell surface (57,58). Interestingly, cytotrophoblasts do not express class Ia genes, which appear to encode negative transcriptional regulatory elements that are absent from HLA-G loci (59,60). It has been suggested that for normal development of the semiallogeneic fetus, cytotrophoblasts must somehow evade inducing a maternal antifetus immune response and that HLA-G may play a role in this (61–63), perhaps by suppressing NK cell responses (64,65). Consistent with an immunological role, HLA-G expression has recently been shown to be upregulated on mononuclear phagocytes in response to IFNγ (66). Moreover, it appears that HLA-G may be an efficient antigen-presenting molecule (67,68).

1.2.3. Class I Transcriptional Regulation

A number of *cis*-acting regulatory elements incorporated into two enhancer regions, in addition to an interferon response element (IRE), are located in the 5′ region of class I genes and are required for normal expression and inducibility (Figure 1.7). Enhancer A appears to regulate constitutive expression of class I genes in a variety of cell types through binding of different factors (Figure 1.8) (69–72). The IRE binds a number of proteins that are both constitutively present and/or interferon inducible, although the IRE on its own does not confer interferon inducibility (73,74). Factors that bind IRE constitute a broad and still emerging family of molecules, which at present include the nine related factors IRF-1 (75,76), IRF-2, IRF-3 (77), LSIRF (Pip, NF-EM5, IRF-4) (78,79), IRF-5, IRF-6, CIRF-3, ICSBP, and ISGF-3γ (80,81). The exact role of these factors, however, in the regulation of class I expression is not clearly understood. Mice deficient in IRF-1 have apparently normal levels of class I expression, although they are less resistant to some infections (75,82), which is similar to observations for IRF-2-deficient mice (82). Although ISGF-3γ (interferon-stimulated gene factor) may be involved in regulating class I expression (81), the temporal regulation of ISGF-3γ expression after IFNγ treatment does not correlate well with class I upregulation (83). On the other hand, ICSBP (interferon consensus binding protein), which is exclusively expressed in cells of the immune system, appears to act only as a negative regulator of class I expression (84–87). Downregulation of class I transcription also occurs after infection with tumorigenic adenovirus, which involves the viral E1A gene product (88–90). E1A appears to interfere with NF-κB p50–p65 binding to elements in the enhancer A region of class I promoters (91–93). This interferes with the efficient presentation of viral antigens and works presumably as an immune evasion tactic.

1.2.4. HLA Class II

Class II molecules are expressed from a 1000-kb stretch of DNA in the D region. The class II genes have been categorized into five families, according to structural similarities and the ability to form heterodimers, and are designated DN(DO), DM, DP, DQ, and DR.

Each family contains separate genes encoding the α (A) and β (B) chains that form the class II αβ heterodimer. Considerable similarity exists between HLA-DR and -DQ family and murine E and A, respectively (94). To date, 67 DPB1, 41 DQB1, and 127 DRB1 alleles have been assigned (Table 1.3) (48). DP and DQ subregions each express a single α-chain and β-chain subunit, whereas the DR locus may express multiple β chains according to haplotype. A total of nine DRB loci (DRB1–DRB9) have been identified and as many as five DRB loci may be present in an individual haplotype, although only DRB1, DRB4, and DRB5 are functional genes (Figure 1.8). However, most individuals express two DR β chains: DRB1 and an additional β chain selected from DRB2 to DRB8 loci. DRB1 and DRB2 are highly polymorphic, whereas those encoded by DRB3 to DRB8 are less so. DR(A) α chains are virtually invariant (95). Both α and β products from DQ regions are polymorphic and HLA-DQ heterodimers from both parental DQ loci can dimerize to form unique HLA-DQ class II molecules (96).

Class II expression and tissue specificity are important in terms of immunoregulation of $CD4^+$ T-helper cells and several models exist indicating a role for class II molecules in autoimmune pathogenesis (97,98) (see Chapter 5). Thus, class II expression is largely confined to professional antigen-presenting cells with dedicated roles in immune response induction (99). Significant levels of class II are constitutively expressed in Langerhans cells, interdigitating cells, follicular dendritic cells, B cells, and macrophages. Class II is also present on epithelial cells of the thymus, where it participates in antigen presentation to and selection of thymocytes. In addition, class II is found on microglial cells of the CNS, where aberrant expression is associated with disease (100–102).

The transcription of both α and β subunits of class II heterodimers is tightly regulated and controlled mainly by regulatory elements in the 5′-flanking regions of their genes. Many of the *cis*-acting elements are shared by all class II genes whereas others are specific for either α or β genes (103–105). Starting from the 5′-proximal end of the promoter, *cis*-acting elements include: TATA and CCAAT motifs, Y, X2, X1, and W/Z/S boxes, all of which appear to be required for normal tissue-specific expression and inducibility (106–109). Several DNA-binding proteins have been described that appear to regulate class II expression, including RFX, X2BP, and NFY (CBF, CP1, YEBP) (103). RFX is a member of a family of related transcription factors that form both homo- and heterodimers that bind X1 boxes and regulate inducible expression of class II molecules (110–112). Interestingly, RFX (EC-2) also transactivates hepatitis B virus (HBV) and polyomavirus (Py) genes through high-affinity binding sites (113–115). The X2 binding protein (X2BP) interacts with the X2 box and is composed of two polypeptide subunits, one of which may be a member of the ATF/CREB family (116). Recent observations indicate that X2BP may form a complex with RFX (116). NFY, also known as CCAAT binding factor (CBF), binds the CCAAT motif in numerous eukaryotic promoters and in Y boxes (which contain inverted CCAAT box sequence) of class II genes. NFY has recently been found to share some primary sequence homology with histone proteins and to require three subunits (CBF-A, -B, and -C) to form DNA-binding complexes (117). The class II transactivator, CIITA, is a critical regulator of both constitutive and inducible class II expression and is absent in the human disease "bare lymphocyte syndrome" (118–120). The induction of class II genes in response to mediators such as IFNγ varies for different cell types and the developmental stage of cells. In some situations, for example, TNFα can synergize with IFNγ to induce class II expression (121–124), whereas in others it can suppress the effects of IFNγ on class II upregulation (125–127). Class II induction by IFNγ has also been shown to be inhibited by TGFβ, which may serve an immunoregulatory role (128–130).

Table 1.3
Class II Alleles

HLA-DR alleles	HLA-DR serological specificities	HLA-D–associated (T-cell–defined) specificities	Previous equivalents	Accession number
DRA*0101	—	—	DRaPDR-a-2	J00194, J00196, J00203
DRA*0102	—	—	DR-H	J00201
DRB1*0101	DR1	Dw1	—	X03069, M1161
DRB1*0102	DR1	Dw20	DR1-NASC	—
DRB1*0103	DR103	Dw'BON'	DR1-CETUS, DRB1*BON	M33600
DRB1*0104	DR1	—	DRB1*01New	X70251
DRB1*1501	DR15(2)	Dw2	DR2B Dw2	M17378, M16957, M29430
DRB1*15021	DR15(2)	Dw12	DR2B Dw12	M16958, M30180
DRB1*15022	DR15(2)	Dw12	DR2MU	L23964
DRB1*1503	DR15(2)	—	—	M35159
DRB1*1504	DR15(2)	—	DR2DAI	L23963
DRB1*1601	DR16(2)	Dw21	DR2B Dw21	M16959, M30179
DRB1*1602	DR16(2)	Dw22	DR2B Dw22	M20504
DRB1*1603	—	—	—	L02545
DRB1*1604	DR16(2)	—	DRB1*16x8	L14582
DRB1*1605	—	—	—	X74343
DRB1*1606	DR2	—	16PRET	X75444
DRB1*03011	DR17(3)	Dw3	—	M17379, X04054
DRB1*03012	DR17(3)	Dw3	DRB1*IMR	M91807, L07767
DRB1*0302	DR18(3)	Dw'RSH'	—	M27689
DRB1*0303	DR18(3)	—	—	M81743
DRB1*0304	DR3	—	03MIT	X75441
DRB1*0401	DR4	Dw4	—	K0776, M17381, M20548-50, M19556
DRB1*0402	DR4	Dw10	—	M15068
DRB1*0403	DR4	Dw13	DR4 Dw13A, 13.1	—
DRB1*0404	DR4	Dw14	DR4 Dw14A, 14.1	X02902, M15073, M1569-74
DRB1*0405	DR4	Dw15	—	M15070, L13875
DRB1*0406	DR4	Dw'KT2'	—	—
DRB1*0407	DR4	Dw13	DR4 Dw13B, 13.2	M37771
DRB1*0408	DR4	Dw14	DR4-CETUS, Dw14B, 14.2	M37770
DRB1*0409	DR4	—	—	M37769, M64794
DRB1*0410	DR4	—	DR4.CB	M81670, M36879
DRB1*0411	DR4	—	DR4.EC	M81700, M55615
DRB1*0412	DR4	—	AB2	M77672
DRB1*0413	DR4	—	DRB1*LEV	M94460

Table 1.3 (Continued)

HLA-DR alleles	HLA-DR serological specificities	HLA-D-associated (T-cell-defined) specificities	Previous equivalents	Accession number
DRB1*0414	DR4	—	DR4 Dw10.2	X65031
DRB1*0415	DR4	—	—	X68272
DRB1*0416	DR4	—	DR4-BELF	X70788
DRB1*0417	DR4	—	DRB1*04SAM	L14481
DRB1*0418	DR4	—	DRB1*04.N	X71610
DRB1*0419	DR4	—	DR4FK	L21985
DRB1*11011	DR11(5)	Dw5	DRw11.1	M11867
DRB1*11012	DR11(5)	Dw5	—	M34316
DRB1*1102	DR11(5)	Dw'JVM'	DRw11.2	M17382
DRB1*1103	DR11(5)	—	DRw11.3	M21966, M22047-49
DRB1*11041	DR11(5)	Dw'FS'	—	—
DRB1*11042	DR11(5)	—	—	M34317
DRB1*1105	DR11(5)	—	—	M84188
DRB1*1106	DR11(5)	—	DR11.CCY,11PMH	M98436, D14352
DRB1*1107	—	—	—	X73027
DRB1*11081	DR11(5)	—	DR11JL	L21984
DRB1*11082	DR11(5)	—	DR11HW	L21983
DRB1*1109	DR11(5)	—	DRB1*MON	X75347
DRB1*1110	—	—	DR11.5	L23986
DRB1*1111	—	—	DR11.6, DR11BRA	L23987, L26306
DRB1*1112	—	—	DR11.7	L23989
DRB1*1113	—	—	DR11-14	X76194, L29081, U09200
DRB1*1201	DR12(5)	Dw'DB6'	—	M27635, M27509
DRB1*1202	DR12(5)	—	DRw12b	M27510
DRB1*1203	DR12(5)	—	DRw12POPE	S48645
DRB1*1301	DR13(6)	Dw18	DRw6a I	M17383, X04056
DRB1*1302	DR13(6)	Dw19	DRw6c I	—
DRB1*1303	DR13(6)	Dw'HAG'	—	X52451, X16649, M34320-23, M57599
DRB1*1304	DR13(6)	—	RB1125-14	M34320-24
DRB1*1305	DR13(6)	—	DRw6'PEV'	M57600
DRB1*1306	DR13(6)	—	DRB1*113.MW	M61899
DRB1*1307	—	—	DRB1*JJY, DRB1*SHN	L06847, D13189
DRB1*1308	DR13(6)	—	—	L03531
DRB1*1309	—	—	DRB1*YUN	L23535
DRB1*1310	DR13(6)	—	13NEW	X75442
DRB1*1311	DR13(6)	—	—	X74313
DRB1*1312	—	—	DR113BRA, DR13.7	L25427, L23988
DRB1*1313	—	—	DRB1*13GDR	D17742

(continued)

Table 1.3 (Continued)

HLA-DR alleles	HLA-DR serological specificities	HLA-D-associated (T-cell-defined) specificities	Previous equivalents	Accession number
DRB1*1401	DR14(6)	Dw9	DRw6b I	X04057
DRB1*1402	DR14(6)	Dw16	—	—
DRB1*1403	DR1403	—	JX6	—
DRB1*1404	DR1404	—	DRB1*LY10, DRw6b.2	M34372
DRB1*1405	DR14(6)	—	DRB1*14c	M33693, M60209
DRB1*1406	DR14(6)	—	DRB1*14GB, 14.6	M63972, M74032
DRB1*1407	DR14(6)	—	14.7	M74030
DRB1*1408	DR14(6)	—	AO1, 14.8	M77673, M74031
DRB1*1409	DR14(6)	—	AB4	M77671
DRB1*1410	—	—	AB3	M77670
DRB1*1411	—	—	DRw14x11	M84238
DRB1*1412	—	—	DRB1*Y0S	D16110
DRB1*1413	—	—	—	L21755
DRB1*1414	—	—	DRB1*14N	U02561
DRB1*1415	—	—	DRB1*af	X766195
DRB1*1416	—	—	—	XX76198
DRB1*1417	—	—	1412T	X76938
DRB1*0701	DR7	Dw17, Dw'DB1'	—	M16941, M17384, U09201
DRB1*0801	DR8	Dw8.1	—	M17386
DRB1*08021	DR8	Dw8.2	DRw8-SPL	—
DRB1*08022	DR8	Dw8.2	DRw8b	—
DRB1*08031	DR8	Dw8.3	DRw8b-TAB	—
DRB1*08032	DR8	Dw8.3	—	M27511
DRB1*08041	DR8	—	RB1066-1, DR8-V86	M84446, M34315
DRB1*08042	DR8	—	—	L10402
DRB1*0805	DR8	—	DR8-A74	M84357
DRB1*0806	DR8	—	DR8.6	M87543, M86590
DRB1*0807	DR8	—	DR8BZ	L22341
DRB1*0808	DR8	—	08New	X75443
DRB1*0809	DR8	—	DR8.7	L23990
DRB1*0810	DR8	—	LP10-1	L19054
DRB1*0811	DR8	—	DR8TL	—
DRB1*09011	DR9	Dw23	—	—
DRB1*09012	DR9	Dw23	—	M17387
DRB1*1001	DR10	—	—	M20138
DRB3*0101	DR52	Dw24	DR3 III, DRw6a III	X04055
DRB3*0201	DR52	Dw25	DRw6b III	M17380, V00522
DRB3*0202	DR52	Dw25	pDR5b.3	—
DRB3*0301	DR52	Dw26	—	—

Table 1.3 (Continued)

HLA-DR alleles	HLA-DR serological specificities	HLA-D-associated (T-cell-defined) specificities	Previous equivalents	Accession number
DRB4*01	DR53	Dw4, Dw10, Dw13, Dw14, Dw15, Dw17, Dw23	—	M17385, M17388, M15071-2, K02775
DRB4*01011	DR53	Dw17	—	M16942
DRB4*01012 N	DR53	Dw11	DRB4 null	—
DRB4*0102	DR53	—	DRB4*ICML	L08621
DRB4*0103	DR53	Dw4	—	M15178-9, M29555, M19556
DRB5*0101	DR51	Dw2	DR2A Dw2	M17377, M16954, M20429
DRB5*0102	DR51	Dw12	DR2A Dw12	M16955, M30182
DRB5*0201	DR51	Dw21	DR2A Dw21	M16956, M30181
DRB5*0202	DR51	Dw22	DR2A Dw22	M20503
DRB5*0203	DR51	—	DRB5*HK	M91001
DRB6*0101	—	—	DRBs*0101, DRBX11	X53357, M83892
DRB6*0201	—	—	DRBX21, DRBV1	M77284-7, X53358, M83893
DRB6*0202	—	—	DRBs*0201,drbx22, DRB6III	M83204, M83894
DRB7*01011	—	—	DRBHY1	K02772-4, L31617
DRB7*01012	—	—	—	L31618
DQA1*0101	—	Dw1	DQA 1.1,1.9	—
DQA1*0102	—	Dw2,w21, w19	DQA 1.2,1.19,1.AZH	—
DQA1*0103	—	Dw18, w12, w8, Dw'FS'	DQA 1.3,1.18, DRw8 DQw1	M34320-3
DQA1*0104	—	Dw9	—	M34314
DQA1*0201	—	Dw7,w11	DQA 2,3.7	—
DQA1*03011	—	Dw4,w10, w13,w14, w15	DQA 3,3.1,3.2	M29613, M29616
DQA1*03012	—	Dw23	DQA 3,3.1,3.2, DR9-DQw3	—
DQA1*0302	—	Dw23	DQA 3,3.1,3.2, DR9-DQw3	M11124
DQA1*0401	—	Dw8, Dw'RSH'	DQA 4.2,3.8	M33906
DQA1*0501	—	Dw3,w5,w22	DQA 4.1,2	—

(continued)

Table 1.3 (Continued)

HLA-DR alleles	HLA-DR serological specificities	HLA-D-associated (T-cell-defined) specificities	Previous equivalents	Accession number
DQA1*0513	—	Dw22	DQA 4.1,2	M20506
DQA1*0502	—	—	—	U03675
DQA1*0601	—	Dw8	DQA 4.3	—
DQB1*0501	DQ 5(1)	Dw1	DQB 1.1, DRw10-DQw1.1	X03068, M65044
DQB1*0502	DQ 5(1)	Dw21	DQB 1.2,1.21	—
DQB1*05031	DQ 5(1)	Dw9	DQB 1.3,1.9,1.3.1	M65047
DQB1*05032	DQ 5(1)	Dw9	DQB 1.3.1.9,1.3.2	—
DQB1*0504	—	—	DQB 1.9	M65046,M94773
DQB1*06011	DQ 6(1)	Dw12,w8	DQB 1.4,1.12	M65048
DQB1*06012	DQ 6(1)	Dw12,w8	DQB1*0601 var.	M86740
DQB1*0602	DQ 6(1)	Dw2	DQB 1.5,1.2	M20432
DQB1*0603	DQ 6(1)	Dw18, Dw'FS'	DQB 1.6,1.18	M65050, M34320
DQB1*0604	DQ 6(1)	Dw19	DQB 1.7,1.19	M65051
DQB1*06051	DQ 6(1)	Dw19	DQB1.8, DQBSLE, 1.19b, 2013-24	M36472, M34320, M65052
DQB1*06052	DQ 6(1)	Dw19	DQB1*MDvRR-1	L26325
DQB1*0606	—	—	DQB1*WA1	M86226
DQB1*0607	—	—	DQB1*06BRI1	M87041
DQB1*0608	—	—	DQB1*06BRI2	M87042
DQB1*0609	—	—	DQB1*06AA	L19951, L27345
DQB1*0201	DQ2	Dw3	DQB 2	K02405, M65043, M81140
DQB1*0202	DQ2	Dw7	DQB 2	M81141, UO7848
DQB1*0301	DQ7(3)	Dw4,w5, w8, w3	DQB 3.1	M65040
DQB1*0302	DQ8(3)	Dw4,w10, w13, w14	DQB 3.2	M65038, K01499
DQB1*03031	DQ9(3)	Dw23	DQB 3.3	—
DQB1*03032	DQ9(3)	Dw23,w11	DQB 3.3	M65039, M60028
DQB1*0304	DQ7(3)	—	DQB1*03HP,*03New	M74842, M83770, X76553
DQB1*0305	—	—	DQB1*03KC	M69169
DQB1*0401	DQ4	Dw15	DQB 4.1 Wa	M13279
DQB1*0402	DQ	Dw8, Dw'RSH'	DQB 4.2 Wa	M33907, M65042

HLA-DP alleles	Associated HLA-DP specificities	Previous equivalents	Accession number
DPA1*0101	—	LB14/LB24,DPA1	X00457, K01506
DPA1*0202	—	pSBa-318	—

Table 1.3 (Continued)

HLA-DP alleles	Associated HLA-DP specificities	Previous equivalents	Accession number
DPA1*0103	—	DPw4a1	X03100
DPA1*0201	—	DPA2,pDAa13B	—
DPA1*02021	—	2.21	M83906, I11642
DPA1*02022	—	2.22	M83907, L11641
DPA1*0301	—	3.1	M83908
DPA1*0401	—	4.1	M83909, L11643
DPB1*01011	DPw1	DPB1,DPw1b	M83129, M83664, M62338, X72070
DPB1*01012	DPw1	DPB1*WA6	L19220, L27662
DPB1*0201	DPw2	DPB2.1	—
DPB1*02011	DPw2	DPB2.1	X01426
DPB1*02012	DPw2	DPB2.1	M62328, X03067
DPB1*0202	DPw2	DPB2.2	M62329, X72071
DPB1*0301	DPw3	DPB3	M62334, X02964, X03023, X78044
DPB1*0401	DPw4	DPB4.1,DPw4a	M62326, M23675, K01615, N00010, M23906-9, X033022, X030025-8, X02228, X00532, X72072
DPB1*0402	DPw4	DPB4.2,DPw4b	M62327, M21886
DPB1*0501	DPw5	DPB5	M62333, X72073
DPB1*0601	DPw6	DPB6	M62335, X72074
DPB1*0801	—	DPB8	M62331
DPB1*0901	—	DPB9,DP'Cp63'	M62341, X72075
DPB1*1001	—	DPB10	M85223, M62342, X072076
DPB1*11011	—	DPB11	M62336, X78046
DPB1*11012	—	—	L23399
DPB1*1301	—	DPB13	M62337, X72077
DPB1*1401	—	DPB14	M31778, M62343, X72077
DPB1*1501	—	DPB15	M31779, M62339, X72079
DPB1*1601	—	DPB16	M31780, M62332
DPB1*1701	—	DPB17	M31781, M62344
DPB1*1801	—	DPB18	M62340
DPB1*1901	—	DPB19	M62330, X72081
DPB1*20011	—	Oos,DPB-JA	M58608, M63508
DPB1*20012	—	DPB1*BR16	M97685
DPB1*2101	—	DPB-GM,DPB30,NewD	M77659, M83915, M84621, M80300
DPB1*2201	—	DPB1*AB1,NewH	M77674, M83919
DPB1*2301	—	DPB32,NewB	M83913, M84014
DPB1*2401	—	DPB33,NewC	M83914
DPB1*2501	—	DPB34,NewE	M83916
DPB1*26011	—	DPB31,WA2	M86229
DPB1*26012	—	DPB1*WA8	L24387
DPB1*2701	—	DPB23,WA3	M84619, M86230
DPB1*2801	—	DPB21,JAVA2	L84617, L00599

(continued)

Table 1.3 (Continued)

HLA-DP alleles	Associated HLA-DP specificities	Previous equivalents	Accession number
DPB1*2901	—	DPB27,NewG	M84625, M83918, L01467
DPB1*3001	—	DPB28	M84620, X78045
DPB1*3101	—	DPB22,NewF,JAVA1	M84618, M83917, L00598
DPB1*3201	—	DPB24,NewI	M84622, M85222
DPB1*3301	—	DPB25	M84623
DPB1*3401	—	DPB26	M84624
DPB1*3501	—	DPB29	M84626
DPB1*3601	—	NewA,SSK2	M83912, D10479, D10882
DPB1*3701	—	DPB18WA4	M87046
DPB1*3801	—	SSK1	D10478
DPB1*3901	—	DPB1*BRI4	M97686, X78043
DPB1*4001	—	DPB1*BRI5,WA5	M97684, L19219, L23400
DPB1*4101	—	DPB2.3	D13174
DPB1*4401	—	STCZ	L01466
DPB1*4501	—	DPB1*NM	L09236
DPB1*4601	—	DPB1*NIB	L07768
DPB1*4701	—	DPB1*02KY,*SUT	D14344, D10834
DPB1*4801	—	—	L17314
DPB1*4901	—	—	L17313
DPB1*5001	—	—	L17311
DPB1*5101	—	DPB1*WA7,*EA1,*JYO	L17310
DPB1*5201	—	—	L22076
DPB1*5301	—	—	L22077
DPB1*5401	—	DPB1 New2	L78042
DPB1*5501	—	DPB1 New3	L80041

1.3. PEPTIDE-BINDING POCKETS

1.3.1. Class I Peptide Binding

Interactions resulting from both conserved and polymorphic residues of peptides and class I molecules are responsible for securing peptides into the binding groove (131). Binding of peptides into the groove is achieved in part by amino and carbonyl main-chain atoms at either end of the peptides, which form noncovalent bonds with highly conserved tyrosine, lysine, and threonine and of class I molecules (132–135). Crystallographic analysis of class I molecules has also revealed that the peptide-binding groove contains a series of depressions that provide steric freedom and unique environments for protruding amino acid side chains (R groups) of the peptides. These depressions, or pockets, are formed by class I residues that exhibit high degrees of polymorphism and thus unique pocket environments are characteristic of the different class I alleles. The peptide-binding groove is formed by β-pleated sheets that make up the floor of the groove and α-helical walls that run the length of the groove, secondary structures that are formed by both α1 and α2 domains of the class I molecules. The pockets that accommodate the peptide R groups are topographically located between the β-pleated floor and the α-helical walls that run the length of the groove (pockets B through E), and are formed at either end of the

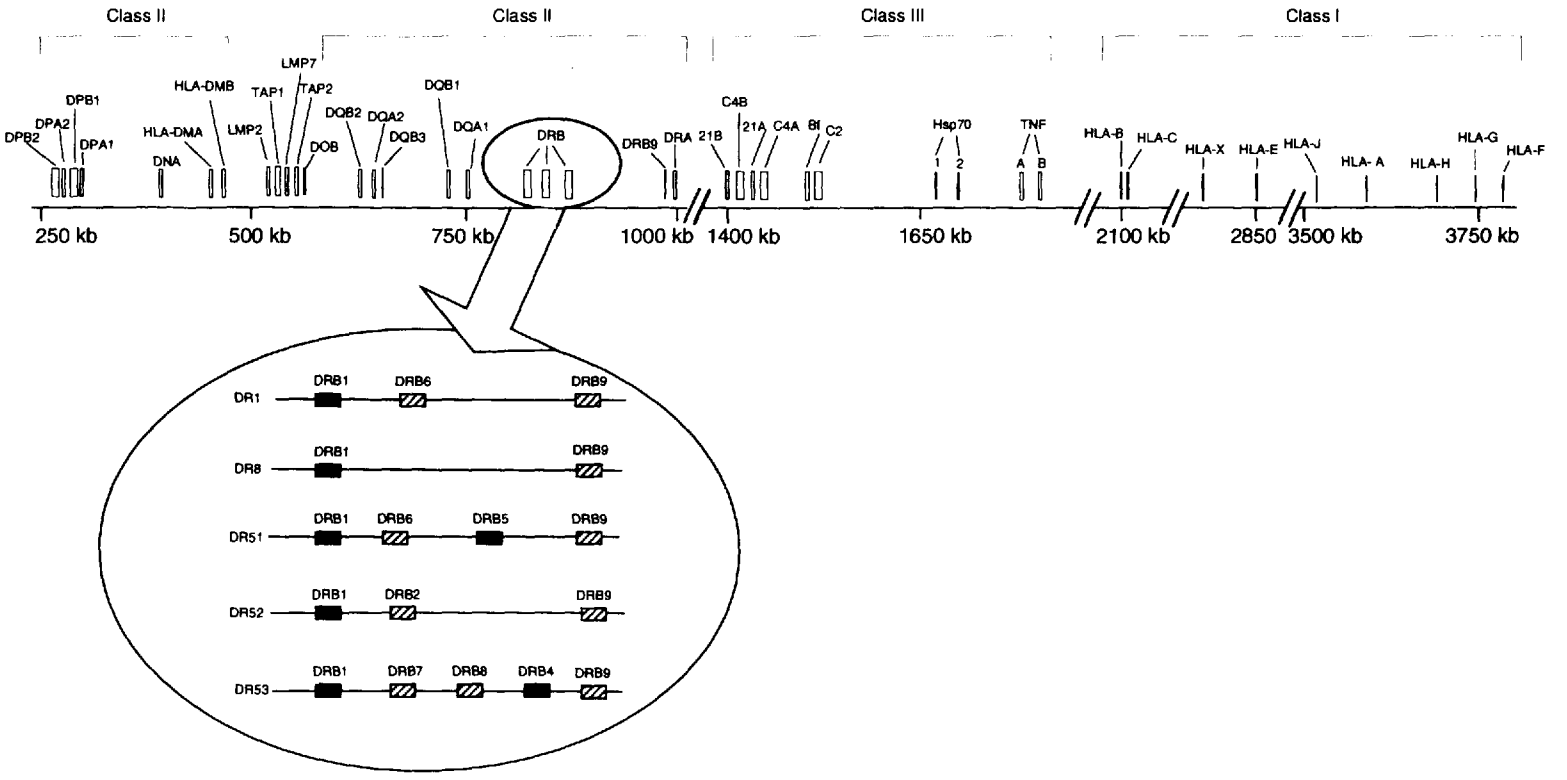

Figure 1.8. A map of the HLA complex. Exploded view provides details of the class II DRB genes associated with different haplotypes. Solid boxes are functional genes; striped boxes are pseudogenes.

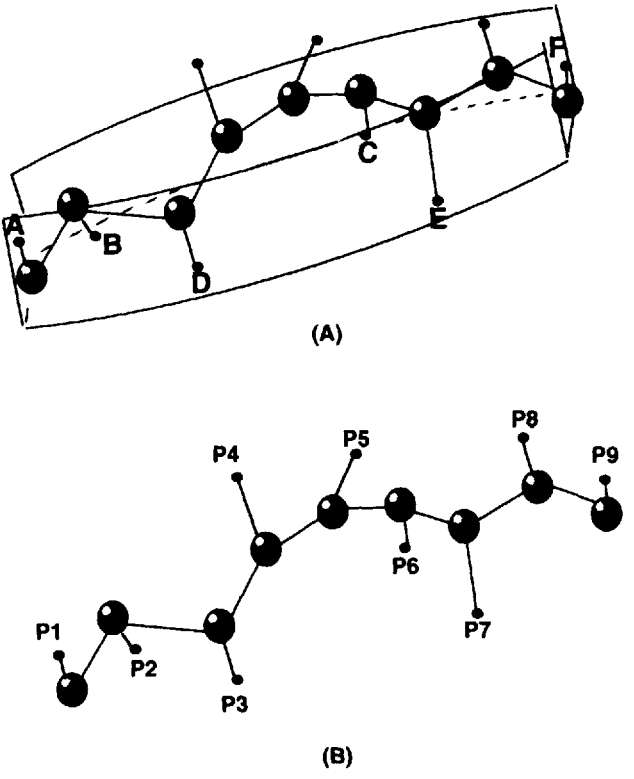

Figure 1.9. Nomenclature of the peptide-binding groove of class I molecule. (A) Peptide-binding pockets are designated A–F. The sides of the canoe-shaped peptide-binding pocket represent the α-helical walls, and the floor represents the β-pleated sheet. Pockets are formed at the intersection of walls and floor. (B) Side chains of class I-binding peptides are typically designated P1–P9.

groove (pockets A and F) where the α-helical walls sandwich the peptide (Figure 1.9). Because the α-helical walls of the class I groove close in at either end of the groove, the potential length of peptides is restricted to α-helical conformations of 8–10 amino acids (136–139). The pockets add selectivity and bonding strength to peptide interactions in the class I peptide-binding groove (140,141) and at the same time define class I allele-specific peptide "anchor" residues, or binding motifs (142,143). Anchor residues are thus amino acids that are preferred by the pocket environment and aligned on peptides to facilitate binding in the class I groove (Table 1.4).

Understanding the nature of the peptide–class I interaction is important to elucidating the role of peptides as antigenic determinants for T cells. Evidence that the middle residues of class I-bound peptides bulged out from the binding groove (Figure 1.10) raised the possibility that this portion of the peptide is highly "visible" to the TCR (201, 202). If this were the case *in vivo*, it might suggest that certain portions of the peptide play a more prominent role as antigenic determinants for T cells. More recent analysis of five peptide–HLA crystal structures has provided a more detailed understanding of class I–peptide interactions (203). It appears that the orientation of R groups at middle positions of the peptide have steric freedom to extend outward (toward the TCR), inward (toward the β-pleated floor of the groove), or laterally (toward the α-helical wall). The orientation of

Table 1.4
Known and Probable Naturally Occurring Peptides[a]

Class I	Peptide	Source	Ref.
H-2D^b	A S N E N M E T M	FLu NP 1934 366-374	(144,145)
	A S N E N M D A M	FLu NP 1968 366-374	(146)
	C K G V N K E Y L	SV-40 T Ag 223-231	(147)
	Q G I N N L D N L	SV-40 T Ag 489 497	(147)
	S G P S N T P P E I	Adenovirus-2 Ela 234-243	(148,149)
	V E N P G G Y C L	LCMV GP 278-286	(150)
	Q P Q N G Q F I H F Y	LCMV NP 397-401	(151)
	A I N N Y A Q K L	SV-40 T Ag 205-215	(147)
H-2D^d	K G P I T V Q I	Unknown	(152)
	V G P Q K N E N L	Unknown	(152)
	S G P R K A I A L	Unknown	(152)
	A G P D R T E K L	Unknown	(152)
	K G P D K G N E F	Unknown	(152)
	I G P E R G H N L	Unknown	(152)
	D G P V R E H N L	Unknown	(152)
	K G P E R A N G L	Unknown	(152)
	S G P E R G E K L	Unknown	(152)
	D G P V R G I S I	Unknown	(152)
	N G P Q R I Y N L	Unknown	(152)
	S G P V A L V N F	Unknown	(152)
	I G P N R A F N F	Unknown	(152)
	S G P E R I L S I	Unknown	(152)
	S G P E R I L S L	Unknown	(152)
	V G P S J K Y F I	Unknown	(152)
	F G P Y K L N R L	Unknown	(152)
	F G P I K F N V L	Unknown	(152)
	F G P Y R F Y V L	Unknown	(152)
	S G P K T D A Q T L	Unknown	(152)
	A G P D R T E K A L	Unknown	(152)
	S G P V A L V N F I	Unknown	(152)
	S G P E R I L S A Y	Unknown	(152)
	V G P S G K Y F I L	Unknown	(152)
	F G P Y R F Y V L T	Unknown	(152)
	R G P G R A F V T I	HIV-1 gb160	(153)
	G P P H S N N F G Y	Tum-P35B 4-13	(154)
H-2K^b	S I I N F E K L	Ovalbumin 257-264	(155)
	R G Y V Y Q G L	VSV G 52-59	(156)
	H I Y E F P Q L	Unknown	(157)
	F A P G N Y P A L	Sendai virus NP 324-332	(158)
H-2K^d	S Y F P E I T H I	Tyrosine kinase IAK1	(157,159)
	K Y Q A V T T T L	Tum-P198 14-22	(160,161)
	T Y Q R T R A L V	Flu NP 147-155	(144,145, 161)
	G Y K D G N E Y I	Listeriolysin O 91-99	(162)

(continued)

Table 1.4 (Continued)

Class I	Peptide	Source	Ref.
	S Y V P S A E Q I	P. yoelii CS 280-288	(161)
	S Y I P S A E K I	P. berghei CS 252-260	(161)
	S Y I G S I N N I	RSV M2 82-90	(163)
	L Y Q N V G T Y V	Flu A/Iap/57 HA 204-212	(161,162, 164,165)
	T Y V S V G T S T L	Flu A/Iap/57 HA 210-219	
	R Y L E N G K E T L	HLA-A24 170-179	
	R Y L K N G K E T L	HLA-Cw3 170-179	
	Y P H F M P T N L	Murine CMV pp80 167-176	
H-2K^k	S D Y E G R L I	Flu NP 50-57	(166)
	F E A N G N L I	Flu HA 259-266	(166)
	E E G A I V G E I	Flu NS1 152-160	(167)
	I E G G W T G M I	Flu HA 354-362	(166)
H-2L^d	L S P F P F D L	Unknown (2C epitope)	(168)
	U P Q P G R E Q	Unknown	(169)
	U P A U A Y P Y	Unknown	(169)
	Y P N V N I H N F	Unknown	(169)
	Q P Q R G R E N F	Unknown	(169)
	U P Q P N I Y Q I	Unknown	(169)
	U P I E A N Y Q U F	Unknown	(169)
	A P Q P G M E N F K	Unknown	(169)
	U P Q K A G G F L M	Unknown	(169)
	L P L G W L V	Tum-P1A 33-46	(170)
	Y P H F M P T N L	Murine CMVpp89 168-176	(165)
	R P Q A S G V Y M	LCMV NP 118-126	(171)
HLA-A1	Y T S D Y F I S Y	Ets-1	[b]
	Y L D D P D L K Y	Cytosine methyl transferase	[b]
	I A D M G H L K Y	Prolif cell nuclear factor	[b]
	S T D H I P I L Y	Fructose-6-amino transferase	[b]
	D S D G S F F L Y	Human IgG4 279-284	[b]
	A T D F K F A M Y	^{x}Cyclin type D	[b]
	G T D E X R N X Y	Unknown	[b]
	V S D P Y N X K Y	Unknown	[b]
	V A D K V H X M Y	Unknown	[b]
	Y T A V V P L V Y	Human J-chain 102-110	[b]
	Y T N P Q F N V Y	Unknown	[b]
	E T X X P D W S Y	Unknown	[b]
	F T D V N S X X R Y	Unknown	[b]

Table 1.4 (Continued)

Class I	Peptide	Source	Ref.
	E T D X X X D R S E Y	Unknown	[b]
	Y T D Y G G L I F N S	Cytochrome c oxides	[b]
	Y E A D P T G H S Y	MAGE-1 161-169	(172)
HLA-A2.1	L L D V P T A A V	IP-30 signal sequence	(173)
	S L L P A I V E L	Protein phosphate 2A	(173)
	Y L L P A I V H I	ATP-dependent RNA helicase	(173)
	T L W V D P Y E V	TIS21	(173)
	S X P S G G X G V	Unknown	(173)
	G X V P F X V S V	Unknown	(173)
	S X X V R A X E V	Unknown	(173)
	K X N E P V X X X	Unknown	(173)
	A X W G F F P V X	Unknown	(173)
	M V D G T L L L L	HLA-E signal sequence	(173)
	Y M N G T M S Q V	Tyrosinase	(174)
	M L L S V P L L L G	Calerticulin signal sequence	(175)
	L L L D V P T A A V	IP-30 signal sequence	(175)
	L L L D V P T A A V Q A	IP-30 signal sequence	(175)
	V L F R G G P R G L L A	SSRα signal sequence	(175)
	V A L F G Y P V Y V	HTLV 1 tax 12-19	(176)
	W L S L L V P F V	Hepatitis B sAg 335-343	(177)
	G I L G F V F T L	Flu A M1 58-66	(178.179)
	I L K E P V H G V	HIV-1 RT 476-484	(180)
	L L F G Y P V Y V	HTLV 1 Tax 11-19	(176)
	I A G N S A Y E Y V	Human CMV gB 619-628	(176)
	F L P S D F F P S V	Hepatitis B cAg 18-27	(181)
	G L S P T V W L S V	Hepatitis B sAg 348-357	(177)
HLA-A3.1	K L F K N I L Y K	Unknown	(182)
	K L H K Q R A K S	Unknown	(182)
	S L F K Q V V T K	Unknown	(182)
	K L F N I M V T Y	Unknown	(182)
	K L F E K V Y N Y	Unknown	(182)
	K L F K V T F S Y	Unknown	(182)
	K L F V K V Y N Y	Unknown	(182)
	K I V R K P G M A	Unknown	(182)
	K M F N I T V T Y	Unknown	(182)
	K L F K V V U N Y	Unknown	(182)
	S L F N T H L U K	Unknown	(182)
	S L U E K T F D Y	Unknown	(182)
	S L F E L V F U Y	Unknown	(182)
	S L H K Y U F E Y	Unknown	(182)
	T L A N D U V V P	Unknown	(182)

(continued)

Table 1.4 (Continued)

Class I	Peptide	Source	Ref.
	K U F K M I L R K	Unknown	(182)
	K U F V K U L U Y	Unknown	(182)
	T U F V K U L U Y	Unknown	(182)
	G L F P U Q F A Y	Unknown	(182)
	K L Y E K V Y T Y K	Unknown	(182)
	S L F D H I L U K H	Unknown	(182)
	Y L U V R U A U I V	Unknown	(182)
	G I F A U U U V K A	Unknown	(182)
	R L R D L L L I V T R	HIV-1 Env 768-778	(183)
HLA-A11	S V L N L V I V K	Ribosomal protein S6	*b*
	K V V N P L F E K	Ribosomal protein L7A	*b*
	R T Q N V L G E K	Ribosomal protein S3	*b*
	G T M T T S X Y K	Unknown	*b*
	A S F D K A K L K	Thymosin b-10	*b*
	A A M X D T V V F K	Unknown	*b*
	R V E Q A V E S M V K	Unknown	*b*
	A T A G D G X X E L R K	Prohibitin	*b*
	I V T D F S V I K	EBNA 4 416-424	(184,185)
HLA-A24	K Y P N E F F L L	Protein phosphatase 1	*b*
	Y Y E E Q H P E L	NK/T-bell activation protein	*b*
	A Y V H M V T H F	Unknown	*b*
	V Y X K H P V S X	Unknown	*b*
	Y L K D Q Q L L	HIV-1 gp41 584-591	(186)
HLA-A31	S T L P E T T V V R R	Hepatitis B cAg 141-151	(187)
HLA-A68.1	A V A A V A A P R	Unknown	(188)
	D V F R D P A L K	Ribosomal 60 S homologue	(188)
	E V A P P E Y H R	Unknown	(188)
	K T G G P I Y K R	Flu NP 91-99	(188,189)
	E V A P P E Y H R K	Unknown	(188)
	E V I L I D P F H K	Unknown	(188)
	T V F D A K R L I G R	Hsp70 protein B/Hsc70	(188)
	S T L P E T T V V R R	Hep Bc 141-151	(187)
HLA-B7	A P R T V A L T A	HLA-DP signal sequence	(190)
	A P R A X X X X X	Unknown	(190)
	A P R X P X T G X	Unknown	(190)
	A P R A S R P S X	Unknown	(190)
	A P R T L V L L L	HLA-A2.1 signal sequence	(190)
	A P R S N G M V X	Unknown	*c*
	A P R Q P G X M A	Unknown	*c*

Table 1.4 (Continued)

Class I	Peptide	Source	Ref.
	A P R P P P K P M	Ribosomal S26 protein	[c]
	M P R G V V V T X	Unknown	(190)
	S P R Y I F T M L	Topoisomerase II	(190)
	A P A P T V A V X	Unknown	(190)
	R P K S N I V L L	CD20	(190)
	R P S G P G P E X	Unknown	(190)
	A P Y G G P X A X	Unknown	[c]
	L V M A P R T V L	HLA-B7 signal sequence	(190)
	R V M A P R A X X	Unknown	(190)
	A P R T V A L T A L	HLA-DP signal sequence	(190)
	A P R A F X P X P V	Unknown	(190)
	A A S K E R S G V S L	Histone H1	(190)
HLA-B8	Y L K D Q Q L L	HIV-1 env 586-593	(191)
	F L R G R A Y G L	EBNA 3 339-347	(192)
	E L R S R Y W A I	Flu A/PR/8/34 NP 380-388	(193,194)
HLA-B14	E R Y L K D Q Q L	HIV-1 Env 582-591	(191)
HLA-B27	R R I K E I V K K	Hsp89α	(195)
	G R I D K P I L K	Ribosomal protein	(195)
	A R L F G I R A K	Unknown	(195)
	R R S K E I T V R	ATP-dependent RNA helicase	(195)
	K R F E G L T Q R	Unknown	(195)
	R R V K E V V K K	Hsp89β	(195)
	F R Y N G L I H R	60 S ribosomal protein	(195)
	R R Y Q K S T E L	Histone H3.3	(195)
	R R W L P A G D A	Elongation factor 2	(195)
	R R I S G V D R Y	Unknown	(195)
	R R F T R P E H —	Unknown	(195)
	K K Y Q K S T E L	Unknown	
	S R Y W A I R T R	Flu A NP 383-391	(196)
	R R R W R R L T V	EBNA LMP2 236-244	(197)
	R R Y P D A V Y L	Measles F protein 438-466	(198)
	R R Y I D L I E L	EBNA 3C 258-266	(197)
	K R W I I L G L N K I V	HIV Gag p24 265-276	(196)
HLA-AB53	K P I V Q Y D N F	P. falciparum LSA-1 1786-1795	(199)
HLA-Cw	F N C G G E F F	HIV-1 gp120	(200)

[a]Used with permission, Victor H. Engelhard, Structure of Peptides Associated with MHC Class I Molecules, *Curr. Opin. Immunol.* **6**:13–23, 1994.

[b]Kubo, R., Sette, A., Gray, M., Appellar, E,. Sakaguchi, K., *et al.* Unpublished data.

[c]Bodoar, W., Huczko, E., Engelhard, V., and Hunt, D. Unpublished data.

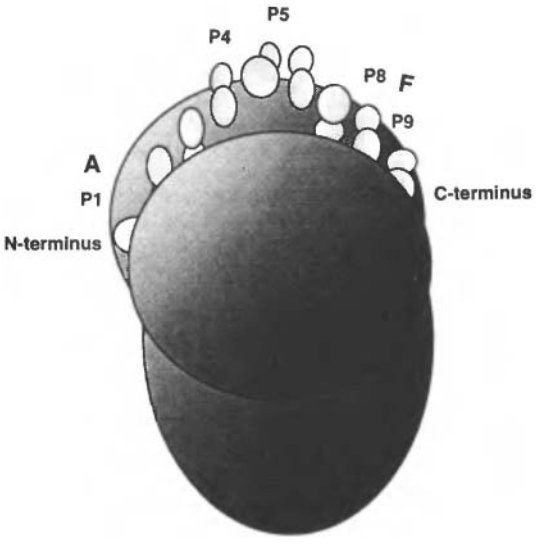

Figure 1.10. Peptide bound in the pocket of class I molecule. The middle portions of peptides in the groove of class I molecules bulge out and have more exposure to the TCR.

these R groups varies according to the composition of the entire peptide sequence, which also dictates the exact positioning of the main-chain atoms of the peptide backbone. Although peptide orientation in the groove is variable, class I molecules themselves appear to be very restricted in their ability to undergo conformational changes in response to different peptides (203). The interpretation drawn from these observations is that antigenic specificity for individual peptides must in large part be determined by discrete interactions between the peptides themselves and TCR. However, other findings suggest that conformational changes in the binding groove can alter the antigenic epitope of HLA-B51 but not the peptide binding characteristics (204).

1.3.2. Class II Peptide Binding

As for class I molecules, the class II binding groove interacts with peptides in a peptide sequence-specific and nonspecific manner. X-ray crystallographic analysis of the class II molecule HLA-DR1 has indicated four peptide-binding pockets (see above) which facilitate interactions with peptide side chains and confer peptide-binding specificity (205, 206). As with class I also, polymorphism of class II molecules is concentrated at pocket-forming residues, resulting in the class II-allele-specific peptide-binding motifs, or anchor residues (207–210). Although these structures are less defined for class II molecules, attempts have been made to identify some important features governing peptide binding for various class II molecules (Table 5). The binding grooves of both class I and class II have similar β-pleated sheet structures on the floor of the groove, but differ significantly in the α-helical strands that form the walls of the pocket. Moreover, the class II molecule lacks the conserved interactions with the N- and C-termini of bound peptides. Thus, a major difference between the class I and class II peptide groove is the open-ended nature of the class II pocket, which has less length restriction on peptides, permitting lengths of between 15 and 24 residues, which "sit" in the groove in an extended conformation (Figure 1.11) (218–221). Although class II peptide-binding grooves lack conserved residues that might interact with N- and C-termini of peptides, conserved positions over the

Table 1.5
Examples of Pocket Specificities for HLA-DR Molecules[a]

Class II molecule	P1	P4	P6	P9
HLA-DRB1*0101				
Polymorphic residues	Gly86	Phe13, Gln70, Arg71, Ala, 74, Tyr78	Leu11, Phe13	Trp9, Asp57
Ligand specificity	**Aromatic,** aliphatic	**Aliphatic,** polar, no positive charge	**A, G,** S, T, P	Aliphatic, aromatic, polar
HLA-DRB1*0301				
Polymorphic residues	Gly86	Ser13, Gln70, Lys71, Arg74, Tyr78	Ser11, Ser13	Glu9, Asp57
Ligand specificity	**Aliphatic**	D,E,F	**K,R,**E,Q,N	Aromatic, aliphatic, polar
HLA-DRB1*0401				
Polymorphic residues	Gly86	His13, Gln70, Lys71, Ala74, Tyr78	Val11, His13	Glu9, Asp57
Ligand specificity	**Aromatic,** aliphatic	Aromatic, aliphatic, negative charges, no positive charges	N,S,T,Q,H,R	Polar, aliphatic, **K**
DRB1*0402				
Polymorphic residues	Val86	His13, Asp70, Gln71, Ala74, Tyr78	Val11, His13	Glu9, Asp57
Ligand specificity	**Aliphatic**	Aromatic, aliphatic, positive charges, no negative charges	N,Q,S,T,K	Polar, aliphatic, H
DRB1*0404				
Polymorphic residues	Val86	His13, Gln70, Arg71, Ala74, Tyr78	Val11, His13	Glu9, Asp57
Ligand specificity	**Aliphatic**	Aromatic, aliphatic, negative charges, no positive charges	N,S,T,Q,K,D	Polar, aliphatic, K
DRB1*0405				
Polymorphic residues	Gly86	His13, Gln70, Arg71, Ala74, Tyr78	Val11, His13	Glu9, Ser57
Ligand specificity	**Aromatic,** aliphatic	V,I,L,M,F,D,E	N,S,T,Q,K,D	**D,E,**Q

[a]Motif information has been obtained from the following references: DRB1*0101 (211–214); DRB1*0301 (215,216); DRB1*040 (212,213,217); DRB1*0401–0405 (T. Friede *et al.*, unpublished data). Preferred residues are shown in bold type. The three-letter code is used for residues of MHC chains and the one-letter code for MHC ligands.

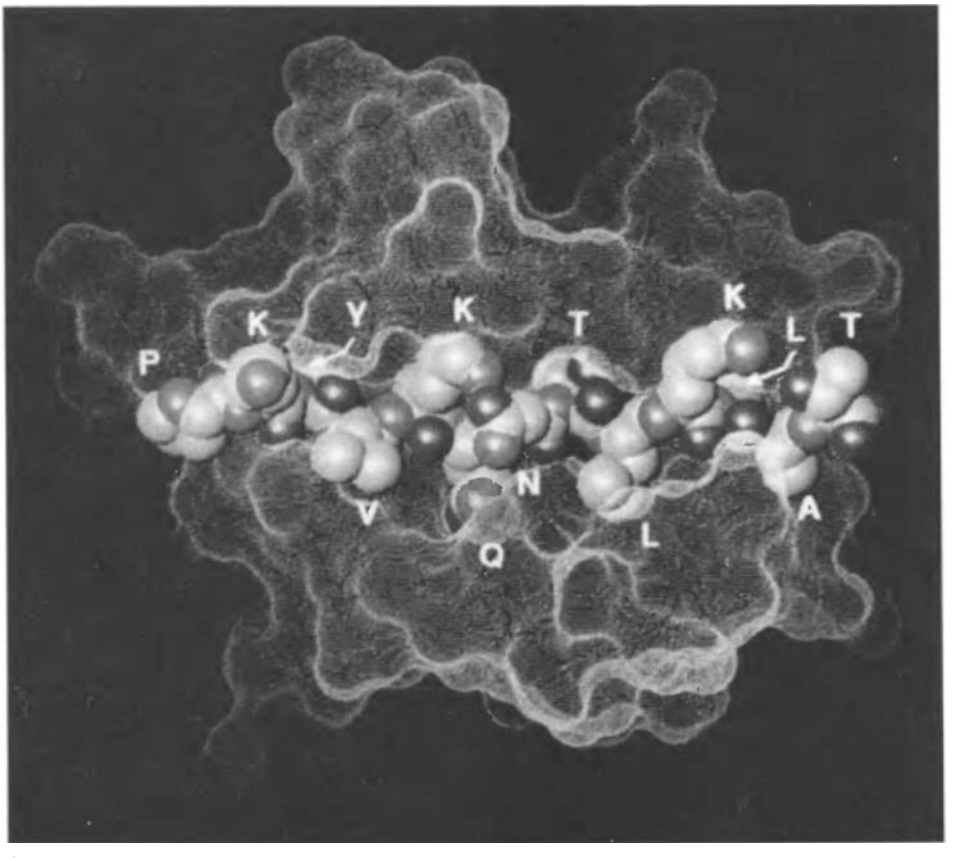

Figure 1.11. Computer-generated image of a viral peptide bound in the groove of the class II molecule HLADR1. Reprinted with permission from *Nature*, Stern *et al.* **368:**215–221, 1994, Macmillan Magazines Limited.

length of the class II groove may function to provide alternate side-chain-independent interactions with peptides (205).

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2

Genes of the Antigen Processing Pathways

There is overwhelming evidence that a bimodal system exists for processing and presenting antigen to T lymphocytes. This system involves the endogenous and exogenous pathways, responsible for processing and targeting antigen from internal and external sources for presentation on class I and class II major histocompatibility complex (MHC) molecules, respectively. The endogenous route supplies antigen predominately from cytosolic sources, such as virus-encoded proteins, whereas the exogenous route facilitates the processing and presentation of antigens captured at the cell surface, such as through endocytosis of antibody-bound (opsonized) pathogens. Such a discrete division of labor in antigen processing is, like most other conceptual models in biology, something of a caricature. However, besides being fundamentally accurate, the bimodal model is an important framework from which to appreciate larger issues of the immune system, such as immunoregulation. For example, distinct and separate pathways for antigen collection and presentation on class I and class II MHC provide an elegantly simple way by which we can imagine the autonomous regulation of antigen presentation to $CD8^+$ and $CD4^+$ T-cell subsets. Nonetheless, reality never quite fully surrenders itself to models and the processing of antigen for class I and class II molecules does appear to overlap. Moreover, the immunoregulatory mechanisms governing CD4 and CD8 T-cell-mediated immunity are considerably more complex than can be explained by understanding antigen presentation alone.

A fundamental strategy that is reflected in the design of the antigen processing machinery is its role to ensure that adequate peptide diversity and numbers are appropriately generated, and that these bits of antigen are made readily available to the immune system via class I and class II molecules. To accomplish this, the two pathways possess several processing stages, each with various levels of selectivity and polymorphism. The result and, perhaps, purpose of this selectivity and polymorphism is to generate an immense peptide repertoire in each individual and to provide for large inherent variability in the repertoire between different individuals. The large repertoire enables the immune system to be both a good protector against invaders and to be nonthreatening to the larger organism in which it operates. Stated differently, the antigen processing apparatus must have the capacity to produce a suitably broad set of peptides such that once all of those self-peptides to which the host must be tolerized are deducted from the total peptide repertoire, there remains enough peptide diversity to represent all encounterable patho-

gens. Although a cellular machinery capable of producing a diverse peptide repertoire solves the problem of survival for the individual, it must also be designed to ensure that no single pathogen, having subverted an individual immune system, might pillage an entire population or species. Thus, genetic polymorphism at various levels of the antigen presentation pathway is critical, the most important of which is likely the immense polymorphism of the MHC class I and class II molecules themselves. However, infectious agents have also learned to manipulate antigen presenting machinery (see Sections 2.1.1 and 2.1.4) and polymorphism in these components is sure to be critically important.

The interferon-inducible class I presentation pathway operates as a three-level system: at one level there is protein machinery dedicated peptide manufacturing, the proteasome complex; on another level there is selective peptide transporters that deliver antigen into the endoplasmic reticulum (ER); and finally there are the class I molecules themselves, which exhibit allele affinities for peptides. Polymorphism at each and every level of this process could help the immune system maintain its responsiveness to a plethora of pathogens that must constantly be striving to maximize antigenic crypticity, and otherwise seeking ways of subverting effective function of the immune system. Additionally, variations between processing systems present in cells of the thymus and of the periphery may be critical in differentially presenting antigen to the preimmune thymocytes and peripheral T cells, maintaining a critical balance between an effective immune repertoire and autoimmunity. The class I pathway starts off in the cytosol, where proteins produced inside the cell are degraded by the multicatalytic proteasome complex. The peptide products are then translocated into the ER via the transporters associated with antigen presentation (TAP). In the lumen of the ER the peptides bind the groove of class I molecules that are complexed with the chaperone p88, β_2-microglobulin, and TAP. After securing a peptide in its binding groove, the class I complex is released from TAP and is transported through the Golgi to the cell membrane surface.

Antigen processing in the class II pathway does not rely on either proteasomal degradation of proteins or peptide delivery by TAP. Rather, the class II pathway sources protein antigen that is taken up by endocytosis and degraded in acidic endosomal compartments. The pathway begins in the ER where class II $\alpha\beta$-heterodimers associate in multimeric complexes with invariant chain (Ii). These class II–Ii complexes are delivered through the Golgi and *trans*-Golgi reticulum where they intersect with the peptides generated in the endosomes. The Ii chaperone is proteolytically excised, leaving a residual CLIP peptide bound to the class II heterodimer. Finally, CLIP is exchanged for the peptides in a process that is regulated by the peptide exchanger HLA-DM/H-2M and the class II–peptide complexes are delivered to the cell surface. Components (Table 2.1) of class I and class II pathways are described below in more detail. The class I and class II molecules are discussed in Chapter 1.

2.1. THE CLASS I PATHWAY FOR ANTIGEN PROCESSING AND PRESENTATION

2.1.1. Proteasome

Degradation of the majority of cellular proteins occurs via a nonlysosomal, ATP-dependent process that involves large multicatalytic protease complexes, or proteasomes, which themselves constitute about 1% of total cellular protein (1–4). Proteasomes can be

Table 2.1
Components of the Antigen Processing Pathways

Component	Function	IFNγ inducible	Polymorphic
	Class I antigen processing pathway		
Proteasome	Regulated cleavage of cytosolic proteins	Yes	Yes
LMP2/LMP7	β-type subunit of 20 S particle; protease function; modulates proteasome function to produce antigenic peptides	Yes	Yes
PA28α/PA28β	Components of the 11 S cap structure of proteasome: enhance rate of protein degradation and alter composition of peptides generated	Yes	?
TAP1/TAP2	Transport of peptides into ER; assembly of peptide–class I complexes	Yes	Yes
Calnexin (p88,IP90)	Folding of class I and assembly of class I–peptide complexes	?	No
	Class II antigen processing pathway		
Invariant chain (Ii)	Assists assembly and folding of class II dimers; controls intracellular transport of class II to endosome; blocks loading of peptide in ER	Yes	—
CLIP	Class II–CLIP complex produced from class II-bound SLIP fragment; prevents peptide loading until sampling can occur in endosome	—	—
HLA-DM	Facilitates dissociation of CLIP and loading of antigenic peptide on class II molecules	Yes	No

isolated as 20 S (700 kDa) and 26 S (2000 kDa) particles from both cytosolic and nuclear compartments, where they degrade proteins linked covalently at carboxy-terminal lysine residues with the polypeptide ubiquitin. A recent report that the 20 and 26 S particles are associated predominately with the ER membrane and the cytoplasm, respectively, and that the 20 S proteasome is a stable complex that exists reversibly as a 26 S particle, suggests that the 20 and 26 S proteasomes may perform different functions (5). Chymotrypsin, trypsin, and peptidylglutamyl-peptide hydrolase-like activities are associated with the proteasome.

Although it is apparently not the only resource for these peptides (6–8), the ubiquitin–proteasome system appears critical for producing much of the peptide fragments needed to supply class I molecules with their antigenic repertoire (9). Proteasomal cleavage patterns have been shown to affect the availability of antigenic epitopes for presentation on class I molecules (10). However, the proteosomal cleavage of endogenous proteins is not necessary for peptides less than 18 amino acids in length, which are presented on class I in the absence of a functional proteasome (11).

X-ray crystallography has been used to establish the structure of a prototypical proteasome complex from *Thermoplasma acidophilum* (12). The 20 S proteasome parti-

cles are comprised of 28 subunits stacked in four rings in a barrel-like structure, each ring comprised of seven polypeptides; outer rings are designated as α-type subunits, and the two middle rings, which possess the proteolytic activity, are the β subunits, with the 20 S complex identified by the nomenclature α7β7β7α7. The α and β rings contain heterologous protein subunits with unique functional characteristics. The 20 S complex is assembled as a 15 S intermediate from pro-β-type subunits that are processed to acquire proteolytic function (5,13,14). Approximately 16 additional proteins (35–110 kDa) form a 19 S cap assembled onto either or both ends (α-subunit rings) of the 20 S core. The 19 S cap, or 19 S regulator, contains several ATPases and at least one subunit that binds ubiquitin and is required for 26 S function to degrade ubiquinated proteins (15). Interestingly, the viral protein TAX has been found to modulate proteasomal binding of proteins, and can thereby indirectly regulate its proteolytic activity (16).

IFNγ induces qualitative and quantitative changes in the make up and function of the proteasome (Figure 2.1). IFNγ causes enhanced expression of PA28α and PA28β, forming a 16-subunit oligomeric complex, called the 11 S regulator, that competes for binding with the 19 S particle at the α ends of the 20 S proteasome. The 11 S regulator appears to activate the proteasome and enhances the efficiency of peptide production (see below). It has been suggested that the 11 and 19 S regulators may bind at opposite ends of the 20 S proteasome thereby achieving a functional unit that both binds ubiquitin-conjugated proteins (19 S) and induces efficient generation of peptides (11 S), although the existence of

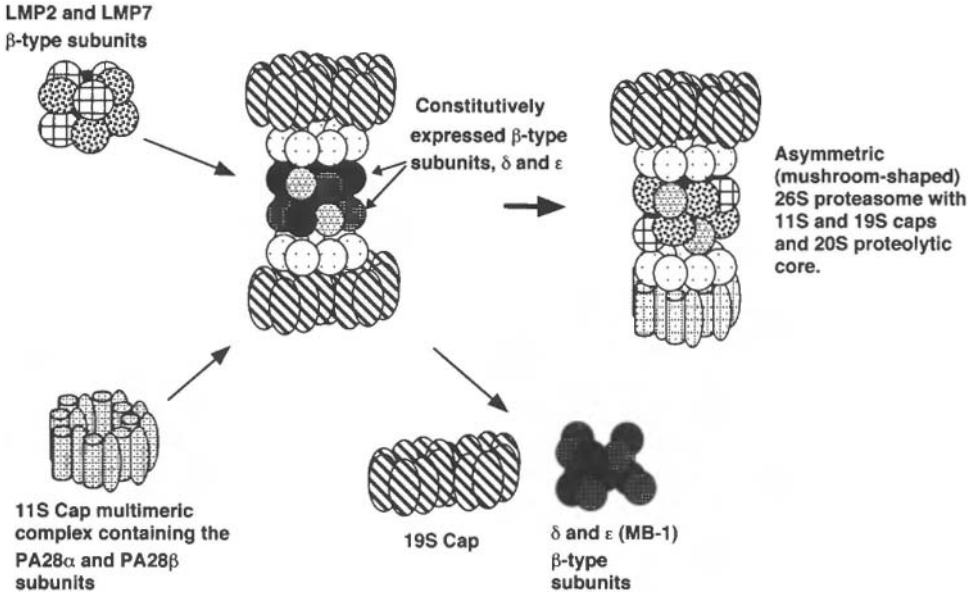

Figure 2.1. A hypothetical depiction of proteasome subunit exchange on induction by IFNγ. Expression of LMP2 and LMP7 subunits are upregulated by IFNγ and are exchanged for two of the three constitutively expressed β-type subunits, δ and ε. The 11 S regulator, composed of IFNγ-inducible PA28α and PA28β subunits, binds an α ring of the 20 S complex. A 26 S proteasome is produced that has an enhanced rate of peptide production and a propensity to generate peptides suitable for TAP transport into the ER for class I loading.

these complexes remains to be demonstrated. IFNγ can also induce changes in the composition of 20 S core proteins, by causing the displacement of β subunits by LMP2 and LMP7 molecules. The insertion of LMP2 and LMP7 into the 20 S core is believed to enhance the production of antigenically relevant peptides (see below). An additional IFNγ-inducible component, LMP10, may also be involved in the production of antigenically relevant peptides from the proteasomal complex (17).

The specificity and regulation of proteasome-mediated proteolysis are facilitated through the regulation of ubiquitin–protein conjugation, mediated by enzyme systems whose complexity is now emerging (18–20). The proteasome and its ubiquitin-conjugating enzyme system provide a system for ridding the cell of unwanted or irregular proteins and generally regulate the life span of other functional proteins—interesting examples being cyclin B (18,21–23) or the cyclin-dependent kinase inhibitor p27 (24); some other proteins regulated by the ubiquitin–proteasome pathway include MATα2, GCN4, c-jun, p50 subunit of NF-κB, IκB, p53, an α subunit of a G protein, and Mos kinase (1,4,25).

2.1.2. LMP2 and LMP7

The 20 S proteasome is a cylindrical-shaped multimeric complex built from a four-layer ring structure, two outer α rings and two middle β rings, each ring incorporating seven protein subunits (see above). In yeast there is a single different gene for each α- and β-type constituent of the 20 S multimer, with 14 different gene products incorporated into a single proteasome complex. The 20 S proteasome in humans constitutively incorporates three proteolytically active and three inactive β-type subunits, the latter inferred from findings using site-directed mutagenesis of β-type homologues in *T. acidophilum* (26). IFNγ induces expression of two β-type subunits, LMP2 and LMP7, which displace two of the three constituent and proteolytic β-type subunits, δ and ε (MB-1), and become incorporated into the 20 S proteasome (Figure 2.1) (27–30). LMP2 and LMP7 genes are closely linked to those of TAP in the MHC class II gene cluster (31–34) (Figure 2.2).

IFN-γ-induced changes in subunit composition enhance both the rate and efficiency of peptide production for class I ligands. LMP2 and LMP7 induction by IFNγ results in simultaneous downregulated expression of the so-called housekeeping subunits, δ and ε (also referred to as X and Y) (29,30), which have a peptidase activity that produces class I binding peptides only inefficiently (27,29,30,35,36). The LMP2 and LMP7-containing complex has a specific protease activity that produces peptides with hydrophobic or basic C-termini (37–40), a peptide configuration that promotes translocation into the ER and, consequently, loading on class I molecules.

LMP2 and LMP7 are synthesized as 24- and 30-kDa precursor proteins, processed to 21- and 23-kDa subunits (13), respectively, on assembly into the 20 S proteasome. LMP7 messenger RNA is constitutively expressed in murine spleen, thymus, lung, heart, liver, and kidney (41). Both LMP2 and LMP7 undergo posttranslational modifications on induction by IFNγ (14,42,43). LMP7-deficient mice have a 25–45% reduction in class I surface expression and APC show about a twofold reduction in their efficiency for presenting endogenous antigen to $CD8^+$ T cells (44). LMP2-deficient mice have normal class I expression but have reduced numbers of $CD8^+$ T cells and lower CTL precursor frequencies after infection with influenza virus than normal mice (45). In addition, peptide cleavage patterns by the proteasome are altered, showing reduced efficiency for generating peptides with C-terminal hydrophobic and basic residues.

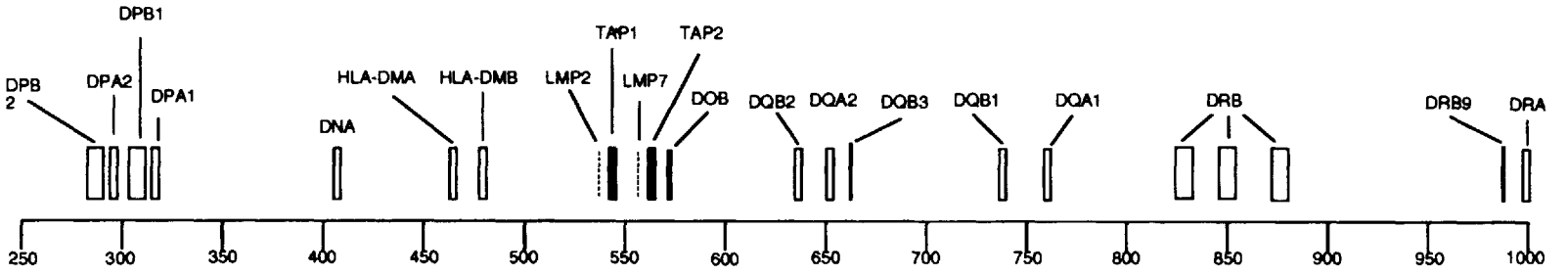

Figure 2.2. Location of the TAP and LMP genes in the human class II MHC gene cluster.

2.1.3. PA28α/PA28β

Stimulation of cells by IFNγ upregulates expression of LMP2, 7, and 10, which replace constitutive subunits present in the proteasome (see above). In addition, IFNγ upregulates two other genes that encode strong activators of the proteasome complex: the PA28α and PA28β subunits of the 11 S regulator (Figure 2.1) (46). PA28 is incorporated into the 11 S regulator and binds to the 20 S proteasome (47), where it induces a 3- to 50-fold enhancement of proteolytic activity, a rate that varies according to the amino acids involved at the cleavage site (48). The PA28α and PA28β subunits have an apparent molecular mass of 29 and 31 kDa, respectively, share about 50% sequence identity, and are phosphorylated during induction (49). Both α and β subunits exhibit about 90% sequence conservation between human and rat (50,51). Recent findings indicate that the 11 S regulators enhance the rate of protein degradation *in vitro*, and that the presence of the 11 S particle on 20 S proteasomes qualitatively alters the composition of peptides generated from the complex (48). The altered peptidase activity by PA28 may be more efficient at producing protein fragment antigens for class I presentation (52,53).

2.1.4. TAP1 and TAP2

The transporters associated with antigen processing (TAP) function as ATP-dependent peptide translocators (54–56), moving proteasome-digested—and other—protein fragments from the cytosol into the ER, where they can bind class I molecules [Although in some cases TAP may provide peptides for loading on class II molecules (57)]. The IFNγ-inducible (58) TAP genes are closely linked to those of LMP2 and LMP7 in the class II MHC gene cluster (Figure 2.2) (59) and belong to a family of molecules involved in ATP-dependent membrane translocation, known as the ABC (ATP-binding cassette) transporters, which include the multidrug resistance molecule P-glycoprotein (60) and the transmembrane regulator protein of cystic fibrosis (61). Unlike these ABC translocators, which operate as single molecules, TAP1 and TAP2 function in the ER membrane as a heterodimer, each subunit having primary sequences of over 500 amino acids, each with two hydrophobic domains, six membrane-spanning regions, and a cytosolic ATP binding motif (Figure 2.3). Both TAP1 and TAP2 subunits are required for peptide binding and translocation. TAP1 appears to be uniquely involved in interactions with class I/β_2 dimers at the luminal membrane of the ER (62), where it interacts with the membrane-proximal region of the α3 domain of class I–β_2-microglobulin complexes prior to peptide loading (62–65). Recent evidence suggests that the interaction between class I and TAP, which is crucial for efficient peptide loading and antigen presentation (66), may be mediated by an additional factor, the 48-kDa glycoprotein tapasin (67). TAP also binds β_2M independently of class I heavy chain, perhaps facilitating rapid assembly of class I peptide-binding complexes (68).

The selection of peptides for transport into the ER has been found to vary with polymorphism in TAP2 subunits (69,70), such that the different TAP2 alleles can alter peptide repertories being presented by a given class I molecule (70–73). In rats, TAP heterodimers have shown a general preference to translocate peptides with basic and hydrophobic C-termini (55), although the putative peptide binding site of TAP exhibits little peptide binding specificity (74). It has been calculated that TAP heterodimers can translocate more than 20,000 peptides/min to supply nascent class I molecules produced at a rate of 10–100/min (75). The TAP heterodimer has also shown a preference for

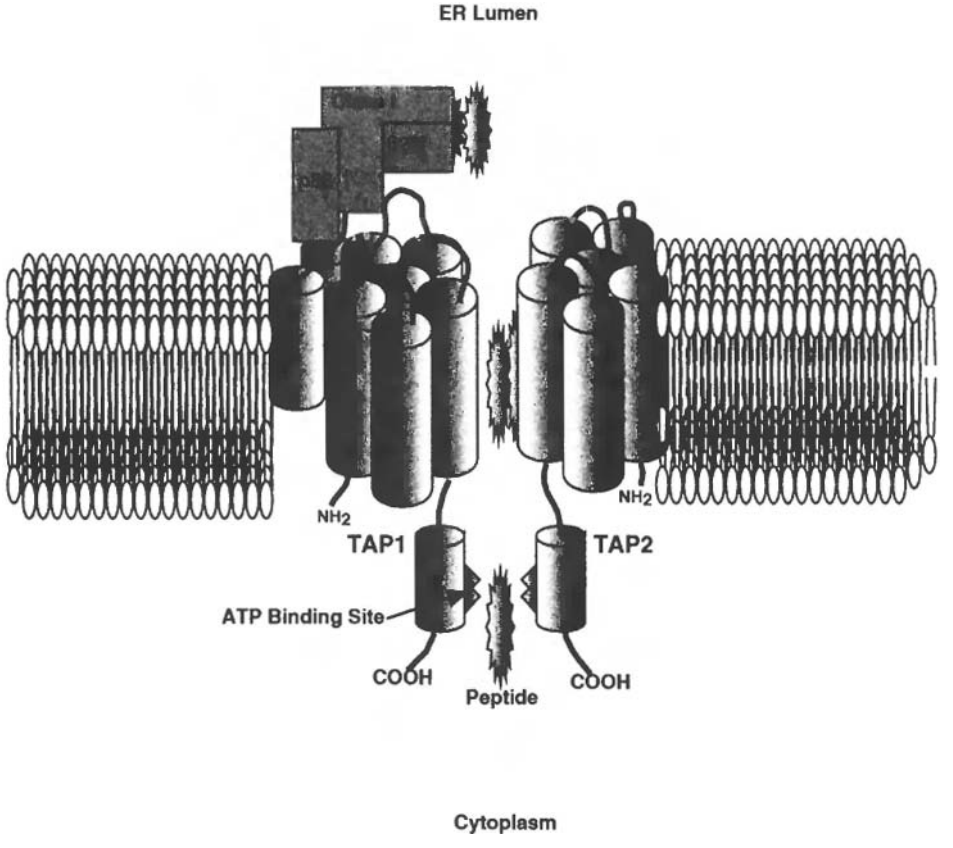

Figure 2.3. A model of TAP transport and loading of peptides onto class I MHC. A promiscuous ATP-dependent binding site captures peptides for transport into the ER. Selectivity of the TAP transporter is imparted by the TAP2 subunit. p88–class I–β_2M complex is associated with TAP1 subunit and dissociates after loading of peptide.

peptides with a restricted number of amino acids, although length restrictions vary with different studies and with *in vitro* and *in vivo* systems. *In vitro* studies indicate that optimal peptide length for TAP is similar to that required for peptide loading on class I, between 8 and 10 residues (76,77), even though TAP can transport peptides ranging from 7 to 40 residues in length. Although the importance (if any) of peptide secondary structure on TAP selectivity is not yet defined, it has been suggested that, like other members of the ABC transporters, TAP may prefer amphipathic molecules. Such selectivity would also make sense in terms of antigen presentation, as T-cell antigenic determinants are often clustered around sequences where amphipathic helical structures are predicted (78–81).

TAP-deficient cell lines also present skewed repertoires of peptides on class I molecules. Peptides present on class I molecules on these cells represent only 1–21% of the species found on normal cells, and are mainly those containing signal sequence domains of translocated and membrane-bound proteins (82). Stated differently, TAP deficiency results in no more than 6 different peptides representing half of the species presented by class I MHC on the cell (82–84), compared to at least 200 major peptide species on normal cells (82).

The involvement of TAP genes in disease is under investigation. The role of TAP in tumor cell evasion of immune surveillance has not been contradicted by observations that mutations in TAP-1, rendering the protein unable to transport peptides into the ER, correlate with reduced class I expression in tumor cells (85–88). Interestingly, cells transformed by oncogenic adenovirus have downregulated TAP expression and reduced surface levels of class I molecules (89). Finally, the herpes simplex virus-encoded protein ICP47 has been shown to interfere with class I presentation (90) through interacting with TAP (91,92) at its peptide-binding domain (93,94). ICP47 appears to prevent peptide translocation into the ER, which results in virus-infected cells going undetected by class I-restricted T cells. TAP is also a candidate susceptibility factor for autoimmune disease (70,73).

2.1.5. Calnexin (p88, IP90)

Calnexin is an 88-kDa lectinlike transmembrane resident of the ER that performs chaperone functions through binding its substrates via N-linked monoglucosylated moieties (95–97). Calnexin is highly conserved (93–98%) among mammals, and is located on the distal end of the long arm of human chromosome 5, at 5q35 (98). Both the cytosolic C-terminus and luminal N-terminus are Ca^{2+} binding. The lectin character of calnexin separates it from other chaperones, although it lacks sequence identity with known lectins and may represent a new family of molecules. Calnexin binds core glycans of oligosaccharide side chains after trimming of outer N-linked sugars by glucosidases I and II, or after glucosylation of a high-mannose glycan (99) (Figure 2.4). As such, calnexin has been shown to exhibit dramatically reduced protein binding in cells lines that are deficient for glucosidase enzymes (100). It is not yet clear whether calnexin can bind nonglycosylated proteins.

An important immunological function of calnexin is to bind nascent class I molecules as they enter the ER (101), keeping them there until the class I molecules are properly folded and capable of loading peptide (65,102,103). Once loaded with peptide, the class I–β_2M–peptide complexes dissociate from TAP and begin the journey through the secretory pathway to the plasma membrane (Figure 2.5). In mice, incomplete formation of class I heavy chain–peptide–β_2M complexes results in retention of the heavy chain by calnexin in the ER (104,105). In humans, it appears that assembly of class I–β_2M heterodimers is sufficient for release from calnexin (106,107), although a portion of human class I–β_2M dimers can be found associated with calnexin (68). A number of different oligomeric proteins are known to associate with calnexin during assembly (108), including membrane immunoglobulin (109), the T-cell receptor (110,111), class I and class II molecules, $\alpha\beta_1$ integrins (112), some viral proteins (97), and monomeric molecules such as α_1-antitrypsin and transferrin (95).

2.2. CLASS II ANTIGEN PRESENTATION PATHWAY

2.2.1. Invariant Chain

Invariant chains (Ii) are transmembrane glycoproteins found in intracellular compartments in association with class II molecules. Multimers consisting of three class II $\alpha\beta$ dimers and three Ii molecules assemble rapidly in the ER (113,114) and travel across Golgi bodies to the *trans*-Golgi network that intersects with the endocytic pathway, where class II molecules reside for about 1–3 hr before transit to the cell surface for display to T

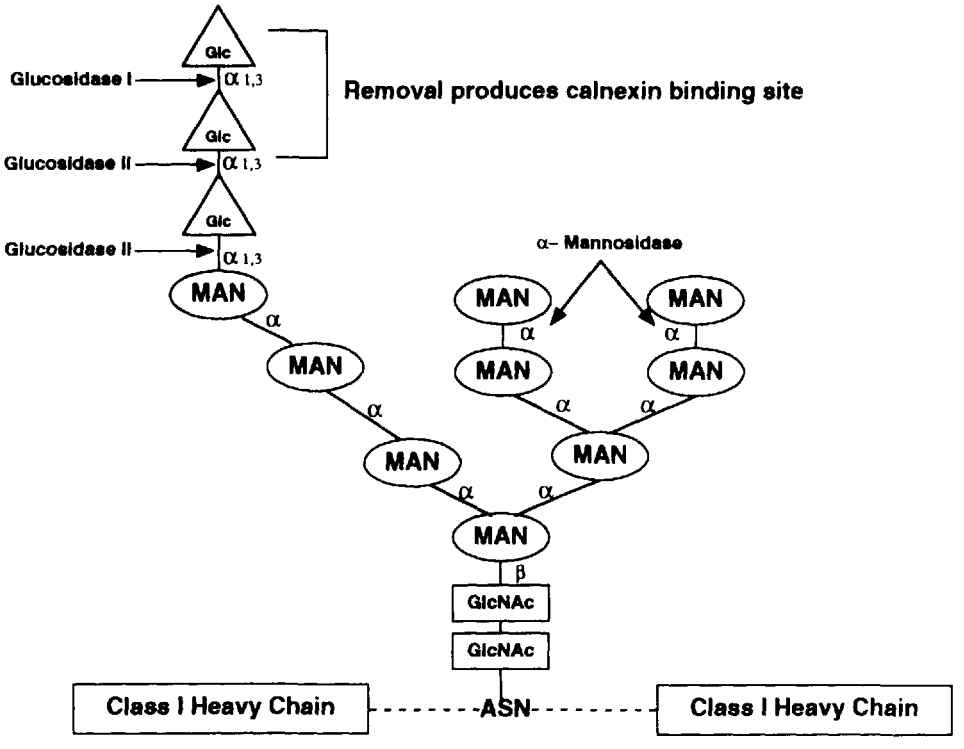

Figure 2.4. A hypothetical structure of an N-linked core oligosaccharide attached to a class I MHC heavy chain. Resident oligosaccharide transferases attach core sugars to nascent class I heavy chains as they emerge into the ER lumen. Cotranslational trimming in the ER by glucosidases I and II sequentially removes the terminal α1,2-glucose and α1,3-glucose moieties, respectively. Trimming of two outer glucose moieties produces a calnexin binding site. Adapted from *Molecular Biology of the Cell* (A. Helenius, **5**:253–265, 1994).

cells (115) (Figure 2.6). Alternative splicing of Ii transcripts produces two Ii isoforms, p31 and p41, both of which can operate to assist in the folding of class II dimers, direct the passage of class II from the ER through an exocytic pathway (116–118), and block loading of peptide until peptide sampling can occur as exocytic–endocytic pathways intersect (119–121).

A four-residue putative endosomal targeting signal was identified at the N-terminus of Ii that is essential for intracellular transport to endosomal compartments (122). The C-terminus (123) and the transmembrane region (124) of Ii are also necessary for sorting of class II–Ii complexes to the endosome. In the endosome of B cells, Ii undergoes proteolytic cleavage by aspartyl and cysteine proteases, activities blocked by the inhibitor leupeptin (125,126). Inhibition with leupeptin produces two Ii fragments called LIP (22 kDa) and SLIP (12 kDa), the leupeptin-induced and small-leupeptin-induced proteins, respectively.

Comparison of p31 and p41 demonstrates similar functions for the two molecules, with various regions essential for class II interactions and sorting common to each of them (127–129; Table 2.2). However, the observation that varying ratios of p31 and p41 are found in cells of different cell types suggests unique roles for the isoforms in antigen presentation: p41 constitutes about 9% of total Ii pools in B cells, 23% in spleen dendritic

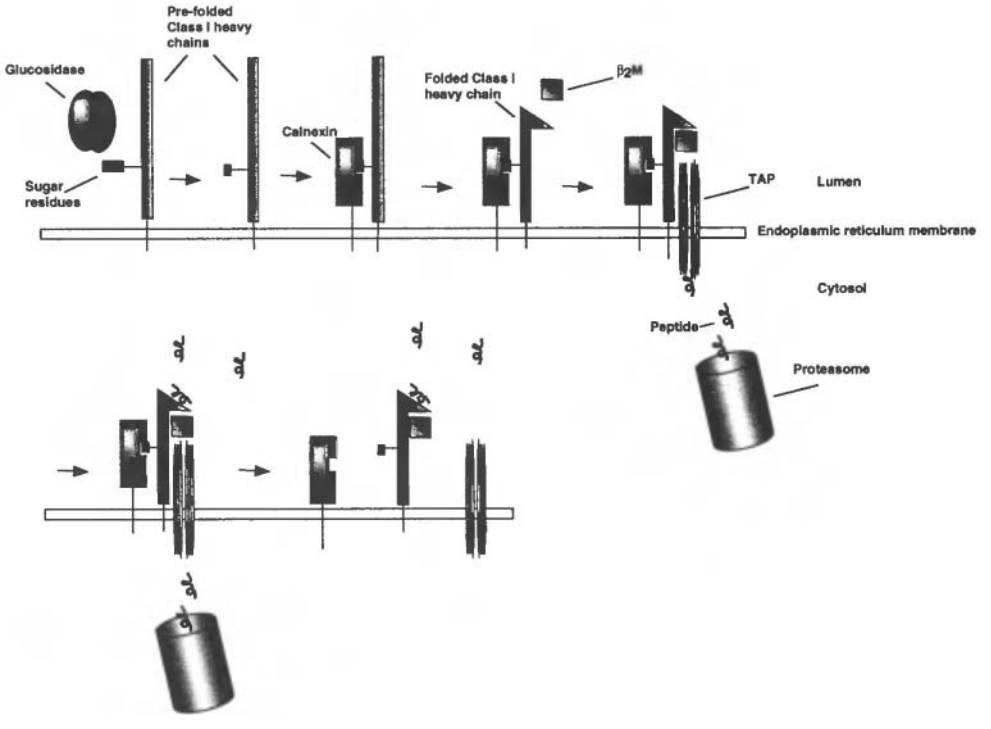

Figure 2.5. Newly synthesized and glycosylated heavy chains undergo trimming of glucose residues in the ER by glucosidases to produce a heavy chain that binds calnexin, which in turn assists the folding of class I heavy chains. Class I heavy chain–calnexin dimer association with TAP coincides with β_2M association and peptide loading. Class I–peptide–β_2M complexes dissociate from TAP and calnexin and begin their journey through the secretory pathway to the plasma membrane.

cells, 30% in macrophages, and 43% in fresh Langerhans cells (155). The p41 form appears to regulate the production of a stable 12-kDa SLIP–class II complex and is capable of enhancing antigen presentation (156,159). A peptide fragment from the p41 subunit has been shown to competitively inhibit the cysteine protease cathepsin L, and may thus be involved in regulating class II-relevant protease activity in lysosomes (158).

2.2.2. CLIP

The class II=associated invariant chain peptide (CLIP) is derived from amino acids 80–110 of Ii, which corresponds to the third exon of the Ii gene. The CLIP region is essential for Ii binding to class II molecules (159,160) and thus it is not surprising that CLIP is critical for Ii's roles in folding, transport, and peptide loading of class II molecules (161). X-ray crystallographic analysis of HLA-DR3–CLIP complexes has confirmed that CLIP peptides bind in the peptide-binding groove, resolving a strenuously debated issue of how CLIP interacts with class II molecules (162,163).

Because efficient presentation of class II peptides requires CLIP binding, the proper display of endocytosed antigen also depends on CLIP dissociation from the class II binding groove. The N-terminus of CLIP, which appears to contribute to a high on–off

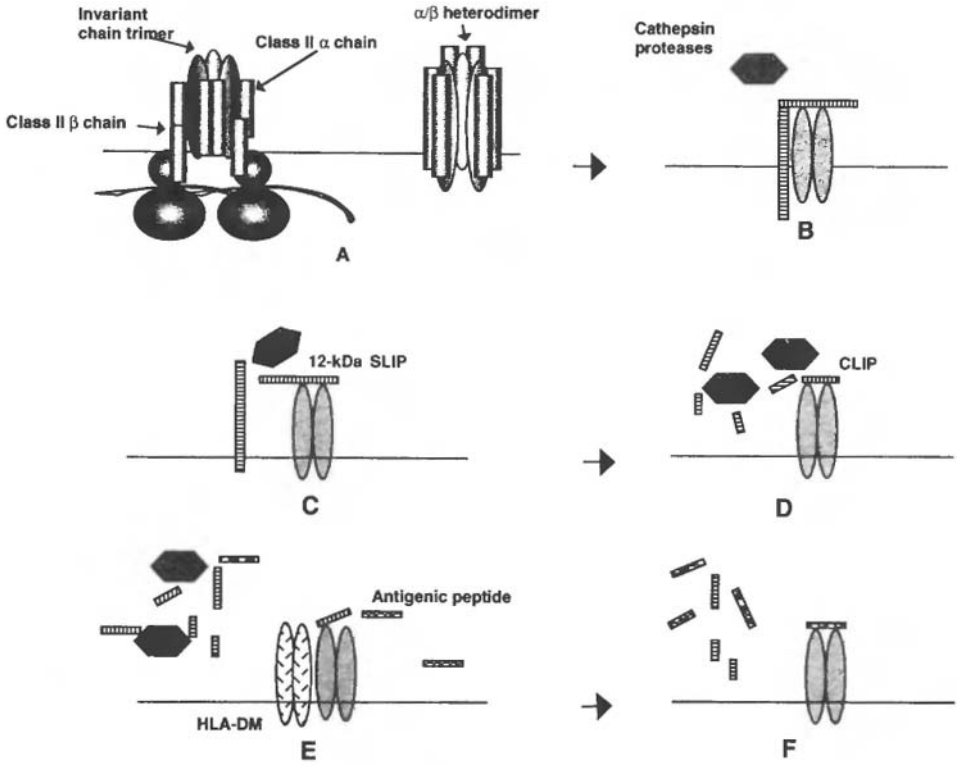

Figure 2.6. A cartoon depiction of invariant chain (Ii) involvement in the assembly, transport, and peptide loading of class II MHC molecules. (A) Newly synthesized class II α chains bind preformed Ii trimers and assemble with β chains. (B) For ease of depiction, class II–Ii complexes are drawn as dimers. Ii draws class II complex from the default secretory pathway through the *trans*-Golgi network and targets molecules to intersect endocytic pathway. (C) Soon after targeting to endosomes, proteases begin degradation of Ii chain, producing SLIP–class II complexes. (D) Further degradation of SLIP produces CLIP–class II trimer. (E) CLIP is displaced from the binding groove as the class II–CLIP complex encounters the HLA-DM/H-2M peptide exchanger. (F) Endocytosed and processed antigen is loaded and mature class II–peptide trimers are delivered to the plasma membrane.

rate observed in the acidic endosomal environment, may facilitate exchange by antigenic peptides (164). Other findings, however, have indicated that both antigenic peptide and CLIP binding to class II are enhanced at endosomal pH, suggesting that a mechanism (e.g., allosteric) for CLIP removal is needed (165). CLIP-derived peptides normally represent a small fraction of the peptides associated with class II molecules (166–168), although in cells lacking expression of HLA-DM (169–191), or in cells with mutant class II heterodimers, as much as 50% of class II molecules can be occupied by CLIP (172,173). It is not yet clear whether CLIP is the residual peptide fragment of an Ii chaperone that remains bound to class II molecules during Ii trimming in the endosome, or whether CLIP binds as a free peptide that has been generated from Ii degradation products after its complete release from class II. The finding that a 12-kDa SLIP fragment bound in the class II groove is a precursor of the class II–CLIP complex suggests that CLIP fragment may be generated as it sits in the binding groove (194). Recently, it has been demonstrated

Table 2.2
Comparison of Invariant Chain Isoforms

Function	Isoform	Region involved	Refs.
Assembly, folding, egress from ER	p31,p41	Unknown	(130–133)
Class II mAb epitopes	p31,p41	Unknown	(134–136)
ER retention	p41>p31	Cytosolic tail	(137–140)
Inhibition of peptide binding	p31,p41	CLIP	(141–143)
Endosomal localization/retention	p31,p41	Cytosolic tail	(137,138,144–149)
Plasma membrane internalization	p31	Cytosolic tail	(150)
Antigen presentation	p41>p31	Unknown	(135,151–153)
Accessory function	Ii-CS	CS at 201	(154)

that cathepsin S, a cysteine protease expressed in lymphocytes and other cells of the immune system, is required for generating CLIP peptides (175).

2.2.3. HLA-DM/H-2M

HLA-DM are IFNγ-inducible nonclassical class II molecules encoded from genes located in the class II HLA gene cluster (Figure 2.2) (171,176). Cell lines [i.e., T2 (DR3), .174 (DR3), and 9.5.3] lacking either the α (DMA) or β (DMB) chains of HLA-DM produce class II molecules bound by a limited repertoire of peptides, with an overrepresentation of class II–CLIP complexes (177). Transfection with HLA-DMA and -DMB expression vectors reduces class II–CLIP complexes and restores presentation of antigenic peptides; and intracellular distribution of class II and invariant chain molecules is also restored to that of wild-type cells (169,170,178). HLA-DM is not significantly associated with class II membrane surface structures, but rather interacts with class II in intracellular compartments where peptide loading occurs (179–181). However, in some cell types HLA-DM is also present in lysosomes that do not contain class II molecules, although its role there is not clear (182). The peptide-binding pocket of HLA-DM is predicted to be similar to class II heterodimers, except that it contains disulfide linkages that appear to limit the range of peptides that might potentially bind (183).

There are a number of possible mechanisms by which HLA-DM/H-2M functions as CLIP–peptide exchanger. Physical interactions between HLA-DM and class II–CLIP complexes in endosomal compartments may induce conformational changes that drive CLIP removal and subsequent reloading by antigenic peptide (Figure 2.6). On the other hand, HLA-DM may sequester CLIP that has dissociated from class II and prevent its reoccupation of the peptide groove. Perhaps HLA-DM is involved in delivering antigenic peptide to a specific compartment where antigenic peptides are preferentially loaded. Antibody blocking and other data have suggested that H-2M interacts directly with class II–CLIP complexes to induce CLIP dissociation (184,185). It has been postulated that HLA-DM might facilitate class II–CLIP dissociation by stabilizing a strained conformation of the complex, thereby lowering the free-energy barrier for CLIP dissociation in a catalyticlike manner (162,186). Although the strained conformation may exist similarly for other antigenic peptides bound in the groove of class II molecules, selective dissociation of CLIP may result from its lack of strong anchor residues (185,187).

HLA-DM of humans appears to be highly similar to H-2M in mice (H-2Ma, Mb1, and Mb2) (176). In H-2M-deficient mice, class II molecules are associated predominately with peptides derived from the class II invariant chain (CLIP), and cells have a reduced ability to present antigens to class II-restricted T cells (188,189). In both mouse strains developed, potential T-cell reactivity also appears to be altered, reinforcing the important role antigen presentation plays in shaping the mature T-cell repertoire.

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3

T-Lymphocyte Genes

Antigen-specific receptors on T lymphocytes are generated by the rearrangement of germline DNA to produce immunoglobulinlike receptor molecules. Unlike the immunoglobulin receptors on B cells, however, T cells do not secrete antigen-specific molecules but rather express them only on the cell surface. Furthermore, unlike immunoglobulins, which can recognize virtually any form of antigen, be it on the cell surface, soluble in the plasma, protein, or carbohydrate, the T-cell receptor (TCR) recognizes protein antigen that is processed into peptides and complexed together with class I or class II molecules on the cell surface. Thus, T cells must be capable of "reading" and interpreting class I/II–peptide complexes, and be capable of determining if these complexes indicate that trouble is lurking within the cell. This remarkable ability of T cells to analyze the actual contents of cells defines their role as highly specialized detectives capable of routing our intracellular pathogens. Once cells harboring intracellular pathogens are discovered, T cells can differentiate specific cytotoxic activity and destroy infected cells.

The TCR genes are organized into multigene families on different chromosomes. They encode a TCR that is a covalently linked heterodimeric glycoprotein, each subunit composed of extracellular V- and C-region Ig-like domains, a charged transmembrane portion, and a short cytoplasmic tail (1). Each polypeptide subunit of the TCR has an N-terminal portion (or V region) that contains the highly variable sequences which form the peptide–MHC recognition sites (2,3), and which are encoded by gene segments that have been recombined to form a contiguous coding region. The different heterodimeric TCR are assembled to form the $\alpha\beta$ or $\gamma\delta$ receptors are expressed in a mutually exclusive manner on mature T cells. β and δ chains are produced by the joining of germline variable (V), diversity (D), and joining (J) genetic elements, whereas complete α and γ chains require only the juxtapositioning of V and J gene segments (4,5). The completed V region is transcribed as a contiguous primary RNA transcript that contains one or more constant (C) region genes and redundant D and J elements. Splicing of transcripts juxtaposes the recombined VJ or V(D)J genes with a C region segment (6) that encodes a proximal C-type Ig-like domain, membrane-spanning and cytoplasmic portions that are almost identical between mice and humans (7,8). From these mature mRNA the polypeptides are assembled into respective $\alpha\beta$ or $\gamma\delta$ TCR heterodimers. The process of recombining different germline segments results in an extremely diverse contiguous TCR gene, a diversity that is further enhanced by imprecision in the joining of segments, by introduc-

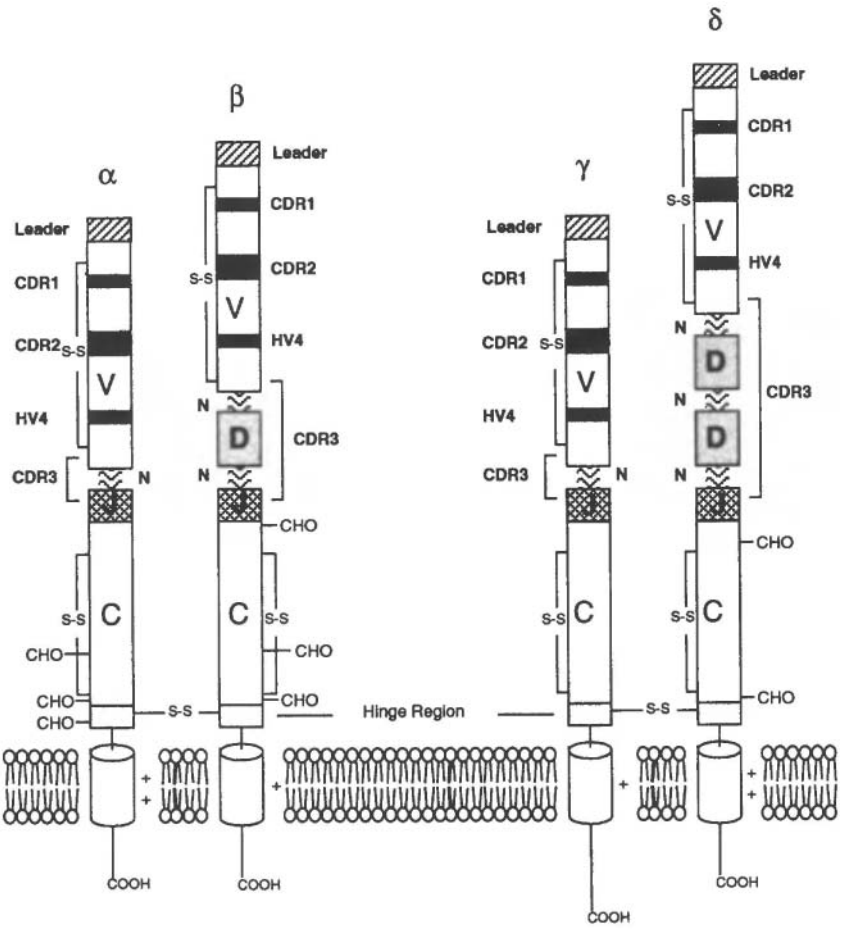

Figure 3.1. The αβ and γδ chains of the TCR. V(D)J segments and CDR regions are highlighted. –CHO indicates glycosylation sites.

tion of nontemplated nucleotide sequences (p-nucleotides) during recombination, and by the unique combination of the different TCR subunits: It has been estimated that with these mechanisms factored together, the recombination process can generate about 10^{16} different αβ TCR and 10^{18} unique γδ receptors (3).

Amino acid variability in the V region of the TCR chains involves a wider range of residue positions (i.e., is less concentrated) compared with the V region of Ig molecules. Nonetheless, three regions with a relatively high degree of polymorphism exist on the TCR that form complementarity-determining regions (CDR) analogous to Ig molecules. There is an additional fourth hypervariable region (HV4) in the TCR V region (Figure 3.1) (9). The CDR and HV4 regions of TCRs—as with the CDRs of immunoglobulins—are important in antigen recognition (3,10). This is supported by observations that conserved variations in otherwise highly polymorphic CDR3 regions occur in T cells with similar peptide–MHC specificities (11–13), although this is not always the case (14). Variation in

TCR sequences is concentrated in the junctional CDR3 region, which spans on average about 10 residues (14) and appears to strongly influence receptor specificity (15,16). The TCR CDR3 region includes a similar number of residues as that of Ig light chains but is considerably less extensive than the CDR3 of Ig heavy chains (14,17,18). It is predicted that residues in TCR CDR3 contact peptide in the binding pocket of class I or class II molecules. It appears that about 75% of CDR3 residues in the TCRα chain are hydrophobic, compared with about 32% of TCRβ-chain CDR3 sequences (14), although the significance of this in terms of peptide–TCR interactions is not clear.

Because T cells express only one of the two TCR heterodimers, the αβ and γδ receptors delineate two fundamental groups of T cells (3). T cells bearing αβ TCR are further subdivided into those expressing the transmembrane coreceptors CD4 or CD8, and are functionally characterized by their ability to recognize peptide antigen bound to class II or class I molecules, respectively. γδ T cells do not appear to rely on coreceptor molecules and have a less stringent mode of antigen recognition, i.e., they are not necessarily restricted to "seeing" only those antigens that are bound in the form of peptides to class I or class II molecules (19–21). Nonetheless, both αβ and γδ TCR must communicate, or signal, the information they "see" and these signals must be interpreted such that an appropriate course of action is taken. Interpretation is critical, as the outcome of TCR interaction with peptide–MHC complexes can range from induction of T cell death, to anergy or tolerization of T cells (22–27), or to proliferation and differentiation of cytotoxic function or helper function. It is not surprising, then, that TCR–ligand interactions induce a complex series of protein modifications and signal transduction events. These events, although triggered by the antigen receptor heterodimer, are mediated by invariant components of the larger oligomeric TCR complex (28). These invariant subunits are collectively the CD3 chains (29,30). Despite intense interest, the X-ray crystal structure of the TCR has not been unambiguously resolved, reflecting difficulties in producing sufficient quantities of soluble nonglycosylated subunits (31–33). To date, only the crystal structure for the β chain (Vβ8.2Jβ2.1Cβ1) (34,35) and a TCR Vα-domain homodimer (36–38) have been determined.

3.1. T-CELL RECEPTOR GENES

The assembly of TCR polypeptides into αβ and γδ heterodimers provides no hint as to the chromosomal organization of the TCR genes. That is, for evolutionary or perhaps functional reasons the α and δ loci are located together on chromosome 14 in both mice (3,39–41) and humans (42,43), where δ sequences in fact interrupt the α locus (Figure 3.2). In humans the γ and β locus are separately located on chromosome 7, whereas the mice β and γ chains are found on chromosomes 6 and 13, respectively.

3.1.1. αβ

The human TCR α locus is contained on the long arm of chromosome 14 and consists of 42 V, 61 J, and 1 C gene (43,44). TCR β genes are clustered on chromosome 7 and include 75–100 V, 2 D, 13 J, and 2 C genes (43). Recently the entire 685-kb human β locus was sequenced, the longest contiguous stretch of DNA sequenced to date (45). The Vβ genes have been categorized into 34 different subfamilies that exhibit ≥ 75% sequence identity at the DNA level (43). Mouse TCR α loci are situated on chromosome

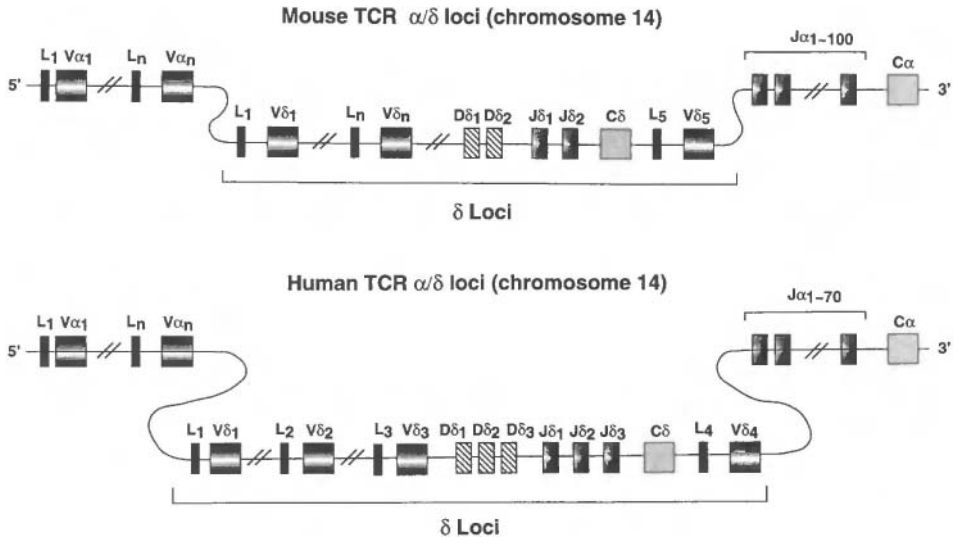

Figure 3.2. Schematic depiction of the α/δ locus. Neither the sizes of the gene segments nor the relative distances are to scale. Location of the δ genes within the α locus means that rearrangements of either locus are mutually exclusive. Humans and mice have a similar arrangement of α/δ loci. There are about 75 Vα and 10 Vδ segments in mice and approximately 50 Vα and 4 Vδ segments in humans. There are extensive Jα segments in mice and humans, including about 70 segments in both species.

14 and are comprised of 75 V, 61 J, and 1 C gene (46). The TCR β genes are located on chromosome 6 and consist of approximately 23 V, 2 D, 12 J, and 2 C gene segments (46).

Cβ in humans and mice exhibit significant sequence similarity at both nucleotide and protein levels. The 2 Cβ genes form clusters with upstream Dβ and Jβ segments: Cβ1 rearranges only with Dβ1/Jβ1 genes, whereas Cβ2 can rearrange with both Dβ1/Jβ1 and Dβ2/Jβ2 gene segments. There is no apparent functional reason why T cells might incorporate one Cβ segment over the other and there are no identified T-cell subsets with preferential Cβ1 or Cβ2 usage. Similarly, functional Vβ genes appear to rearrange to both Jβ clusters in a random fashion (47) (Figure 3.3). Expression of a functionally rearranged β chain suppresses further rearrangement at β gene loci to induce a so-called allelic exclusion (48,49), which ensures that the production of a functional contiguous TCR gene is not destroyed by further realignments and that only a single clonotypic chain is expressed on each T cell. In contrast, allelic exclusion at the α locus is probably induced by a functional TCR and may involve multiple rearrangements that are arrested on positive selection (50).

There are differences between the α and β chains in terms of the important CDR3 regions they contain, which span the V–J and V(D)J joints in the transcripts, respectively. Analysis in antigen-specific cells has revealed that significant variability exists for the number of residues and N additions present in CDR3 of the α chain. However, the β-chain transcripts of antigen-specific T-cell clones appear to contain little length variation and harbor conserved N additions (14).

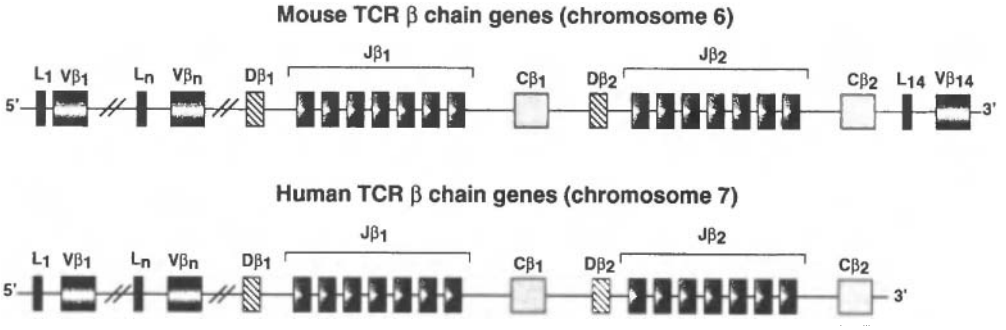

Figure 3.3. Similarity of the TCR β-chain region in mice and humans. The organization of the locus is conserved among all mammalian species studied to date. There are 20–30 Vβ segments in mice and approximately 75 in humans.

3.1.2. γδ

Human TCR γ genes are located on chromosome 7 over a stretch of 150 kb. There are at least 14 different γ genes making up six subfamilies; however, only 6 Vγ genes appear to be functional (V2–V5,V8–V11), and the remaining 6 genes are pseudogenes (43). The Vγ genes are followed at the 3′ end by 5 Jγ and 2 Cγ genes (21,51). There are at least 10 Vδ, 3 Dδ, 3 Jδ, and 1 Cδ gene segment. Only 5 Vδ genes are considered to be functional. The γδ T cells in humans use either Vδ1 or Vδ2 chains, with over 70% of peripheral γδT cells expressing the Vδ2 (52). Vδ2 expression is typically accompanied by a Vγ9 chain, whereas Vδ1 chains can be coexpressed with the various Vγ chains. The mouse TCR γ locus is contained on chromosome 13 in four discrete clusters including 7 Vγ, 4 Jγ, and 4 Cγ genes (39,53–55) (Figure 3.4). Vγ genes undergo recombination with Jγ–Cγ elements that are proximal and in the same orientation; as a result, Vγ1.1 joins to Jγ4/Cγ4, Vγ1.2 joins to Jγ2/Cγ2, Vγ1.3 joins to Jγ3/Cγ3, and Vγ2, Vγ3, Vγ4, or Vγ5 joins to Jγ1/Cγ1. In mice, Cγ3 is a pseudogene with a splicing defect and is deleted in some strains, thus only 6 Vγ genes are potentially expressed (55,56). As in humans, the TCR δ locus in mice is located within the α gene cluster and contains approximately 12 Vδ, 2 Dδ, 2 Jδ, and 1 Cδ gene segment (3,39–41,46). Short homology repeats near the ends of V–D–J genes function to align the segments for fusion during rearrangement (57–59). The repeats may be important in regulating recombination and junctional diversity at V–J and V–D junctions in γ and δ loci, respectively (60,61).

A mechanism for achieving diversity in variable (antigen-specific) regions of the TCR is thought to involve the random addition of nucleotides, inserted at junctional positions during the joining of V(D)J segments. TCR γδ T cells have been thought to contain limited N-nucleotide insertions, which supported the notion that these T cells had a restricted repertoire of antigen-specific receptors (61,62). More recent studies, however, suggest that junctional diversity related to N insertions accounts for significant diversity in at least three segments of the CDR3, and that such insertions might facilitate TCR γδ interactions with a broad variety of antigenic structures akin to those of immunoglobulins (63–65). This compares with the stringent class I and class II restriction of the αβ TCR.

γδ T cells can develop in the thymus or within the tissues in which they reside (Figure 3.5). Despite their overall inferior contribution to the T-cell repertoire in the

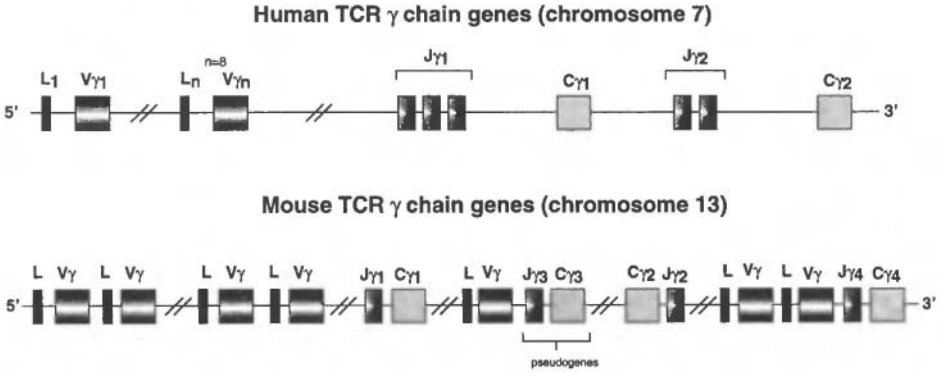

Figure 3.4. Murine and human γ loci are organized differently. There are seven Vγ segments in mice and eight in humans.

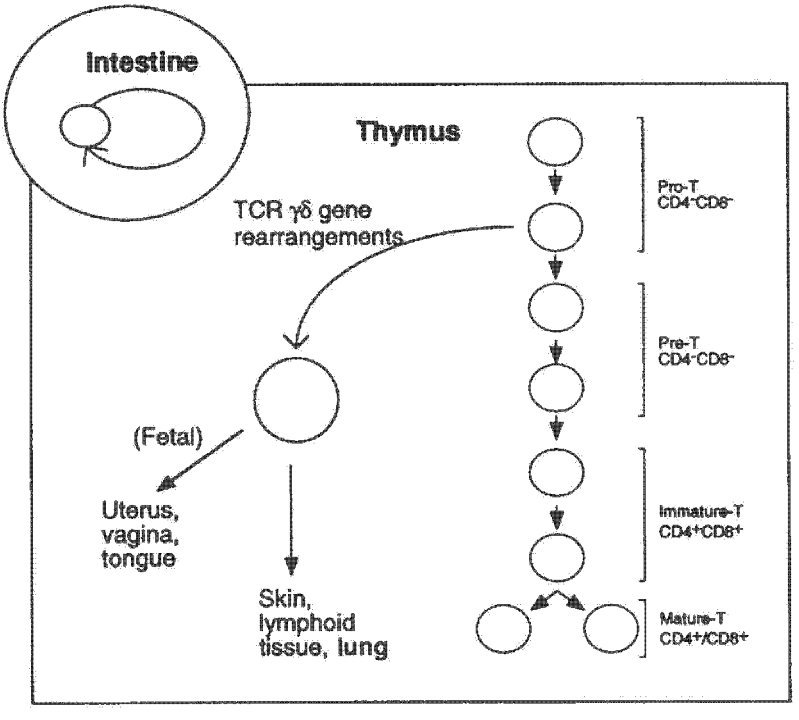

Figure 3.5. Ontogeny of murine γδ T cells. Such T cells represent multiple cell lineages that develop in a temporally and spatially regulated manner, exhibit biased expression of antigen receptor genes, and exclusive tissue surveillance. γδ T cells that develop in the thymus are found principally in the skin, lung, and lymphoid tissues, whereas intraepithelial γδ T lymphocytes (IEL) develop and reside in the intestinal epithelium (460–462).

Table 3.1
Preferential Gene Rearrangements and Tissue Specificity of γδ T Cells

Tissue	Preferential γ use	Preferential δ use
Lactating mammary gland	Vγ3Jγ1Cγ1, Vγ2Jγ1Cγ1	Vδ4Dδ2Jδ1Cδ
Tongue/vagina/uterus	Vγ4Jγ1Cγ1	Vδ1Dδ2Jδ2Cδ
PBL/adult thymus	Vγ2Jγ1Cγ1 .	Vδ5Dδ1Dδ1JδxCδ
Spleen	Vγ2Jγ1Cγ1, Vγ1.1Jγ4Cγ4	Vδ5Dδ1Dδ2JδxCδ
Lymph nodes	Vγ2Jγ1Cγ1	Vδ5Dδ1Dδ2JδxCδ
Skin (DEC)	Vγ3Jγ1Cγ1	Vδ1Dδ2Jδ2Cδ
Lung (RPL)	Vγ2Jγ1Cγ1, Vγ2Jγ1Cγ1	Vδ6 > Vδ5 > Vδ7/Vδ4 > Vδ1/Vδ3
Gut (IEL)	Vγ5Jγ1Cγ1	Vδ6Jδ1, Vδ7Jδ1

periphery, TCR γδ cells make up a significant lymphocyte population in the epithelial tissues of the lung, gut, tongue, epidermis, and reproductive organs (66–72). Interestingly, TCR γδ cells resident in different tissues appear to have preferential V gene usage (Table 3.1). For example, dendritic epidermal cells (DEC) in mice are a population of TCR γδ T cells residing in the epidermal layers of the skin and which preferentially express Vγ3Jγ1Cγ1 and Vδ1Dδ2Jδ2Cδ (61), whereas those resident in the tongue or uterus express Vγ4Jγ1Cγ1/Vδ1Dδ2Jδ2Cδ (69).

In adult mice, more than 95% of thymocytes and most mature T cells express the TCR αβ receptor. The remainder of T cells express TCR γδ receptors for which the function remains enigmatic (52,73,74). γδ T cells from both mice and humans can be stimulated by conventional class I or class II molecules (75–78) or by nonclassical MHC molecules such as Qa-1 (79–81). However, normal numbers of γδ T cells are observed in class I-deficient animals and γδ T cells have been shown to respond to antigen independently of class I or class II MHC (65,82–85). Activated γδ T cells can secrete the cytokines IFNγ (86–88) and IL-4 (89) and can differentiate cytotoxic effector function (86,90–93). T cells expressing TCR γδ receptors were in fact initially described to have anti-tumor cell activity (52) and recent experiments with mice expressing a transgenic TCR Vγ1.1Jγ4Cγ4 showed that γδ T cells can confer spontaneous resistance to hematopoietic tumors *in vivo* (94). TCR γδ cells have also been implicated in protection against bacterial infection such as *Listeria monocytogenes, Mycobacterium tuberculosis*, and *Mycobacterium leprae* (95,96). Finally, there is evidence that γδ T cells may have some involvement in autoimmune disease (76,97–101).

3.2. RECOMBINATION AND EXPRESSION OF TCR GENES

Genetic Control Elements (RSS)

Similar to immunoglobulins, germline TCR genes must undergo rearrangement to produce a mature transcript and a functional antigen receptor. Rearrangement is achieved by recombination signal sequences (RSS; see Section 4.2.1) that direct a process whereby sequences intervening V(D)J segments are looped out and deleted, juxtaposing V(D)J segments and allowing them to be joined (102,103) (Figure 3.6). Another RSS-dependent recombination mechanism exists whereby gene segments located 3′ to their respective

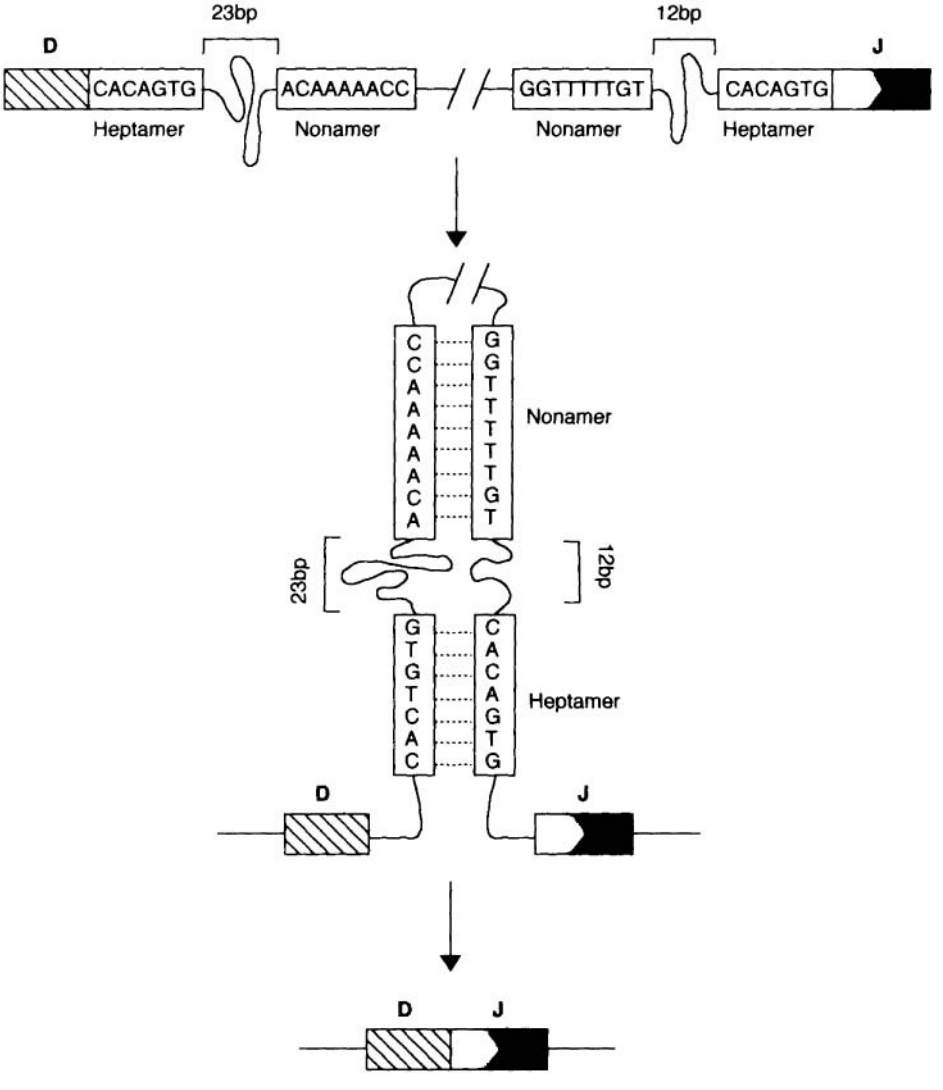

Figure 3.6. Recombination signal sequences direct the rearrangement of V–D–J segments. Here, complementarity between the nonamer and heptamer sequences is shown to guide juxtapositioning of D and J segments.

constant regions rearrange by inversion (41,43,104). RSS consist of conserved heptamer and nonamer sequences separated by less conserved regions of 12 or 23 bp (105), equivalent to one or two turns of the DNA helix, respectively. RSS with long spacers can only rearrange to short spacers, thus these signals limit and direct the possible rearrangements.

T-lineage progenitor cells from bone marrow enter the thymus with TCR genes in a germline configuration. These progenitor cells, capable of rearranging either $\alpha\beta$ or $\gamma\delta$ genes, make a decision to recombine one or the other locus early during the pro-T-cell stage (3,106–109). Because δ genes reside within the α locus, rearrangement of the α locus physically disrupts the δ locus and precludes its rearrangement on that chromosome.

However, as β and γ loci are independent of each other, γδ T cells typically rearrange γ, δ, and β genes, whereas αβ T cells have the potential to rearrange at α, β, and γ loci.

The rearrangement process is organized at two levels, namely, with respect to the timing of rearrangement at each locus and the order of V(D)J recombination. Rearrangements at δ, β, and γ loci are initiated prior to α genes in the fetal thymus (106,110–112) and at earlier stages of T-cell development in postnatal thymus (113–115). Furthermore, rearrangement at the TCR β locus typically proceeds in an orderly fashion, first involving D→J followed by V→DJ alignment, whereas δ loci undergo rearrangement at V→D loci followed by VD→J. Considerable effort has been directed to understanding how TCR recombination is regulated. What has emerged is the importance of transcriptional enhancer and promoter elements at α, β, δ, and γ loci (116–122). Enhancer elements contain multiple sequences that bind both T-cell-specific and ubiquitously expressed nuclear proteins and transcription factors (123–126). For example, the transcription factor c-MYB binds the Eδ enhancer (127–129) and is important for regulating δ gene rearrangement (130). Ultimately, regulation of TCR rearrangement appears to reflect accessibility of the loci to recombinational machinery (129,131) and the presence of transcriptional activity (132).

3.3. MACHINERY

3.3.1. Recombination Activating Genes 1 and 2 (RAG1 and RAG2)

In mice and humans RAG genes are first expressed in immature thymocytes (133,134). Phosphorylation of RAG at serine/threonine residues regulates the activity and stability of the protein which probably has a relatively short half-life once transported into the nucleus (135,136). RAG are essential for the initiation of rearrangement of TCR genes (133,134) (see Section 4.3.1), and targeted disruptions of RAG1 or RAG2 genes in mice result in a profound lack of mature T cells (137,138) with thymocyte development being blocked very early at a $TCR^-CD4^-CD8^-IL\text{-}2R\alpha^+$ stage. Because RAG genes initiate rearrangement of V(D)J loci, it is not surprising that RAG genes are regulated in a temporal manner during thymocyte ontogeny (139). Expression levels peak during thymocyte development at the $CD4^-CD8^-$ stage, which coincides with recombination of TCR β, δ, and γ genes. RAG is then actively downregulated by receptor signaling (50,140) (through a pre-TCR complex) before being upregulated in $CD4^+CD8^+$ thymocytes to facilitate α-chain rearrangements (Figure 3.7). Recombination mediated by wild-type RAG1 appears to be unaffected by a wide range of coding sequences adjacent to the recombination signal. However, a mutant RAG1 only initiates rearrangement when specific dinucleotides are next to the signal sequence heptamer, suggesting that RAG1 protein may physically interact with target sequences located at the border of the coding–signal junction (141).

3.3.2. Terminal Deoxynucleotidyl Transferase (TdT)

Murine T cells deficient for TdT have a loss in diversity of TCR genes reflecting a lack of N additions at V→(D)→J junctions (142,143). Conversely, overexpression of TdT expressed transgenically from a CD2 promoter can induce enhanced N-region diversity of TCR genes (60). Thymocyte selection is altered in the TdT-deficient mice, which have highly elevated numbers of $CD4^+/CD8^+$ single-positive thymocytes (144). Interestingly,

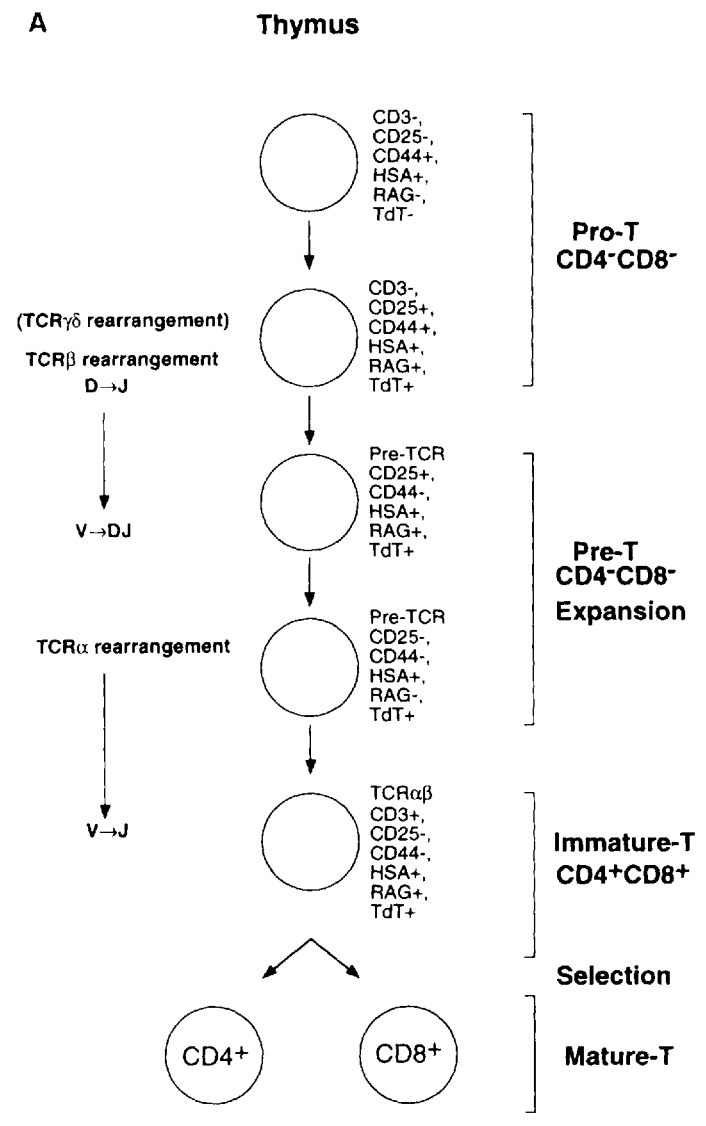

Figure 3.7. (A) The stages of T-cell development are illustrated with respect to the rearrangement of T-cell receptor genes and expression of important developmentally regulated molecules.

however, the lack of N-diversity does not appear to hamper immune responses to a variety of infectious agents (145). (See Section 4.3.2.)

3.3.3. DNA-Dependent Protein Kinase (DNA-PK)

Rejoining of DNA after chromosomal double-stand breaks (DSB) generated during V(D)J recombination of TCR genes requires the activity of a three-subunit DNA-dependent protein kinase (DNA-PK) (146–150). The DNA-binding subunit dubbed Ku, a heterodimer composed of 70- and 86-kDa chains, is essential for the DSB repair function

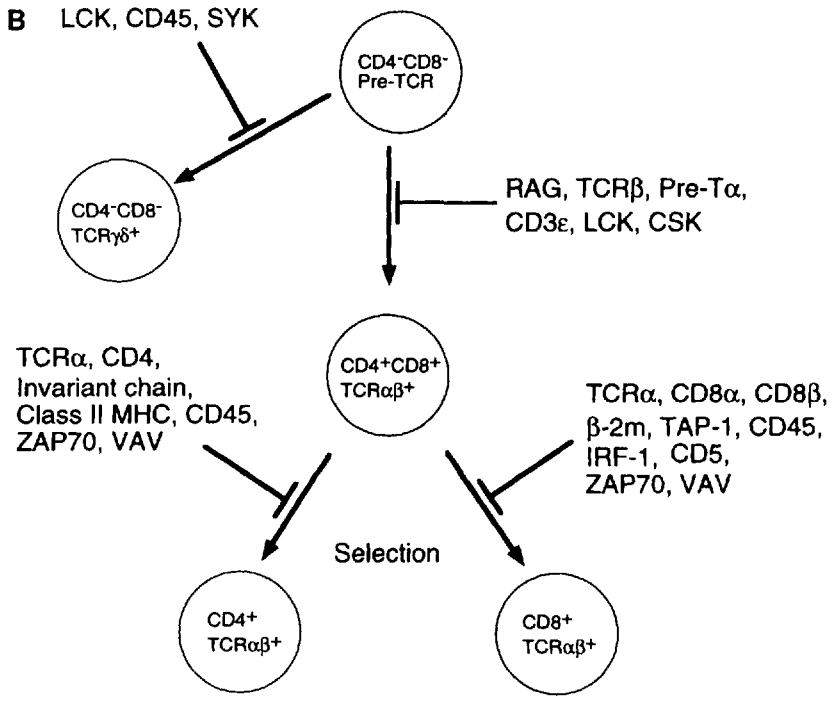

Figure 3.7. (B) A number of molecules that are developmentally regulated during T-cell ontogeny have been gene-targeted. Resulting blocks in T-cell differentiation are indicated.

of the complex (151,152). Ku associates with a catalytic subunit (DNA-PKCS) which is deficient in SCID mice and is critical for DSB repair and for normal V(D)J recombination (153–156). Mice with gene-targeted deletions for the DNA-binding subunit Ku80 have recently been shown to have a block in V(D)J rearrangement in both B- and T-lineage cells (157). T-cell ontogeny in these mice is blocked at the early progenitor $CD4^-$ $CD8^-$ stage of development, reminiscent of RAG-deficient mice. Thus, DNA-PK appears to be critical to the recombination process.

3.4. SIGNALING AND CORECEPTORS

3.4.1. CD3 Complex

The TCR is an oligomeric complex that contains either αβ or γδ antigen-specific heterodimers associated noncovalently with at least four nonpolymorphic transmembrane proteins, which include CD3γ, δ, ε, ζ, and η chains and the γ chain of the Fcε receptor I (FcεRIγ) (158). Structural and functional studies suggest that the CD3 subunits are mainly arranged at the cell membrane as homo- and heterodimers (29,30,159–162). A typical configuration includes noncovalently associated CD3γε and CD3δε heterodimers, and a disulfide-linked dimer consisting of a ζ subunit and one of either ζ (163), η (164–166), or FcεRIγ chain subunits (Figure 3.8) (167–171). The CD3ζ and CD3η proteins are structurally similar to FcεRIγ and may form disulfide-linked heterodimers in association

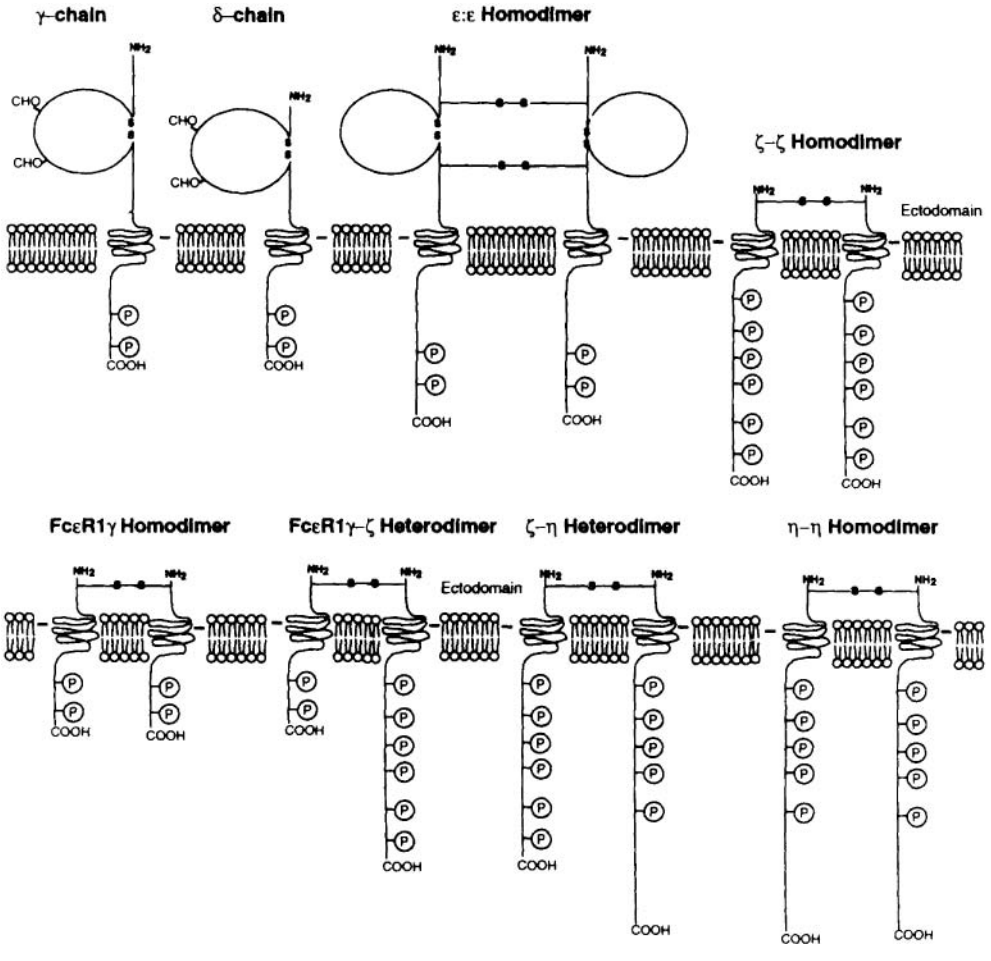

Figure 3.8. The principle CD3 components of the αβ TCR. CD3γ and δ glycoproteins and the ε polypeptide are clustered on human chromosome 11q23 and mouse chromosome 9. The δ chain contains extracellular Ig-like domains and the ε chain has a short (nine amino acid) extracellular ectodomain. The CD3ζ chain gene is on chromosome 1 in mice and humans (1q22). ζ mRNA can be alternatively spliced in mice to produce an η-polypeptide, which can form a homodimer or can heterodimerize with the ζ chain. Thus, ζ–η dimers can be found in murine TCR complexes. Intestinal epithelial lymphocytes (IEL) can express an FcεRIγ chain polypeptide, which has a transmembrane portion homologous to the ζ chain, and which can substitute for the ζ chain in the TCR complex of IEL. FcεRIγ–ζ heterodimers are also present in TCR. All transmembrane regions are negatively charged. The P designations on the cytoplasmic tails represent phosphorylation sites in antigen receptor activation motifs (ARAMs).

with the TCR complex or the immunoglobulin FcεRI (171–173). The FcεRIγ chain gene is located on chromosome 1 and shares similar structural features as the CD3ζ gene (163,174). ζ–ζ homodimers are found in about 90% of all T cells, whereas ζ–η heterodimers are found in only about 10% of T cells. A single antigen receptor chain preferentially interacts with different CD3 components, such that a TCRα chain will associate with CD3δ or ε whereas TCRβ will associate with δε or γ chains (167,175). Recent detailed stoichiometric analysis suggests that T-cell antigen receptor might also contain more than

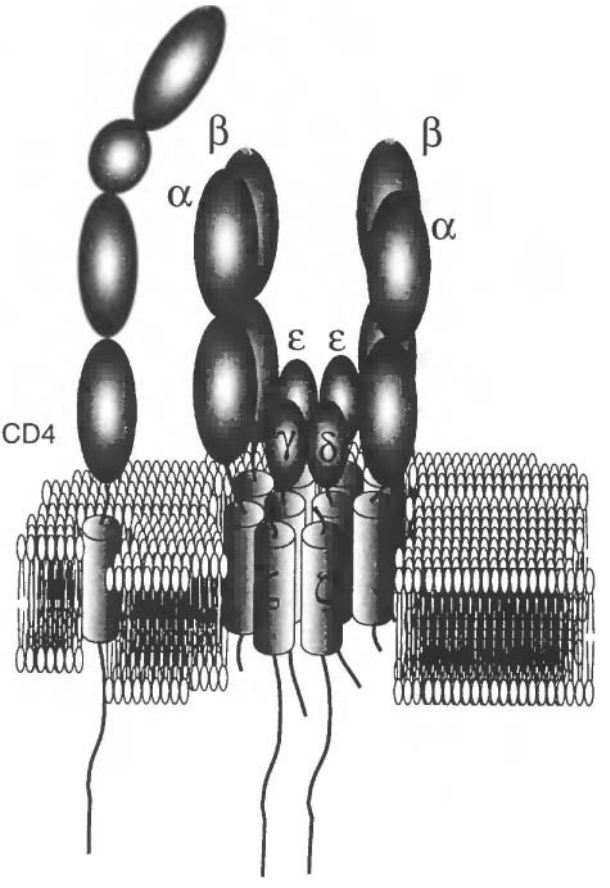

Figure 3.9. Oligomeric structure of the T-cell receptor. The CD3γ and δ chains typically exist as single-copy polypeptides in the αβ TCR complex. Two ε chains, usually disulfide linked, are present in the αβ TCR. There are probably two disulfide-linked antigen-specific α and β chains in the TCR complex. The same oligomeric structure may apply to the γδ TCR complex (463).

one α–β heterodimer in a 10-chain oligomeric complex (Figure 3.9) (176). These interactions involve both transmembrane regions and extracellular domains (175).

Genes encoding CD3γ, δ, and ε have extensive sequence similarities and are clustered on chromosome 11q23 in humans and chromosome 9 in mice, and in both species appear to be the result of gene duplication events (158,177). These CD3 molecules also have similar protein structures, each containing an N-terminal IgC2-like extracellular domain, a single transmembrane portion, and a relatively long cytoplasmic tail of 44–55 amino acids. The cytoplasmic regions of CD3γ, δ, and ε contain antigen receptor activation motifs (ARAMs), which consist of six conserved amino acids (D/E-X_7-D/E-X_2-Y-X_2-L/I-X_7-Y-X_2-L/I) (178,179). Whereas CD3γ, δ, and ε contain only a single motif, the η and ζ chains contain two and three motifs, respectively. Multiple motifs may increase the affinity of these CD3 molecules to other signaling kinases like ZAP70 (180–182). The clonotypic TCR is not expressed on the cell surface of a mouse T-cell line that lacks CD3δ expression (183) or in a human T-cell line deficient for CD3γ (184). Thus, in addition to their role in antigen receptor signaling, the CD3 subunits regulate surface expression of the TCR.

The CD3ζ gene is located on chromosome 1 and contains 10 exons that are alternatively spliced to produce ζ, η, θ chains (166,185–188). Tyrosine phosphorylation of the CD3ζ chain is an early event after TCR stimulation (189) and is critical for normal signal

transduction after antigenic stimulation (178,190–193). The ζ chain is also involved in transport and assembly of TCR–CD3 complexes (194–196). Unlike the other CD3 components, there appears to be a high turnover rate of the ζ chain in the TCR complex (197). The human CD3ζ chain contains a GTP/GDP binding site, suggesting that CD3ζ may regulate PLCγ1 activation via a G protein (198–201).

3.4.2. CD4 (T4, Leu3, L3T4)

CD4 is a 55-kDa transmembrane glycoprotein expressed as monomers on the surface of class II-restricted T cells (202). CD4 expression can also be found on some monocytes, macrophages, follicular and reticular dendritic cells, Langerhans cells, dendritic cells of the thymus, a small portion of B cells, and brain microglial cells (203,204). CD4 crystal structure has been resolved (205,206) and the molecule contains four extracellular Ig-like domains (177,207) and a highly basic cytoplasmic tail. The gene is located on chromosome 6 in mice and chromosome 12 in humans (203). In its function as a coreceptor on T cells, CD4 is thought to interact via its N-terminal Ig-like domain with the nonpolymorphic α2 and β2 domains of MHC class II molecules (203,204,208–210). In addition to its role in increasing adhesion between the TCR and MHC–peptide complexes, CD4 is involved in intracellular signaling in T cells through its physical association with the tyrosine kinase $p56^{lck}$ (204,211–213). Association of CD4 with the TCR–CD3 complex may in fact depend on CD4 interactions with $p56^{lck}$ (214–217). Site-directed mutagenesis suggests that either CD4 or MHC receptors may interact as oligomers during T-cell activation (218). Activation through different regions of CD4 appears to deliver different activatory signal to T cells (219). CD4 downregulation after T-cell activation may involve serine phosphorylation (220), which is accompanied by CD4 dissociation from $p56^{lck}$ (221). The HIV protein NEF interacts with CD4 and downregulates CD4 expression by enhancing the rate of CD4 internalization (222–225). NEF also appears to interact with CD4-associated $p56^{lck}$ (226). The N-terminus and extracellular region of CD4 also acts as a high-affinity receptor for the HIV envelope glycoprotein gp 120 (207,209,227,228) and is the initial point for viral entry into $CD4^+$ T cells (229–231).

3.4.3. CD8

CD8 is a transmembrane disulfide-linked heterodimer, composed of a 38-kDa α chain (Lyt-2) and a 30-kDa β chain (Lyt-3) (202). It has an important immunological role as a coreceptor on class I-restricted T cells (203,232,233). In mice, the α-chain gene is alternatively spliced producing a 34-kDa protein (α′) that can also form a CD8 heterodimer (234). The CD8 αβ heterodimer is expressed on virtually all class I-restricted T cells with the exception of intestinal intraepithelial lymphocytes (IEL), which express a CD8α homodimer (235). CD8 serves two discrete roles on T cells. It functions as an adhesion molecule binding class I molecules on cells targeted for cell-mediated lysis, or performs the same function during interactions with target cells (236–238). It is also a coreceptor participating in antigen signaling in response to antigen-specific signaling through the TCR (237,239–244). CD8 is required for normal maturation of thymocytes (245–247), and mice deficient for the CD8α gene have dramatic reductions in class I-restricted T cells and mount poor cytotoxic T-cell responses (247). During cell–cell interaction, the CD8 coreceptor function appears to engage the same class I molecule on target cells as the TCR (239,240,242–244). The CD8α subunit is reportedly involved in

engaging the α3 domain of the class I molecule (239,240,248–250). The cytoplasmic domain of CD8 associates with $p56^{lck}$ (238,241,251).

3.4.4. CD28

CD28 is a surface glycoprotein that functions as a costimulator of T cells that are activated through the TCR–CD3 complex. In humans about half of all $CD8^+$ T cells and virtually all $CD4^+$ T cells express CD28. In mice all T cells are $CD28^+$ (252–254). Developing $CD4^+CD8^+$ thymocytes express low levels of CD28 (255,256) and mature T cells upregulate the molecule after activation through the TCR (257). The natural ligands for CD28 are the B7 family of molecules on APC (25,252,258). CD28 binds at least two different ligands, designated CD80 (B7/B7-1 (259) and CD86 (B70/B7-2) (260) expressed on the surface of APC; the ligands costimulate T-cell proliferation, cytokine production, and the generation of CTL (261,262). On ligand binding of CD28, its cytoplasmic tail becomes tyrosine phosphorylated and has been thought to bind phosphatidylinositol 3-kinase (263), although the role of PI3 in CD28-mediated signaling is not clear (264,265). A lack of CD28 signaling can be compensated for by a persistent antigenic stimulation (266).

Signals delivered through CD28 "constimulate" the T cell in conjunction with those signals delivered through the TCR, and can prevent the induction of cell death or T-cell anergy (267). Perhaps the most important feature of costimulation is its role in inducing transcriptional activation and secretion of IL-2 (268,269), although costimulation also enhances the production of a number of other cytokines such as IFNγ, IL-1, TNF, IL-4, and IL-5 (252,270,271). CD28 triggering helps sustain TCR-mediated proliferation and is important for Th-dependent B-cell responses (268,272–274). CD28 is probably required for both Th1 and Th2 responses (275–277). However, in the absence of CD28 signaling, T cells tend to develop a Th1 phenotype (275). But the role of CD28 in developing Th responses appears to be more complicated, as CD28-deficient mice have enhanced susceptibility to vesicular stomatitis virus (VSV), which is normally cleared by Th2 humoral responses, whereas mutant mice clear LCMV infections without difficulty, an immune response that relies on a Th1 immune response (254).

3.4.5. IL-2/IL-2R System

IL-2 is a critical paracrine and autocrine mediator that delivers activation signals to T cells via the IL-2R complex (278,279). There are three different IL-2R chains, α (CD25), β (CD122) and γ, that are differentially regulated on T cells (278) and can be expressed individually or together in different combinations, forming dimeric or trimeric receptor complexes with varying affinities for IL-2 (see Chapter 7). T cells constitutively express the intermediate-affinity IL-2Rβ chain (280) and the non-IL-2-binding γ chain. On activation, T cells upregulate the low-affinity IL-2Rα chain and form a high-affinity IL-2Rαβ complex. Binding of IL-2 to its receptor promotes antigen-induced expansion of T cells, whereas a block in IL-2 transcription and secretion renders $CD4^+$ and $CD8^+$ T-cell lines anergic, or nonresponsive, to stimulation through the TCR (281,282). IL-2 and IL-2R are expressed in thymocytes (283–286) and may be important in proliferative events during ontogeny (287). However, although anti-IL-2 antibody treatment has in certain cases been shown to block thymocyte development (288,289), IL-2-deficient mice appear to have a normal thymus profile and to develop mature T cells (290,291).

In addition to its role in supporting T-cell activation and proliferation, the IL-2 system appears to have an essential role in downregulating T-cell activation. Interestingly,

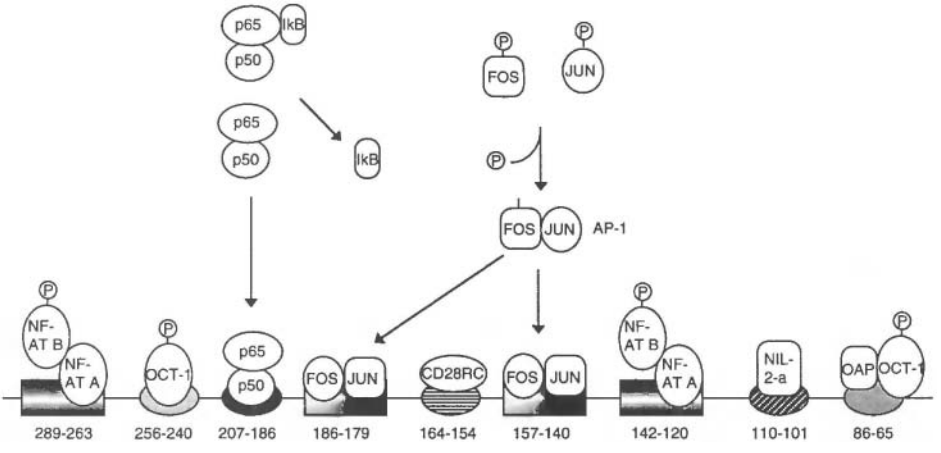

Figure 3.10. Regulatory elements of the IL-2 gene. Transcriptional regulation and upstream signaling (464–466) for IL-2 gene expression are particularly well characterized (467–475). The position of regulatory sequences (in relation to the transcriptional start site, 0) and the transactivating factors that bind them are illustrated.

mice deficient for either IL-2 (292) or IL-2Rβ (293) have hyperactive T cells that appear to drive a generalized and severe autoimmune pathology. In IL-2-deficient mice, the defect has been attributed to $CD4^+$ T cells (294,295); in IL-2Rβ-deficient mice, T cells can be brought under control—and the phenotype reversed—by the presence of normal IL-2Rβ-expressing T cells (H. Suzuki, personal communication).

Signaling through the IL-2Rβ cytoplasmic tail of the β chain is currently under investigation (296,297). An "acid-rich" domain between amino acids 315 and 384 of the β-chain cytoplasmic tail binds the tyrosine kinase SHC (298); JAK kinases have also been shown to associate with the β and γ chains of the IL-2R (299) and induction of IL-2 in T cells requires the activation of $p21^{ras}$ (300,301). A lack of IL-2 production in T cells activated without costimulation has been attributed to inadequate $p21^{ras}$ activation (302). A block in $p21^{ras}$ induction is thought to result in reduced kinase activity of the mitogen-activated protein kinases (MAPK) (303–305), ERK and JNK, and a subsequent lack of activation of the transcription factor AP-1 (302,306). Inadequate IL-2 production under such circumstances may also reflect transcriptional repression involving NIL-2a (307,308) (Figure 3.10).

3.4.6. CD45

CD45 is critical for normal activation of T cells through the antigen receptor (309–311). CD45 phosphatase activity is essential for proximal and distal signaling events after TCR ligation (312–314), including tyrosine phosphorylation, phosphoinositol hydrolysis, Ca^{2+} flux into cells, and induction of IL-2 synthesis and proliferation of cells, respectively (311,315,316). CD45-deficient mice have a dramatic block in thymocyte differentiation of mature single-positive $CD4^+$ or $CD8^+$ T cells and consequently lack a normal peripheral T-cell compartment (317). Although B-cell development appeared unimpaired in these mice, recent data suggest that CD45 also regulates selection processes of B cells (318).

Activated T cells switch expression of CD45 from the high-molecular-weight isoform CD45R to the low-molecular-weight form CD45RO (319,320). Although T cells can

Table 3.2
Exon Usage for the Various CD45 Isoforms

Isoform	Exons used						Antibody specificity A	B	C	O
CD45α	123	4	5	6	7	8	+	+	+	
CD45β	123	4	5		7	8	+	+		
CD45γ	123	4		6	7	8	+		+	
CD45δ	123		5	6	7	8		+	+	
CD45ε	123	4			7	8	+			
CD45ζ	123		5		7	8		+		
CD45η	123			6	7	8			+	
CD45θ	123				7	8				+
CD45τ	123					8				

switch back from CD45RO expression to CD45R (321), the CD45 isoform expressed has been used to distinguish memory (CD45RO) from virgin (CD45RA,-B,-C) T cells (322,323) and to characterize certain functional subsets of T cells (324–329). The various isoforms appear to bind to CD22β (330,331), although this molecule probably interacts with additional sialic acid-containing moeities on T cells. The role for the different CD45 isoforms in T-cell subsets has yet to emerge (Table 3.2).

CD45 resides in close proximity to the TCR complex, where it represents about 90% of the membrane-associated protein tyrosine phosphatase (PTP) activity (189,332). In nonactivated T cells, basal levels of CD45 phosphatase activity remove phosphate groups from the signal-transducing kinases, negatively regulating their activity. Stimulation of the T cell induces tyrosine kinase activity, resulting in a rapid accumulation of phosphorylated tyrosine residues at regulatory sites of important signaling kinases, which become active and initiate signaling kinase activity. Phosphatase activity is attributed to its cytoplasmic domain (333–337), which in T cells dephosphorylates C-terminal regulatory tyrosine residues on SRC-PTKs (e.g., $p56^{lck}$ and $p59^{fyn}$) (338–345).

3.4.7. CTLA-4

CTLA-4 is an essential surface molecule that acts as a negative regulator of T-cell activation. Although they have opposing roles, CTLA-4 has significant similarities with CD28. Both are disulfide-linked homodimer glycoproteins, sharing about 76% sequence identity in mice (346–348), both have a single extracellular Ig-V-like domain, both are expressed on T cells and bind the ligands CD80 (B7.1) and CD86 (B7.2,B70), and finally their genes exhibit similar organization, are located in close proximity on mouse chromosome 1, and appear to be the product of a gene duplication event (349–355). Despite the similarities, CTLA-4 binds CD80 with a 20-fold greater affinity than CD28 (348) and contains two binding sites for its costimulatory ligands (356). Functional studies on CTLA-4 have led to a variety of interpretations and have demonstrated both positive and negative signaling features for the molecule (347,357–359). The recent production of a CTLA-4-deficient mouse strain has highlighted the importance of CTLA-4 in lymphocyte

homeostasis, and in downregulating T-cell activity (360). T cells from CTLA-4 mutant animals undergo spontaneous activation and proliferation, spleen and lymph nodes are grossly enlarged, serum immunoglobulin levels are elevated and autoimmune disorders are prevalent. The downregulation may be mediated by the recruitment of tyrosine phosphatase SHP-2 (through an SH2 domain interaction) by CTLA-4 to the membrane where dephosphorylation of substrates can reverse the T-cell activation events (361).

3.5. T-CELL ACCESSORY MOLECULES

3.5.1. CD2 (LFA-2, Leu-5, Tp50)

The 45- to 50-kDa transmembrane glycoprotein CD2 is a monomeric Ig-superfamily molecule with two extracellular Ig-like domains and a long proline-rich (116) cytoplasmic tail (362–364) (see Figure 4.1). CD2 is expressed early during T-cell ontogeny in the thymus and on most peripheral T cells (365). In mice, CD2 is also expressed on some B cells (366). A high-affinity receptor for CD2 has been identified as the widely expressed LFA-3 (CD58) molecule, an Ig-superfamily molecule that is alternatively spliced and exists in either GPI-anchored forms or with a short cytoplasmic tail (362,363). CD2–CD58 binding is thought to stabilize cell–cell interactions to facilitate efficient ligation of TCR and MHC–peptide complexes; at the same time, stimulation through the TCR mediates upregulation of CD2 expression (363,364,367). CD2–CD58 interactions may thus be important in T-cell binding to APC and to their target cells, and perhaps are important in thymocyte contact with endothelial or bone marrow-derived stromal cells, where CD2 might mediate signals such as apoptosis (368). CD2 binding by its ligand also induces upregulation of CD40 and may thus be important in cognate T–B interactions (369). The CD2 structure (370,371) and CD2–CD58 binding have been studied in detail (370,372). Anti-CD2 or -CD58 antibodies inhibit IL-12-induced proliferation and IFNγ production by phytohemagglutinin-activated T cells (373). Signals resulting from CD2 engagement may play an essential role in the regulation of the Th1–Th2 effector equilibrium (374,375). CD2 perturbation results in the phosphorylation of CD3γ and ζ chains, and the latter appears crucial for sustaining CD2-induced activation (28). Activation of CD2 by monoclonal antibody or soluble CD58 also results in tyrosine phosphorylation of PLCγ1 and PKC activation (376). CD45 phosphatase activity is critical for CD2-induced tyrosine kinase activity, PLCγ1 activation, and IL-2 production (376,377).

3.5.2. CD5

CD5 is a pan-T-cell marker expressed on thymocytes and mature T cells in association with TCR complexes and is phosphorylated in responses to antigen receptor stimulation (378,379). Anti-CD5 antibodies have been found to potentiate T-cell proliferation (380) and IL-2 secretion and IL-2R (CD25) expression (380,381). HIV-infected individuals have a population of $CD5^-$ T cells (382) and increased numbers of $CD5^+$ B cells are observed in autoaggressive immune disorders such as rheumatoid arthritis (383) and myasthenia gravis (384,385). The natural ligand for CD5 is CD72 (Lyb-2) (386), which is expressed on pre-B and mature B cells but absent from Ig-secreting plasma cells (387).

3.5.3. FAS (CD95)/FASL

The cell-surface protein FAS (APO-1) is a member of the tumor necrosis factor receptor (TNFR) superfamily, which includes TNF, LTα, LTβ, their shared receptors

TNFR p55, TNFR p75, and TNFR-RP, and the receptor ligand systems of CD27/CD27L, CD30/CD30L, CD40/CD40L, 4-1BB/4-1BBL, and OX40/gp34 (388,389). Members of this superfamily are in general involved in interactions between lymphoid cells and other hematopoietic cells (including lymphocytes), where they can mediate activation, inhibition, or cell death. CD95 triggering via interaction with its ligand FASL can induce apoptosis in $CD4^+CD8^+$ thymocytes (390) and mature peripheral T cells (391–393). This mechanism of eliminating autoreactive T cells may be an important inducer of T-cell tolerance in the periphery (394–396), where CD95 has been shown to play a prominent role in preventing graft rejection (397). Whereas FAS is expressed on a variety of lymphocyte subsets (398), in addition to other nonlymphoid cells such as monocytes and neutrophils (399), FASL is predominately induced on activated T cells (393,400). However, FASL is also expressed in thymus, in addition to nonlymphoid organs such as testis and eye, where expression may be a means of facilitating immune privilege (395).

Despite the presence of FASL in thymus, transgenic mice overexpressing CD95 have supported a role for the FAS–FASL system in peripheral—but not thymus-induced—tolerance (401). Peripheral deletion of T cells by superantigen may also involve CD95 (402). Autoreactive B cells are also subject to CD95-mediated cell death, delivered via interactions with FASL-expressing $CD4^+$ T cells (403–405). CD95 is an integral component of the cytotoxic machinery used by T and NK cells to kill their targets (406–413). Autoimmune mice (gld) harbor a mutation in the FASL gene (414) and mutations in CD95 are associated with both human and murine lymphoproliferative disorders (396,415). Human immunodeficiency virus (HIV) appears to induce upregulation of CD95, which may have the effect of sensitizing infected T cells for apoptosis (416).

3.5.4. LFA-1 (CD18/CD11a)

The CD11a/CD18 (LFA-1) complex is a cell adhesion molecule that has for some time been considered essential for normal cell-mediated cytotoxicity by T lymphocytes (CTL) and NK cells (417,418). Interactions between cytotoxic T cells and target cells (364,419,420) or APC (421,422) are thought to rely significantly on LFA-1 binding of its ligands ICAM-1, ICAM-2, and ICAM-3. Although LFA-1 appears to have a predominate role in lymphocyte function (362), it is also expressed on monocytes, granulocytes, and bone marrow cells. Lymphocytes require LFA-1 for normal inflammatory responses *in vivo* (364,423). Earlier studies suggested that LFA-1 probably was crucial to early phase induction of immune responses but was not as important for lymphocyte proliferation and effector phase (417,424). Other studies suggested LFA-1 function in T-cell recirculation and delayed-type hypersensitivity (425,426). Anti-LFA-1 antibody treatment inhibits *in vitro* adherence of lymphocytes to lymph node HEV and reduces *in vivo* migration into lymph nodes and Peyer's patches (427,428). Priming and expansion of lymphocytes has been shown to require LFA-1 (422,429). Interestingly, however, CD11a-deficient mice were found to mount normal T-cell responses to virus and to exhibit normal CTL function *ex vivo,* but were defective in responding to and clearing tumors (430).

LFA-1 is a β_2-integrin family member, which include MAC-1 (CD11b/CD18), p150,95 (CD11c/CD18), and a putative heterodimer recently described (431). CD11b/CD18 is important for granulocyte and monocyte function and CD11c/CD18 is reportedly a phagocyte receptor (419,432). Mutations in CD18 result in a lack of functional CD11a/CD18 (LFA-1), CD11b/CD18, and CD11c/CD18 heterodimers and so-called lym-

phocyte adhesion deficiency (LAD), manifesting as extreme susceptibility to infections (433–436).

3.5.5. Very Late Activation (VLA) Integrins ($CD49_{a-f}$/CD29)

VLA molecules incorporate the 130-kDa β_1 integrin (CD29) chain and one of a variety of 120- to 210-kDa α subunits (VLA1–VLA6). VLA integrins are widely expressed on leukocytes where they bind a variety of ligands that include components of the extracellular matrix, such as laminin, collagen, fibronectin, and epilegrin (437,438). VLA4 is expressed on the majority of thymocytes and VLA5 is upregulated on single-positive thymocytes (439,440). Interaction of these cell-surface integrins with fibronectin may be important for thymocyte migration and T-cell development in the thymus (441,442). VLA–ligand interactions can enhance stimulation through the TCR/CD3 such that, for example, subthreshold stimulation through CD3 cross-linking can induce proliferation when combined with VLA activation (438,443–446). Induction of tyrosine phosphorylation as a consequence of VLA signaling involves numerous substrates such as PLCγ, pp125 focal adhesion kinase, paxillin (pp70 and pp50), $p59^{fyn}$, $p56^{lck}$, and MAP kinase (445,447–449).

3.6. THYMIC DEVELOPMENT OF T CELLS

Both $\alpha\beta$ and $\gamma\delta$ T cells develop in the thymus from common precursor cells that have migrated from the bone marrow. $\gamma\delta$ T cells can also undergo extrathymic development. T-lineage progenitor cells in the thymus are thus capable of rearranging $\alpha\beta$ or $\gamma\delta$ genes and recombining one or the other locus early during the pro-T-cell stage (3,106–109). Although β-chain expression in the absence of the α chain has no receptor activity in mature T cells, immature thymocytes coexpress a temporally regulated 33-kDa protein that heterodimerizes with the β chain to form a functional pre-TCR complex (450–452). Expression of a β-chain transgene can rescue rearrangement-deficient $CD4^-$ $CD8^-$ thymocytes, facilitate their expansion, and advance them to the $CD4^+CD8^+$ stage of development (453–455). The β chain may also help induce assembly and expression of α-chain genes (106,453,456). Only about 5% of $\alpha\beta$ TCR $CD4^+CD8^+$ thymocytes become mature $CD4^+$ or $CD8^+$ cells (Figure 3.7) (457–459).

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4

B-Lymphocyte Genes

Once a pathogen has penetrated the body there are two possible sites where replication can occur and where host defenses can mount a counterattack, namely, in intracellular or extracellular compartments. It is the job of B cells and the humoral arm of the immune system to manage the battle against extracellular stages of infection, to minimize the spread of infection, to antibody-label extracellular organisms and inactivate or target them for destruction, and to provide mechanisms of specific capture of antigen for presentation and support of T-cell responses—thereby providing a critical link between the humoral and cell-mediated arms of the immune system. The production of large amounts of clonotypic antibodies, or immunoglobulins (Ig), that both form membrane surface receptors and are secreted from B cells, is the cornerstone of the humoral response. The immunoglobulins are thus noted for their ability both to function as surface receptors on cells and to act as critical soluble mediators of adaptive immunity in blood and lymph.

Ig molecules synthesized from B cells must exhibit an enormous amount of variability such that they can function as specific ligands for a plethora of antigens. But the proteins must also be engineered in such a way as to be readily synthesized in both membrane-bound and soluble forms, be able to switch effector functions while maintaining antigen specificity, mediate carefully regulated complement activation, be efficient ligands for an array of surface receptors, and be capable of hypermutation to fine-tune specificity and increase affinity to antigens during an immunological challenge.

Ig molecules contain four or five related extracellular regions, or immunoglobulin superfamily (IGSF) domains, that can be further subdivided into variable (V) or constant (C) Ig domains. Although both V and C-type Ig domains structurally have much in common, the V region is longer by about 16 amino acid residues, contains two extra β-strands, and exhibits significant differences in quaternary structure. The Ig superfamily domain contains about 100 amino acids that make up the characteristic Ig-fold, a structure that is featured in a large number of surface molecules that exist in one form or another on the plasma membrane of most, if not all, cells. The IGSF members perform a multitude of functions, and include well-characterized immunological molecules such as CD4, CD8, CD28, Fc, and T-cell receptors, to mention a few (Figure 4.1).

Immunoglobulins are composed of two identical and relatively high-molecular-weight chains, called heavy chains (H), and two identical smaller light chains (L), ex-

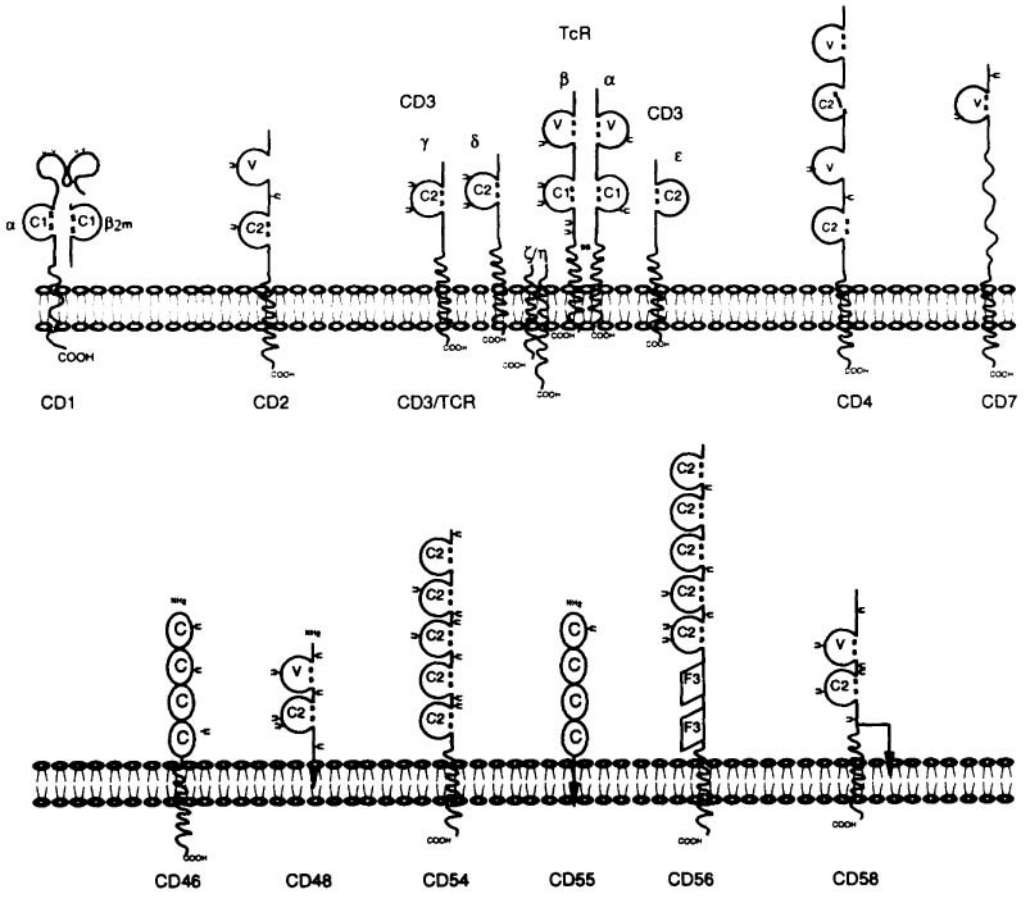


Figure 4.1. A highly schematic representation of surface molecules containing Ig-like domains. The Ig-fold can be described as a sandwich, one half of which is a three-stranded, and the other half a four-stranded antiparallel β-pleated sheet. Each β-strand is composed on average of about six amino acids, and in most cases, both halves of the sandwich are held together by a disulfide bond. Sequence identity between IGSF molecules is mainly conserved in the β-strands whereas considerable variability exists in the loops. The Ig molecule is comprised in equal parts by β-sheets and loops. C1 domains have similar sequences to Ig domains contained in antigen receptors on B and T cells, and the membrane-proximal domains of MHC molecules. C2 domains have similarities to both V and C domains. Differences between C and V regions largely reflect an extra polypeptide loop in the three-stranded β-sheet of V regions (523). For details about functions of molecules in this diagram, see Chapter 8.

pressed from either the κ or λ light chain genes—a receptor system exploited by virtually all vertebrates (1). Thus, a total of four polypeptide chains transcribed from separate genes are linked to form the mature Ig molecule. Both heavy and light chain polypeptides possess the N-terminal V domains that contain most of the sequence variability of the Ig molecule. V-region amino acid variability is further localized into three clusters, known as the complementarity-determining regions (CDRs), encoded by hypervariable regions (HVRs) that result from the assemblies of light chain and heavy chain gene segments. The

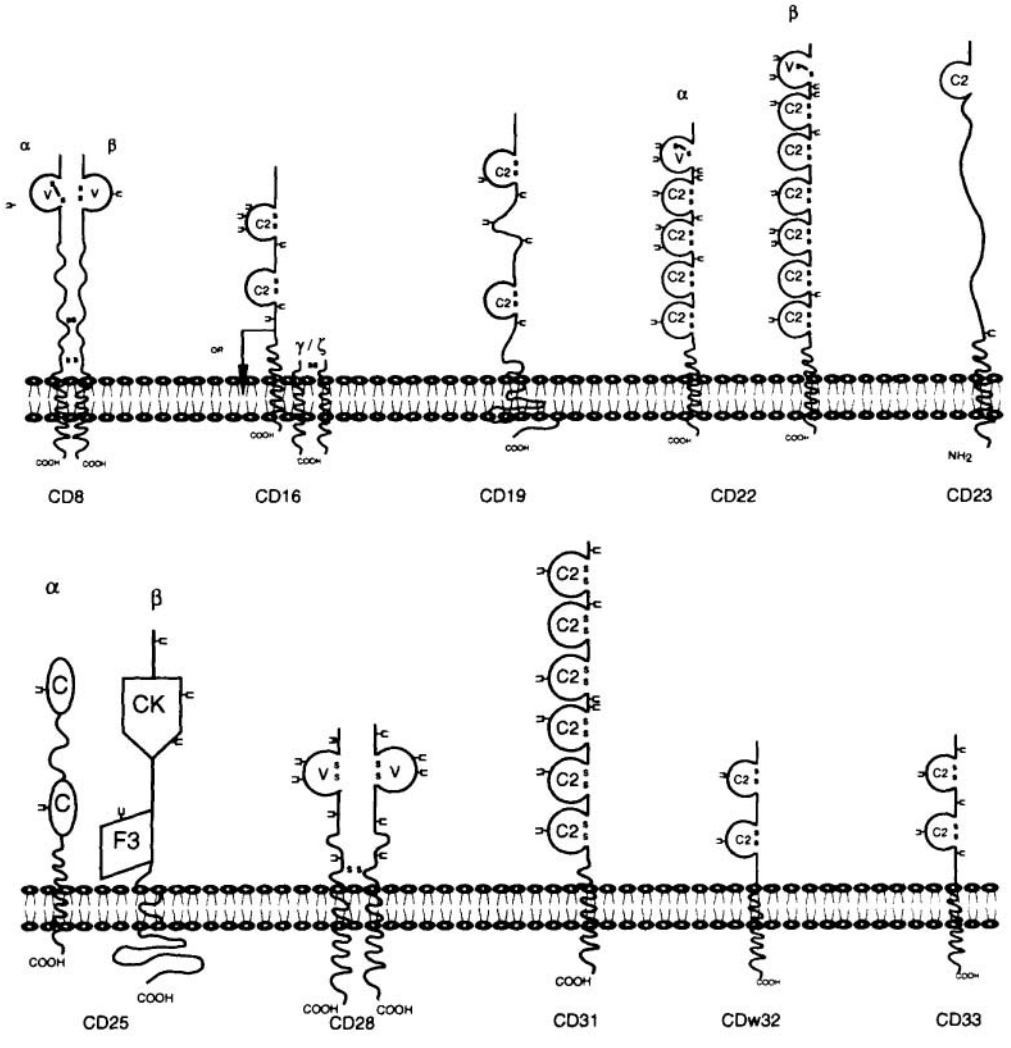


Figure 4.1. (*Continued*).

CDRs of the light chains and heavy chains make up the actual antigen-binding sites, occurring mainly in the *loops* that connect the antiparallel *strands* of the β-pleated sheets. Each unique antigenic determinant formed by a CDR is referred to as an *idiotope*, and the specificity of the antibody as a whole is referred to as an *idiotype*. Conserved amino acid sequences in strands and loops not forming the antigen-binding sites are termed *framework regions* (FRs) (Figure 4.2).

Heavy chain genes encode both constant (C) regions and variable (V) regions of the Ig (Figure 4.2). Because the biological properties of Igs are determined by the Fc portion (isotype) encoded by the C-region segments, it is fitting that the nomenclature for the various Ig classes reflects differences in the Fc regions (Figure 4.3A,B, Table 4.1). In the

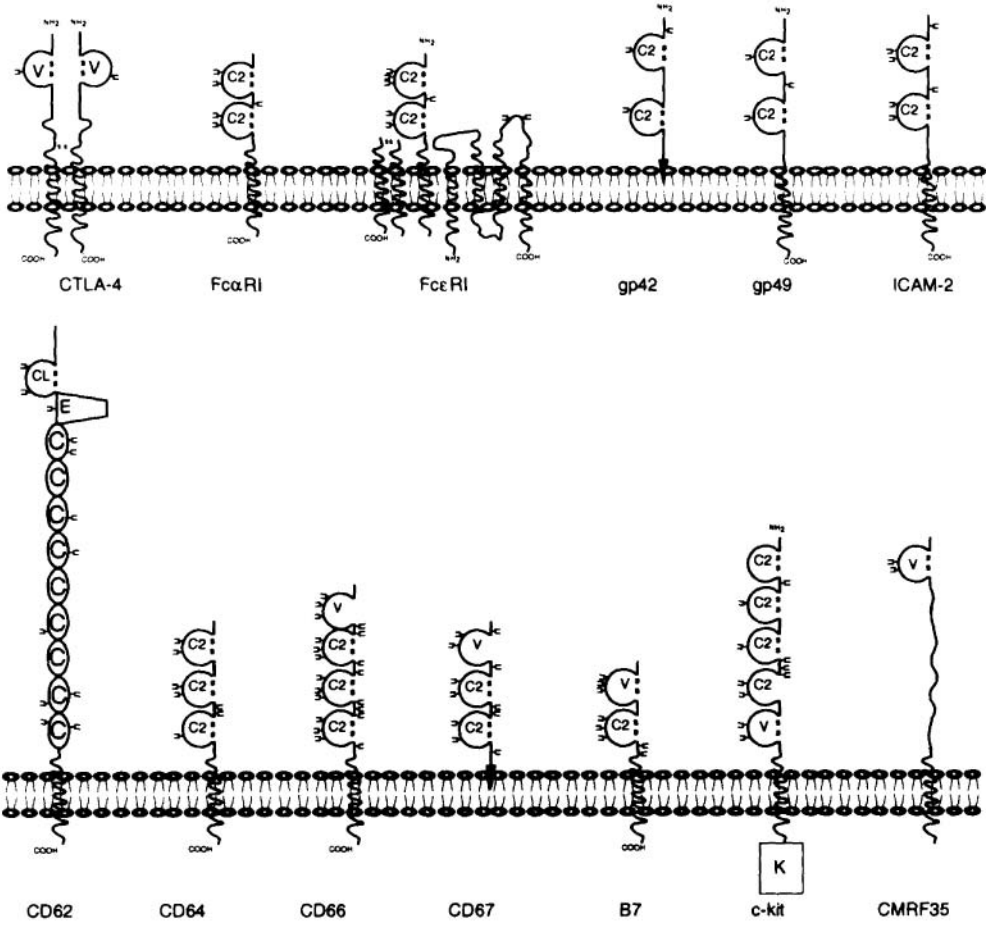


Figure 4.1. (*Continued*).

nomenclature for murine heavy chains, α, δ, ϵ, γ1, γ2a, γ2b, and γ3 genes correspond to IgA, IgD, IgE, IgG1, IgG2a, IgG2b, and IgG3, respectively. Humans have two IgA subclasses, IgA1 and IgA2, single IgD and IgE isoforms, and four major IgG subclasses, IgG1, IgG2, IgG3, and IgG4, that correspond to genes α1, α2, δ, ϵ, γ1, γ2, γ3, and γ4, respectively.

4.1. IMMUNOGLOBULIN GENES

4.1.1. Heavy Chain Genes

Rearrangement of Ig genes begins in B-cell ontogeny during pro-B development (2), where functional heavy chain genes are produced from variable (V_H), diversity (D), and joining (J_H) gene segments. The heavy chain genes D and J_H are the initial substrates for

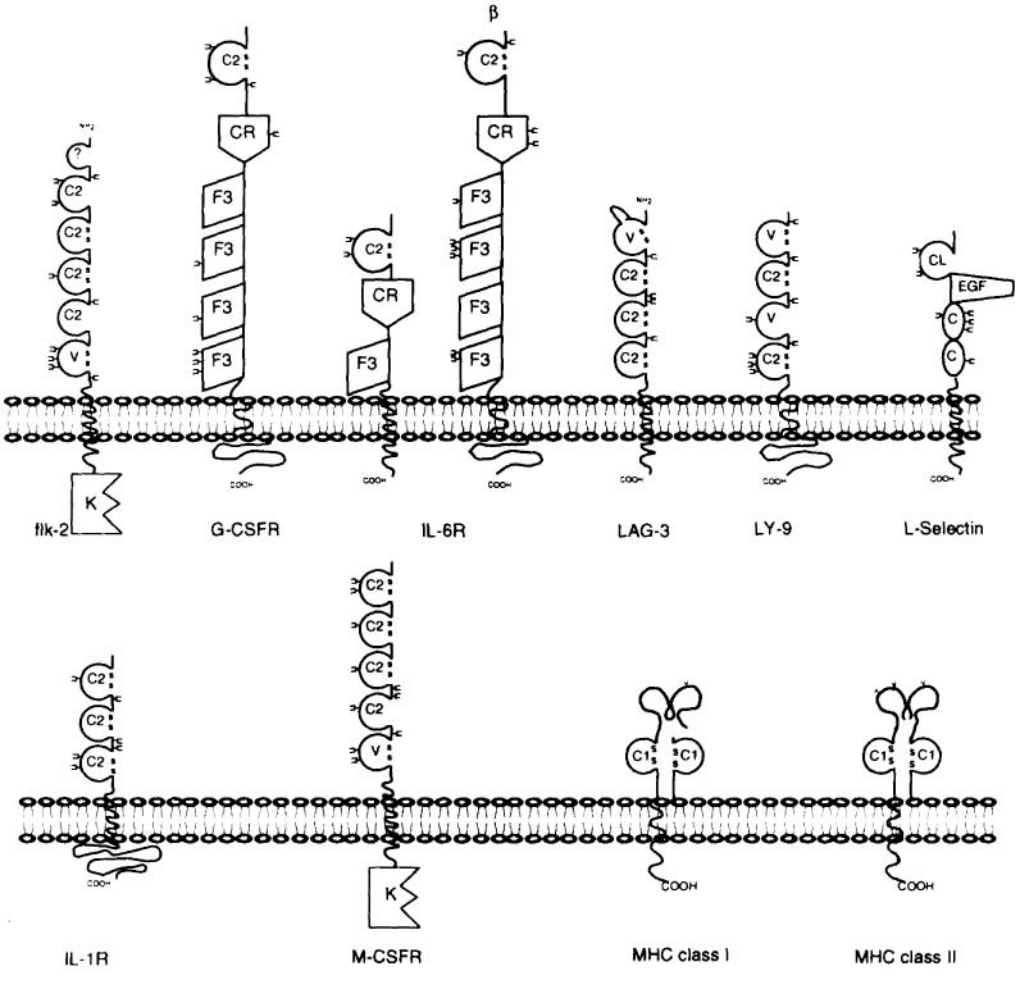


Figure 4.1. (*Continued*).

the rearrangement process and are realigned ($D \rightarrow J_H$) next to each other (DJ_H). Next a V_H segment is added ($V_H \rightarrow DJ_H$) to form the complete V region (V_HDJ_H) (Figure 4.4A,B). The C gene segments, aligned in series 3′ to the combined VDJ_H region, are differentially spliced to produce intact Cμ or Cδ mRNA transcripts (3). Thus, two complete heavy chain mRNAs (Igμ and Igδ) are generated following heavy chain VDJ_H rearrangement. The Igμ chain is expressed early in ontogeny whereas mature B cells express both isotypes. The mechanism of heavy chain transport to the surface of B cells has been extensively studied, albeit less so during the process of ontogeny. In early B cells, μ heavy chains have been found to associate with a number of proteins including surrogate light chains (see below), Igα and Igβ (see below), and the chaperones GRP94, BiP/GRP78, and calnexin (4–7). These proteins and others appear also to be involved in assembly of heavy chain and κ or λ light chains in mature B cells (4,5,8–12).

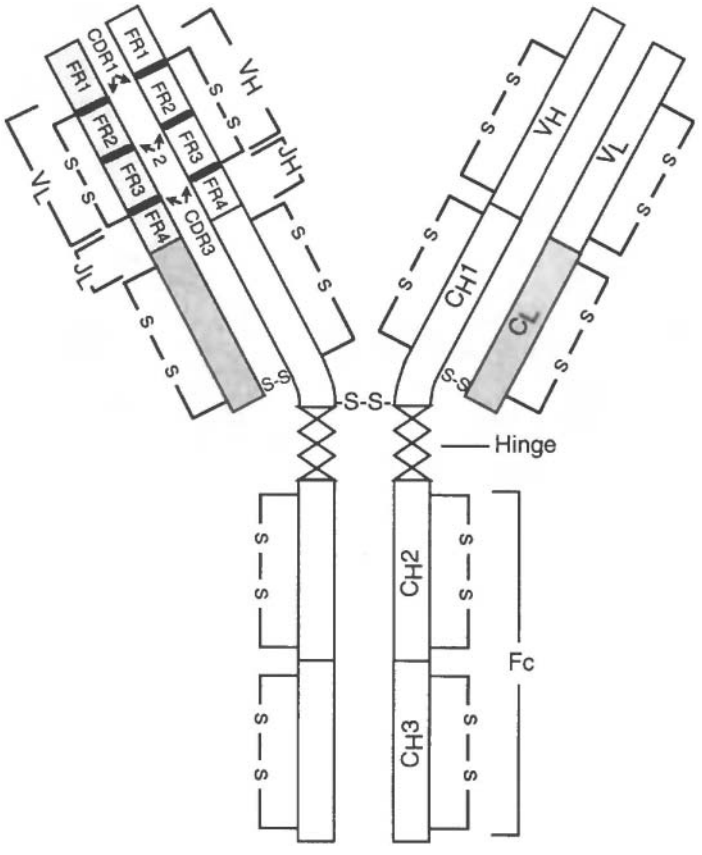


Figure 4.2. Schematic depiction of an Ig molecule bearing a λ light chain, illustrating the relative positions of CDRs and FRs. In addition to variations in primary sequences, N-glycosylation in V domains can alter the conformation of the polypeptide loops and modify antigen-binding properties (524–526). Bold lines indicate CDRs, stippled boxes represent FRs.

Isotype switching to IgG, IgA, or IgE occurs through a process by which the variable gene regions (initially proximal to Cμ) are rearranged to other C-region segments (13,14). C-region recombination is directed by repetitive switch sequences, incorporated into 2- to 10- kb switch regions, located immediately upstream of the C-region genes (15). It has not been established how the recombinational machinery differentially selects C regions in order for B cells to choose expression of a specific isotype (16,17). It has been noted that exogenous factors (i.e., LPS, IL-4, IL-10) induce transcription at unrearranged C genes prior to switching to the same C_H genes (18,19) and that isotype switching is correlated temporally with transcriptional activation of a targeted switch region (20). Mice deficient for NF-κB or IgH enhancers also fail to normally rearrange C-region genes (21). These results may indicate that switch recombination is in part regulated by transcriptional machinery (22).

In humans the V_H gene segments are categorized into 7 families that vary in size from V_{H3}, which has more than 30 members, to V_{H6}, which contains a single gene segment (23–25). Each family contains unique 5′ flanking regions, and each family

member shares about 80% identity in terms of nucleotide sequences. The total V_H repertoire—including both functional and nonfunctional genes—occupies a total of about 3 mbp of DNA on chromosomes 14q32.3 (1.1 mbp), 15q11.2 (1.1 mbp), and 16p11.2 (0.8 mbp), although only chromosome 14 has segments that are known to participate in functional rearrangements (24). In humans, the V_H genes are not necessarily clustered in groups with other family members, but rather V_H clusters often contain members of different families (26–28). Mouse V_H genes are grouped into 14 families (29) and are mostly clustered according to family groupings (30,31). The human V_H-III family shows the greatest homology with mouse V_H genes (32). Nonfunctional clusters of Ig gene segments on human chromosomes 14, 15, and 16 have been dubbed *orphan regions;* orphans on chromosomes 15 and 16 appear to have been duplicated by interchromosomal translocation of functional segments from chromosome 14 (24,33). Of the orphan V_H segments on chromosomes 15 and 16, there are at least 10 genes with open reading frames, one of which appears to contain typical recombination signal sequences (RSS) (24) (Section 4.2.1).

Finally, alterations in heavy chains are used to generate membrane-bound (mIg) and secreted Ig (sIg). The replacement of a stretch of 26 hydrophilic amino acids at the C-terminus of sIg by a 41-residue hydrophobic anchor results in the generation of mIg. The conversion from sIg to mIg expression is achieved by differential processing that involves alternate splicing and polyadenylation of the primary RNA transcript (34,35). This may be controlled in part by intron length (36) and by exon recognition sequences (ERS) that denote splicing points in transcripts (37–39). The ratio of mIg versus sIg changes during B-cell differentiation: Early B cells mostly produce mIg, whereas plasma cells predominately express sIg.

4.1.2. κ Light Chain

The human κ light chain genes occupy roughly 300 kbp on chromosome 2p11-p12, which includes about 50–100 Vκ genes, 5 Jκ segments, and a single Cκ gene (40–42). In humans Vκ genes are grouped into four major families, VκI–VκIV, although what appear to be nonfunctional orphon Vκ regions have been described on 2p18 and chromosomes 1 and 22 (43,44). Mice have a more extensive set of Vκ genes (~300) categorized into about 20 interspersed families (45), which rearrange with four functional Jκ segments and a Cκ gene (29). Despite differences in the total numbers of genes, a high degree of sequence similarity exists (greater than 74%) between human and murine Vκ families. About 95% of B cells in mice have κ light chains on their surface (46,47) compared with about 60% of human B cells (48). The light chain present in serum Ig reflects the dominant κ expression seen for antigen receptors on B cells. Moreover, there is a significant skewing of Vκ gene expression in B cells in favor of a limited number of Vκ families. The marked bias for κ-chain expression may reflect superior recombination efficiency of κ genes (49), or an antigen-driven preferential selection of κ-gene products (50). In addition, mice rendered defective for κ light chain loci (46,47,51,52) express a strictly limited repertoire of λ genes. About 0.2–0.5% of peripheral B cells in humans express antigen receptors with both κ and λ light chains (53).

Compared with heavy chain genes, the light chain genes are thought to have little variation imparted by N-nucleotide addition (see Section 4.3.2). A corollary is the expectation that junctional diversity in the $V_L \rightarrow J_L$ joint, which encodes the CDR3 of the light chain, reflects mainly variation encoded by the combination of germline sequences at the

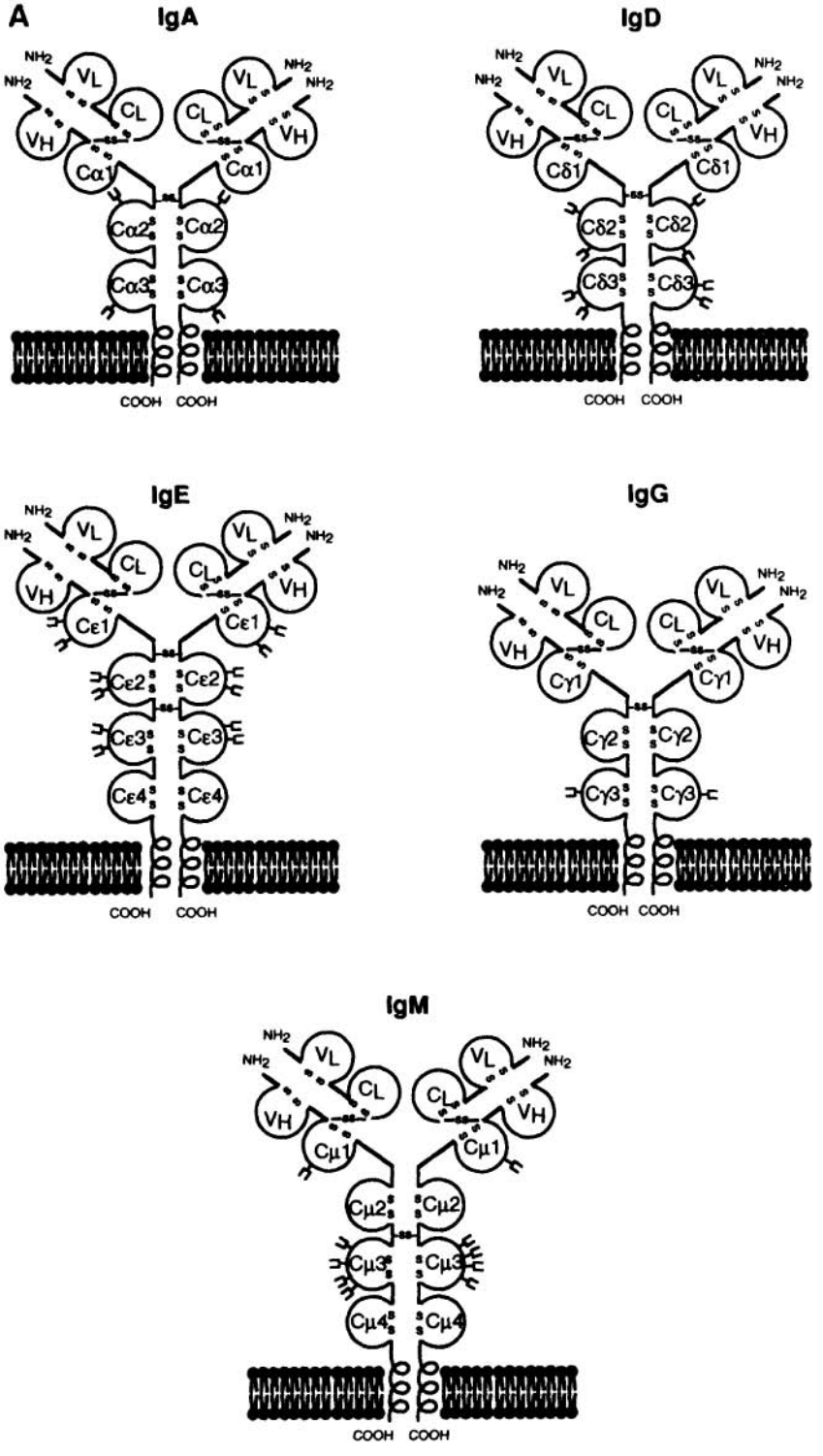


Figure 4.3. (A) Ig isotypes. IgE and IgM have additional C-region domains in the Fc portion of the molecule. The proteins contain various sites for N- and O-linked glycosylation, as depicted by the stick symbol (—|). Differential glycosylation of C-region domains may play a role in modifying antigen specificity (see Figure 4.2), complement fixing activity (527,528), half-life in serum (529), and antibody-mediated autoimmune diseases (530–532).

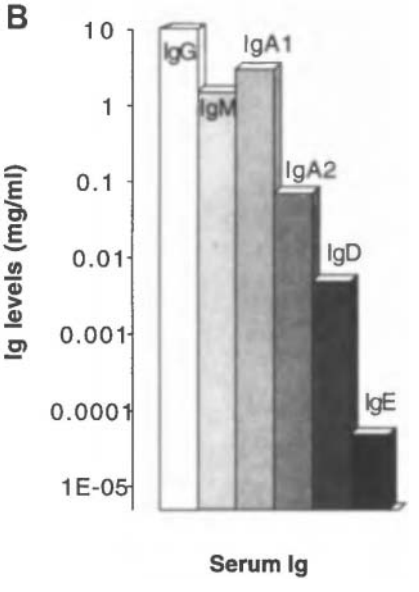


Figure 4.3. (B) Levels of human Igs in serum.

Table 4.1
Properties of Human Igs

	IgG	IgA	IgM	IgD	IgE
Molecular weight	150 kDa	160 kDa	190 kDa	175 kDa	190 kDa
Sedimentation coefficient (S)	7	7	19	7	8
Carbohydrate (%)	3	10	13	15	15
Heavy chain isotypes	4	2	2	—	—
Heavy chain allotypes	23	2	1	—	—
Adult serum level (%)	80	13	6	<1	<1
Placental transfer	+	—	—	—	—
Half-life in serum (days)	9–23	6	5	5	2.5
Bacterial lysis	+	+++IgA1 −IgA2	+	?	?
Classical pathway complement activation	++	—	+	—	—
Alternative pathway complement activation	—	+IgA1 −IgA2	—	—	—
High-affinity binding to mast cells and basophils	—	—	—	—	+++
Macrophage binding	+				

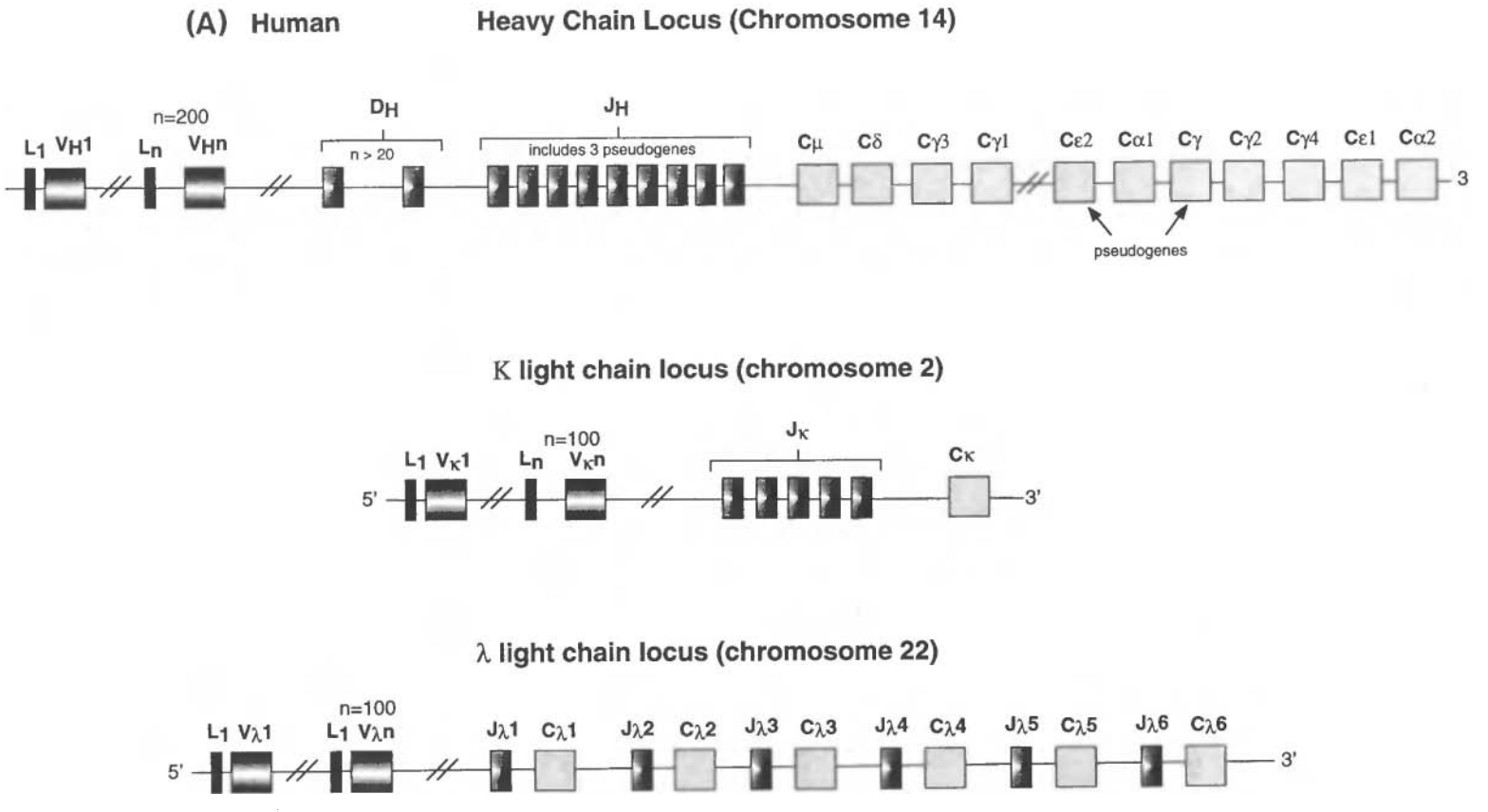


Figure 4.4. Schematic representation of the human (A) and mouse (B) loci involved in producing the heavy and light chain components of the Igs.

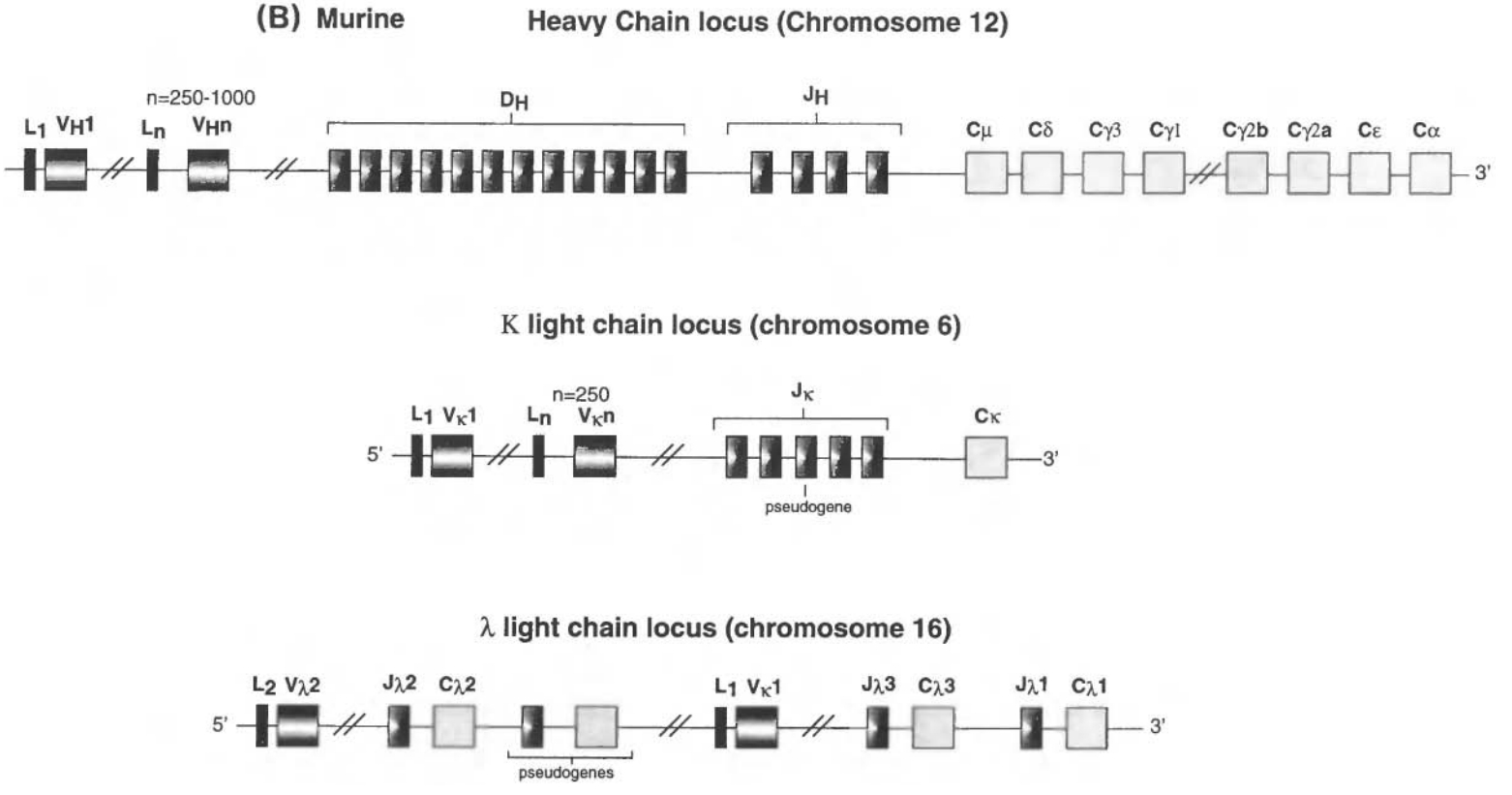


Figure 4.4. (*Continued*).

joints. Sequence analysis has confirmed that most Vκ–Jκ joints (CDR3 variation) are encoded by germline sequences, although about one in five $V_L \rightarrow J_L$ joints appear to contain some N additions (54). Interestingly, the assumption that N-region diversity is necessary for antigen receptor diversity and strong immune responses has been challenged by reports that immune responses are normal in mice lacking terminal deoxynucleotidyl transferase (55) (see Section 4.3.2).

Light chain rearrangement is thought to be arrested by the expression of a functional antigen receptor (56–58). However, in situations where κ and λ genes are nonproductively rearranged, or where they assemble with a heavy chain to produce an antigen receptor with a high avidity for self-antigens, it has been suggested that a process of additional rearrangement, or *editing*, of the light chain loci can occur (59,60). Although both κ and λ genes appear to undergo editing after nonproductive rearrangement, kappa gene editing appears to have a major role in rescuing B cells with autoreactive antigen receptors from deletion (61,62).

The regulatory mechanisms involved in receptor editing, and more generally, Ig gene rearrangement, are not well understood. The control of switch recombination of C-region genes has been linked to transcriptional regulation of switch region genes, and general models that explain how rearrangement is directed have been proposed. Mice deficient for a κ intron enhancer element are defective for V→Jκ rearrangement (47,52). A recent study of Vκ–Jκ genes has found a Vκ–Jκ *cis*-acting recombination-enhancing sequence that is involved in regulating gene rearrangement *without* affecting transcription (63).

4.1.3. λ Light Chain

The human λ light chain genes occupy about 3000 kbp in three separate clusters on the short arm of chromosome 22q11 (48). They include about 20–70 functional Vλ genes grouped into 10 Vλ families (>75% identity) (64–66), and 7 Cλ constant-region genes in tandem array each adjacent to a Jλ segment (48,67–69), the latter grouped into three clusters that reflect family affiliations (67). The presence of alternating pairs of J-region and C genes is unique among Ig loci, but is seen in both human and murine λ loci. The mouse λ locus stretches over 2000 kbp and incorporates 3 Vλ genes and 4 Cλ segments, each of the latter accompanied by a functional J segment.

Only a small proportion of B cells express λ light chains in mice (see Section 4.1.2), despite the observation that both λ and κ loci of mature B cells contain DNase hypersensitive sites and appear to have active chromatin structure (70). B cells expressing λ light chains usually show extensive rearrangement of the κ locus (the reverse is not true), even though rearrangement of the κ locus is not required for λ rearrangement (46,47,51,52) and the events appear to occur independently of one another (71). κ-chain-deficient mice produce a compensatory amount of λ-bearing B cells (46,47).

The joined V–Jλ segment contains the HVRs, whereas the Cλ regions code for different λ-chain subclasses. Sequences surrounding the λ genes lack sequences with similarity to the enhancer elements present in heavy chain and κ light chain genes (72–74), although functional regions are characterized in the mouse that do facilitate lymphoid-specific expression (75–77). Mice deficient for κ light chains express a strictly limited repertoire of λ genes (46,47,51,52,78,79), notably λ1, λ2(V2), λ2(Vx), and λ3. An unambiguous mechanistic or functional explanation for the preferential use of λ genes is forthcoming (51,80).

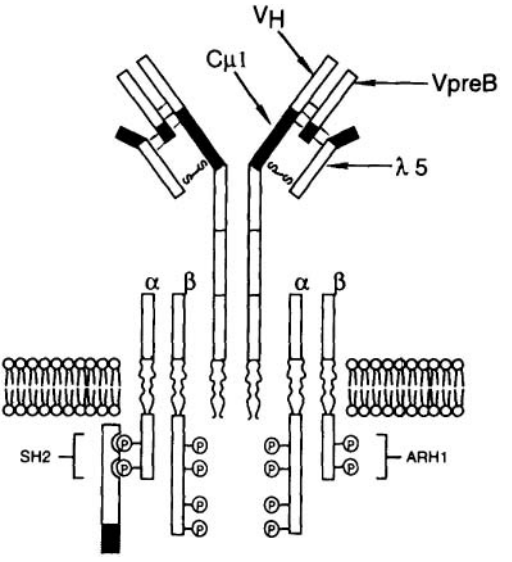


Figure 4.5. The B-cell antigen receptor complex (BCR) incorporates membrane-bound Ig and the transmembrane heterodimer CD79a (Igα) and CD79b (Igβ). BCR cross-linking results in phosphorylation of Igα/Igβ tyrosine residues, docking sites for SRC-homology-2 (SH2) proteins. The receptor depicted here is that of an immature B cell, including VpreB/λ5 light chains associated with a μ heavy chain. Dotted lines indicate noncovalent interactions.

4.1.4. Surrogate Light Chain (VpreB/λ5)

The VpreB and λ5 genes encode 16- and 22-kDa proteins that share significant sequence similarity with V-region (both heavy and light) and J–Cλ genes, respectively (81–83). VpreB and λ5 expression is specific for precursor B-lineage cells, where they are found prior to κ or λ light chain synthesis (Figure 4.5) (81,82,84–87). VpreB- and λ5-encoded proteins are noncovalently associated with each other, and covalently linked via a penultimate Cys of λ5 to the C-terminus of μ_H (83,88). VpreB/λ5 form a light chain-like protein, so-called surrogate light chain (SLC), that assembles with μ heavy chains forming an immature-B-cell receptor complex on pre-B cells (89–91). VpreB/λ5 genes are both transcribed from a TATA-less promoter (as are TdT, mb-1, and B29, see below) with multiple initiation start sites (92,93). Putative promoter and enhancer elements responsible for positive regulation, developmental and tissue specificity, appear to lie within a -210 to -22 region of the λ5 gene (94).

About 5 and 18% of immature B cells in bone marrow of mice and humans express receptors containing VpreB/λ5, respectively (95). The μH–SLC receptor complex signals to prevent V(D)J rearrangement of the second allelic set of heavy chain gene segments, thereby mediating heavy chain allelic exclusion (96,97), which may involve accompanying alterations in chromatin structure (98). The complex also induces the pre-B cell to proliferate and to continue B-cell developmental programs (99–101). Mice with gene-targeted mutations at λ5 loci show a block in B-cell development at the pre-B-cell stage resulting in a 95% reduction in the numbers of recirculating B cells (99,102).

In the endoplasmic reticulum, newly synthesized SLC proteins transiently associate with a number of proteins, including uncharacterized 40-, 60-, and 98-kDa species and BiP, a heat shock protein (6). Cell surface expression of VpreB and λ5 has been described for B-cell lines that do not express μ heavy chains (90,103), although a more recent report

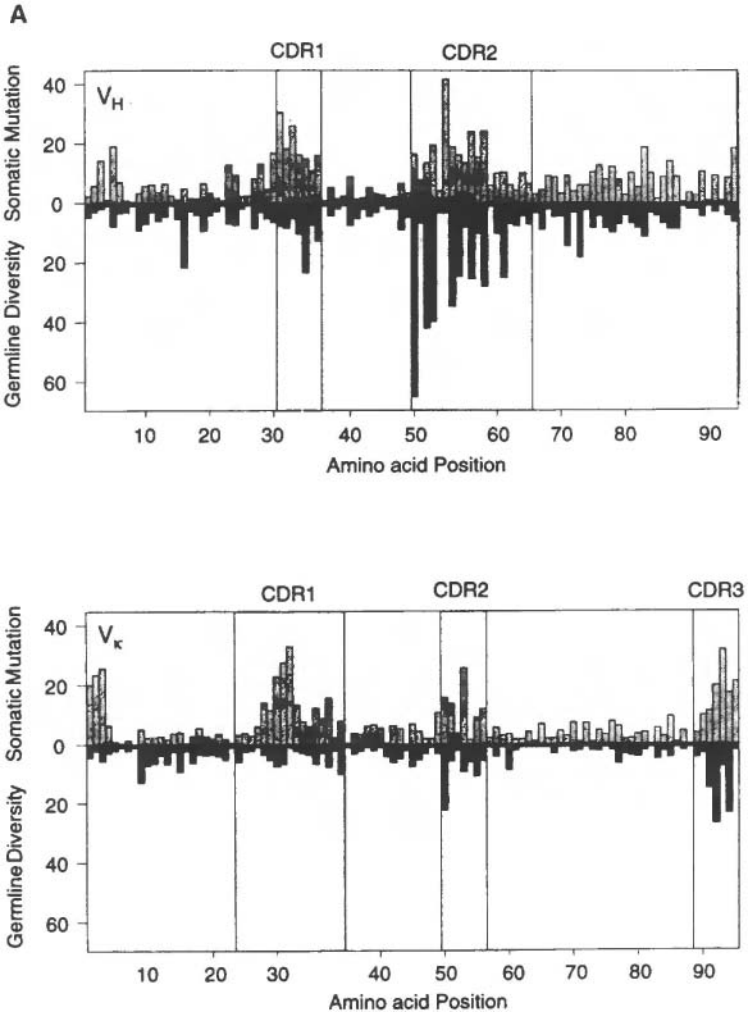


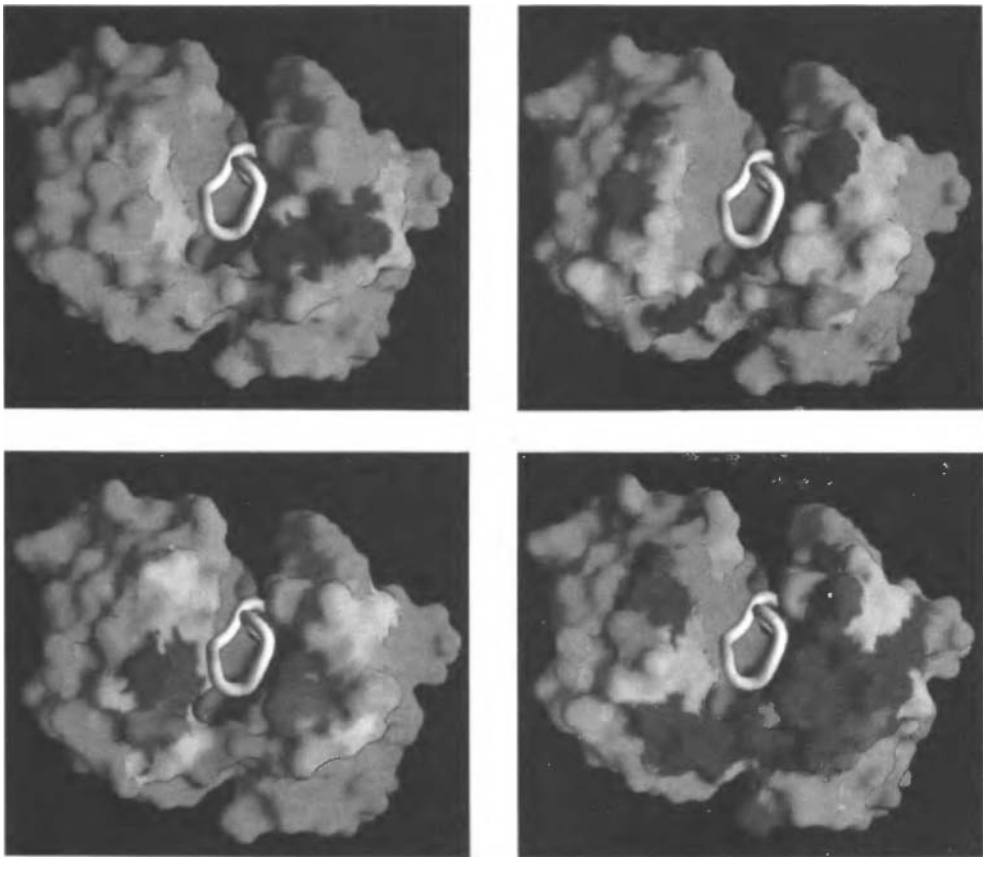
Figure 4.6. (A) Germline diversity and somatic hypermutations were assessed for rearranged V_H and $V\kappa$ sequences (533). Variation was calculated by comparing the total number of differences between the rearranged sequences and corresponding germline V segments for 1181 V_H and 736 $V\kappa$ sequences.

has suggested that successful surface expression of VpreB/λ5 requires the presence of heavy chain (6).

4.2. GENETIC ELEMENTS REGULATING RECOMBINATION AND RECEPTOR DIVERSITY

4.2.1. Recombination Signal Sequences (RSS)

The rearrangement process is organized at two levels: with respect to the timing of rearrangement at each locus and the order of V(D)J recombination. Ultimately, regulation



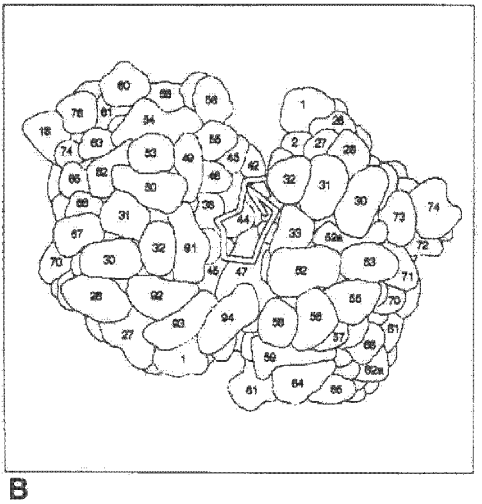


Figure 4.6. (B) A three-dimensional representation of the Ig antigen-binding pocket. V_H sequences occupy the right half of the pocket and Vκ the left. Sequence variation is represented as a gradient form light (conserved) to dark (variable) for (a) germline sequences, (b) diversity created by somatic hypermutation, and (c) total diversity after somatic hypermutation. (d) Vκ residues that are expected to make direct contact with antigen: light has no contacts, dark has up to 16 contact points. A and B reproduced with permission from the *Journal of Molecular Biology*, Tomlinson *et al.*, **256:**813–817, 1996.

of the rearrangement process probably reflects accessibility of loci to recombinational machinery and/or the presence of transcriptional activity. V(D)J rearrangement is regulated at least in part by two motifs known as recombination signal sequences. RSS are located 5′ to each J and 3′ to each V segment and are present at both 5′ and 3′ ends of D segments (104). The sequences consist of two conserved motifs, a palindromic 7-mer and an A–T-rich 9-mer, separated by 12- or 23-spacer sequences. Prior to the juxtaposition of V(D)J segments, the outer portion of the RSS heptamer bordering the coding region must undergo a double-strand (ds) cleavage (105–107), and recombination fuses the coding regions of the two segments together in so-called *coding joints,* leading to a deletion or inversion of intervening DNA (see Section 3.2). Defective V(D)J recombination resulting from faulty repair mechanism of ds breaks is linked to severe combined immunodeficiency syndrome in mice, which may reflect deficiency in a DNA-dependent protein kinase (108). Although RSS are the only known elements that direct V(D)J recombination (109,110), DNA sequences both adjacent to cleavage sites (111,112) and coding sequences in segments being joined have been shown to change the efficiency (113) [but not the specificity (114)] of the recombination process. Differences in the frequency of expression of κ and λ light chains have been suggested to reflect differences in the strength of the RSS signals associated with the respective chains (49). The V(D)J recombination process is not very sensitive to variations in intervening distances—from hundreds of bases to kilobases—between segments (115). It is speculated that the recombinase complex might be sensitive to structural aspects conveyed by sequences contained near RSS, evidenced by the fact that A/T homopolymers, which induce deformation or narrowing of the minor groove (116,117), also affect the efficiency of V(D)J recombination (114,118). Recent findings have suggested that chromatin structure may play a critical role in regulating and directing V(D)J recombinase activity (98).

4.2.2. Somatic Hypermutation: Enhancer/Matrix Attachment Regions (Ei/MARs)

Somatic mutation of Ig genes in B cells before or after antigen challenge could conceivably function to provide a larger preimmune repertoire or a higher-affinity antigen-specific response, respectively (119–121). To effect subtle alterations in antibody affinity, the hypermutation process directs (mostly) point mutations (122) in CDRs of V_H and V_L genes, although hypermutation of Cλ-region sequences has been reported (123). The hypermutation process occurs over 5–10 cell cycles (124,125), introducing mutations at about 100,000-fold above background, or at a frequency of about 10^{-3} base pairs per generation—the result is to raise the affinity of specific antibodies from the primary response level ($K_d = 10^{-7}$ M) to that of typical secondary responses ($K_d = 10^{-9}$ M). But mutational hotspots are also observed in mouse lambda light chain J–Cλ intron (126,127) and transgenes expressing non-Ig genes replacing V-region segments (128). The frequency of somatic mutations at different CDRs has been extensively compared for V_H and Vκ genes (Figure 4.6A,B).

The frequency of B cells with V regions containing somatic hypermutations, and the extent of the mutations in V genes, increases with age (129), which is presumably indicative of an accumulating pool of memory B cells. In the κ light chain of mice (VκOX-1) mutations are frequently found in CDR1, whereas in λ light chains these mutations are also common in CDR2 and CDR3, as well as in the joining constant-region intron proximal to the intron enhancer/matric attachment region (Ei/MAR) (123,126,130–132). Enhancers are important in the recruitment of hypermutation. The demonstration

that an absence of Ei/MAR sequences from a κ gene abrogates hypermutation without a loss in transcriptional activity has suggested that transcription and hypermutation processes may in some circumstances occur independently and involve different machinery (133). Consistent with this, more recent findings have shown that active transcription of a λ transgene can occur in the absence of hypermutation (134,135). On the other hand, the introduction of hypermutations has been correlated with transcription (136). Single-strand nicks introduced at topoisomerase II binding sites that lie within Ei/MAR have been suggested as a possible means of directing hypermutations, which occur as a result of repair mechanisms that are subject to error (119). Such a model finds support in the demonstration that DNA repair enzymes are included in the RNA polymerase II transcriptional complex (137).

4.3. MACHINERY

4.3.1. Recombination Activating Genes (RAG1 and RAG2)

RAG1 and RAG2 have an essential role in V(D)J recombination (138,139). The RAG genes have almost identical expression patterns exclusive to lymphoid cells during periods of active recombination of antigen receptor genes, the notable exception to this being the expression of RAG1 in neurons (140). The RAG genes are positioned next to each other on chromosome 11p13 in humans (2p in mice). RAG1 and RAG2 exhibit extensive sequence similarity in all species in which the genes have been identified, although the two genes show no similarity to each other (141–145). The RAG1 and RAG2 genes are continuous coding sequences that contain no introns (146), encoding 119- and 59-kDa proteins, respectively. RAG1 is involved in both initiation of V(D)J recombination and resolution of coding ends (147), and both RAG genes are required to initiate DNA breaks (148). Mutagenesis and deletion of RAG1 and RAG2 have identified regions required for normal activity, which span residues 330–1008 and 1–388, respectively (142,143,145). The RAG1 basic domains mediate nuclear and nucleolar localization. The two halves of RAG1 each contain multiple regions that mediate interactions with the nuclear-pore-associated protein Rch1 (human homologue of yeast SRP1) and facilitate RNA binding (149–152). RAG1- and RAG2-deficient mice have confirmed the requirement for both genes in the initiation of recombination (138,139) and cutting of RSS (107,153). In mice deficient of RAG genes, B cells in the bone marrow are arrested developmentally, exhibiting a large ($B220^+$) pre-B-cell-like appearance with no evidence of V(D)J rearrangements (138,139,154).

Despite the critical involvement of RAG proteins in the recombination process, it has not been clear whether RAG1 and RAG2 actually encode components of a recombinase machinery or whether they merely potentiate recombinase activity. In cells expressing a high level of RAG proteins, RAG1 and RAG2 have been found as complexes in the nucleus in the form of large aggregates, which appear to contain multiple RAG1 and RAG2 subunits in a 1:4 ratio (149,155). Recent analysis of RAG activity in a cell-free system also suggests that RAG1 and RAG2 likely represent at least part of a recombinase complex (156).

RAG genes are under translational and posttranslational control (146,157). RAG2 is phosphorylated at two serine residues, one of which appears to regulate its activity *in vivo* (158). An additional phosphorylation by $p34^{cdc2}$ at a threonine residue may regulate the rate of proteolytic degradation of RAG2 (158). RAG expression has been found to be

upregulated after stimulation of the BCR, which may be an initial link between receptor editing of B-cell receptor during development and RAG expression (60,159–162). Expression of RAG genes in B cells may in part be regulated by signals delivered through CD19 and IL-7 receptor (163).

Lymphoid malignancies often contain translocations involving antigen receptor genes and oncogenes, particularly in cells of immature phenotype (164). This raises the possibility that infidelity of recombination events, of which RAG genes are sufficient to induce (146), may be linked to early events in transformation. Chromosomal breakpoints around translocated oncogenes have been found to contain sequences similar to the heptamer–nonamer RSS of V, D, and J regions (165–167) (see Chapter 6). Interestingly, recent evidence suggests that cells infected with Epstein–Barr virus, which is associated with tumors such as Hodgkin's disease or nasopharyngeal carcinoma, show dysregulated expression of both RAG1 and RAG2 (168,169). Expression of RAG genes in non-lymphoid cells has been shown to facilitate rearrangement of genes (170,171).

4.3.2. Terminal Deoxynucleotidyl Transferase (TdT)

TdT is the only known template-independent DNA polymerase, catalyzing the random addition of deoxynucleoside 5′-triphosphates (N nucleotides) to the 3′-hydroxyl group of a DNA strand (172). TdT exhibits preference for deoxyguanine (G) and deoxycytosine (C) substrates and is more active during recombination of heavy chain than light chain segments; it also has a minor endonuclease activity (22). In both humans and mice, TdT is a 58-kDa monomeric protein encoded by a single gene and is expressed with high specificity in pro-B cells and in immature T cells, correlating with rearrangement of Ig (161,173) and TCR genes (174), respectively. TdT is also frequently expressed in lymphoblastic [and to a lesser extent myeloblastic (175)] leukemia cells (176). Limited proteolysis of TdT has revealed two separate regions localized in the C-terminus that appear to be responsible for DNA binding (aa 221–249) and nucleotide binding and polymerase activity (aa 359–381) (177–179). In addition, an Asp residue at position 343 has been identified as critical to both binding of nucleotides and polymerase activity (180). Splenic B cells in adult mice have been shown to have N insertions with a frequency of 83% in at least one of the two V–D–J junctions, in 71% of V–D junctions, and in 56% of D–J junctions (181). As N addition occurs at either end of D-region segments, it modifies the CDR3 determinant of Igs, on average with an addition of 4–5 nucleotides (182).

In mice, short (509 aa) and long (529 aa) alternatively spliced TdT isoforms have been identified (183), differing in their TdT activity and in subcellular localization (184). The long isoform, which contains an additional 20 amino acids at its C-terminus and has a shorter turnover rate, is localized cytoplasmically and shows lower polymerase activity (184). The TdT promoter region, which does not contain a customary TATA box, has been investigated in detail and tissue specificity has been attributed in part to elements about 60 bp upstream of the transcriptional start site (185–188).

Gene-targeted mice have confirmed that TdT is involved in the addition of nucleotides (N regions) to V–D, D–J joints (189,190). Interestingly, positive selection of T cells in these mice appears to be more efficient (191,192), whereas the B-cell repertoire in adult mice remains similar to that seen in normal fetal mice. It is very intriguing that a loss of antigen receptor diversity that accompanies TdT deficiency does not appear to render animals more susceptible to infection by common laboratory pathogens (55,191). At the same time, however, nonobese diabetic mice with TdT deficiency are less susceptible to

diabetes, implying that under certain circumstances a restricted antigen-receptor diversity can reduce T-cell reactivity to some antigens (191).

4.3.3. DNA-Dependent Protein Kinase (DNA-PK)

Rejoining of DNA after chromosomal double-strand breaks (DSB) generated during V(D)J recombination has been found to require the activity of a three-subunit DNA-dependent protein kinase (DNA-PK) (193–197). The heterodimeric (70/86 kDa) DNA-binding subunit, Ku, is essential for the DSB repair function of the complex (198,199). The Ku DNA-binding unit is associated with a catalytic subunit (DNA-PKCS) that is deficient in SCID mice. DNA-PKCS is also critical for DSB repair and for normal V(D)J recombination (108,200–202). Mice with gene-targeted deletions for the 86-kDa Ku subunit have recently been shown to have a block in V(D)J rearrangement for antigen receptors in both B and T cells similar to that seen in RAG-deficient mice (203).

4.4. B-CELL SIGNALING

4.4.1. B-Cell Receptor Complex (Igα/Igβ; CD79a/CD79b)

The B-cell antigen receptor complex (BCR) incorporates membrane-bound Ig and a transmembrane heterodimer (204–207) that contains the disulfide-linked glycoproteins Igα (42 kDa) and Igβ (37 kDa) (Figure 4.5), respective products of the mb-1 and B-29 genes (Figure 4.7) (208–212). Expression of mb-1 and B29 is confined to B cells and is controlled at least in part by regulatory sequences in the 5′ region of the genes similar to those found in Ig genes (209,210,211). Both genes are expressed prior to heavy chain rearrangement and in all nonplasma B cells (207). Plasma cells, however, express only Igβ (213). An alternatively spliced version of Ig β, which is truncated (34 kDa) and lacks about 30 C-terminal residues encoded in the full-length transcript, has been dubbed the Igγ chain; two differentially glycosylated full-length Igβ chains also exist, the under-glycosylated form appearing also as a 34-kDa protein (214). Extensive sequence comparisons in humans and mice have been made for Igα and Igβ, which in general show high conservation in transmembrane and cytoplasmic regions and less collinearity in external domains (Table 4.2) (213). Igα and Igβ may play different roles in BCR signaling (215,216).

Cytoplasmic portions of Igα and Igβ are 61 and 48 amino acids in length and contain 4 and 2 tyrosines, respectively. Both chains have a 22-amino-acid membrane-spanning region that is either polar (Igβ) or negatively charged (Igα). The cytoplasmic tails of the heterodimer are phosphorylated immediately after BCR cross-linking at tyrosine residues in antigen-recognition homology 1 (ARH1) motifs (also called I-TAM or ARAM for immunoreceptor tyrosine activation motif and antigen receptor activation motif, respectively) (217–221), docking sites for SRC-homology-2 (SH2) proteins (222). SRC kinases are constitutively associated with the Igα/Igβ chains via interactions at cytoplasmic ARH1 motifs (223,224). Phosphorylation results in the recruitment of additional SRC-family kinases that bind via SH2 domains (225), which, in turn, results in the induction of signaling kinase activity (226).

4.4.2. CD19

CD19 is a 540-amino-acid glycoprotein (95 kDa) exclusively expressed on B cells (227). It is a member of the IGSF (see Figure 4.1) with two extracellular C2-type Ig

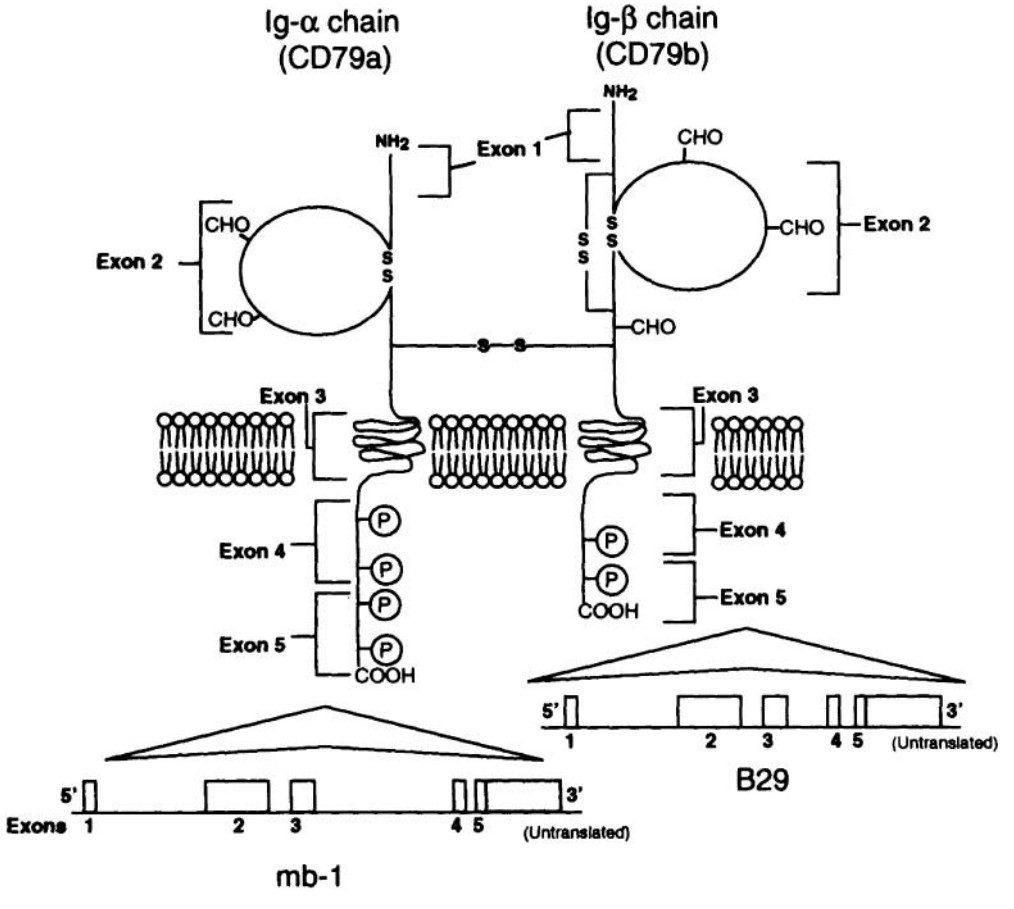


Figure 4.7. Schematic representation of the exon and protein structure of Igα (CD79a) and Igβ (CD79b) chains. The heterodimer is disulfide linked in the membrane-proximal regions of the molecules.

domains; a long 242-residue cytoplasmic tail contains 9 tyrosine residues (228,229), two of which form motifs that bind the SH2 domain of PI-3 kinase, and another two tyrosines form motifs that bind FYN, perhaps through an SH2 domain (230). CD19 coimmunoprecipitates with FYN, LYN, and PI-3 kinases (231–233) and is required for normal signal transduction through BCR (234,235), for which it lowers the threshold for BCR-mediated activation (234).

CD19 first appears on B cells prior to rearrangement of Ig heavy chain genes, is one of the first markers to identify B-lineage cells (236), and is present on mature B cells but is downregulated and undetectable on plasma cells (227,237). CD19 interacts noncovalently with other B-cell surface molecules such as CD21 and CD81 and probably mediates adhesion interactions through binding with CD77 (expressed on B cells and endothelium) (238). Antibody ligation of CD19 has been shown to induce proliferation of immature B cells and homotypic adhesion in tonsilar B cells (239,240), although the effects of cross-linking appear to have varied consequences depending on additional signals and stage of

Table 4.2
CD79b Gene and Protein Sequence Comparison for Humans and Mice[a]

Region	Gene (%)	Protein (%)
Leader peptide	74.7	60.0
Extracellular portion	70.0	56.0
Ig-like domain	68.3	52.9
Connecting peptide	83.3	87.5
Transmembrane portion	84.8	95.5
Intracytoplasmic domain	90.3	95.8
Entire coding region	74.25	68.6

[a]"The high degree of homology in the cytoplasmic region of the protein (95.8%) is consistent with a vital role for the molecule in B-cell signaling. Data from Ref. 534.

differentiation (241–244). Cross-linking of CD19 results in Ca^{2+} mobilization, activation of phospholipase C and protein tyrosine and serine kinases, binding of PI-3 kinase, and NF-κB activity activity (233,239,245–248). CD19 stimulation has also been found to block IL-7-mediated downregulation of RAG genes (163). CD19 may be involved in BCR-mediated apoptosis (249).

4.4.3. CD20

The nonglycosylated CD20 molecule, alternatively spliced to generate three isoforms (33, 35, 37 kDa), appears to form part of a multimeric cell-surface receptor complex on B cells (250). The CD20 gene itself contains eight exons and is located on chromosome 11q12-13 in humans and chromosome 19 in mice (251,252), encoding a protein with four transmembrane-spanning regions that appears to form homodimeric and homotetrameric oligomeric structures on the cell surface (253). CD20 and the β-chain high-affinity IgE receptor (FcεRI) share significant sequence similarity and their genes are colocalized on respective chromosomes in mice and humans (251,252,254).

Antibody cross-linking studies suggest that CD20 plays a role in cell cycling (255–257). Perturbation of CD20 induces serine and threonine phosphorylation and Ca^{2+} flux (258), and structural and functional data suggest that CD20 probably acts as a calcium channel (253,259–261). Expression of CD20 in Balb/c 3TC cells results in constitutive Ca^{2+} permeability and $G_0 \rightarrow G_1$ progression (261). CD20 appears also to associate with the tyrosine kinases LYN, FYN, and LCK, which may be mediated by a 75- to 80-kDA phosphoprotein (262).

CD20 is expressed prior to cytoplasmic Igμ chains and is found on mature B cells, although, similar to CD19, it is not detected on plasma B cells (255,263). Binding of CD20 by the monoclonal antibody 1F5 has been found to protect germinal center B cells *in vitro* from apoptosis (264). Activated B cells shift expression from 33-kDa to 35- and 37-kDa isoforms of CD20 (258,265). Treatment of resting B cells with CD20 antibody results in elevated levels of c-MYC mRNA and phosphorylation of phospholipase C γ (259). B-cell- and stage-specific expression of CD20 has been reported to involve a PU.1/PIP transcriptional factor binding site (266).

4.4.4. CD22

CD22 is a B-lineage-specific 130-kDa surface phosphoglycoprotein that mediates homotypic and heterotypic adhesions through interactions with various N-linked sialoglycoproteins (267–272). CD22 is present on the surface of a majority of mature B cells, associates with BCR, and appears to be involved in BCR-mediated activation and is coupled to cytoplasmic tyrosine kinases (269,273–276). CD22 binds proteins containing α2,6-linked sialic acids, which makes it a sialic- acid-binding lectin such as sialoadhesin and selectins (277,278). CD22 is associated with surface Ig at low stoichiometric proportions (274,275) and is protein tyrosine phosphorylated at tyrosine residues following antibody stimulation of surface Ig (273–275). Expression of CD22 correlates with Ig surface expression, particularly surface IgD (267,279). After BCR stimulation, CD22 associates with the protein tyrosine phosphatase PTP1C (280), which acts as a negative feedback regulator of B-cell activation (281,282). CD22 is thought to bind the sialoglycoprotein CD45 (271,272,278,283), a lymphocyte-specific phosphatase that couples antigen-receptor complexes to intracellular signaling pathways (see CD45). If this is true, interactions between CD22 on B cells and CD45 on T cells may be important in regulating B-cell-induced T-cell activation (271,284–287). Human B cells express two isoforms, CD22a and CD22b, which contain 5 and 7 Ig extracellular domains, respectively, the latter the most commonly expressed isoform found on B cells (268,269,283). The cytoplasmic domain of CD22 contains two YXXL motifs similar to the ARH1 (ARAM, I-TAM) motif (269), which are phosphorylated after BCR triggering (273,279).

4.4.5. CD45

Critical to the function of the BCR complex is the transmembrane protein tyrosine phosphatase CD45. CD45 makes up about 10% of the surface glycoprotein of B cells, which express the high-molecular-weight (220 kDa) isoform (288,289). The protein tyrosine phosphatase activity of CD45 is required for normal BCR-initiated signal transduction (290,291), where it functions to couple antigen-receptor signaling to downstream signaling events (288,292,293). As one of its functions in B cells, CD45 may dephosphorylate the regulatory C-terminal phosphotyrosines of receptor-associated protein tyrosine kinases (294–298); it may also regulate phosphorylation of Igα and Igβ subunits of the BCR (290,299). Interestingly, B cells in mice deficient for CD45 develop normally but have defective proliferative responses after IgM perturbation (300). CD45 appears to have an important function in regulating selection/deletion of B cells during maturation in the bone marrow (301). (See Section 3.4.6 and Chapter 8 for additional information on CD45.)

4.4.6. Signaling Kinases and Phosphatases

Regardless of the ultimate outcome, early events after BCR perturbation involve activation of protein tyrosine kinases (PTKs) (219,302,303) (within seconds), hydrolysis of inositol phospholipids (217,304–306), and Ca^{2+} flux (peaking about 2 min after receptor stimulation) (215,307–309). Kinases participating in the earliest signaling events include SRC-family members BLK, FYN, LYN, and LCK (219,220,223,302,310–313). SRC-family kinases contain a single SH2 domain and an additional SH3 region, which allows them to interact with phosphorylated tyrosine residues in ARH1 motifs of Igα/Igβ (314) and proline-rich sequences in other signaling molecules such as PI-3 kinase (315–

317), respectively. The SYK-family members have two SH2 domains in addition to the tyrosine kinase domain, but lack an N-terminal myristoylation (membrane anchor) and C-terminal negative regulator tyrosine residue (318–320). SYK may be considered to have analogous responsibilities in BCR signaling (321–323) to those of ZAP70 in T lymphocytes (see Chapter 3).

There are several non-SRC kinases that are involved in BCR signaling. These include SYK (220,223,313,324), CSK (325), CBL (326), and BTK (226,327–329). BTK [also called BPK, B-cell progenitor kinase (330)] is a 77-kDa nonreceptor tyrosine kinase (NRTK) that, like other BTK-family members, contains a critical N-terminal pleckstrin homology (PH) (331) and a proline rich sequence, in addition to SH3, SH2, and catalytic kinase domains (330,332). BTK is defective in human X-linked agammaglobulinemia where there is less than 1% normal numbers of peripheral B cells (330,333), whereas in mice the disorder is less severe with about a 50% reduction in B cells (334,335). The SRC and non-SRC kinases work together in a functional BCR signaling pathway, a case in point being the phosphorylation of BTK by SRC kinases after BCR stimulation (336).

Regulation of BCR signaling activity may also involve nontransmembrane protein tyrosine phosphatases. SHP-1 (HCP, PTP1C, SH-PTP1, and PTPN6) contains two tandem SH2 domains (337), an N-terminal SH2 domain that acts both as a regulatory domain and as a recruiting unit and a C-terminal SH2 domain that functions in molecular recruitment (337,338). SHP-1 has been found to constitutively associate with BCR and possibly acts to regulate phosphorylation of the Igα chain (339). SHP-1 can bind various signaling molecules involved in the activation of RAS or RAS-related proteins and this may involve its regulation of signaling in B cells (340). SHP-1 associates with CD22 (280) and may be involved in cell death signaling (341). It has also been reported to regulate B-cell selection through interactions with the BCR (342). Moth-eaten mice, characterized by patchy fur, immunodeficiency with paradoxical autoimmunity, and early death, contain mutations in the SHP-1 gene (343,344), although this defect was recently reported to occur in the absence of B or T cells (345).

4.5. THE IMMUNOGLOBULINS

4.5.1. IgA

IgA is the predominate Ig molecule in mucosal secretions and represents about 10–15% of total Ig in serum. IgA synthesis is highly compartmentalized. B lymphocytes located in specialized sites in the gastrointestinal, mammary, pulmonary, and genitourinary systems produce the IgA found in secretions, whereas serum IgA is produced by B cells in bone marrow, spleen, and lymph nodes (346–350). IgA is also an important Ig present in mother's milk, supplying newborns with virtually all of their gut mucosal IgA defenses (351–355,356). IgA deficiency is the most common defect of the humoral immune system in humans (357). Total IgA synthesized on a daily basis exceeds that of the other Igs combined, which in humans amounts to about 70 mg/kg body weight (Table 4.3) (350). Two thirds of the IgA produced is in mucosal secretions, the majority of IgA-secreting plasma cells ($\sim 10^{10}$) being found in subepithelial mucosa of the jejunum and small intestine.

Secreted IgA exists mainly as a dimer (55–75%), in addition to larger complexes such as trimers, tetramers, pentamers, and hexamers. IgA polymers (pIgA) synthesized from plasma B cells are covalently modified prior to secretion by the addition of the 16-

Table 4.3
Estimated Daily Production of IgA versus IgG[a,b]

Location	IgA (mg)	IgG (mg)
Circulation	1295–2100	2100
Saliva	100–200	1–2
Tears	1.25–5.5	?
Bile	54–400	160
Large intestine	2100–5234	587
Small intestine	1170	137
Urine	1–3	1–3
Respiratory (nasopharynx)	45	15
Total	3600–9100	~3000

[a]Used with permission, *Clin. Immunol. Immunopathol.*, Mestecky *et al.*, **40**:105–114 (1986).

[b]The total daily synthesis of IgA from all tissues can exceed that of all other immunoglobulins combined.

kDa polypeptide J- chain. Once secreted, pIgA–J chain complexes are free to bind the 70-kDa polymeric Ig receptors (pIgR), present on basolateral surfaces of virtually all epithelial cells associated with mucosal surfaces (358–363). On pIgA–J chain binding of pIgR, it is internalized in clathrin-coated vesicles, transported across the cell, and assembled on the apical (luminal) surfaces. On the luminal surface, the C-terminal portion of pIgR is cleaved releasing a highly stable pIgR–IgA complex, or secretory component, into mucosal secretions (Figure 4.8). Trancytosis is induced by binding of pIgR, which requires Ser664 of its cytoplasmic domain (364,365). IgA in plasma is mainly monomeric, and to a lesser extent pentameric. IgA is vigorously synthesized systemically, although its rapid catabolism results in relatively low serum levels (366). In mice, serum IgA levels are at least in part regulated by IgA flux into bile, which is facilitated by pIgR binding and translocation into hepatocytes (346,367).

In humans, there are two subclasses, IgA1 and IgA2, which exist primarily as monomeric and polymeric molecules, respectively. IgA1 is the main IgA constituent of serum, secreted mostly from plasma cells in bone marrow (346,366,367) where about 90% of IgA-secreting cells are IgA1 positive (Table 4.4) (350). Primary sequences are very similar for the two subclasses in the $\alpha 1$ and $\alpha 2$ domains of the constant regions. However, IgA1 has more extensive glycosylation in the hinge region, which may be relevant in disease (368), and is highly susceptible to proteolysis by bacterial IgA1-specific proteases (367,369,370). IgA2 allotypes have been identified and designated as A2m(1) and A2m(2), the former missing interchain disulfide bonds between heavy and light chains (371).

IgA does not efficiently induce inflammatory responses. This is critical to its function in front-line defenses against pathogens entering at mucosal membranes. It is generally accepted that IgA protects by exclusion, binding and cross-linking pathogens to prevent their uptake across epithelial linings and thereby facilitating their expulsion in mucous (i.e., gastrointestinal) excretions. With this in mind, the induction of inflammatory responses is expected to be counterproductive, leading to tissue damage jeopardizing the

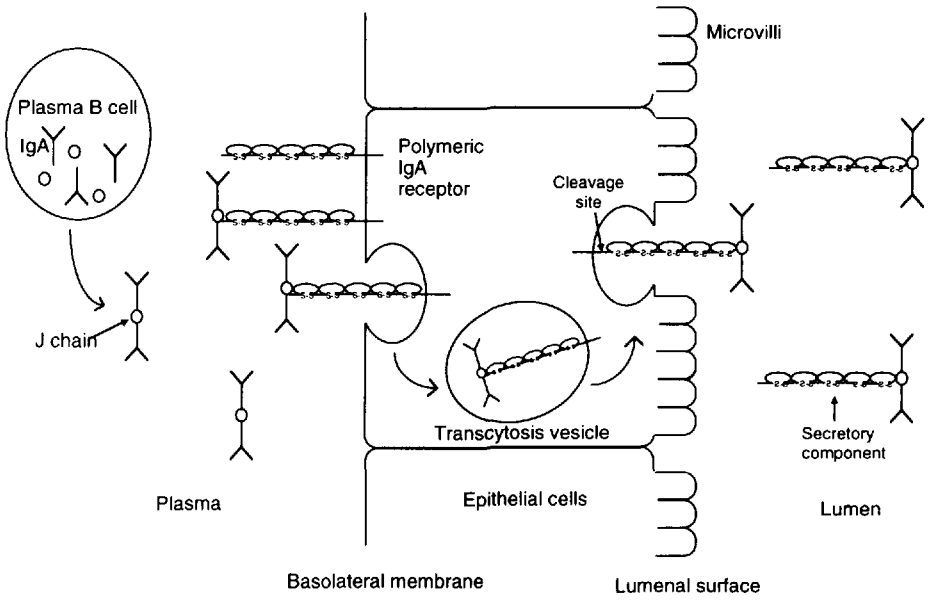


Figure 4.8. The function of the polymeric IgA receptor is to transport IgA–J chain complexes across epithelial cells at mucosal membranes, such as the intestines, delivering IgA complexes into the lumen.

integrity of the epithelial barrier to infection. Shigella is an example of an infectious agent that may take advantage of immune-mediated epithelial damage to penetrate the gut wall (372). In various gut diseases, altered immune regulation results in a disproportionately increased number of J chain-negative IgG-producing cells in the mucosa. Inflammatory reactions induced by IgG might cause a breakdown in the gut epithelial barrier and

Table 4.4
Distribution of IgA1- and IgA2-Expressing Cells in Human Tissues[a]

Tissue	IgA1 (%)	IgA2 (%)
Bone marrow	88	12
Spleen	85	15
Tonsils	86	14
Lymph nodes	69–94	6–31
Nasal mucosa	95	5
Lacrimal glands	54–80	20–46
Salivary glands	51–65	35–49
Mammary glands	65	35
Duodenum	80	20
Ileum	56	44
Colon	37	63

[a]Used with permission, *American Journal of Kidney Disease*, Mestecky, **12**:378–383, 1988 [Ref. 535].

provide an entryway for pathogens. Such altered regulation of Ig isotypes may contribute to the pathology of inflammatory bowel diseases (373,374).

Although the synthesis of secretory and plasma IgA is compartmentalized, IgA responses to antigenic challenge delivered to either mucosal or peripheral sites overlap. That is, immunization through mucosal routes (i.e., oral or urethral routes) results in specific plasma IgA responses, whereas systemic immunization (i.e., intramuscular) generates both secretory and serum IgA responses (375). The issue of IgA protective antibodies in mucosal genitourinary secretions has become relevant to the development of vaccines for sexually transmitted diseases, in particular for protection against HIV. It has been suggested that IgA antibodies, directed against HIV epitopes involved in binding and infectivity, may protect against host penetration by the virus. Results thus far have lent support to the concept that such a vaccine might prove useful (375–378).

4.5.2. IgD

It has not been easy to ascribe a clear role for IgD in the immune system despite its paradoxical presence on the great majority of peripheral B cells and the high level of δ heavy chain conservation among different species (379). IgD is expressed on the surface of immature B cells during ontogeny. Constant-region genes for both IgD and IgM heavy chains are transcribed into a single primary RNA transcript that is alternatively spliced to produce either δ or μ message (380). Thus, IgD and IgM are coexpressed on mature B cells emerging from the bone marrow and entering the pool of naive recirculating B cells (381). IgM/IgD-positive B cells appear and begin increasing in frequency in the peripheral blood about 4 days postparturition, plateauing at adult levels by about 6 weeks of age (380,382–384) when they constitute about 90% of peripheral B cells in mice and humans. IgD is not secreted during an immune response or after mitogenic stimulation of the IgD-positive B cells. The IgD molecule also lacks complement fixing properties and is present in extremely low levels in serum or other body fluids. Cross-linking of IgD on B cells induces them to become efficient APC (385).

B cells in primary follicles coexpress IgM and IgD, whereas B cells in marginal zones and a proportion of memory B cells express only IgM (386,387). Although most mature B cells are both IgM/IgD-positive, the surface levels of IgD on splenic B cells are reported to be about 10-fold higher than those of IgM (388). This relatively high IgD-receptor density is observed despite significantly lower δ mRNA relative to μ, suggesting that one or all of translational rate, transport rate, or cell surface stability is greater for IgD than for IgM (389). Consistent with this apparent highly efficient IgD surface expression is the finding that unlike other Ig isotypes, IgD does not need to associate with any other proteins for transport to the cell surface (390). Nonetheless, IgD transport is normally associated with Igα/Igβ heterodimers.

IgM and IgD BCR display a number of functional similarities. Both Igs elicit common signals following cross-linking (217,309,391,392). Either can independently facilitate normal activation responses to antigen *in vivo* (393–395). Both signal to upregulate the B-cell coreceptors CD80 (B7-1) and CD86 (B7-2) (389,396) and are noncovalently associated with the same Igα/Igβ heterodimers in BCR complexes (390). IgD and IgM signaling induces activation of protein tyrosine kinases (219,302) including SRC-related BLK, FYN, LCK, LYN, and SYK/PTK72 (220,223,312). Both Ig receptors also induce hydrolysis of inositol phospholipids (305,309). However, the kinetics and intensity of phosphorylation in response to IgM- or IgD-receptor cross-linking have been shown to

differ significantly, the latter being both stronger and longer lasting (397). Activation of B cells to become Ig-secreting plasma cells results in the loss of Ig from the cell surface, beginning with a rapid loss of IgD expression as cells exit G_0 and transit G_1 (398,399). Consequently, both germinal center and antigen-specific B cells lack sIgD (400,401), and the sIgD-negative B-cell pool is considered to represent differentiated memory B cells, as characterized by somatic hypermutation of variable-region genes (402,403). However, early reports that some memory B cells were sIgD-positive were convincingly demonstrated by adoptive transfer of B-cell memory using sIgD-sorted B cells (387,399). It has also been argued that the number of IgG-positive B cells present in spleen is not adequate to account for the diverse memory-B-cell repertoire (404); and it has been speculated that splenic IgD-positive B-cell populations may represent partially differentiated memory cells (404). However, recent studies using human (403) and murine (405,406) models have indicated that sIgD-positive peripheral B cells show little evidence of hypermutation—the trademark of memory B cells—suggesting that few if any memory B cells express sIgD. A subset of germinal center sIgD-expressing cells have been found to accumulate up to 80 mutations per heavy chain variable region (δVH), although these cells do not appear to exit the germinal centers (407).

At different times the IgD receptor has been proposed as a critical element for the induction of B-cell responses to T-independent (408) or T-dependent (409) antigens; in maintaining or inducing B-cell tolerance (394); or in B-cell development and maturation. If IgD is involved in these processes, it was not generally supported by observations in two separately developed strains of IgD-deficient mice (410,411). However, in the knockout strain carrying a translational stop codon inserted into the Cδ3 domain (411), there is a 30–50% reduction in the number of peripheral B cells. In IgD-deficient containing a targeted insertion in the Cδ1 exon and a frameshift mutation in Cδ3, there is delayed affinity maturation of B cells during T-dependent primary responses (410), but no other obvious defects (412). It has been suggested that structural flexibility inherent in IgD (413) (it contains only a single interchain disulfide bond toward the carboxyl end of the hinge region) may allow it to interact with particularly high avidity with antigen (410) and that the high density of IgD on B cells may also enhance its antigen-binding efficiency (389). Both of these mechanisms may facilitate earlier responses to antigen.

Depending on the antibody used, cross-linking IgD has been shown to induce IgM, IgG1, IgG2, IgG3, and IgA class switching (414). Additionally, anti-IgD antibodies have been reported to induce IgE synthesis (415–417). It has been observed that increased serum IgD levels often parallel elevated IgE levels in diseases such as atopic disorders and hyper-IgE syndrome (418–420).

4.5.3. IgE

IgE is present in only trace amounts in serum (see Figure 4.3B). The IgE molecule does not contain a hinge region characteristic of the other Ig isotypes, lacks the ability to activate complement cascades, and plays no significant role in opsonizing antigens. However, through receptor-mediated events, IgE is a very potent inducer of inflammatory reactions. IgE-secreting B cells are found in lung and skin where they have been considered as part of the front-line defense against parasites, although the exact function of IgE in this role remains the subject of debate (421,422). The protective effect of IgE has been attributed to its ability to induce rapid responses—such as inflammation, mucous secretion, coughing, vomiting, diarrhea—to pathogens. Conversely, in IgE-mediated disorders,

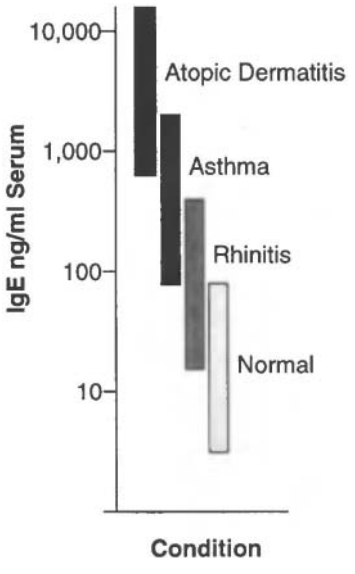


Figure 4.9. IgE levels in tissues are elevated in some disease conditions.

which affect more than 20% of the population in industrialized countries (423), disease correlates both with elevated levels of IgE (Figure 4.9) and with FcεR$^+$ effector cells such as basophils and mast cells (424).

4.5.4. IgG

The level of serum Ig provides the only reliable measure to date to assess the efficacy of long-term immunization (Table 4.5) (425). Because about 80% of serum Ig is of the γ isotype, it would probably be difficult to overstate the immunological significance of IgG. In humans there are four isotypes (subclasses) of IgG, denoted IgG1, IgG2, IgG3, and IgG4, listed in order of decreasing concentration in serum (Figure 4.10). The preponderance of IgG subclasses varies in response to antigenic challenges, suggesting unique roles for the isotypes in the immune response to specific pathogens (Table 4.6); as a corollary, deficiency of specific IgG subclasses is manifested as characteristic immunodeficiencies (Table 4.7). In addition to the four isotypes, allotypic variation, the result of polymorphic IgG genes, exists to increase IgG diversity, although this is mostly the case for IgG1 (426). In mice the IgG genes are designated IgG3, IgG1, IgG2b, and IgG2a listed in order of alignment on chromosome 12. Allotypic variations also exist for mice IgG: 2 IgG3 alleles, 2 IgG1, 6 IgG2b, and 12 IgG2a alleles (427). The significance of these isoforms is not entirely clear despite relatively long-held observations that the preponderance of different IgG subclasses in individuals correlates with allotype, which would suggest a functional implication for the different allotypes in the immune response (428,429).

Differences in primary sequences in the IgG classes exist mainly for the C1 and C2 domains of the heavy chain hinge region, which exhibit only about 50–60% collinearity between the classes, whereas the C1, C2, and C3 domains are highly collinear (90–96%) (426). The unique amino acid sequences in the hinge region of the IgG subclasses may reflect their differential activation of complement C1q and the classical pathway, critical

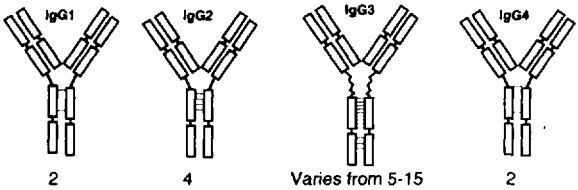
Table 4.5
Licensed Vaccines Evaluated in Terms of Serum Immunoglobulin[a]

Vaccine	Type	Route
Adenovirus	Live virus	Oral
Anthrax	Inactivated bacteria	SC
BCG	Attenuated live bacteria	ID
Cholera	Inactivated bacteria	SC
	Attenuated live bacteria	ID
DTP	Toxoids, inactivated bacteria	IM
Hib conjugate	Polysaccharide–protein	IM
Influenza	Inactivated virus, components	IM
Japanese encephalitis	Inactivated virus	SC
Measles–mumps–rubella	Inactivated virus	SC
Meningococcus	A,C,Y,W135 polysaccharides	SC
Plague	Inactivated bacteria	IM
Pneumococcus	23-valency polysaccharides	SC
Polio		
OPV	Attenuated, three types	Oral
IPV	Inactivated, three virus types	SC
Rabies	Inactivated virus	IM
Typhoid	Inactivated bacteria	SC
Ty21a	Activated bacteria	Oral
Varicella	Attenuated virus	SC
Yellow fever	Attenuated virus	SC

[a]Used with permission, Robbins *et al.*, *J. Infect. Dis.* **171**:1387–1398, 1995, University of Chicago Press [Ref. 425].

role for the immune function of IgG molecules (430). The C1q-binding motif is contained in the C2 domain and typically is represented in murine IgG by Glu318–X–Lys320–X–Lys322. The size and flexibility of the hinge have traditionally been considered important factors in determining complement activation potential of IgG, with molecules containing short–rigid hinges being less able to fix complement than those with longer–flexible hinges (431). This has been attributed to the effect of hinge size/rigidity on the accessibility of complement reactive sites on C_H1/C_H2 domains, which may or may not be sterically obstructed by Fab regions depending on the hinge (426,432). Glycosylation in the C_H2 domain at Asn297 in human IgG has been shown to be required for complement fixing function (433).

The hinge regions for IgG1/IgG2 and IgG4 span 12 and 15 amino acids, respectively. Each hinge region is encoded by a single exon. The hinge region for IgG3 is, however, encoded in a series of four separate exons, resulting in a hinge spanning more than four times as many residues as the other subclasses (434)—which is attributed to IgG3 having the highest affinity for C1q. Conversely, the lack of complement fixing activity of IgG4 is attributed to its short proline-rich hinge (426). Interestingly, a mouse–human chimeric IgG3 gene that has had the four hinge exons deleted, still expresses an IgG3 molecule efficient at fixing complement (435); in addition, an IgG3 molecule containing an IgG4 hinge retains its IgG3-like C1q binding ability (436) and, in fact, facilitates complement-mediated lysis more efficiently than IgG3 (437). These findings clearly challenge the



Immunoglobulin γ subclasses and characteristics				
Heavy-chain disulfide linkages	2	4	Varies from 5-15	2
Molecular weight (kDa)	146	146	165	146
Activates alternative pathway	↑	↑	↑	↑↑↑
Activates classical pathway	↑↑↑	↑↑	↑↑↑↑	↑
Binds FcγR on macrophages	↑	–	↑	↑
Placental transfer	↑	↑↑	↑	↑↑
Concentrations in healthy adult serum (mg/ml)	5.91±2.64	3.04±2.52	0.61±0.56	0.24±0.90
(Fraction)	33-87%	5-56%	0.5-12%	7-12%

Figure 4.10. The function and biochemistry of IgG subclasses.

Table 4.6
Induction of IgG Subclasses by Different Antigenic Stimuli[a]

Antigen	IgG1	IgG2	IgG3	IgG4
Polysaccharide				
Corynebacterium (levan)	—	↑↑	—	—
Haemophilus	↑/—	↑↑	—	—
Klebsiella	↑/↑↑	—/↑↑	—	—
Meningococcus	↑↑	↑/↑↑	—	—
Pneumococcus	—/↑	↑↑	—	—
Staphylococcus (techoic acid)	↑	↑↑	—	—
Streptococcus	—/↑	↑↑	—	—
Lipopolysaccharide				
Salmonella	↑	↑↑	—	—
Vibrio	↑/↑↑	↑/↑↑	—	—
Protein				
Bacillus (tetanus toxoid)	↑↑	—	↑	↑
Corynebacterium (diphtheria toxin)	↑/↑↑	—	↑/↑↑	↑
Haemophilus (outer membrane)	↑↑	—	↑	—
Staphylococcus (alpha toxin)	↑↑	—	—	↑
Streptococcus (protein M)	—	—	↑↑	—
Vibrio (endotoxin)	↑↑	↑	—	↑
Virus				
Cytomegalovirus	↑↑	—	↑↑	—
Epstein–Barr	↑↑	—	—	—
Hepatitis B	↑↑	—	↑↑	↑
Herpes simplex	↑↑	—	↑↑	↑
HTLV III	↑↑	↑/—	↑↑	↑/—
Rubella	↑↑	—	↑↑	↑
Varicella zoster	↑↑	—	↑↑	—
Other antigens				
Filariasis	—	—	—	↑
Nucleoproteins (DNA, Sm, RNP)	↑	—	↑	—

[a]Used with permission, *Critical Review in Clinical Laboratory Sciences*, Papadea and Check, **27**:27–58, 1989 [Ref. 536].

Table 4.7
Immunodeficiencies Related to IgG Subclass Deficiencies[a]

Clinical conditions	IgG1	IgG2	IgG3	IgG4
Acquired immunodeficiencies				
Nonallergic chronic chest symptoms (children)	↓	↓	↓	
Recurrent sinopulmonary infections		↓	↓	
Recurrent otitis media (children)		↓		
Recurrent upper-respiratory-tract infections		↓		
Bronchiectasis				↓
Primary immunodeficiencies				
Common variable immunodeficiency	↓	↓	↓	↓
X-linked agammaglobulinemia	↓	↓	↓	↓
Ataxia telangiectasia		↓		↓
Deficiencies with concomitant IgA deficiency		↓		
Wiskott–Aldrich syndrome			↓	

[a]Used with permission, *Critical Reviews in Clinical Laboratory Sciences*, Papadea and Check, **27**:27–58, 1989 [Ref. 536].

conventional paradigm of a critical regulatory role involving the hinge region in complement activation. Nonetheless, the ability of IgG to induce complement activation and inflammation is clearly important in disease and health, the latter evidenced by the finding that mice lacking FcγR are resistant to some kinds of IgG-induced autoimmune disease (438).

4.5.5. IgM

The IgM heavy chain is the first isotype expressed during B-cell development (439). It is also present on most mature B cells and is the isotype involved in the induction of primary immune responses. IgM comprises 5–10% of total serum Ig and is a major component of mucosal secretions. IgM is the first antigen receptor expressed on developing B cells. It is normally required for progression of B cells through early stages of ontogeny (100), although B cells mature in transgenic mice expressing IgD but not IgM (393). During pre-B stages IgM is associated with surrogate light chains and later in immature B cells with one of either λ or κ light chains. Most mature B cells in the peripheral lymphoid organs in both mice and humans coexpress IgM and IgD (382). Coexpression of IgM and IgD is the result of alternative splicing of a functionally rearranged heavy chain locus that produces message containing exons for both μ and δ C regions; coexpressed molecules thus have identical V regions (see Section 4.1.1). Cross-linking of either IgM or IgD has been shown to result in similar signaling (217, 309,391,392) and responses to antigen (389,393) (see Section 4.7.2). Stimulation of the IgM receptor on mature B cells quickly results in its downregulation (389,440), which may be important for the induction of tolerance in peripheral B cells (441). IgM antibodies are the first to be secreted from plasma cells into the blood during antigenic challenge. Because IgM is not secreted from memory B cells, elevated IgM levels are indicative of recent antigen exposure.

4.6. FC RECEPTORS

4.6.1. IgA Receptors

It is clear that IgA plays a protective role through binding to invading organisms in the luminal environment thereby preventing pathogen penetration into the host. This mode of action requires secretion of large amounts of IgA across epithelial cells involving the pIgA receptor (see Section 4.7.1). In addition to its function as a secretory protein, however, IgA also binds two IgA-specific Fc-type receptors, FcαR and FcαRb, differentially expressed on hematopoietic cells of the peripheral blood and alveolar macrophages.

4.6.1.1. FcαR (CD89). The major form of the FcαR (CD89) is a 32-kDa protein with an apparent molecular mass of 55–100 kDa reflecting heavy glycosylation (442,443). It exists in at least five alternate splice variants that are differentially expressed on hematopoietic cells (444) (Figure 4.11A,B). FcαR is expressed on mucosal myeloid cells such as alveolar macrophages (445) and on eosinophils (442), monocytes (443), and

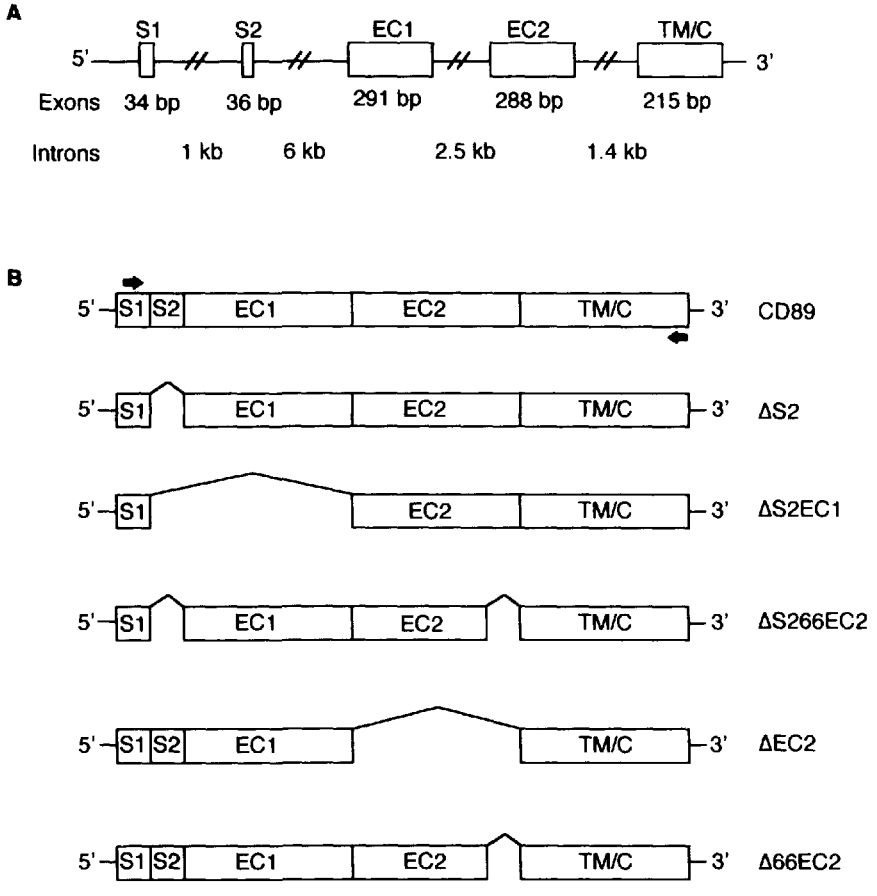


Figure 4.11. (A) Structural organization of the human FcαR gene. (B) Schematic representation of the five splice variants for the FcαR. S1 and S2 encode leader peptide, EC1 and EC2 encode the extracellular Ig-like domains, and TM/C encodes transmembrane and cytoplasmic regions.

neutrophils (446). FcαR associates with the shared FcγR subunit, which is likely important for FcαR-mediated signaling (447). IgA binding to FcαR-expressing cells can induce the production of cytokine mediators, such as TNFα and IL-6 (448), antibody-dependent cell-mediated cytotoxicity (ADCC), and phagocytosis (449). TNFα is itself capable of upregulating FcαR expression (450), whereas TGFβ has a negative effect (451). Reduced expression of FcαR on peripheral blood monocytes has been observed in HIV-infected patients, and correlates with elevated serum levels of IgA and disease progression (452). IgA binding to the receptor involves residues at the boundary between Cα2 and Cα3 domains of IgA (453).

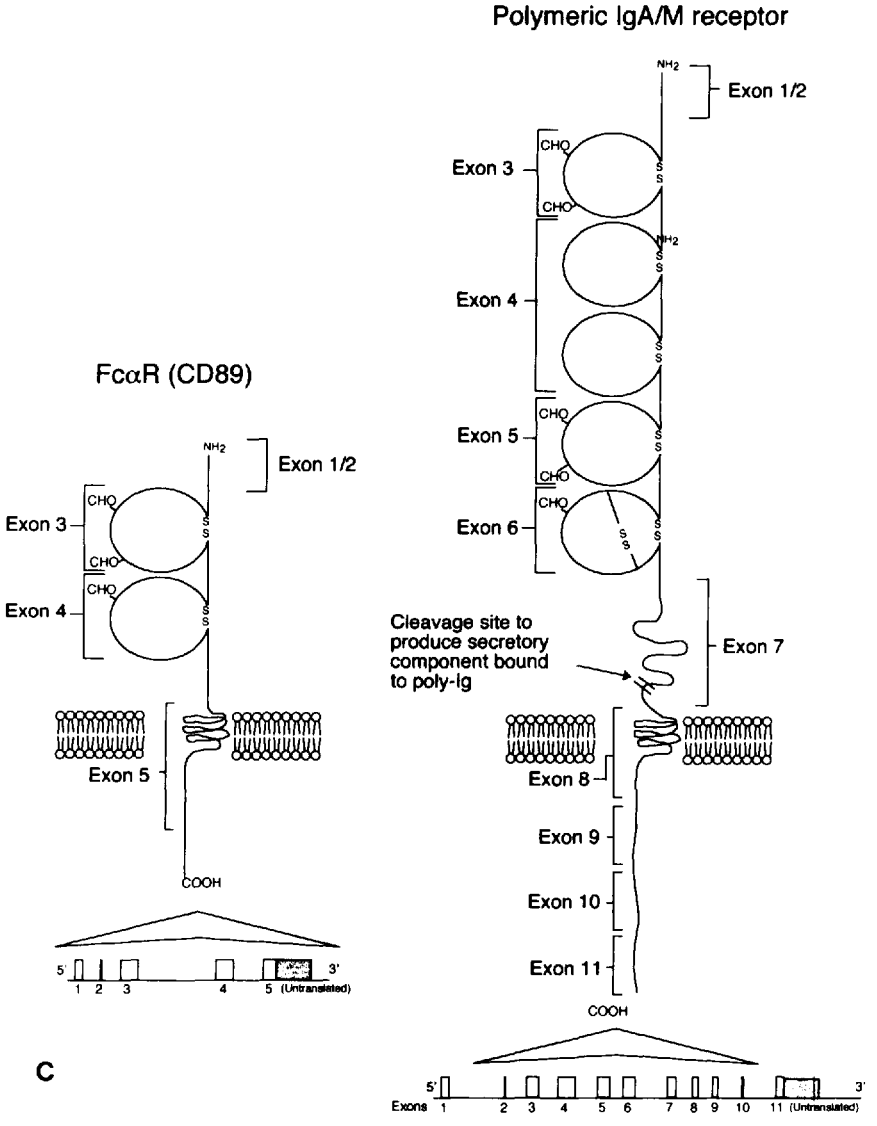


Figure 4.11. (C) Exon structure of FcαR gene shown with corresponding protein structure. A and B used with permission from *Immunogenetics*, Morton *et al.*, **43**:246, 1996.

4.6.1.2. FcαRb. Recently the identification of an additional Fc receptor for IgA has been made. FcαRb lacks the transmembrane/intracellular regions of FcαR (454). Instead it has a 23-amino-acid region that facilitates both secretion and expression at the cell surface. Affinity of FcαRb for IgA-coated beads is comparable to that of FcαR. FcαRb transcripts are present in eosinophils and neutrophils (454).

4.6.2. IgE Receptors

The two FcεRs are structurally distinct and have unique tissue distributions and biological roles (Figure 4.12). The receptors exhibit differential expression on mast cells (455–457), Langerhans cells (458–461), basophils (462,463), eosinophils (422,464,465), and monocytes (466–469). A receptor with high affinity for IgE, FcεRI, has been identified on cells involved in degranulation and release of preformed inflammatory mediators, a process that occurs during allergic responses. Stimulation through these receptors, which are expressed on mast cells, basophils, and eosinophils, also induces arachidonic acid metabolism and biosynthesis of leukotrienes. The low-affinity receptor, FcεRII expressed on lymphocytes, may play a specific role in regulating IgE levels in plasma.

4.6.2.1. FcεRI. The functional high-affinity receptor FcεRI requires the association of four subunits, α, β, and two γ [which is shared with the FcγR (470)], and is expressed predominately on basophils and mast cells (471,472). Mice deficient for the α chain of the receptor do not mount IgE-mediated anaphylaxis, suggesting a critical role for FcεRI in this reaction *in vivo* (473). At the same time, a deficiency in FcεRI does not result in altered levels of IgE in serum, which may indicate that these receptors play a minor role in regulating IgE synthesis or uptake. Gene-targeted deletions have also been generated at the γ-chain locus, resulting in a similar dysfunction in addition to loss in function of Fcγ receptors and defects in host resistance to infection (474).

4.6.2.2. FcεRII (CD23). A low-affinity receptor, FcεRII (CD23), is also expressed on multiple hematopoietic lineages where it may play a role in B-cell ontogeny and immune defense against some pathogens, i.e., parasites. FcεRII is a 48-kDa glycoprotein receptor expressed on monocytes, eosinophils, and B and T lymphocytes (475–477). It exists as two alternate splice variants, with FcεRIIa being expressed on B cells and FcεRIIb on monocytes and eosinophils (478,479). FcεRII may be involved in regulating IgE synthesis (480) via interactions with CD21 on B cells (481), although CD23-deficient mice produce normal levels of IgE (482). FcεRII recognizes at least four different ligands via its lectin domain, including IgE, Epstein–Barr virus receptor (CD21) (483,484), and the B_2 integrins CD11b and CD11c. FcεRII is an unusual lectin-binding molecule as it exhibits lectinlike calcium-dependent binding of carbohydrate moieties (i.e., on CD21 and CD11b/c) but also specifically interacts with protein epitopes, such as those on IgE. CD23 triggering may be an important stimulator of NO production and IL-10 synthesis from macrophages and monocytes (485,486). LPS and IL-4 upregulate FcεRII expression in B cells, whereas IL-7 and GM-CSF induce its expression on T cells (477) and polymorphonuclear neutrophils, respectively (487). CD40 perturbation can trigger FcεRII expression on B cells (488–490). IL-10 downregulates CD23 expression on B cells (491).

4.6.3. IgG Receptors

The IgGs play a fundamental role in host immunity via their interplay with Fcγ receptors (492,493). IgG binding to Fcγ receptors can induce phagocytosis (494), ADCC

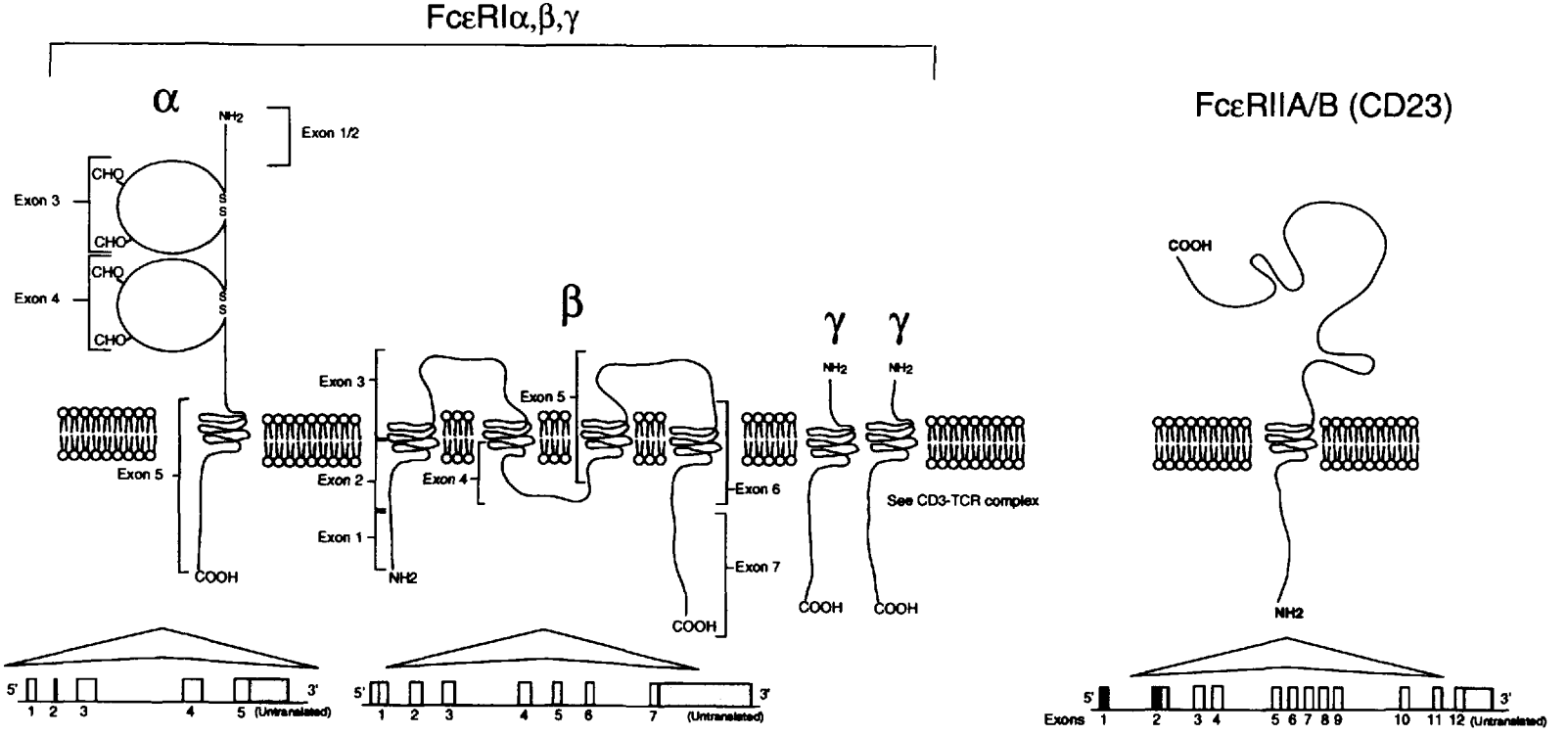


Figure 4.12. Exon and protein structure of the receptors for IgE.

(495,496), and transfer across the placenta (497,498). IgG also binds soluble FcγR (466,499). The Fcγ receptors are structurally similar, each having two or three Ig-like extracellular domains (Figure 4.13), but do exhibit differences in their subunit composition and IgG affinity. Humans contain a number of different isoforms for the various FcγR subclasses clustered on chromosome 1 (Figure 4.14). Mice lack the isoforms, with the genes for FcγR1 being located on chromosome 3 and those for FcγRII and FcγRIII situated on chromosome 1.

4.6.3.1. FcγRI (CD64). The FcγRI is a glycosylated 55-kDa protein expressed predominately on monocytes and macrophages where it binds monomeric IgG with high affinity. FcγRI contains three extracellular Ig domains, with the membrane-distal domain being involved in binding of IgG. Humans have three subclasses, FcγRIA, FcγRIB (which exists in isoforms 1 and 2), and FcγRIC, that are expressed from separate genes. The human FcγRIA isoform has been found to associate with the γ subunit of FcεRI, FcγRIII, and the TCR–CD3 complex. FcγRI is constitutively expressed on macrophages and monocytes and is upregulated on neutrophils and eosinophils (500,501). FcγRI is also expressed on $CD34^+$ granulo-monocytic progenitors (502). Mice express only a single FcγRI receptor found on macrophages and monocytes that is upregulated by IFNγ (503, 504). FcγRI binds both aggregated and monomeric IgG with high affinity, but with variable affinities for the different IgG subclasses. FcγRI polymorphism is associated with diabetes in the NOD mouse strain, perhaps reflecting the poor efficiency with which this receptor variation sequesters immune complexes (505).

4.6.3.2. FcγRII (CD32). Both humans and mice express multiple isoforms of the low-affinity IgG receptor FcγRII. Both species also express a soluble form of the receptor (506). Mouse and human receptors bind monomeric IgG with low affinity but also bind IgE (507). The human isoforms of the receptor bind IgG subclasses with varying affinities, whereas the murine FcγRII binds IgG1, IgG2a, and IgG2b but has no affinity for IgG3 (508). Human FcγRII is expressed widely on hematopoietic cells including B cells, basophils, eosinophils, Langerhans cells, monocytes, neutrophils, and platelets and trophoblasts (509–511). In humans there are three forms of FcγRII that have similar extracellular regions but differ in their transmembrane and cytoplasmic domains. The three forms are transcribed from individual genes that are differentially expressed: FcγRIIA and C are expressed mainly on neutrophils and the B form is found on lymphocytes. Mice have only a single FcγRII gene of which they express alternate splice variants.

4.6.3.3. FcγRIII (CD16). In humans the low-affinity FcγRIII is transcribed from two separate genes, FcγRIIIA and FcγRIIIB, which are transmembrane and GPI-anchored glycoproteins, respectively. In mice there is only a single FcγRIII with similarities to the human FcγRIIIA, both with two extracellular Ig-like domains, a transmembrane region, and surface expression that is dependent on associations with additional subunits. FcγRIII molecules are found on macrophages, γδ T cells, mast cells, and NK cells (512–514). The receptor may be involved in sequestering immune complexes and mediates clearance of erythrocytes cross-linked with IgG (515). The human FcγRIII isoforms have differential affinities for IgG subclasses, whereas FcγRIIIB can also interact with lectins. Mouse FcγRIII binds IgG1, IgG2a, and IgG2b with highest affinities and similar to FcγRII, may also bind IgE (507). Expression is upregulated by IFNγ (500,514,516).

4.6.4. IgM Receptors

IgM is efficient at activating the classical complement cascade. The polymeric structure of IgM allows high-avidity antigen-specific binding of an otherwise relatively low-

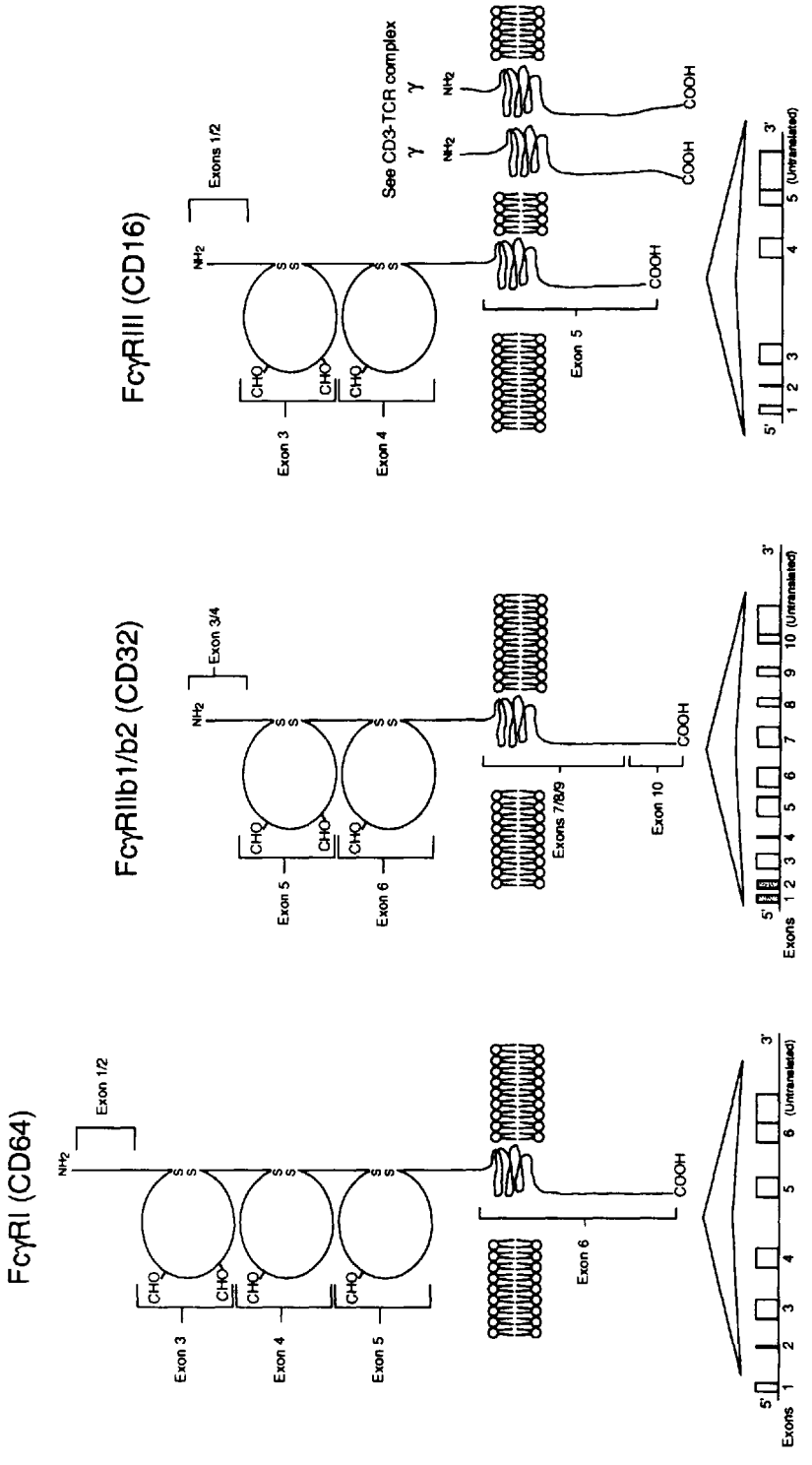


Figure 4.13. Exon and protein structure of the receptors for IgG.

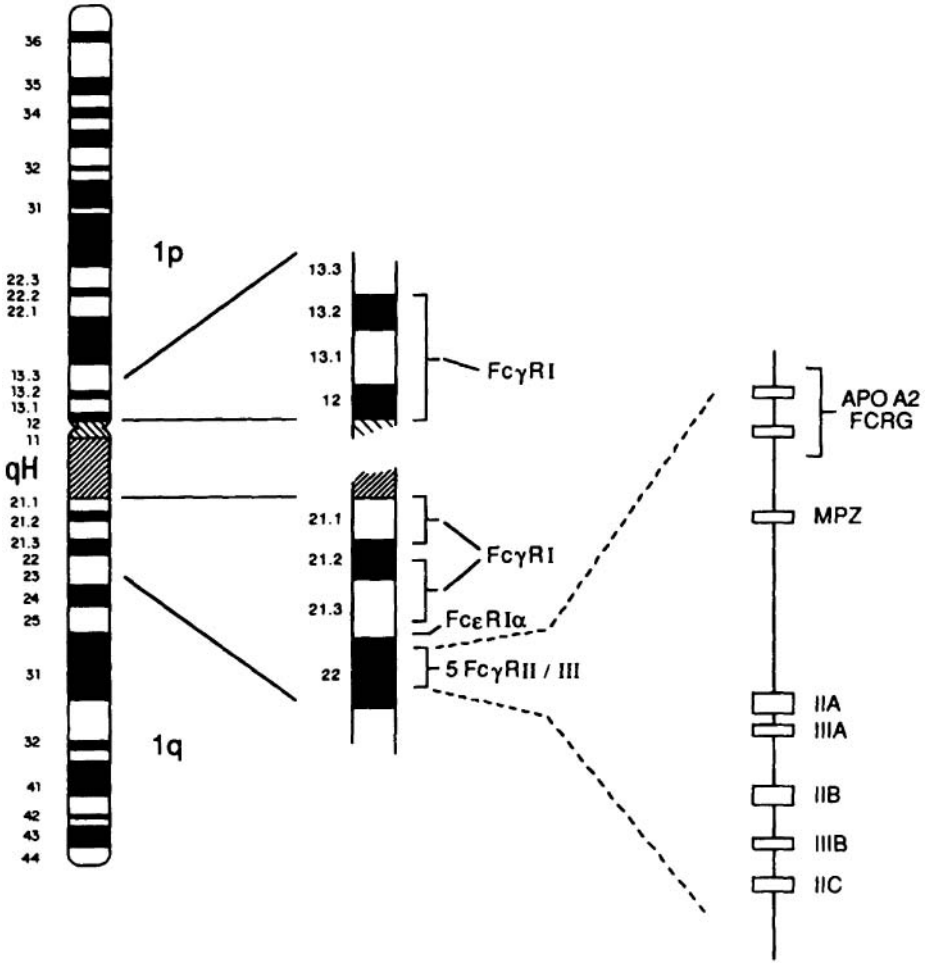


Figure 4.14. Organization of the FcγR gene cluster on human chromosome 1. Used with permission from *Cell*, Jeffrey V. Ravetch, **78**:553–560, 1994.

affinity IgM monomer. Its high avidity and complement fixing activity make it critically important in front-line defense. IgM is present in secretions and, like IgA, is transported across mucosal epithelial cells by the pIgR (see Section 4.8.1). Secretory IgM may exert a similar protective function in the gut as its local synthesis sometimes is markedly increased, especially in selective IgA deficiency.

4.7. B-CELL DEVELOPMENT

During embryonic development of mice and humans, B cells differentiate from multipotential precursors in spleen and liver (517,518). B-cell production shifts shortly after birth to the bone marrow (519,520). In the bone marrow, there are an estimated 1 million of the earliest committed B-cell precursors, the pro-B cells, which expand and give

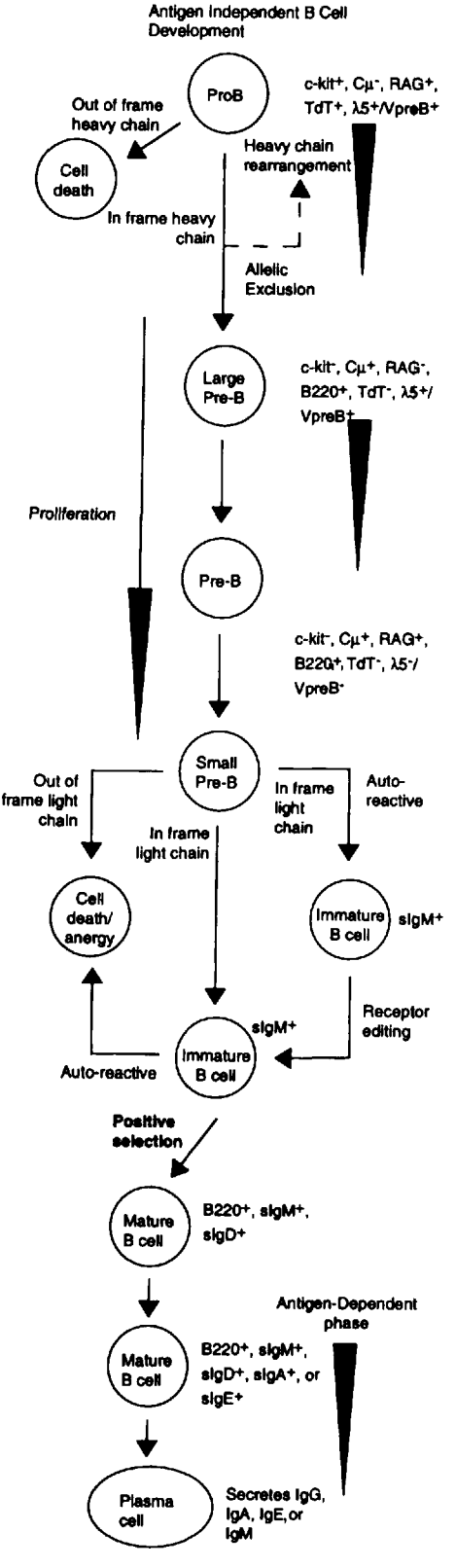


Figure 4.15. Differential expression of developmentally important genes during B-cell ontogeny. Rearrangement and expression of a functional Ig receptor is a critical process in B lymphopoiesis. Rearrangement of Ig genes coincides with expression of several other genes, such as the recombinase activating genes (RAG) and terminal deoxynucleotidyl transferase (TdT) (see relevant sections in text for details).

rise to 40 million pre-B cells. Only about half of the pre-B cells successfully rearrange functional receptors that are not autoreactive and proceed to develop into mature B cells. Antigen-receptor-driven expansion of the mature B cells results in the emergence each day of more than 3 million B cells from the bone marrow into the peripheral pool, where there is a cumulative population of over 500 million B cells (521,522). During differentiation, all B cells express membrane IgM at immature and mature stages of development and coexpress IgD once they are selected and become mature cells. However, IgD expression is lost after the mature resting cell is activated and interestingly is not expressed again except on a proportion of memory B cells. The pre-B-cell receptor contains the μ heavy chain, but lacks κ or λ light chains. In place of the light chains found on immature or mature B cells, are the surrogate light chains, λ5 and VpreB (CD89a,CD89b) (see Section 4.14). Deficiency in the λ5 gene results in a block in B-cell lymphopoiesis (99). Numerous other genes are developmentally regulated during B-cell development and are critical for normal B lymphopoiesis (Figure 4.15). Many of these genes are discussed under relevant headings in other sections.

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5

Autoimmune Disorders

HLA, Genetic Predisposition, and the Immune System

Many diseases with autoaggressive immune components appear to have predisposing genetic factors. Such a contention is supported by the observation of an increased prevalence of many autoimmune diseases among family members and among ethnic or racial groups (1). Moreover, autoimmune diseases are more often shared among monozygotic twins than among dizygotic twins or nonrelated individuals (1,2). Ultimately, disease association with genetic factors has often been defined in terms of human leukocyte antigens (HLA), particularly those for the highly polymorphic class I and class II genes. Yet most HLA-associated diseases (which include infectious diseases and some forms of cancer) do not reveal a simple Mendelian mode of inheritance, either recessive or dominant, are only partially penetrant, and may involve a number of different HLA alleles in addition to non-HLA loci (3). Taken together, these observations indicate that autoimmune diseases have a genetic basis, but that they also have environmental components and that multiple genetic loci are probably critical to disease onset.

Although there are no unequivocal explanations why class I and class II alleles associate with disease, there are a number of diseases, particularly those with autoimmune components, that are worth discussing in terms of their associations with class I or class II HLA (3–6). Class I and class II HLA genes are encoded in a region that spans about 3500 kb (about 0.03% of the total human genome) and incorporates more than 100 known genes, clustered on the distal portion of chromosome 6 (6p21.3) (7,8) (see Chapter 1). Because there is great expectation that the role of class I and class II molecules in disease may reveal itself in part from studies in mice, it is important to note that the three class I HLA categories HLA-A, HLA-B, and HLA-C roughly correspond to murine MHC class I groups H-2K, H-2D and H-2L, respectively, and that the human class II HLA groupings HLA-DQ and HLA-DR show considerable molecular, genetic, and serological identity with murine I-A and I-E, respectively (Figure 5.1). The functional similarities between human and murine class I or class II can indeed be striking: For example, a comparison of class II molecules associated with insulin-dependent diabetes mellitus (IDDM) and murine nonobese diabetes (NOD) reveals that in both cases susceptibility to disease involves the amino acid residue at position 57 of the class II molecule, which is a residue involved in peptide binding (4,10).

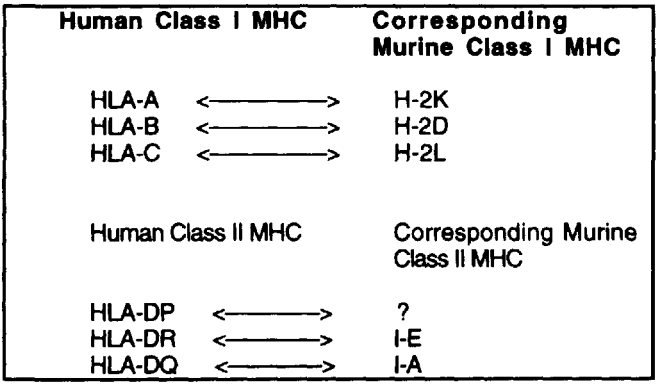

Figure 5.1. Molecular and genetic similarities exist between mouse and human class I and class II MHC.

Because it is the function of HLA class I and class II molecules to display peptides in their polymorphic peptide-binding grooves, the observation that certain HLA haplotypes were associated with specific autoimmune diseases clearly hinted that certain peptide binding characteristics may ultimately reflect disease susceptibility (Table 5.1). What is perhaps a logical extension of this thinking has become known as the molecular "mimicry" hypothesis (11–13). Each class I and class II allele displays a unique affinity for a set of peptides, which are derived from either invading pathogens or from endogenous pro-

Table 5.1
HLA Serotypes that Segregate with Disease[a]

Disease	Associated HLA	Relative risk
Addison's disease	DR3/DQ	6.3
Ankylosing spondylitis	B27	87.4
Autoimmune liver disease		3–15
Autoimmune hepatitis		
Primary biliary cirrhosis	DP/DQ	
Primary sclerosing cholangitis	DR/Dw2	
Behcet's disease	B5	6.3
Celiac disease	DR3	
Cicatrical pemphigoid	DQ/DR	
Dermatitis herpetiformis	DR3	15.4
Insulin-dependent diabetes mellitus	DR3	5.3
Multiple sclerosis	DR2	
Myasthenia gravis	B8/DR3	2.7/2.5
Pemphigus vulgaris	DR4	14.4
Reiter's syndrome	B27	37.0
Rheumatoid arthritis	DR4	4.2
Systemic lupus erythematosus	DR3	5.8

[a]See text for a more detailed discussion of various alleles and their associations with disease.

teins. However, in the absence of infection, most peptides displayed on the surface of cells on class I or class II molecules are presumably derived from *self-proteins*, which include those derived from fragments of class I or class II molecules themselves (see discussion on antigen processing, Chapter 2). Problems may arise after an infectious organism is processed into peptides and displayed on class I or class II molecules. If these peptides are a close match, or even identical, to any one of the *self-peptides* normally displayed on the cell surface (derived from endogenous proteins), the ensuing antigen-specific immune response may attack not only these foreign peptides but also may target those displaying self-peptides. As HLA class I and class II polymorphisms largely involve residues that determine peptide binding characteristics, the result is an association between autoimmune disease and the HLA allele involved in presenting the "mimicking" peptide. The model is further validated by the reasoning that if self-peptides described are largely derived from endogenous proteins that are expressed in a tissue-specific manner, these antigens would not be involved in negative selection (tolerance induction) in the thymus and thus potentially autoreactive T cells might indeed be part of the normal peripheral T-cell repertoire. Although teleological in design, transgenic murine models of autoimmunity are not inconsistent with a molecular mimicry hypothesis. Such a model exists for T-cell-mediated autoimmune destruction of pancreatic β-islet cells, where mice transgenically express a viral protein exclusively on β-islet cells, and where islet destruction is induced by infection with the intact virus (14). There are a number of reports that reveal much of the current thinking on the subject of how mimicry might arise (15–17).

Another intriguing role for class I and class II HLA in autoimmune disease involves their possible function in positive and negative selection of thymocytes. Certain HLA alleles might facilitate positive selection of an αβ TCR repertoire prone to self-reactive T cells. Conversely, disease-related HLA alleles may not function properly to induce negative selection of potentially autoreactive T cells (18), resulting in a mature T-cell compartment predisposed to attacking self-epitopes. Explanations for autoaggressive diseases that point to "mimicry" and "selection" may both be correct: HLA association may result from involvement of class I and II molecules at both levels of central and peripheral tolerance.

Mimicry between self- and foreign antigens has been thought of in terms of primary sequence collinearity between different antigens. Nonetheless, T cells that are cross-reactive with epitopes contained in self- and foreign antigens have been difficult to demonstrate (12,19,20). Interestingly, in one report, using synthetic peptides from myelin basic protein (MBP), seven viral and a single bacterial peptide were all able to stimulate cross-reactive MBP-specific T-cell clones, whereas only one of the foreign peptides showed collinear sequence alignment with those from MBP (11). Thus, it appears that "mimicry" of self-epitopes by foreign antigens may occur despite a lack of primary sequence coidentity. This may suggest that TCR "read" antigenic surfaces of peptide–MHC complexes that are only partially defined by the sequence of the bound peptide (21–24). The exact role of the class I and class II MHC molecules in determining antigenicity and cross-reactivity of these antigens is still forthcoming.

5.1. HLA CLASS I

A compilation and nomenclature for HLA antigens has been established by the World Health Organization (WHO) (see Section 1.2). There are at present at least 50 HLA-A, 97 HLA-B, and 34 HLA-C alleles known (25). Originally defined through

serological methods, the alleles are now additionally defined based on nucleotide sequencing, restriction fragment length polymorphism (RFLP), and other means, such as cytotoxic T-cell reactivity (25). Although the class I HLA molecules consist of both α and β chains (β_2-microglobulin), polymorphism is only a feature of the α chain, particularly the α1 and α2 domains of the peptide-binding groove. Among the three broad groups of class I HLA molecules, it has been determined that the HLA-B molecules contain the largest number of positions with high variability, HLA-A is intermediate, and HLA-C molecules have the least variability (26). HLA-A, -B, and -C have highly variable positions in the α1 domain at amino acid positions 9 and 116 and in the α2 domain at position 156. X-ray crystallographic analyses have been performed for class I molecules (i.e., HLA-B27) (27,28) and the basic principles governing class I peptide binding have been relatively well defined (see Section 1.3).

5.2. HLA CLASS II

The class II HLA molecule is a heterodimer, with each α and β subunit containing two external domains of about 90 amino acids each. The α1 and β1 domains form a β-pleated sheet that is believed to create the floor of the peptide-binding groove (29). Typical regions or sites with high degrees of polymorphism vary between different HLA-DP, -DQ, and -DR molecules. In class II nomenclature the first uppercase letter to appear after DR, DQ, and DP designations refers to either α or β chains: For example, DRB refers to the β chain of HLA-DR and DQA, the α chain of HLA-DQ.

5.2.1. HLA-DP

Both α and β chains of DP are polymorphic. Polymorphic residues, clustered around five locations on the β chain, are known as hypervariable regions (HVRs). These regions form part of the β-pleated sheet and include amino acids at positions 8–11, 35–36, 55–57, 65–69, and 84–88 (30). Additional diversity arises from the ability of α and β chains to mix and match with chains expressed from both parental alleles, permitting the production of four different DP heterodimers in individuals heterozygous at DP loci (which is almost always the case in an outbred, i.e., human, population).

5.2.2. HLA-DQ

Both α and β chains of DQ contain polymorphism. Variability has been detected at numerous amino acid positions spanning the entire length of the α1 domain, and an HVR in the DQ α chain occurs at positions 40–56. For DQB1, HVRs have been identified at positions 26–37, 52–57, and 70–74. Identical DQ serological specificity can occur for DQ dimers composed of different α- (DQA) and β-chain (DQB) alleles: Thus, DQ serological designations suggest a much lower diversity than actually exists for DQ molecules. In addition, as with the DP class II molecules, α and β chains can mix and match with those expressed from both parental loci. Although the peptide-binding pockets and peptide motifs for HLA-DR have been well characterized, those for HLA-DQ remain relatively uncharted (31–33). DQ polymorphisms in the peptide-binding cleft have been documented as they associate with different autoimmune disorders, such as IDDM (10,34), and may involve an Ala→Asp polymorphism at codon 57 (23,35).

5.2.3. HLA-DR

Polymorphic residues are clustered around three HVRs on the β chain, which accounts for virtually all of the observed allelic variation in the DR group (36). The α chain essentially lacks polymorphism. DR molecules have highly conserved peptide-binding grooves, formed predominately by the α chain, although a critical Val/Gly dimorphism exists at position 86 in the β chain which regulates peptide specificity (37). Of the nine genomic DRB loci, only six are known to be expressed (B1, B3, B4, B5, B6, and B7), and 85% of all DRB polymorphism is found at DRB1. It has been suggested that hypervariable coding regions might exist as intact cassettes, such that HVRs could be mixed and matched to form various class II HLA allelic variants (38). On DRB1, polymorphism predominates at positions 9–13, 25–28, and 67–74. The HLA-DR molecules have been studied by X-ray crystallography; peptide-binding motifs have been generated for several important disease-related alleles (23,29,39). In addition to expression on APC, HLA-DR has been detected under normal conditions in tissues from salivary (40) and mammary glands (40,41), kidney tubules (42), small intestine (43,44), endometrium and fallopian tubes (43), and adrenal cortex (45).

5.3. CALCULATING RELATIVE RISK VALUES FOR HLA DISEASE ASSOCIATIONS

The relative risk calculations that appear with many of the HLA associations reflect the frequency that a particular allele or haplotype occurs with a disease relative to its occurrence in normal healthy individuals. That is, relative risk compares the frequency of disease in a group of randomly selected persons (who have the allele of interest) with that in persons who do not carry the allele (Figure 5.2). For example, if 20% of a population carries a specific allele, and half of persons with disease carry the same allele while the other half with disease do not carry the allele, the allele has a relative disease risk of about 4.

5.4. ADDISON'S DISEASE

Addison's disease (AD) is an organ-specific disease of the adrenal cortex characterized by circulating cortex-specific autoantibodies (46) and lymphocyte infiltration into areas where adrenocortical destruction occurs (47,48). Autoantibodies to adrenocortical

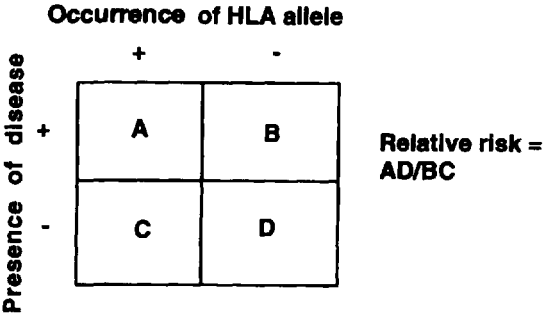

Figure 5.2. The simple relationship illustrated can be used to calculate relative disease risks for HLA class I and II association.

microsomal and plasma membrane antigens are detected in about two thirds of patients with the disease (46,49–51). The major target of autoantibodies is the p450 steroidogenic enzyme 21-hydroxylase (21-OH) (52,53). Autoantibodies from patient sera have been shown to bind a conserved epitope at the 21-OH hormonal binding site, inhibiting its enzyme activity (54).

In autoimmune AD there is class II expression on about 50–100% of adrenocortical cells (55). Interestingly, under normal conditions a portion (~10%) of adrenocortical cells express class II molecules (45); moreover, there is some degree of lymphocytic infiltration in normal adrenal glands by $CD4^+$ T cells, particularly in persons over 60 years of age (56). Thus, it would appear that factors besides upregulated class II expression play a role in disease. The disease has been associated with DR3 and DR4 subgroups (57,58). Expression of the HLA DQA1*0501 allele is associated with AD and a variety of other endocrine autoimmune diseases, such as IDDM and Grave's disease (59). AD has also been associated with HLA-DR3 class II molecules, as have a number of other endocrinopathies (60), and almost half of AD patients have one or more concurrent autoimmune diseases (61).

5.5. ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is an inflammatory condition that affects joints of the spine (62,63). HLA-B27 alleles B*2702 and B*2705 have long been associated with AS (64,65) and the peptide binding characteristics of these alleles have been studied in detail (66). Mimicry involving bacterium-derived peptides has been suggested in disease etiology (67), and may involve an epitope on the disease-related HLA-B27 molecule itself (68). Interestingly, five HLA alleles (B*2701, B*2702, B*2704, B*2705, and B*2706) associated with AS have been shown capable of presenting the same immunodominant peptide derived from Epstein–Barr virus (EBV) (69), indicating conserved antigen presentation function among various disease-associated alleles. A line of rats doubly transgenic for the HLA-B27 molecule and β_2- microglobulin spontaneously develop disease similar to AS seen in humans (70). However, some murine lines expressing the transgenes did not develop disease. Because AS-associated alleles are also found in healthy subjects, other genes located in class I and class II regions, such as TNFα, LMP2, and TAP, have been investigated for polymorphisms that might predispose to disease, although conflicting results have been reported (71–75).

5.6. AUTOIMMUNE LIVER DISEASE

Autoimmune hepatitis (AIH), primary biliary sclerosis (PBS), and primary sclerosing cholangitis (PSC) are major liver diseases with autoaggressive immune components. All three diseases are characterized by circulating autoantibodies and an association with class II genotypes (76,77). Interestingly, there are a number of concurrent immunological diseases that present with these liver conditions (Table 5.2). Nonetheless, as with all other autoimmune diseases, the HLA associations are not complete, and it is unclear whether the HLA linkage to the disease is a direct one. In addition, for the liver diseases discussed below, all can have complement abnormalities associated with them (78–80).

Table 5.2
Immunological Diseases that Present with Liver Disease[a]

	Liver disease		
Concurrent autoimmune disease	Chronic viral hepatitis	PBC[b]	PSC[c]
Asthma			1
Crohn's			1
Dermatitis herpetiformis	1		
Diabetes type I		1	
Graves'	1		
Idiopathic thrombocytopenic purpura	1		
Keratoconjunctivitis sicca		3	
Lichen planus		1	
Nephritis	1		
Rheumatoid arthritis	2		
Sjogren's syndrome		1	
Synovitis	4	1	
Thyroiditis	8	1	
Ulcerative colitis	1		7
Vasculitis	6		
Total	25	8	9

[a]Patients with chronic liver diseases and concurrent immunological disease are more commonly HLA-DR4 (51 versus 30%, $p = 0.02$) and are more likely to be heterozygous for HLA-DR3 and DR4 (13 versus 2%, $p = 0.04$) compared with normal subjects [Ref. 368].
[b]PBC, primary biliary cholangitis.
[c]PSC, primary sclerosing cholangitis.

5.6.1. Autoimmune Hepatitis

AIH also referred to as chronic active hepatitis, is characterized by hypergammaglobulinemia, circulating autoantibodies against liver-specific antigen, inflammatory infiltrate in periportal regions of the liver, and in most forms of the disease, treatment response to immunosuppressive agents such as corticosteroids (81,82). In AIH, these symptoms occur in the absence of viral infection, which is seen in other forms of liver disease. Spontaneous remission in AIH has been reported to be associated with generalized autoimmunosuppression in AIH patients (83). Over 50% of AIH patients express a DR3 subtype, compared with about 20% of healthy persons, and most patients express one of either DR3 or DR4 subgroups (84). The DR4 subtypes have been found to have a high frequency of DRB1*0401 and DRB3*0101 alleles, which share a common string of residues at positions 67–72 (85). Arg or Lys at position 71, which points from the α-helical domain toward the peptide-binding groove, interacting with both peptide and TCR (86), correlates with reduced or elevated risk (77,87) for AIH, respectively. In one study, 94% of AIH patients had the motif LLEQKR at positions 67–72 with lysine at position 71, which translated into a ninefold increased risk for the disease (77). The HLA associations for AIH are similar to those for PSC (88,89).

5.6.2. Primary Biliary Cirrhosis

PBC is a chronic granulomatous inflammatory disease that affects small bile ducts of the liver, resulting in scarring, progressive liver damage, and organ failure (90,91). Antimitochondrial antibodies (AMA) are present in about 90% of patients with PBC (92,93). Both IgM and IgG AMA-specific antibodies are present, with highly elevated levels of IgG3 (94,95). The target autoantigens include subunits of the pyruvate dehydrogenase complex (PDC), 2-oxo-acid dehydrogenase and 2-oxo-glutarate dehydrogenase complexes, Eα1, and protein X (96–103). Both $CD4^+$ and $CD8^+$ T cells are involved in bile duct pathogenesis (104–109). T-cell clones specific for pyruvate dehydrogenase antigens have been cloned from liver of PBC patients (110). On the other hand, there are reduced numbers of γδ T cells in the peripheral blood of PBC patients (111).

Elevated levels of class II HLA molecules are detected on PBC bile duct epithelium (112–114). However, abnormal PDC-E2 expression on luminal surfaces of biliary epithelium has been reported to occur prior to class II or BB1/B7 expression (115). HLA-DR8 and DPB1*0301 have been associated with PBC and the concurrent immunological disease manifestations (116–119). In a study in Japan, PBC patients were found to have a significantly higher frequency of DPB1*0501 and DQ3 alleles (120). A Leu residue at position 35 of the peptide-binding groove of the DP β subunit was found in 91.4% of PBC patients and appeared to be important in disease susceptibility. A more recent study in Britain, however, has failed to find a significant association between DPB1 and PBC (121). Other studies have found a DRB1*08 association with disease (77).

5.6.3. Primary Sclerosing Cholangitis

Sclerosis, inflammation, destruction, and fibrosis of intra- and extrahepatic bile ducts are characteristic features of PSC, a disease that largely (70%) afflicts men (122,123). There is a frequent concurrence with inflammatory bowel disease, which occurs in about 70% of PSC patients (124,125). HLA-DR3 may be associated with PSC (88,89,126). A recent report indicated that compared with normal subjects, frequencies of HLA-DR3 (B1*0304), DR2 (B1*1606), Dw2 (B1*1501), and DR52a (B3*0101) were all significantly increased in PSC patients, and that DR52a was associated with those ultimately requiring liver transplants (89). HLA-DR4 association corresponds with accelerated disease progression (89), and the DRB3*0101 allele in this group was most often associated with both disease and poor prognosis. A second allele, DRB5*0101, also conferred susceptibility. Both of these alleles contain a leucine residue at position 38 of the DR β chain. The DRB4*0101 allele, which correlates with a lower risk for PSC, contains alanine at position 38. The highest relative risk for PSC has been reported for two DR molecules with Leu38 in the β chain, and lowest risk was observed for two molecules with alanine at this position (127,128).

5.7. BEHCET'S DISEASE

BD is a multisystemic inflammatory disorder that involves lesions in the eyes, mouth, skin, vasculature, and genitals characterized by marked infiltration with functionally abnormal neutrophils (129). T cells from patients with BD have been found to respond to four synthetic peptides corresponding to mycobacterial heat shock proteins (HSP), and to peptides from homologous human HSP (130). Sera from patients also contain antibodies

against epitopes that overlap with previously defined HSP T-cell epitopes (131). $CD4^+$ T cells from BD patients show abnormally low levels of the apoptosis-inducing Fas antigen (132). HSP-reactive γδ T cells have also been reported in patients with BD (133). The disease has been associated with HLA-B51 (134,135) and HLA-B52 expression (134,136,137), particularly the B*5101 allele, which was found, without exception, in all patients in a Japanese cohort with BD (138). Recent findings have shown that HLA-B51 expression correlates with neutrophil hyper activity regardless of whether BD is present or absent; and that HLA-B51 transgenic mice show elevated superoxide production by neutrophils (129). Individuals with B*5102 and B*5103 do not have elevated risk for BD, whereas these alleles differ from the risk-associated molecule B*1501 only by single amino acid substitutions at residues 171 and 167, respectively (138,139). Interestingly, allelic polymorphism in transporters associated with antigen processing (TAP) and low-molecular-weight polypeptide (LMP) have been found to associate with disease (140,141).

5.8. CELIAC DISEASE

Autoimmune celiac disease (CD) is a gut disorder precipitated by the ingestion of gluten (142–144). CD manifests with chronic diarrhea, weight loss, edema, and other findings suggestive of gastrointestinal malabsorption; histologically, it is characterized by crypt hyperplasia and villous atrophy. There is about 70% concordance for the disease in identical twins (145), suggesting a strong genetic element in disease susceptibility. Serum antigliadin, antireticulin, and antiendomysial antibodies are often present (146–148) as are highly elevated numbers of intraepithelial γδ cells (149). Most CD patients (~90%) carry the class II HLA alleles DQA1*0501 and DQB1*020 (DQ2), which are present in about 20% of the general population, and thus the gene pair appears to confer significant disease risk (150–153). The two genes may appear in *cis* or in *trans*, as in each case expression results in the formation of a functional class II heterodimer (see Section 1.2). As a corollary, there appear to be gene dosage effects for the disease-related DQ alleles (154); more recently, elevated expression levels, which reflect promoter polymorphisms, have been suggested to increase susceptibility (155). There may also be involvement of another class II MHC locus, HLA-DPB1, located about 400 kb centromeric of DQ (156,157), although this relationship may merely reflect linkage disequilibrium between DQ and DP loci (153,158).

CD may also be associated with DQ-restricted gliadin-specific T cells (159,160). The N-terminal portion of α-gliadin has been proposed as a potential autoantigen, as T cells from CD patients recognize peptides mimicking this region when presented in the context of DR7 and DQ2 (161,162). A more recent study has found that α-gliadin peptides do not efficiently bind DQ2 (163). Patients with CD have increased risk for a number of other diseases (150) such as asthma (164), atopy (165), arthritis (166), diabetes (167), and malignancies such as non-Hodgkin's lymphoma (168,169).

5.9. CICATRICIAL PEMPHIGOID

CP is a chronic disease affecting mucous membranes such as the mouth and eyes, characterized by subepidermal and mucosal blistering (170). Immunoglobulin deposition

at basement membrane zones (BMZ) (171,172) has been suggested as the pathogenic mechanism by which the disease progresses. However, BMZ antibodies are not detected in all cases of CP and the cause of tissue destruction is not entirely clear (170). The occurrence of CP has been noted in patients with rheumatoid arthritis treated with D-penicillamine, and it has been suggested that the antibiotic might induce BMZ antibodies in genetically susceptible individuals (170). A genetic link for class II loci has been found for ocular and oral forms of the disease, involving the DQB1*0301 allele (173,174) and the DRB1*04-DRB4*0101-DQA1*03-DQB0301 haplotype (175). Amino acid sequence analysis of DQB1 alleles from patients with CP suggested that positions 57 and 71–77 may be critical to disease association (175).

5.10. DERMATITIS HERPETIFORMIS

Immunopathological lesions afflict both the skin and small intestine in dermatitis herpetiformis (DH) (176). The disease is characterized by IgA deposits in the upper dermis of uninvolved skin, about two thirds of patients have intestinal disorders with villous atrophy similar to those seen in DC, and gluten sensitivity and lymphocytic infiltration of gut epithelium (177). DH is also complicated by a high incidence of malignancies, particularly lymphomas that appear to originate in the gastrointestinal tract (177,178). The presence of antibodies against the cereal-derived protein gliadin (179), and resolution of disease in gliadin-free diets, implicates this protein in disease pathogenesis. This is similar for CD and the two diseases have been considered to possibly reflect a common genetic lesion, although genetic linkage for DH and CD has been reported to reflect different regions of the MHC (180). T-cell infiltrates in lesions are mainly $CD4^+CD45RO^+$ memory cells, but significant numbers of $CD8^+$ T cells are also present (181). Positive associations with class I and II HLA haplotypes have been reported, but the strongest correlations are with DR3 and DQw2, carried by almost 100% of patients with DH (182).

5.11. INSULIN-DEPENDENT DIABETES MELLITUS

IDDM occurs as a consequence of destruction of the insulin-producing β-islet cells of the pancreas (183,184). Circulating islet autoantibodies and lymphocytic infiltration into islets suggest an immune component to islet destruction. Low concordance among identical twins also indicates the importance of environmental factors in the disease (185). There also appear to be multiple genetic loci involved in the disease, although linkage analyses indicate that the MHC loci are probably the most critical for disease susceptibility (186). $CD8^+$ T cells likely play an important role in islet destruction, as they infiltrate affected tissue early in disease onset, show restricted Vβ usage, and appear to be capable of attacking β islets, which display upregulated class I expression in IDDM (187–189). Moreover, negative selection in the thymus against β-islet antigens appears to protect susceptible animals from diabetes (190). $IL\text{-}2R^+$ oligoclonal T-cell populations are present in the peripheral blood (191). T cells from peripheral blood of patients or those at risk for IDDM (i.e., first-degree relatives) were reported to proliferate in coculture with either islet cells or purified insulin (192,193), or glutamic acid decarboxylase (GAD65) (194,195).

Coxsackievirus has been implicated as a candidate etiological agent in IDDM (196–200). The enzyme carboxypeptidase H expressed in the β-islet cells of the pancreas, has possible antigenic sequence homology with a peptide processed from the β chain of the class II allele HLA-Dq3.2, which is displayed on the HLA-DR4 subgroup (185,201,202). It is of interest that carboxypeptidase H can be processed into peptides with sequence alignments similar to the coat protein of coxsackievirus and the nucleoprotein of influenza A. Islet cell antigen 512 (ICA512) is a CD45-related molecule, found from an islet cDNA expression library screened with human IDDM sera (203). Antibodies against ICA512, expressed in insulin-producing pancreatic β islets and other cells (204), are prevalent in IDDM individuals (205,206) and the protein contains sequences shared with HLA-DQB alleles. Similarity between a GAD65 and proinsulin peptide sequences has been noted, and representative synthetic peptides have been shown to stimulate T cells from patients at risk for IDDM (207). A retrovirus component behaving like a superantigen has been isolated and may represent an autoantigen involved in type I diabetes (208).

The DR3 (B1*0301,B1*0302) and DR4 (B*0401,B*0402) class II alleles are associated with IDDM; when DR3/DR4 molecules are found together, the relative risk is significantly increased (209). DQβ chains are also associated with IDDM susceptibility (DQw3.2, DQw2, DQQw1.1, DQw1.19), and these alleles share a common Val or Ser residue at position 57 (4). The actual charge of the amino acid at position 57 has been correlated with disease susceptibility (210), and modeling studies have predicted that the negative correlation observed with Asp at position 57 may result from the formation of a salt bridge at one end of the peptide-binding groove (10). IDDM is also frequently associated with autoimmune thyroid disease (ATD), in which case it segregates with the DQB1*0201 allele (211). A TAP1 allele has been associated with IDDM albeit with low relative risk (212). Another report has shown an IDDM-protective effect for a TAP allele (213).

NOD mice serve as a murine model for IDDM (214). The NOD phenotype involves over a dozen loci (215) including, in an obligatory way, genes of the MHC (216). The disease can be transferred from NOD mice to healthy recipients using NOD-derived $CD4^+$ or $CD8^+$ T cells (217–219) and athymic nude mice are resistant to NOD (220). Monoclonal T cells expressing Vβ TCR have also been identified in young prediabetic NOD mice, suggesting a possible role for T cells in disease onset (221).

5.12. MULTIPLE SCLEROSIS

Chronic inflammatory reactions of the central nervous system with concomitant degeneration of myelinated cells are the hallmark of MS (222–224). A concordance rate of 26–31% for MS is observed in monozygotic twins versus about 3% in dizygotic pairs, indicating a genetic predisposition for the disease but also a critical environmental component (2,225,226). Recent evidence also supports the involvement of multiple genetic loci in disease susceptibility (227). The role of T cells in disease pathogenesis has been widely investigated and restricted TCR usage in patients with MS has been observed (228,230). Analysis of mRNA from T cells of patients with MS revealed restricted V-region usage in brain tissues (231,232), oligoclonal αβ T-cell populations in cerebrospinal fluid (233, 234), and preferential usage in blood (235–237). Nevertheless, myelin basic protein (MBP)-specific T-cells precursors are reported to occur with similar frequency in individuals with MS and healthy subjects (238,239).

T- and B-cell IgG responses in MS patients possessing the HLA-DR2 subgroup, which represents about two thirds of patients, are targeted at MBP epitopes, involving residues 84–103 (240). Retroviral infections have been suggested as a trigger for MS, but definitive evidence remains to be presented (11,241), HLA-DR-restricted T cells cross-reactive with coronavirus and MBP have been proposed as a possible immune mediator of disease (242). Association of MS with the haplotype DRB1*1501-DQA1*0102-DQB1*0602 has been reported (243–246). Detailed analysis of this haplotype has established the importance of the DRB1*1501 allele in the positive association with MS, and the highest correlation with disease is observed when both DRB1*1501 and DRB1*0400 appear together (247). Other HLA associations have been made when both DRB1*1501 and DRB1*0400 appear together (247). Other HLA associations have been made with MS but these vary according to populations studied (247,248). Murine experimental autoimmune encephalomyelitis, which involves immunization with MBP, has been used as a model to study the possible pathogenic role of T cells in MS (249,250), which can be blocked using T-cell TCR antagonist peptides (251).

5.13. MYASTHENIA GRAVIS

Circulating IgG specific for the acetylcholine receptor (AChR) is a common feature of myasthenia gravis (MG) (252–254), accompanied by progressive deterioration of striated muscle fiber. However, anti-AChR antibody levels do not correlate with disease manifestations and some patients with MG have no demonstrable AChR antibodies (255). Hyperplasia of the thymus and risk of thymoma are common features of MG, suggesting a role for the thymus and T cells in the disease (256,257). MG associations have been found with both class I and class II MHC, although correlation varies for different alleles depending on age of onset, sex, and accompanying clinical symptoms (258–262). Patients with MG frequently demonstrate B and T lymphocytes with reactivity against AChR (263–265), including $CD4^+$ T cells specific for embryonic forms of the AChR complex (eAChR) (266,267), which is also expressed in the thymus (268,269). Also, $CD4^+$ T cells reactive against epitopes of the γ subunit of AChR (270,271) have been identified from patients (266,267), some with different HLA haplotypes. However, AChR-specific T cells are also present in the normal immune repertoire (272). $CD4^+$ T cells from MG patients are largely restricted by HLA-DR molecules (273–276). Natural peptide ligands binding MG-associated HLA-DR3 molecules have been identified (277).

The class II HLA-DQ alleles DQB*0301, B*0302, B*0303, and DPB1*0201 have been observed with elevated frequency in female patients with early onset disease, and association was especially high for carriers of both of the (unlinked) DQB1*03 and DPB1*0201 alleles (278). Another study has shown susceptibility when the heterodimers DQA1*01-DQB1*0201 or DQA1*01-DQB1*0301 are present (relative risk 6.2) (279). DQA1*01 alleles DQA1*0101, 0102, and 0103 have glycine and arginine residues at positions 55 and 64, respectively, while DQB1*0301 and DQB1*0201 contain a negatively charged glutamic acid at positions 45 and 46, respectively. In MG patients with thymic hyperplasia, DQA1*0501 was in linkage disequilibrium with DQB1*0201 and DQB1*0301 (relative risk 17.2) (279).

An experimental MG can be induced in rats by immunization with AChR protein. Rats depleted of $CD8^+$ T cells have significantly reduced disease severity, as is antibody

against the AChR (280); however, these results are in conflict with an earlier study in class I-deficient mice (281). Treatment of animals with IFNα, which downregulates class II expression, reduces disease in experimental autoimmune MG (282).

5.14. PEMPHIGUS VULGARIS

PV is a chronic blistering disease of the skin characterized by high levels of circulating autoantibodies specific for desmogleins (Dsg), a member of the cadherin family of molecules (283–285). Antibodies and immune complexes appear to mediate breakdown of epidermal cell adhesion; and sera from PV patients, affinity purified using Dsg-fusion proteins, induce blistering in mice (286). This disease is associated with the class II DR4 subtype among others. Interestingly, the DR4 subtypes involved in PV and rheumatoid arthritis show differences only for amino acids in the DR β chain at positions 67–71 (287–289). PV has been associated with several different haplotypes, including HLA-DQ5, DQ8, DR4, and DR6 class II subgroups (290–293).

5.15. REITER'S SYNDROME

RS, a form of reactive arthritis that attacks peripheral joints, is a classic spondylarthropathy that includes other inflammatory diseases such as AS (63,294,295). Bacterial antigens have been detected in the synovial joints and membranes of patients with RS (296,297). Specific T cells have been isolated from synovium that respond to bacterial antigens associated with disease (298–305). Although RS shows a strong association with the class I alleles HLA-B27, the specific T cells isolated from patients have been $CD4^+$ and presumably class II restricted. It has been suggested that the HLA-B27 correlation with disease may reflect the inability of the molecule to adequately present disease-causative bacterial antigens, prolonging infection and resulting in autoimmune disease (306–308). Interestingly, although transgenic lineages of rats expressing cDNA of human HLA-B27 develop reactive arthritis, disease is dependent on the copy number of HLA-B27 genes expressed in the animals (309,310).

5.16. RHEUMATOID ARTHRITIS

Inflammation of the synovial membrane, cartilage destruction, and bone erosion are characteristic features of rheumatoid arthritis (RA), which, in a subset of individuals, is also accompanied by vasculitis (311). Autoantibodies against type II collagen (CII) are found in serum and joints of RA patients (312,313). Extensive somatic mutations of autoantibodies, or RF factors (314), also suggest an antigen-driven immune response (315,316). CII-specific T cells have been reported in the synovial membrane of an RA patient (317) and there are numerous reports of preferential usage of T-cell V-region genes in patients with RA (318–325), although $CD4^+$ T-cell depletion in RA patients provides little relief from disease (326). There is a strong association between RA and expression of the MHC class II DR1 and DR4 molecules B1*0101, and B1*0401, B1*0404, and B1*0405, respectively (4,327–330). Homozygosity for DR4 molecules has been found to

significantly increase risk for disease and may be linked to severity and vasculitis (331,332). The DRB1*0404 allele associated with RA and the DRB1*0402 allele, which correlates with less risk of disease, differ only in residues found at positions 67–71 of the β chain (327). Collinear sequence identity at positions 67–71 of the DR β chain, shared by HLA-DR disease-associated molecules (333–336), is likely involved in peptide binding (23,29,37). The peptide binding characteristics of disease-associated alleles have been studied in detail and may lead to identification of the autoantigens involved (39,328). Molecular mimicry has been suggested in the etiology of RA and may involve sequences in Epstein–Barr virus glycoprotein B (201), or in heat shock proteins from *E. coli* (337).

A murine model of arthritis involves immunization with CII and is associated with class II I-A^q (338). The I-A^q CII epitope involved in strong activation of specific T cells is an octamer (IAG*FKGEQ*) (339), which overlaps with the DRB1*0401-restricted epitope 263–270 (*FKGEQ*GPK) (340). Mice transgenic for HLA-DRB1*0401 have also been used to determine the T-cell epitope involved in CII reactivity, which appears to involve CII 261–273, a conserved region of CII involved in I-A^q-restricted T-cell responses in experimental RA in mice (340). A recent report of changing patterns of dominant T-cell clones in synovial tissue, however, suggests a growing use of different antigenic determinants over the course of RA (341).

5.17. SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is characterized by immunologogical abnormalities such as autoantibodies to DNA and nuclear proteins (342–345). Concordance among monozygotic twins has been reported at 70% (346) and 24% (347). The disease predominately afflicts females (348). Alleles from the HLA-DR2 and DR3 group have for some time been considered associated with SLE, although the relative risk for these alleles has never been shown to be high (349,350). Persistent B-lymphocyte activation has been suggested to have a pathogenic role in SLE, supported by the finding that B cells isolated from patients with quiescent disease spontaneously secrete DNA autoantibodies *in vitro* (351). Blocking cognate T–B-cell interactions can ameliorate disease exacerbation in SLE patients (352–354), underpinning a critical role for T-cell-driven B-cell autoimmunity in the disease. There are reports of hyperactive T-cell compartments in SLE, as evidenced by increased levels of soluble IL-2R and class II HLA-DR on T cells (355,356). An HLA-DR-restricted T-cell clone has been found that induces anti-dsDNA antibody secretion by SLE-derived B cells (357), and both $CD4^+$ and $CD8^+$ T cells appear to support polyclonal antibody synthesis *in vitro* (358). Paradoxically, lymphocytes from SLE patients show higher rates of apoptosis *in vitro* compared with normal lymphocytes (359). Restricted junctional diversity has also been reported in γδ T cells from SLE patients (360).

There have been demonstrations of SLE associations with DRQ genes (361,362). HLA-DP associations have been made, although a more recent study suggests no link exists (363). A relative risk of 2.0 has also been found for the class I molecule HLA-B*08 (364,365). More recently, the occurrence of an HLA-DR3-B8 haplotype with a TNF-α polymorphism was found to have increased relative risk of SLE (364). Deficiencies at the class III region complement genes may also have a role in disease (350,366). A recent report found that all of 22 SLE patients investigated, and 12 of 15 normal subjects who had C4A and CYP21A gene deletions (the most common cause of C4A null alleles in SLE), had an allele from the HLA-DR3 group (367).

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6

Neoplasias Involving Translocation of Antigen Receptor Genes

Cytogenetic analysis of neoplastic lymphoid tissues isolated from humans typically reveals chromosomal abnormalities. Although direct causal relationships between specific genetic anomalies and tumorigenesis are complex, these relationships are probably better defined for hematological diseases than for solid tumors. Observations on large numbers of hematological tumors have resulted in the description of numerous nonrandom genetic lesions that are associated with specific and well-defined tumors.

Malignancy in cells of hematological origin represents about 10% of all cancer cases. Typical lesions found in many of these cancers of lymphoid lineages involve translocations of proto-oncogenes with T- or B-cell receptor genes (TCR/BCR). Infidelity in recombination of TCR and BCR genes is presumably behind these oncogenic translocations (1,2). A translocation event bringing a proto-oncogene under the influence of enhancer/promoter sequences of BCR or TCR can result in dysregulated expression of the proto-oncogene, possibly resulting in elevated transcriptional activity, loss of temporal regulation, ectopic expression in an inappropriate cell or tissue. Any or all of these events may provide the basis for an early lesion in tumorigenesis. Below are descriptions of the proto-oncogenes that undergo recurrent translocations with TCR or BCR loci (Table 6.1).

6.1. NEOPLASIAS INVOLVING THE T-CELL RECEPTOR

6.1.1. HOX11 (TLX1)

About 1% of ALL and 5–10% of T-ALL carry translocations between TCR αδ/β loci and a gene encoding the homeobox protein, HOX11, at 10q24 (3–7). Tlx1 (T-cell leukemia homeobox), the murine homologue, was deleted in mice and found to be crucial for the development of the spleen during embryogenesis; it was consequently dubbed a "master gene," as its expression appears to be capable of regulating an entire differentiation pathway (8). A number of 10q24 breakpoints have been identified, most of which reside in a 15-kb region (9). The HOX11 mRNA produced from the translocation appears

Table 6.1
Oncogenic Translocations Involving Lymphocyte Receptor Genes

Translocation	Ch	Deregulating region	Ch	Deregulated gene product	Malignant disorder[a]
TCR					
t(10;14)(q24;q11)	14	TCRδ	10	HOX11 (TLX1)	T-ALL
t(9;14)(p21-22;q11)	14	TCRδ	9	INK4 (MTS1)	B-ALL
t(1;7)(p34;q34)	7	TCRβ	1	LCK	T-ALL
t(7;19)(q35;p13)	7	TCRβ	19	LYL1	T-ALL
t(8;14)(q24;q11)	14	TCRα	8	c-MYC	T-ALL
t(X;14)(q28;q11)	14	TCRα	X	MTCP/C6.B	T-PLL
t(1;14)(p32;q11)	14	TCRα	1	TAL1 (SCL)	T-ALL
t(7;9)(q35;q34)	7	TCRβ	9	TAL2	T-ALL
t(7;14)(q35;q32.1)	14	TCRα	14	TCL1	T-CLL
t(7;9)(q34;q34.3)	7	TCRβ	9	TCL3 (NOTCH1, TAN1)	T-ALL
t(11;14)(p15;q11)	14	TCRα	11	TTG1 (RBTN1)	T-ALL
t(11;14)(p13;q11)	14	TCRα/δ	11	TTG2 (RBTN2)	T-ALL
t(7;11)(q35;p13)	7	TCRβ	11	TTG2 (RBTN2)	T-ALL
BCR					
t(11;14)(q13;q32)	14	IgH	11	BCL1 (PRAD1)	B-CLL and others
t(14;18)(q32;q21)	18	IgH	14	BCL2	PL
t(14;19)(q32;q13.1)	14	IgH	19	BCL3	B-CLL
t(3;14)(q27;q32)	14	IgH	3	BCL6 (LAZ3, BCL5)	NHL, DLCL
t(8;14;12) (q24;q32;q24)	14	IgH	12	BCL7a	B-NHL
t(8;14)(q24;q32)	14	IgH	8	c-MYC	BL, ALL
t(2;8)(p12;q24)	2	Igκ	8	c-MYC	BL, ALL
t(8;22)(q24;q11)	22	Igλ	8	c-MYC	BL, ALL
t(10;14)(q24;q32)	14	IgH	10	NF-κB2 (Lyt-10)	BL

[a]Disease nomenclature: AL, acute leukemia; ALL, acute lymphocytic leukemia (T- or B-cell); BL, Burkitt's lymphoma; CL, chronic leukemia; CLL, chronic lymphocytic leukemia (T- or B-cell); DLCL, diffuse large-cell lymphoma; NHL, non-Hodgkin's lymphoma; PLL, prolymphocytic leukemia.

unaltered from the native form expressed as a rare transcript in lymphoid cells (10), and rearrangement of HOX11 to the TCRδ loci results in abundant expression. Transgenic mice expressing HOX11 from an lck proximal promoter (i.e., T-lineage-specific expression) have been found to develop T-cell lymphomas (11). These mice also show marked reduction of $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ double-positive cells in the thymus. A transfection study of bone marrow cells suggested that constitutive expression of HOX11 interferes with cellular differentiation but that secondary mutations were likely required for malignant transformation of cells (12).

Table 6.2
Frequency of p16 Deletions in Hematological Malignancies[a,b]

T-ALL	62%
B-ALL	6%
Pre-B-ALL	17%
AML	6%
ATL	17%
Non-Hodgkin's lymphoma	
T cell origin	34%
B cell origin	10%

[a]Adapted from Hirama and Koeffler (141).

[b]Mutations in p16 (also known as p16CDKN2, p16INK4, p16INK4A, p16CDK4I, and p16MTS1) are frequently observed in leukemias and lymphomas and are reported as the most frequent genetic lesion in ALL (141–144). p16 is composed of 156 amino acids and four ankyrin motifs. The ankyrin repeats appear to account for the functionality of the molecule: They facilitate interaction of the protein with its target cyclin D-CDK4 holoenzyme and are necessary for inhibitory function of the molecule (145); site-directed mutations at nonankyrin positions do not impair its CDK inhibitory abilities (146). The role of p16 in mice and humans appears to be similar (149).

6.1.2. *p16INK4 (MTS1)*

p16 is a highly specific inhibitor of cyclin-dependent serine/threonine kinase activity that facilitates transit through G_1 during eukaryotic cell division and plays a key role in regulating cell growth and differentiation. Loss of p16INK4 (p16) expression caused by a t(9;14)(p21-22;q11) translocation is associated with acute B-cell lymphoblastic leukemia (13). Loss of p16 expression is also found in childhood T-cell ALL where it is not necessarily revealed as cytogenetically detectable 9p aberrations (14), and loss of p16 function is found in numerous other hematological and nonhematological malignancies (Table 6.2) (13,15–21). The t(9;14) translocation was shown to result in interruption of the p16 gene 1.0 kb upstream of the first exon close to a recombination heptamer, suggesting errant recombinase activity (13).

6.1.3. *p56^{LCK}*

Translocations involving the protein tyrosine kinase LCK gene (1p34) and the TCRβ locus (7q35) are associated with T-ALL (22). Translocation results in constant-region enhancer sequences of a TCRβ chain being juxtaposed upstream of the LCK gene without disruption of LCK coding sequences. LCK is an SRC-family protein tyrosine kinase that is normally expressed in T cells and is associated with molecules including CD4, CD8,

CD2, and IL-2Rβ chain, where it is triggered to transduce kinase signals so as to induce T-cell activation and differentiation programs (23–28). In addition to increased expression, somatic mutations following translocation of LCK may contribute to its oncogenic activity (29). Analysis of a cell line containing the t(1;7)(p34;q34) translocation showed that the sequences proximal to the 1p34 breakpoint contained a heptamer–nonamer recognition motif with a 12-bp spacer, supporting the hypothesis that errant recombinase activity might underlie LCK–TCRβ translocations *in vivo* (30).

6.1.4. c-MYC

c-MYC (8q24) contains a basic helix–loop–helix (bHLH) dimerization motif and a basic DNA-binding region and is found to undergo rearrangement close to the joining sequences of the TCRα locus at 14q11 (31). Both constant and variable regions of the TCRα locus are translocated to the 3′ end of the c-MYC gene on chromosome 8 (31). This translocation has been reported in 15% of T-ALL, whereas 90% of Burkitt's lymphoma cases are characterized by translocation of c-MYC with Ig genes (see below). Somatic mutations in c-MYC often accompany translocation, although their significance is not understood (32). c-MYC is involved in the regulation of growth and differentiation of cells, plays an important role in apoptosis, and can induce tumor formation *in vitro* and in transgenic mice (33). c-MYC exists as a heterodimer in association with Max or other proteins, forming a complex regulatory network of transactivating proteins (34–40). Thus, its overexpression after translocation with the TCRα locus may result in dysregulation of numerous genes and provide a primary lesion in tumorigenesis.

6.1.5. MTCP1 (C6.1B)

Translocation of the recently described mature T-cell proliferation (MTCP1) gene on chromosome Xq28 with the TCRα locus leads to ectopic and/or overexpression of MTCP1 transcripts (41–43). As the name suggests, the MTCP1 translocation is associated with neoplasia of mature T cells. The translocation can be seen in clonal proliferating T cells in ataxia telangiectasia (an autosomal recessive disease characterized by progressive neurological symptoms, humoral and cellular immunodeficiency, and highly elevated risk of malignancies) years before leukemic transformation, suggesting that this lesion occurs early in leukemogenesis (44). Multiple MTCP1 mRNAs are produced through alternate splicing, which code for two unique proteins of 8 kDa (68 aa) or 13 kDa (107 aa), designated $p8^{MTCP1}$ and $p13^{MTCP1}$, respectively. The $P8^{MTCP1}$ shows high expression levels in proliferating T cells bearing the t(X;14) lesion and is localized in the mitochondria (45). MTCP1 has considerable sequence similarity to the TCL1 proto-oncogene (see below) (46).

6.1.6. TAL1 (SCL/TCL5)/TAL2/LYL1

Based on their high degree of similarity in bHLH sequences, TAL1 (7p32), TAL2, and LYL1 appear to encode a subgroup of transcription factors. All three molecules appear to play similar roles in leukemogenesis (47). Alterations of the TAL1 gene are found in about 25% of patients with T-ALL, making it the most common genetic lesion seen in this disease (47–49). However, only about 3% of T-ALL involve translocations with TCR genes (50). TAL1 protein is transcriptionally active after rearrangement with

the TCRα locus, or after an intralocus rearrangement of the TAL gene that results in deletion of about 100 kbp of DNA upstream of the TAL1 gene. Loss of TAL1 in mice results in defective hematopoiesis (51). Although LYL1 and TAL1 share 80% identity in their bHLH regions and have similar expression patterns in cell lines, findings in TAL1-deficient mice indicate that LYL1 function does not replace that of TAL1. TAL2 and LYL1 lesions are uncommon compared with TAL1, as they are present in less than 2% of T-ALL (48). The TAL2 gene is located 33 kb from the t(7;9)(q34;q32) breakpoint on chromosome 9, which results in TAL2 being juxtaposed with TCRβ loci on chromosome 7 (49).

6.1.7. TCL1

The TCL1 gene (14q32.1) is deregulated by inversions and translocations involving the TCRα loci and is associated with clonal proliferating T cells in ataxia telangiectasia and the development of leukemia (52,53). Chromosomal abnormalities involving 14q11-q32 breakpoints have been detected in over 75% of T-prolymphocytic leukemia (T-PLL) (54). TCL1 expression occurs early in normal T- and B-cell differentiation and is restricted to lymphoid cells, but is found at especially high levels in leukemic cells carrying 14q32 rearrangements (52,55). The TCL1 protein shares significant (61%) sequence identity with $p13^{MTCP1}$ and hydropathy plots indicate that their secondary structure in solution is similar (46). It has been proposed that MTCP1 and TCL1 may represent a novel family of molecules regulating cell survival and/or proliferation (46). TCL1 deregulation under the influence of TCRα regulatory sequences may act to facilitate enhanced T-cell proliferation, leading to an accumulation of secondary mutations and ultimate tumor progression (55).

6.1.8. TCL3 (TAN1/NOTCH1)

A leukemogenic rearrangement with NOTCH1 (9q34.3) (a name originally given to its homologue in *Drosophila*) results after a truncated NOTCH1 gene becomes fused to the TCRβ-chain gene. NOTCH1 is a transmembrane receptor protein and a natural NOTCH1 ligand has recently been described in vertebrates (56). Translocation results in the loss of most of its regulatory extracellular domain (57). The intracellular domain, which contains six ankyrin repeats, is constitutively active in the absence of the extracellular portion. This deregulated "on" position could provide the basis of its leukemogenic activity (58). Human NOTCH1 mRNA is present in adults, where it is expressed mainly in lymphoid tissues. During embryogenesis it has a crucial role in regulating development and cellular differentiation, perhaps functioning to arrest cells at certain developmental stages until such time that they can undergo appropriate differentiation programs (56,59–61). NOTCH1 deficiency is an embryonic lethal mutation in mice (62). Three NOTCH1 homologous genes exist in humans, and are located at positions 9q34.3, 1p13-p11, and 19p13.2-p13.1, respectively, with all three regions known as areas subject to neoplasia-related rearrangements (63).

6.1.9. TTG1 (RBTN1)/TTG2 (RBTN2)

The most prevalent translocation in T-ALL involves TCR α/δ/β loci and genes coding for two similar proteins, the T-cell translocation genes 1 and 2, or TTG1 (RBTN1)

and TTG2 (RBTN2). TTG1 and TTG2 share 50% sequence identity and either of their encoded genes is rearranged in 10% of T-ALL patients (64–66). The TTG proteins contain two tandem LIM domains but are unique from other LIM-containing proteins in that they contain no DNA-binding homeodomain. TTG1 and TTG2 can interact with TAL1, TAL2, and LYL1 proteins but not with other bHLH molecules and simultaneous alterations in both TTG2 and TAL1 genes occur in some cases of T-ALL (67). Transgenic mice overexpressing either TTG1 or TTG2 driven by an lck promoter manifest T-ALL-like disease (68), and TTG2 has also been found to be necessary for normal erythroid development in gene-targeted mutant mice (69). TTG1 is a nuclear protein found mainly in the central nervous system and, although detected in the thymus, is not found in individual thymocytes (70–72). TTG2 also has limited expression in T cells but is abundant in human fetal spleen, liver, kidney, bone marrow, pancreas, testes, and brain (73). The breakpoints in the TTG2 t(11;14)(p13;q11) translocation map to a region between 2 and 30 kb upstream of TTG2 on chromosome 11p13. Alternative transcripts initiating from two different promoter sites (P1 and P2), but encoding the same protein, have been detected in fetal tissue. All known chromosomal translocations occur upstream of the proximal promoter P2, which results in the loss of P1 and putative upstream regulatory sequences (74).

6.2. NEOPLASIAS INVOLVING THE B-CELL RECEPTOR

6.2.1. BCL1 (Cyclin D1/PRAD1)

Translocation of the bcl1 locus (11q13) with the Ig heavy chain locus at 14q32 is found in over 30% of centrocytic lymphomas (75,76) and 2–5% of CLL (77). In addition, the BCL1 gene is overexpressed in numerous solid tissue malignancies (78,79), with amplification correlating with proliferative activity (80). Mice expressing a bcl1 transgene from mammary tumor virus promoter develop mammary hyperplasia and adenocarcinoma (81), whereas coexpression of BCL1 and c-MYC in lymphoid cells in double-transgenic mice results in lymphomas (82,83). The three D-type cyclins (D1, D2, D3) control progression through the G_1 phase of the cell cycle, mediating their activity through assembly with cyclin-dependent kinases CDK4 and CDK6, which form holoenzymes and phosphorylate substrates such as retinoblastoma protein (RB) (Figure 6.1) (84). Strikingly, a cyclin-dependent kinase inhibitor, p16, involved in regulating the cyclin D1 pathway, is mutated in a large number of hematological malignancies.

6.2.2. BCL2

The breakpoint region that encompasses the BCL2 (18q21) gene is the most frequent translocation site associated with lymphoid tumors. Translocations of the BCL2 gene are seen in most cases of follicular lymphoma and are frequent in DLCL and CLL (77,85,86). Translocation of BCL2 in these malignancies reportedly occurs early in B-cell transformation, where deregulation and overexpression of BCL2 results from IgH enhancer elements being juxtaposed near the BCL2 locus (87,88). The bcl2 gene is a homologue of the ced9 gene of *C. elegans*, where the protein is involved in preventing cell death by apoptosis (89,90). BCL2 enhances cell survival without affecting proliferation and is needed for normal survival of B and T cells (91). BCL2 transgenic mice show extended follicular

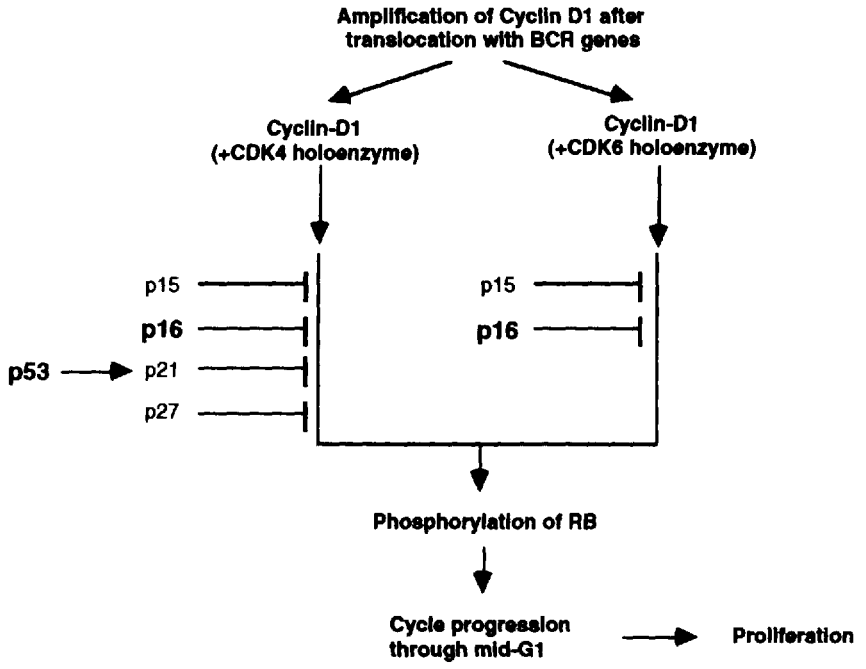

Figure 6.1. Cyclin D1 translocations to Ig loci are found in about one third of centrocytic lymphomas, where the translocated gene is deregulated and overexpressed. Interestingly, in lymphomas where translocations are not apparent, elevated expression of cyclin D1 has been observed (148,149). As schematically illustrated, p16 plays a role along with other cyclin-dependent kinase inhibitors (CDKIs) in regulating activity of cyclin D1 holoenzymes. Adapted for use with permission from W. B. Saunders, Mirama *et al.*, *Blood* **86**:841–854, 1995.

lymphoproliferation (92) whereas transgenic mice expressing BCL2 as a t(14;18) translocation develop high-grade lymphomas (93,94).

6.2.3. BCL3

The BCL3 gene (19q13.1) is involved in recurrent translocations with the Ig heavy chain locus and is associated with B-CLL and other B-cell neoplasias (95). About 10% of cases of CLL demonstrate BCL3 translocations at the IgH locus, which is reported to result in overexpression of BCL3 without alteration of the encoded protein. BCL3 is a member of the IκB family of proteins (96,97), which bind NF-κB transcription factors and keep them as inactive cytoplasmic complexes, blocking their nuclear localization and preventing their transactivation of NF-κB motifs. BCL3 proteins can both inhibit NF-κB translocation into the nucleus and block its DNA binding (98–101). BCL3 contains seven ankyrin repeats, similar to NOTCH1, binds several members of the REL/NF-κB family (96,102), and has intrinsic transactivational ability (103). BCL3 is likely involved in differentiation and cell cycle control (104). It can bind homodimers of the proto-oncogene NF-κB2 (Lyt-10) to generate an active transcription factor complex (103,105).

6.2.4. BCL6 (LAZ3, BCL5)

Rearrangement of the BCL6 gene (3q27) has been found in as many as 20% of patients with non-Hodgkin's lymphoma, and it is also associated with DLCL and follicu-

lar lymphoma (106,107). BCL6 codes for a 79-kDa protein that contains six Cys2-His2 motifs (zinc finger) and shares significant N-terminal homology with transcription factors such as *Drosophila* tramtrack and Broad-complex genes, both of which are developmental regulators (108–110). At least two mRNAs are produced through alternative splicing of the BCL6 gene, which is expressed in most normal tissues, but high levels are found in muscle (111,112). In about 30% of patients with DLCL the BCL6 gene is truncated at its 5′ noncoding region. Translocation may result in the loss of a putative regulatory region and the loss of a transcriptional start site, resulting in overexpression of an aberrant BCL6 transcript (111,113). Consensus sequences for DNA binding of the zinc-finger domain of BCL6 have been determined (108,114). The sequence of the central portion of the consensus site matches binding sequences for NF-κB and interferon regulatory factors, IRF-1 and IFR-2 (108).

6.2.5. BCL7a

The 12q24.1 breakpoint is a common feature of high-grade B-cell non-Hodgkin's lymphomas (B-NHL). Investigation of a translocation t(8;14;12)(q24.1;q32.3;q24.1) involving rearranged Ig heavy chain V_H4DJ_H5 recently resulted in the identification of a new gene BCL7a, encoding a predicted serine-rich protein with homology to the actin-binding protein caldesmon (115). Caldesmon may function to organize microfilaments during mitotic events and is perhaps involved in cell transformation (116,117). Disruption of BCL7a may reveal a new mechanism by which transformation of lymphoid tumors occurs.

6.2.6. Interleukin 3 (IL-3)

Translocations involving the IgH locus and the cytokine gene IL-3 can result in excessive expression of the cytokine that correlates with disease (118). The t(5;14)(q31;q32) translocation, which links the Ig heavy chain joining (J_H) region to the promoter region of the IL-3 gene, placing the IL-3 gene under the control of the Ig heavy chain enhancer, is associated with B-ALL and peripheral blood eosinophilia (118,119). The role of IL-3 in transformation of hematopoietic cells can also involve enhanced expression resulting from deregulation by inserted viral sequences and altered mRNA stability region (see Section 7.1.2). IL-3 also upregulates expression of cell cycle regulators such as the G1 cyclins and cyclin-dependent kinases (CDKs) and induces activation of the proto-oncogene product c-VAV. The multiple effects of IL-3 on hematopoiesis suggest that overexpression of IL-3 may play a role in leukemogenesis.

6.2.7. c-MYC

The translocation between c-myc (8q24) and the Ig heavy chain loci (14q32) was the first genetic alteration of its kind to be identified. Additional translocations involve κ (2p12) and λ (22q11) chain constant regions, which become juxtaposed to c-myc sequences at 8q24 (120). The consequence of these translocations is deregulated expression of high levels of MYC and an association with Burkitt's lymphoma (121,122). Numerous genetically engineered mice have been generated to study the role of c-myc in tumorigenesis. Transgenic mice expressing MYC under the control of an Ig heavy chain enhancer (Eμ-myc mice) develop B-lineage malignancies (123,124), although tumor inci-

dence is significantly reduced when mice coexpress a human μ chain (125); c-MYC and BCL-2 have been shown to operate synergistically to induce tumors in double-transgenic mice (126); and mice expressing a Thy1–myc construct develop thymic tumors involving both thymocytes and epithelial cells (127). c-MYC is among a small family of transcription factors first identified by their identity with virus-encoded transforming genes (128). c-MYC promotes cell cycle progression and inhibits differentiation (34). (See Section 6.1.4.)

6.2.8. NF-κB2 (Lyt-10, p50B)

The NF-κB2p100 gene (10q24) is translocated with the Ig heavy chain locus in a small percentage of patients with B-cell lymphomas, where it is joined to an out-of-frame Ig Cα domain resulting in an NF-κB2 molecule that is constitutively localized in the nucleus (129–132). The NF-κB2p100 gene spans about 8 kb on chromosome 10q24, contains 24 exons (130), and is transcribed as a 3.2-kb mRNA that produces a 100-kDa protein product, which contains an N-terminal DNA-binding REL domain, a poly(G) hinge, and an ankyrin domain at its C-terminus (132,133). The immature 100-kDa cytoplasmic molecule is cleaved at its hinge region, splitting ankyrin and REL domains (134). NF-κB2p100 rearranged with the Ig locus still undergoes this processing. NF-κB2p50 has no intrinsic transcriptional activation, and transactivates genes only through dimerizing with Rel-Ap65; it can thus block transcription as a homodimer, by binding to κB DNA motifs located in enhancers and promoters and thereby preventing their use by other transcription factors (133,135). NF-κB2 homodimers can also interact with the proto-oncogene BCL-3 to produce a transcriptionally active complex—which may be important in tumorigenesis (see Section 6.2.3). NF-κB is inducible in T cells and regulates the expression of numerous immune response genes, such as MHC class I, IL-2, IL-6, IL-8, GM-CSF, IFNβ, Igκ, and TCRβ genes (136–138). The NF-κB2/RelA heterodimer can also regulate the inducible expression of HIV proteins (139). NF-κB2 promoter regions are regulated by NF-κB factors (140).

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7

Cytokines of the Immune Response

The elaboration of an immune response to infection or tissue damage is orchestrated by a myriad of different cells and cell types, the activities of which must be under precise temporal and spatial control. On a cellular basis, this requires an efficient means of self-regulating activation programs and of communicating activities between cells. The soluble mediators of this cellular information network are the cytokines.

Cytokines are low-molecular-weight proteins (<80 kDa). Basal levels of cytokine expression are typically very low, and under transient and specific upregulation in response to certain stimuli. Although the actions of cytokines are local, exerting autocrine and paracrine effects, they are also extremely potent, and are active in picomolar concentrations with high affinity for their specific receptors. Each cytokine induces multiple activities on target cells *in vivo*, and many cytokines appear to have redundant or overlapping functions. The particular outcome of cytokine action on a target cell is highly dependent on the milieu, history of the target cell, concentration of the cytokine, and other contexts in which they operate. In addition, different portions of the cytokine molecules can be responsible for effecting specific biological outcomes, as dramatically demonstrated for MCP-1 (1).

The central role of cytokines in the immune system has resulted in their exploitation by clinicians and infectious agents alike. Because of their ability to modulate cytotoxic and antigen-specific responses, various cytokine genes have been investigated for anti-tumor activity. Transfection into tumor cells has revealed a broad tumor-inhibiting effect for a range of tumors and cytokines (Table 7.1). It is nothing less than remarkable how viruses (and other intracellular parasites) have "learned" to manipulate the enormously complex vertebrate immune system. In what must be a long evolutionary coexistence between viruses and their hosts, viruses have incorporated cytokine genes or homologues with immunoregulatory functions that might best subvert the immune system according to their individual replication strategies (Table 7.2).

There were several possibilities for organizing this chapter. Most commonly, a discussion on cytokines proceeds alphabetically, according to the name of the cytokine, or numerically, according to the designation IL-1, IL-2, IL-3, and so on. Another strategy is to present the cytokines according to their major biological roles, for example, to categorize them according to whether they are pro- or anti-inflammatory, or whether they direct Th1 versus Th2-type immune responses (Figure 7.1). But the pleiotropic activity of

Table 7.1
Antitumor Effects of Cytokines[a]

Cytokine gene expressed	Tumor cell	Growth inhibition (syngeneic mice)	Effector cells involved
	IL-1		
mIL-1α	Transformed NIH-3T3	Yes	—
	IL-2		
mIL-2	Colon carcinoma	Yes	$CD8^+$
mIL-2	Melanoma	Yes	—
hIL-2	Fibrosarcom	Yes	CTL
mIL-2	Mastocytoma	Yes	CTL
hIL-2	Rat sarcoma	Yes	most $CD8^+$
mIL-2	Mammary adenocarcinoma	Weak	—
mIL-2	Mammary adenocarcinoma	Yes	$CD8^+$, N^b
hIL-2	Fibrosarcoma	Yes	$CD8^+$, NK
hIL-2	Bladder carcinoma	Yes	CTL
hIL-2	Lung carcinoma	Yes	CTL
	IL-4		
mIL-4	Plasmocytoma	Yes	E, M
mIL-4	Mammary adenocarcinoma	Yes	—
mIL-4	Renal cell carcinoma	Yes	T, E
mIL-4	Hamster ovary	Yes (nude mice)	M
	IL-5		
mIL-5	Plasmocytoma	No	E
	IL-6		
hIL-6	Melanoma	Yes	M, N
hIL-6	Lung carcinoma	Yes	CTL
mIL-6	Sarcoma	Yes	T
	IL-7		
mIL-7	Plasmocytoma	Yes	$CD4^+$, M
mIL-7	Mammary adenocarcinoma	Yes	$CD4^+$
mIL-7	Fibrosarcoma	Yes	T, E
	IFNs		
mIFNα	Friend leukemia	Yes	—
mIFNγ	Neuroblastoma	Yes	$CD8^+$
mIFNγ	Fibrosarcoma	Yes	CTL
mIFNγ	Adenocarcinoma	Yes	CTL
mIFNγ	Colon carcinoma	Yes	CTL
mIFNγ	Lung carcinoma	Yes	CTL
mIFNγ	Bladder carcinoma	Yes	CTL
mIFNγ	Mammary adenocarcinoma	Weak	M

Table 7.1
(Continued)

Cytokine gene expressed	Tumor cell	Growth inhibition (syngeneic mice)	Tumor reactive cells
		TNFα	
hTNF-α	Skin tumor	Yes (nude mice)	—
mTNF-α	Plasmocytoma	Yes	M
hTNF-α	Sarcoma	Yes	$CD4^+$, $CD8^+$
hTNF-α	Sarcoma	No	—

[a]Table used with permission, Colombo, M. P., and Forni, G., 1994. Cytokine gene transfer in tumor inhibition and tumor therapy: Where are we now? *Immunol. Today* **15**:48–51.
[b]Key: N, neutrophils; E, eosinophils; M, macrophages; T, T cells; CTL, cytotoxic T lymphocyte.

cytokines necessarily limits the logic of any such categorization. Yet another possibility is to group the cytokines according to their structural relationships. In grouping the cytokines this way, a structure–function relationship has emerged that is intriguing, informative, and practical, in the sense that it makes remembering their various roles and interrelationships a little simpler, and thus this is how the cytokines will be presented below (Table 7.3). More than 60 cytokines have been characterized to date. Only those considered directly involved as immune response genes are discussed. For a more complete list of cytokines see Nicola (2).

7.1. SHORT-CHAIN HELICAL BUNDLE

7.1.1. Interleukin 2

Human IL-2 is a 15.5-kDa glycoprotein with a primary sequence of 133 amino acids and a single intrachain disulfide bond, encoded on chromosome 4q26. The IL-2 protein is organized into a largely hydrophobic series of five α-helical domains and two short β-strands, although the exact tertiary structure remains under investigation (3,4). Correct secondary and tertiary structure of IL-2 appears crucial to its function and depends on amino acids Leu17, Trp121 and the disulfide link between Cys58 and Cys140 (5,6). Murine IL-2 is very similar to human IL-2 (7,8), although the murine gene contains unique CAG repeats that encode 12 N-terminal glutamine residues, which may be important in receptor interactions (9). IL-2 is predominantly secreted by activated T-helper ($CD4^+$) cells (10–13). However, IL-2 expression has also been reported in eosinophils (14), stimulated murine splenic B cells and B-cell lines, B-cell lymphomas, and virus-transformed B cells (15,16). IL-2 expression in lymphocytes may in part be regulated by the CD45 isoforms (17). Optimal activation of the IL-2 gene in lymphocytes requires both

Table 7.2
Viral Manipulation of Immune Response Using Cytokine Homologues[a]

Virus	Viral gene product	Function of viral product
Adenovirus	VA RNA	Blocks IFN
	E3-gp19K	Binds Class I molecules
	E1A	Increases sensitivity to TNF
	E3-14, 7K	Blocks TNF
	E3-10.4K/14.5K	Blocks TNF
	E1B-19K	Blocks TNF
Hepatitis B	PreS2	Sequesters IL-6
Herpes Virus		
EBV	BCRF1(IL-10 homolog)	Immunoregulatory
	EBER RNA	Blocks IFN
Cytomegalovirus	UL18	Binds β2 microglobulin
	US28	RANTES receptor homologue
HSV I/II	gC-1	Binds C3b
	gE-gI	Binds Fc and blocks C′
	ORF4	Blocks C′
	IL-10 homologue	Blocks synthesis
Herpes saimiri	ecrf3	Binds IL-8
	CCPH1	Binds C4a
Pox Virus		
Cowpox	crmA	Blocks activation IL-1β
Myxoma	M-T7	Binds IFN-γ
Shope fibroma/myxoma	T2	Binds TNF
Swinepox	ecrf3	Binds IL-8
	K3L	Homologue of eIF2α
	C61	Binds IFN-γ
	K2R	Binds IL-8
Vaccinia	VCP	Binds C4b
	B15R	Blocks IL-1β
	B5R	C′ homologue
	E3L	Blocks IFN
Vaccinia/cowpox	crmA	Blocks activation IL-1β & apoptosis
Reovirus	δ3	Blocks IFN
Retrovirus		
FeLv, MuLv & HTLV	p15E	Inhibits PKC transduction

[a]See text for more details. Table adapted for use with permission from AlphaMed Press, Evans, C. H. 1996. Cytokines and viral anti-immune genes. *Stem Cells* **14**:177–184.

signals from the antigen receptor and secondary, costimulatory signals (18–20), which involves the induction of CREB (21) and the enhancement of IL-2 mRNA stability (22). IL-2 promotes growth proliferation, and differentiation of respective effector functions in T and B lymphocytes (10–13). IL-2 costimulation of $CD4^+$ T cells is important in their differentiation of IL-4 and IFNγ secreting function (23–25). Suboptimal IL-2 production during activation may be responsible for T-cell unresponsiveness or anergy (26–28). Regulation of IL-2 production during anergy induction may predominately reflect a trans-

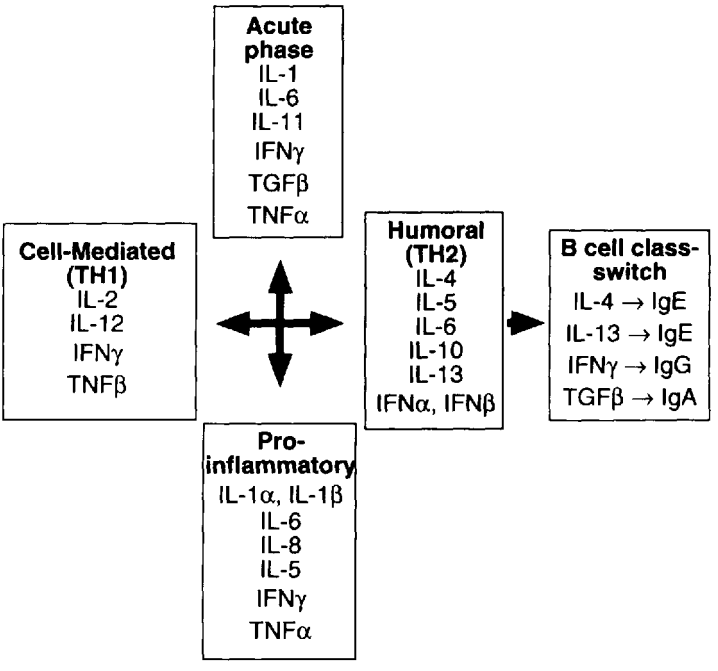

Figure 7.1. Despite their pleiotropic and often overlapping effects, cytokines can be broadly grouped according to their respective major biological roles.

Table 7.3
Cytokine Structure–Function Relationship

Structure	Cytokine	Target cells	Strategic function
Short Chain 4 α-helix	IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-13, IFNγ	Lymphocytes, macrophages, leukocytes, mast cells	Antigen-specific immune responses, immunoregulation, hematopoiesis
Long Chain 4 α-helix	IL-6, IL-10, IL-11, IL-12, IFNα, IFNβ	Organ systems, i.e., liver, muscle nerves, macrophages, neutrophils, T cells	Innate immunity, immunoregulation, hematopoiesis
β-Trefoil	IL-1α, IL-1β	Most cells, hepatocytes	Acute phase responses
β-Jelly roll	TNFα, TNFβ	Leukocytes, T cells	Immunoregulation, inflammation, growth inhibition
Cystine knot	TGF-β	Leukocytes, fibroblasts	Downregulation of immune response, immunosuppression, collagen synthesis
α-Chemokines (C-X-C)	IL-8	Leukocytes	Chemotaxis, inflammation
Others	IL-14, IL-16, IL-17, IL-18	Leukocytes	Immunoregulation, hematopoiesis

lational block (29). Inhibition of IL-2 synthesis in proliferating T cells may also reflect downregulation through CTLA-4 signaling (30).

In addition to its effects on T and B cells, IL-2 facilitates the differentiation of cytotoxic responses from NK cells (31–33) and monocytes (34). Mice rendered deficient for IL-2 expression show normal clonal expansion of T cells but exhibit impaired FAS-mediated cell death (35). IL-2-deficient mice develop $CD4^+$ T-cell-dependent autoimmune disease including hemolytic anemia and chronic inflammatory bowel disease (36–38). IL-2 deficiency has been suggested to disengage the apoptotic pathway in activated T cells, thereby leading to an accumulation of "experienced" T cells and susceptibility to chronic activation and inflammation (35,39). Nonetheless, mice deficient for IL-2 have a remarkably normal thymus and responses to viral and other infections (40,41); such findings appear to contradict earlier thinking that IL-2 was critical for cycle progression and differentiation of lymphocytes. IL-2 has been investigated thoroughly for antitumor activities. Recent success has been achieved in tumor eradication using specific IL-2-delivery systems to the tumor site (42,43).

Receptor. There are three IL-2 receptor chains: α, β, and γ. IL-2Rβ and γ are constitutively expressed on most mature lymphocytes (44–46) whereas the α chain is normally absent but is upregulated after activation (47–49). The IL-2Rβ and γ chains form a functional low-affinity receptor (50,51); addition of the α chain results in high binding affinity for IL-2 (Table 7.4). IL-2 binding of the IL-2R signaling complex results in internalization and induction of various activation programs. Both α and β chains of the IL-2R are required for immunoregulation of T and B lymphocytes, as mice with gene-targeted deletions at either locus have hyperactive lymphoid compartments with severe autoimmunity (52,53). The α chain is expressed in the absence of either β or γ chains early during development of T cells in the thymus (54,55) and B cells in the bone marrow (56,57). However, IL-2Rα-deficient mice have a phenotypically normal thymus (53) and overtly normal B-cell development; its function, if any, in lymphocyte development remains obscure. IL-2Rβ is part of an IL-15 receptor, and both the IL-2 and IL-15 receptor complex exert a number of overlapping biological effects (58), such as the rapid induction of STAT and JAK kinases (59–63). The IL-2Rγ chain is an important component of the cytokine receptors for IL-4, IL-7, IL-9, and IL-15 (Figure 7.2, Table 7.5), and mutations in the γ chain result in an X-linked severe combined immunodeficiency (XSCID) in humans. Gene targeting of the γ-chain gene mimics the XSCID defect in mice (64,65).

7.1.2. Interleukin 3

IL-3 is located 9 kb from the granulocyte-macrophage colony-stimulating factor (GM-CSF) on chromosome 5q21-31 in humans (Figure 7.3) (66). The IL-3 gene shares 29% similarity between mice and humans, and the promoter region is 59% identical (67). At different times IL-3 was described as various entities including multilineage colony-stimulating factor (multi-CSF), mast cell growth factor, WEHI-3 growth factor, P-cell stimulating factor, and burst-promoting activity factor, reflecting its various roles in supporting growth and/or differentiation of multipotential bone marrow and committed progenitor cells (68,69). IL-3 expression is restricted to T cells where it is upregulated after activation through the antigen receptor (70–73). The cytokine supports growth and differentiation of early hematological progenitors (74,75) and of committed cells of myeloid lineages, including megakaryocytes (76,77) and mast cells (78) (Figure 7.4). IL-3 does not play an entirely unique role in these growth-promoting functions (79,80), al-

Table 7.4
Effect of IL-2R Subunit Composition on Binding Affinity and Receptor Signaling

Subunits	IL-2 binding (K_d) affinity (M)	Receptor signaling
α	10^{-8}	No
β	10^{-7}	No
γ	None	No
αβ	10^{-10}	No
αγ	10^{-8}	No
βγ	10^{-9}	Yes
αβγ	10^{-11}	Yes

though it may be unique in its ability to induce the differentiation of mast cell subsets (81,82) [a committed mast cell precursor has recently been identified (83)]. IL-3 pretreatment potentiates the effects of G-CSF to induce elevated numbers of peripheral blood progenitor cells (PBPC) (84), whereas IL-1, IL-6, G-CSF, SCF, IFNγ, and TNFα enhance IL-3-dependent colony formation. IL-3 regulates the 5-lipoxygenase/leukotriene C-4 synthase pathway in mast cells and monocytes (85,86). IL-3 enhances IgE responses in a mast cell-independent way (87), and binding of IgE to its high-affinity Fc receptors on mast cells also induces IL-3 expression (88). Interestingly, IL-3 seems to play a critical role in fighting some kinds of parasitic infections (89) where host protection may involve IgE-mediated responses.

IL-3 may influence Th2-type development via its effects on IL-10 production (90) and may exert a negative regulatory effect on T cells through inhibition of T-cell-lineage development (91). cAMP signaling pathways, induced by activation with mitogen, downregulate IL-3 production in human T cells (92). Impaired humoral immunity in Rel-deficient mice has been attributed in part to its role in the induction of IL-3 and GM-CSF in T lymphocytes (93). IL-3 upregulates endothelial adhesion molecules (94) and enhances antigen presentation of tumor antigens, promoting tumor-specific CTL responses (95).

Transgenic mice expressing IL-3 in astrocytes develop demyelinating neurological disease, associated with activated foamy macrophage/microglial cells, which may mimic diseases such as multiple sclerosis and HIV leukoencephalopathy (96). Deregulated expression of IL-3 in hematopoietic cells can result from translocations involving B-cell receptor genes (see Section 6.2), or as a consequence of the proximal insertion of viral sequences that upregulate transcription and enhance stability of IL-3 mRNA (97,98), which can result in malignant transformation.This may reflect the potential of IL-3 to induce cell cycle regulators, such as G_1 cyclins and cyclin-dependent kinases (CDKs) (99). IL-3 also activates the proto-oncogene product c-VAV (100). It can also upregulate Bcl-2 expression, which may help explain its ability to block apoptosis in some murine cell lines (101).

Receptor. Both humans and mice possess the β chain (β_c) in receptors for GM-CSF, IL-5, and IL-3; in addition, mice express an alternate but redundant IL-3R-specific β chain (β_{IL-3}) (102–104). β_c does not bind IL-3. However, murine β_{IL-3} has significant independent affinity for the cytokine (103). β_c is upregulated in response to IL-1, TNFα, and

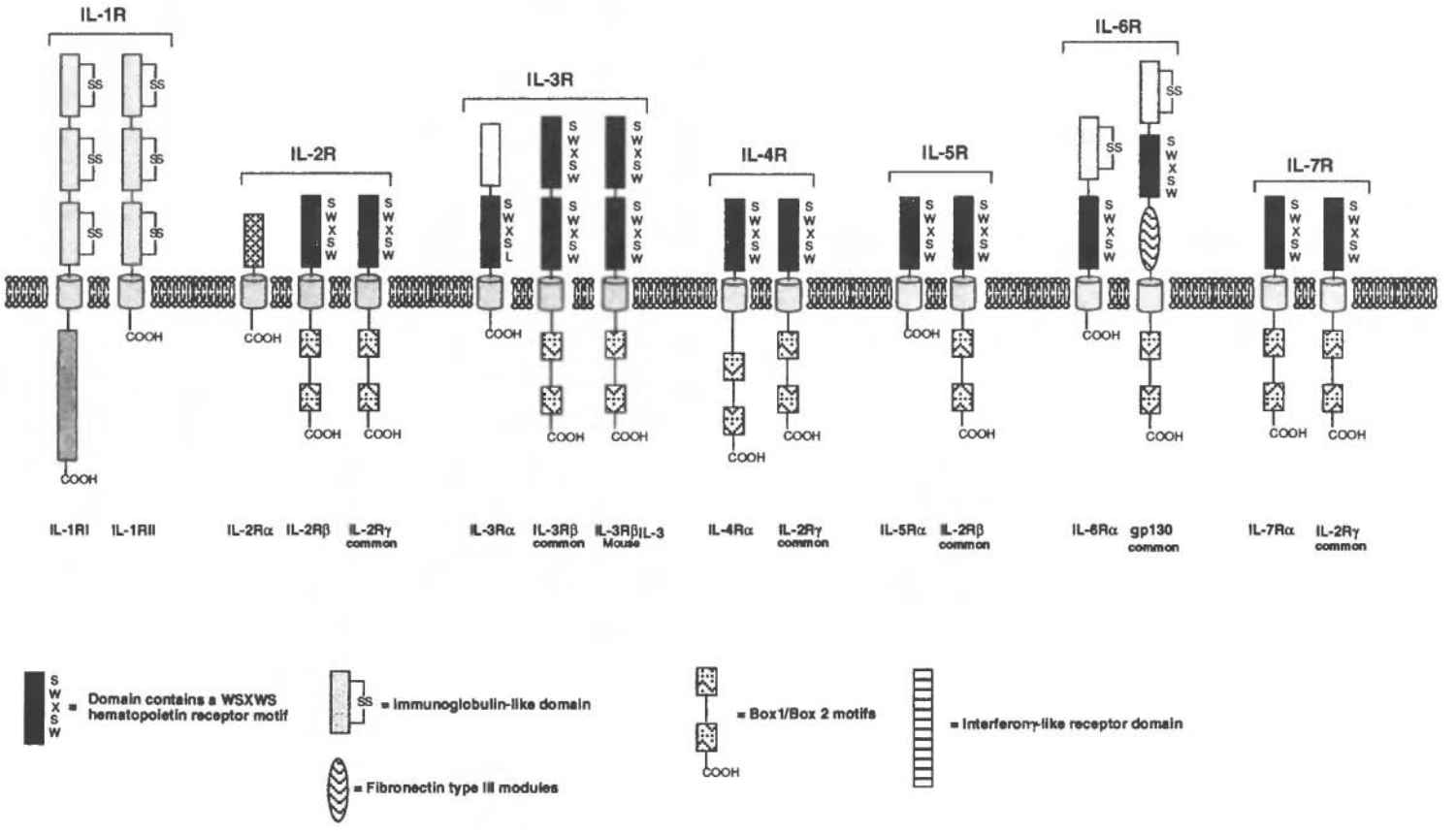

Figure 7.2. Many cytokines possess common receptor chains. The receptor subunits are schematically represented for the various cytokines discussed. The individual receptors are not drawn to scale.

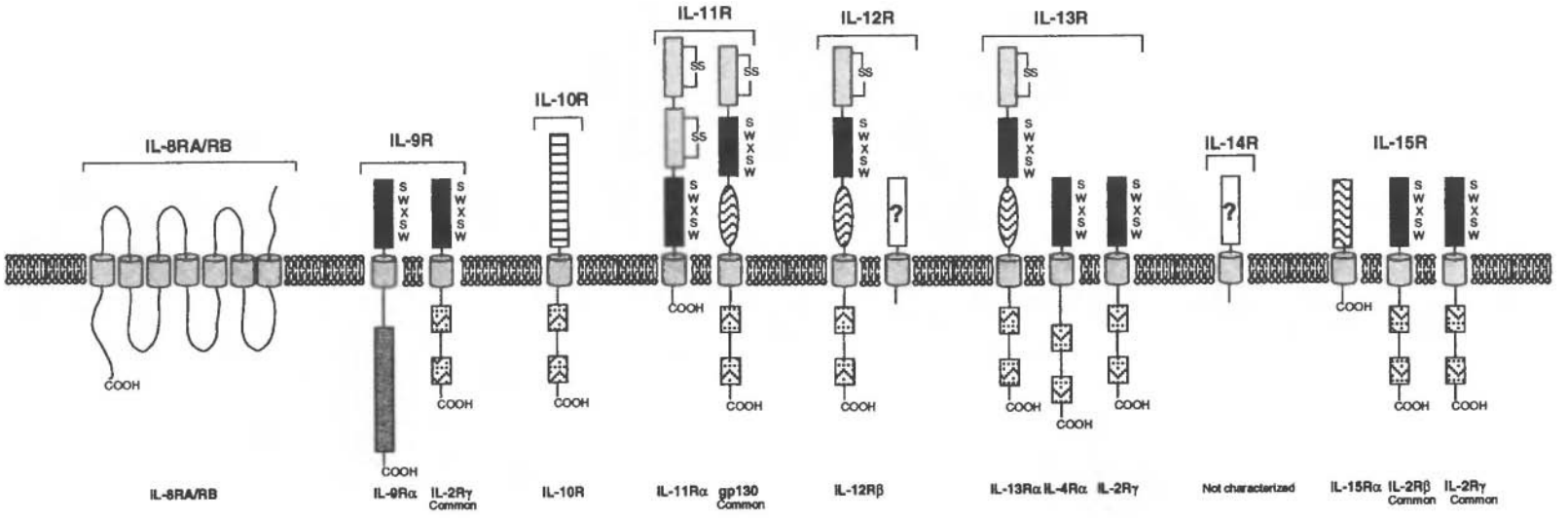

Figure 7.2. (*Continued*).

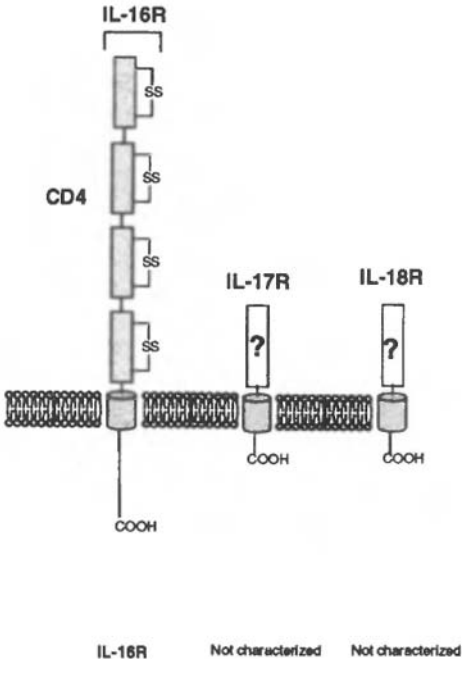

Figure 7.2. (*Continued*).

IFNγ (105), and GM-CSF induces IL-3R on neutrophils (106). With B_c being common for the different cytokines, it may be that the α chain is the critical receptor component that facilitates cytokine-specific signals (107–109). The α subunit independently exhibits low-affinity IL-3 binding capacity in both mice and humans (103,110,111). Residues at the N-terminus of the α chain are critical for binding IL-3 (112) and saturation mutagenesis of IL-3 suggests that only a few key residues are important in its receptor-binding activity (113). There is low-level IL-3R α expression on a subset of peripheral B cells (114) and on monocytes (115). Human IL-3 induces heterodimerization of α and β_c, which involves formation of a disulfide bond between the two chains (116). Expression patterns for IL-3R in mice and humans are similar, with the αβ heterodimer found on early hematopoietic progenitor cells and most myeloid lineages and on a proportion of B cells (104,108). T

Table 7.5
Interleukins that Possess Common β and γ Chains

Cytokine	Receptor subunits		
IL-2	α_{IL-2}	β_c	γ_c
IL-4	α_{IL-4}		γ_c
IL-7	α_{IL-7}		γ_c
IL-9	α_{IL-9}		γ_c
IL-15	α_{IL-15}	β_c	γ_c

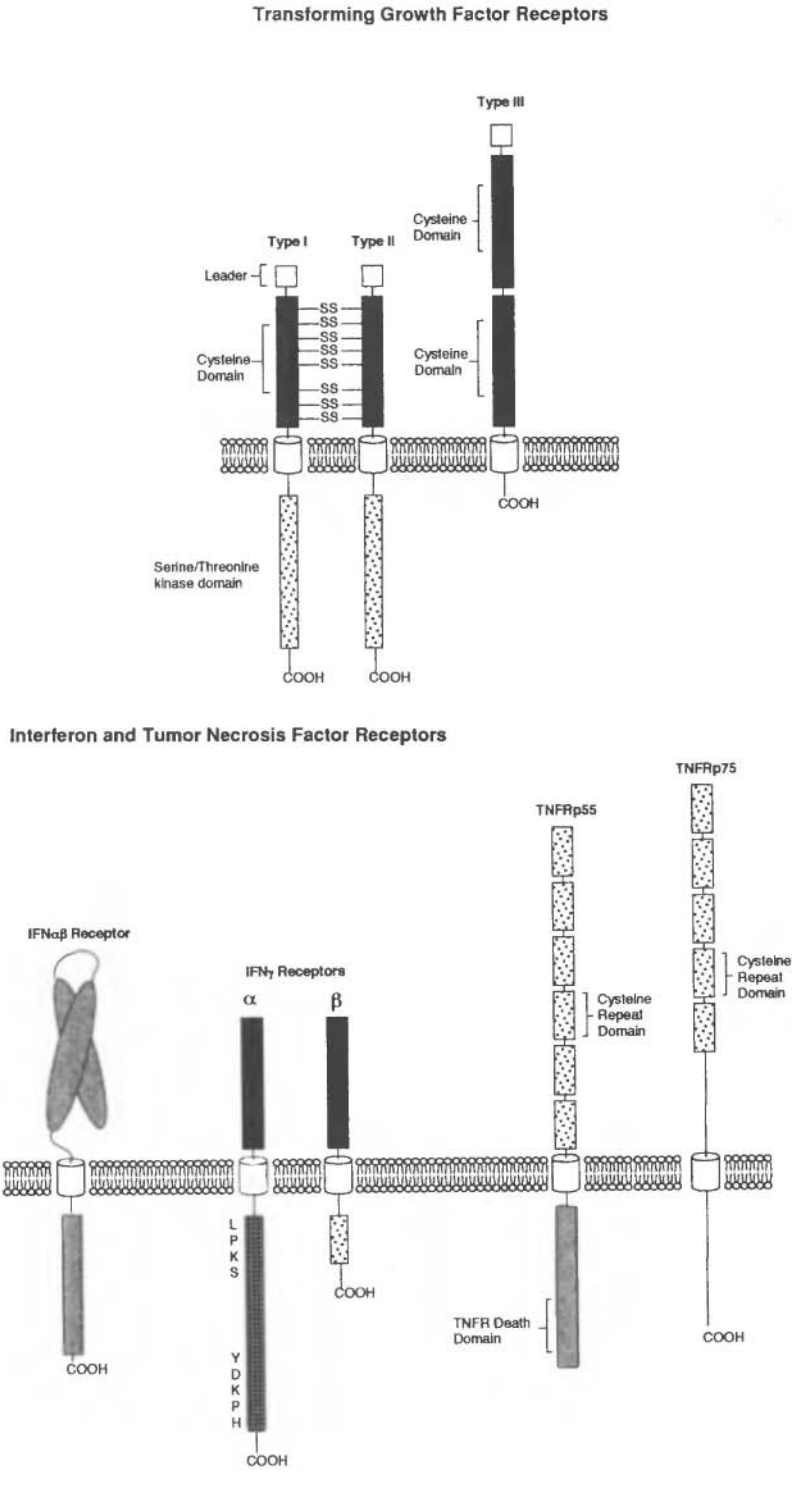

Figure 7.2. (*Continued*).

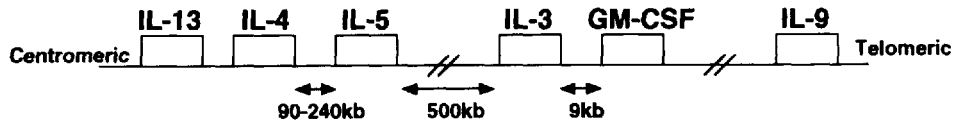

Figure 7.3. The short-chain α-helical cytokines have common biological and structural features. Some of the genes for this structural category of cytokines are also clustered together on human chromosome 5q21-31.

cells do not normally express IL-3R. Overexpression of IL-3R in cell lines can result in factor-independent growth, suggesting a possible role for deregulated IL-3R expression in malignant transformation (117).

IL-3 stimulation results in phosphorylation of the murine β chain at tyrosine and serine/threonine residues, the latter perhaps reflecting activity of a newly identified receptor-associated serine/threonine kinase (118). LYN, SYK, and JAK2 associate with a membrane-proximal region of β_c (119,120). In addition to SRC-related protein tyrosine kinases, MAP kinase and STAT DNA-binding proteins are activated after IL-3R signaling (121–124). RAS-dependent pathways (i.e., Raf/MAPK/Fos pathway) have been reported to be dispensable for IL-3-induced growth stimulation in the BAF3 cell line (125). Otherwise, MAP appears to be a central component of the IL-3R signaling pathway (124).

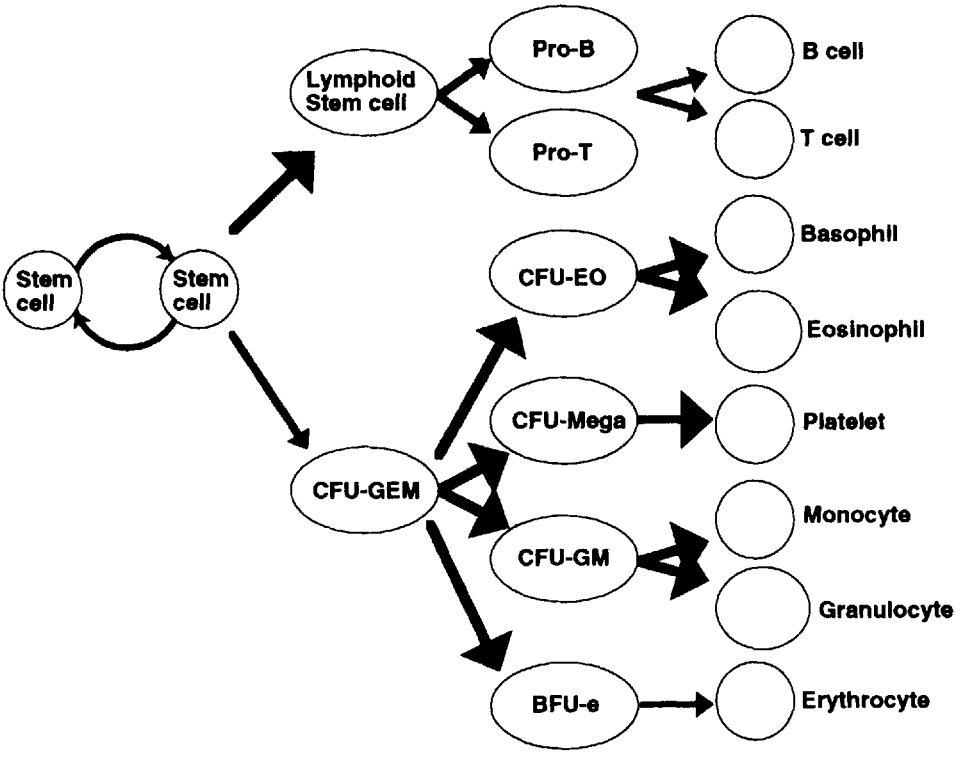

Figure 7.4. IL-3 induces cell growth and differentiation at various points of hematopoiesis. Large arrows indicate the stages where IL-3 has potent effects in supporting growth and differentiation.

7.1.3. Interleukin 4

IL-4 was originally dubbed B-cell growth factor (BCGF) identifying its role in B-cell growth and development. IL-4 is produced predominately by Th2 $CD4^+$ T-cell subsets (126,127), but is also expressed by mast cells and basophils (128–130), and $CD8^+$ T cells *in vitro* (131). A $CD4^-CD8^-TCR\alpha\beta^+NK1.1^+$ T-cell population has also been found to secrete IL-4 (132). CD40L cross-linking on human $CD4^+$ cells induces upregulation of IL-4 synthesis (133) as does costimulation through CTLA-4 (134), whereas IFNγ and IL-12 downregulate IL-4 production (135,136). An alternatively spliced form of IL-4 (IL-4δ2) has recently been identified that antagonizes IL-4-augmented T-cell proliferation (137). IL-4 is a prototypical pleiotropic cytokine. It induces the upregulation of class II molecules and CD23 on B cells (138,139), drives B-cell class switching from IgM to isotypes such as IgA, IgE, and IgG, and induces B cells *in vitro* to switch to IgG1 and IgE production while inhibiting the synthesis of IgG2a, IgG2b, and IgG3 (140–144). IL-4 supports the development of $CD4^+$ T cells *in vitro* and *in vivo* (126,145–148), directs a Th2-type phenotype (149–154), and plays a critical role in directing immune responses to infection (155–157) (Figure 7.5). The elaboration of a Th2 phenotype and the secretion of IL-4 by T cells may reflect antigen dose and strength of the signals received through the TCR (158,159). IL-4 modulates differentiation of $CD8^+$ effector T cells and stimulates specific cytokine secretion in $CD8^+$ T cells (131,154,160–163). In IL-4-deficient mice, IgG1 and IgE responses are delayed or diminished after infection with parasitic organisms (153,156,157,164). Conversely, treatment with IL-4 can enhance resistance to infections (165) or can exacerbate those dependent on Th1-type immunity (166–169). The role of IL-4 in IgE synthesis also suggests its involvement in allergic-type responses (170–172). IL-4-dependent mechanisms may play an important role in the regress or perpetuation of inflammatory infiltrate in autoimmune lesions (173–175). IL-4 has recently been found to support the differentiation of dendritic cells from monocytes (176).

Receptor. The IL-4 receptor is a heterodimer composed of an IL-4 specific 140-kDa α chain (177–179) and a common γ chain (180,181). In different cell types, the IL-4R may incorporate an IL-13R subunit (182–184). Growth regulation and gene expression are controlled by distinct regions of the hIL-4Rα chain (185). IL-4Rα is a member of the hematopoietin superfamily of receptors, characterized by a WS X WS motif in its membrane-proximal extracellular domain which facilitates ligand interactions (178,186). As with other hematopoietin receptors, IL-4R does not have intrinsic kinase activity although it induces tyrosine phosphorylation on ligand binding. This includes phosphorylation

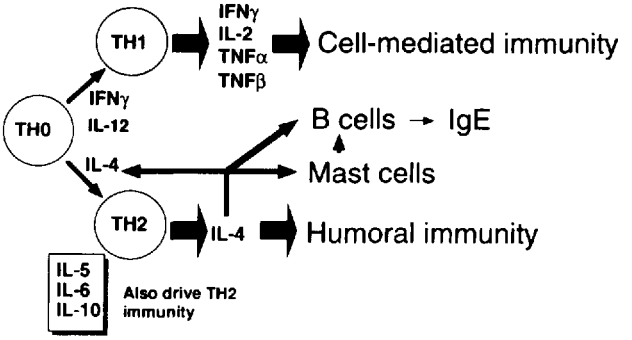

Figure 7.5. IL-4 supports humoral immune responses by regulating Th2 development and B-cell growth and differentiation. IL-4 secreted by Th2 cells acts as a positive feedback to support Th0 → Th2 differentiation.

of STAT6 (187–189) and activation of Janus kinases JAK1 and JAK3 (190–192). In STAT6-deficient mice, the transcription factor is required for IL-4 responsiveness and for the differentiation of Th2-type responses (193,194). B cells deficient for the γ chain also have impaired IL-4 responses (195). IL-4R stimulation results in phosphorylation of receptor-associated 70- and 140-kDa proteins, one of which is the insulin receptor substrate (IRS) 4PS (196,197). IRS is necessary for normal IL-4-mediated mitogenic signals in cell lines (196,198). Interestingly, IL-2R can be endowed with IL-4R function by introducing tyrosine-containing sequences found in the IL-4Rα chain (199).

7.1.4. Interleukin 5

Unlike the other short-chain helical bundle cytokines, IL-5 normally functions only as a homodimer, despite the fact that protein engineering has been used to generate a biologically active monomer (200,201). Similar to IL-4, IL-5 is secreted by activated $CD4^+$ T cells (202) and mast cells (128,203,204). IL-5 is also produced by eosinophils (205,206), for which it promotes survival, differentiation, chemotaxis (207–211), and degranulation (212,213). With its potent effects on eosinophil hemostasis, it is not surprising that transgenic mice expressing IL-5 from CD2 or metallothionein promoters have eosinophilia (214,215). These mice also exhibit elevated levels of IgA, IgE and contain IgM autoantibodies. IL-5 also acts on basophils to promote histamine release (216); it upregulates IL-2R on B cells (217,218) and supports the growth and differentiation of Ig-secreting B cells (219–221). IL-5 has been reported to enhance the growth and differentiation of cytotoxic T cells (222,223). The importance of IL-5 in regulating eosinophil activity has suggested a role for the cytokine in protecting against selective parasitic infections (224–231). At the same time, IL-5 has been implicated in hypersensitivity reactions such as asthma (232–236), although a recent report suggests otherwise (237). Finally, IL-5 may be an important mediator of microglial proliferation in response to inflammation (238).

Receptor. The IL-5 receptor is a heterodimer composed of an IL-5-specific α chain and a shared β, subunit, which is found in receptors for IL-3 and GM-CSF. The IL-5 specific α chain independently binds IL-5 but has no capacity to transduce signals (109,239–241). On the other hand, the α chain appears to confer signaling specificity to the IL-5R complex (242). IL-5R is expressed on human basophils and eosinophils (243,244). CD38 ligation on B cells also upregulates α-chain surface expression (245). Stimulation of the IL-5R results in tyrosine phosphorylation of multiple substrates and activation of RAS, MAP, ERK, LYN, FYN, STAT1α, and JAK2 (246–253). Recently, IL-5R signaling has been shown to include STAT3 and to involve the C-terminal portions of both α and β subunits (254). Soluble IL-5Rα isoforms are expressed from eosinophils. These isoforms may function to antagonize IL-5 activity (255,256). The structural requirements for IL-5 receptor–ligand interaction have been studied in detail (236,257,260).

7.1.5. Interleukin 9

The IL-9 gene is located on human chromosome 5q within a cluster of genes including the growth factors IL-3, IL-4, IL-5, IL-13, and GM-CSF. IL-9 activity was initially detected in supernatant from mouse $CD4^+$ T cells stimulated with concanavalin A, where it was found to support antigen-independent T-cell proliferation of certain $CD4^+$ clones (261). IL-9 does not appear to act on most T cells (262) and may be a more potent

stimulator of thymocytes during fetal development (263). However, IL-9 upregulates the synthesis of the T-cell proteases granzymes A and B and the α chain of the high-affinity receptor for IgE (264). IL-9 is in fact expressed from T-cell subsets, where it appears to be under autocrine regulation by IL-2, IL-4, and IL-10 (265). IL-9 synergizes with IL-4 to enhance the synthesis of IgE and IgG1 in murine and human B cells (266). It has also been found to support the proliferation of murine and human erythroid progenitor cells (267–271). IL-9 was also known as mast cell growth-enhancing activity (MEA), which described its effect on bone marrow-derived mast cells, where it induces proliferation and gene transcription (272–275). IL-9 is not expressed until day 5–7 of infection with *Leishmania major*, is elevated in susceptible strains of mice, and is not detected when mice are depleted of $CD4^+$ T cells (276). In infections with nematode parasite, IL-9 is associated with a protective Th2-type immune response in resistant BALB/K mouse strains (277).

IL-9 appears to play a role in tumor growth (275). T cells transformed with human T-cell leukemia virus type I (HTLV-1), a retrovirus that causes leukemia in humans, show constitutive expression of IL-9 (278). In myeloid leukemic cells, IL-9 induces cells to enter into S phase and proliferate (279), whereas in thymic lymphomas IL-9 is reported to enhance tumor growth, a mechanism that may include the prevention of apoptosis (280,281). Hodgkin's and Reed–Sternberg (H&RS) cell lines have been found to constitutively express IL-9 and to proliferate in response to the cytokine (282,283). About 7% of IL-9 transgenic mice develop thymic lymphomas by 3–9 months of age (284).

Receptor. The IL-9 receptor contains the WSXWS motif and lacks intrinsic kinase activity as do other hematopoietic receptors. It associates with the common γ chain of the IL-2R to form a signaling complex. Human and murine receptors share about 53% identity in primary amino acid sequence of the IL-9R (285). Gene transcripts are alternatively spliced and generate a soluble receptor. A single cytoplasmic tyrosine residue at position 116 is required for IL-9R signaling, including IL-9-induced receptor phosphorylation and STAT activation (286). JAK1 constitutively associates with IL-9R and STAT1 and STAT3 associate on activation (286,287). In contrast to most other hematopoietic cytokines other than IL-4, IL-9-induced signaling also results in tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1) (287). JAK3 deficiency, which has similar manifestations as X-linked SCID defect, may be caused in part by signaling defects of the common γ present in the IL-9 receptor complex.

7.1.6. Interleukin 13

Murine and human IL-13 genes are located within a cluster of genes including IL-3, IL-4, IL-5, and GM-CSF, located on chromosomes 11 and 5q31, respectively (288). IL-13 was recently isolated from a subtracted cDNA library generated from peripheral blood mononuclear cells (PBMC) that had been stimulated with anti-CD28 antibody (289). Because CD28 is a costimulating receptor on T cells, IL-13 was thus discovered as a secretory product of activated T cells (289,290). Activated mast cells also produce IL-13 (291) and more recently it has been found that most basophils secrete the cytokine after stimulation with anti-FcεRIα antibodies or IL-3 (292). Initial findings showed that IL-13 inhibited cytokine production by stimulated PBMC (289,293), upregulated class II molecules and CD23 (low-affinity FcεRII) (290), and stimulated proliferation of activated B cells to upregulate class II, CD23, and IgE synthesis (290,294,295). Using fetal B cells, IL-13 induced isotype switching, proliferation, and Ig synthesis (296). IL-13 has been

shown to inhibit cytokine production (297) and ADCC in macrophages without blocking phagocytosis (290,297). IL-13 can also upregulate vascular cell adhesion molecule-1 expression on endothelial cells (298).

Mice given oral dosages of immunogenic *E. coli* heat-labile enterotoxin revealed significant reductions in humoral systemic and intestinal immune responses when previously treated with anti-IL-13 antibodies (299). Administration of IL-13 to mice using a transplanted cell line expressing recombinant IL-13 resulted in enlarged spleens with conspicuous presence of erythroblasts and megakaryocytes (300). Although CFU-E and CFU-C were elevated in spleens and mice had monocytosis, suggestive of elevated extramedullary hematopoiesis, mice were also anemic. Another report has found IL-13 to simulate megakaryocyte colony formation and to inhibit granulocyte-macrophage and erythroid progenitors (301). IL-13 can protect leukemic cells from apoptosis, raising the possibility of a pathogenic role in supporting tumor growth (302). On the other hand, IL-13 has been shown to suppress growth of breast cancer cells, and to enhance CTL responses in tumor-bearing rats (303). IL-13 production at the sites of allergen challenge has suggested a role for IL-13 in allergen-induced inflammatory responses (304). Largely because of its ability to direct IgE class switching and Ig production, a role for IL-13 in autoimmune disease has been proposed (305,306).

Receptor. A variety of observations have suggested that IL-4 and IL-13 signaling involve common receptor chains. IL-4 mutant proteins can antagonize IL-13 activity (307,308) and anti-IL-4R antibodies inhibit IL-13 activity (307,309,310). In certain cell lines, IL-13 exhibits competitive inhibition of IL-4 binding to its receptor (311,312). Both IL-4 and IL-13 induce tyrosine phosphorylation of IL-4R chains (313) and signaling events induced appear to involve similar substrates (309,314,315). However, the recent cloning of an IL-13-specific receptor chain was demonstrated by expression of a putative IL-13R cDNA in COS cells, which facilitated IL-13 but not IL-4 binding.

7.1.7. Interleukin 15

The murine and human IL-15 gene consists of eight exons that span about 34 kb on chromosomes 8 and 4q31, respectively (316). IL-15 was identified as an activity in supernatants of T-cell and kidney epithelial cell lines that induced the proliferation of T cells and potently activated NK (317–319). IL-15 has also been shown to support the growth of T cells including γδ lineages (319,320) and to upregulate IFNγ production in NK cells and enhance NK cytotoxicity (321,322). IL-15 specifically upregulates the IL-2Rα chain on T cells but acts to negatively regulate its own specific receptor on T cells (323). IL-15 also acts as a costimulator of B cells, enhancing their proliferation and differentiation (324). An important source of IL-15 seems to be activated monocytes and macrophages (322,325). The T-cell chemoattractant activity of IL-15 has been implicated in a possible pathogenic role in rheumatoid arthritis, where IL-15 expression in synovial tissue may be involved in T-cell recruitment and disease (326). Consistent with its role in chemotaxis, IL-15 also modulates levels of adhesion molecules on T cells (327). IL-15 has been demonstrated to support growth of leukemic cells, and an alternatively spliced tumor isoform has been identified (328,329). Although IL-15 appears to have many of the effects of IL-2, IL-15 mRNA is uniquely abundant in numerous other cells such as epithelial cells, fibroblasts, heart, kidney, and lung (330,331). Although abundant IL-15 message may exist in these cells, IL-15 cytokine expression is mainly regulated at the translational

level, thus mRNA expression does not necessarily result in cytokine production (330,332). Indeed, deregulated expression of IL-15 from the tumor cell line HuT-102 reflects in part a loss of translational regulation (333). The strategy behind active synthesis of mRNA in the absence of translation is not clear, which is at least in part a testimony to the early stage of investigation into the biological role of IL-15.

Receptors. T-cell activation induced by IL-15 was shown to be blocked by antibodies against the IL-2Rβ chain (319). IL-15 also binds IL-2Rγ, whereas both IL-2Rβ and γ chains are necessary for IL-15 internalization and signaling (334–336). The IL-15Rα chain is specific for IL-15 and binds the cytokine with high affinity in the absence of either β or γ subunits (337). IL-15Rα is expressed on murine T-helper, macrophage, B-cell, and thymic and bone marrow stromal cell lines (337). Similar to the expression patterns of IL-15 in nonhematopoietic tissues, IL-15Rα mRNA is abundant in heart, lung, skeletal muscle, spleen, and especially liver, which may represent a major target tissue for IL-15. In T cells, IL-15 rapidly induces phosphorylation of JAK1 and JAK3 (323), in addition to tyrosine phosphorylation of STAT3 and STAT5 (59).

7.1.8. Interferon γ

IFNγ was initially described in 1965 as an activity in supernatants of stimulated T cells that *interfered* with virus replication (338), an activity that had been noted for IFNs α and β about 8 years earlier (339). IFNγ is synthesized as a 166-amino-acid proprotein that is proteolytically processed prior to secretion (340). IFNγ is biologically active as a homodimer that is capable of cross-linking the IFN receptor (341,342) and is produced almost exclusively from $CD4^+$ and $CD8^+$ T cells (343,344). The cytokine can also be present as a bound form on the cell surface of T cells (345). In addition to T cells, another important source of IFNγ is NK cells, which secrete the cytokine after cross-linking of CD45 (346) or NKR-P1 (347) surface receptors, or after interactions with B cells (348) and T cells (349). IFNγ directs the development of cell-mediated immunity by inducing Th1-type differentiation and impeding a Th2 phenotype (350–352). IFNγ downregulates the IFNγ receptor β-chain expression in Th1-type cells and renders them unresponsive to IFNγ (352). It has recently emerged that IFNγ plays an important immunoregulatory function by modulating the levels of B7 costimulation on the surface of APC (353–356). IFNγ activates monocytes and macrophages (357–360), synergizes with TNFα and IL-1 to regulate NO (361–364), and is required to upregulate NO production in response to viral (365) and parasitic infections (364,366,367). IFNγ induces mRNA stabilization and production of complement proteins C3 and C4 in liver cell lines and primary fibroblasts (368) and downregulates PECAM-1 (369). Important inducers of IFNγ secretion are IL-12 and IL-18 (see respective sections).

Class I upregulation by IFNγ is essential for control of viral infection (370). IFNγ gene-targeted mice have differential irregularities in class I and class II MHC expression that varies with tissues and inducing stimuli, and are generally deficient in both molecules after inflammatory stimuli (360,371). IFNγ upregulates both class II expression and the high-affinity FcεR on mast cells (372,373). Its role in acute antiviral responses has been strongly confirmed in gene-targeted mice deficient for normal IFNγ activity (374,375). Animals infected with virus develop heavy viral loads and are susceptible to encephalomyelogenic and other complications. Mice require IFNγ for antiparasite defenses, although being protected in its absence by prior immunization against the pathogen (376).

Interestingly, IFNγ has been found to stimulate the growth of *Trypanosoma brucei* in cell cultures (377), and *Trypanosoma* infections result in high levels of anti-IFNγ antibodies (378). IFNγ-deficient animals have reduced parasite loads and enhanced survival (377).

Receptor. The human IFNγR consists of α and β subunits of 472 and 316 amino acids respectively, both of which are required for signal transduction. There is considerable structural and primary sequence similarity between murine and human receptors (379–384). α and β chains are not bound together on unstimulated cells but rather associate in response to IFNγ binding (385–388). The high-affinity α chain mediates specificity of the receptor and is required for signaling (389,390). The 4-amino-acid motif LPKS at positions 266–269 in the cytoplasmic portion of the α chain binds JAK1 and is critical for kinase activation and physiological responses (391,392). Other elements of the cytoplasmic tail are also functionally important (390,393) and both JAK1 and JAK2 are required for mediating IFNγ activity (394,395). IFNγ induction of antiviral signaling depends on both JAK2 and STAT1 activation (396,397). JAK2 also associates constitutively with cytoplasmic sequences of the β chain (385). STAT1-deficient mice have a complete block in response to IFNγ and lack resistance to viral infection (398,399).

7.2. LONG-CHAIN HELICAL BUNDLE

7.2.1. Interleukin 6

IL-6 was initially described as a secretory product from fibroblasts and dubbed IFNβ-2 (400). Later, it became known as B-cell stimulatory factor (BSF-2), reflecting its ability to induce B-cell differentiation into Ig-secreting cells (401,402). Given the appropriate stimulation, IL-6 is produced from most cell types, including B and T lymphocytes, monocytes, macrophages, neutrophils, mast cells, osteoblasts, chondrocytes, dendritic cells (403,404), endothelial cells, keratinocytes, fibroblasts, and microglial cells (405–409). IL-6 is also produced during embryonic development in the mouse although its role is unknown (410). IL-6 provides an accessory or costimulatory signal for T cells (411–414), perhaps by upregulating IL-2R expression (415,416). IL-6 also augments NK cell activity (417). IL-6-deficient mice have a 50% reduction in the number of thymocytes and reduced numbers of mature T cells in the periphery (418). IL-6 deficiency also results in fewer numbers of progenitor cells of granulocytic-monocytic, megakaryocytic, and erythroid lineages compared with wild-type animals (419). Although IL-6 does not appear to be required for normal B-cell development and regulation in gene-targeted mice, immunized mice fail to generate normal total levels of IgG and are almost completely deficient for isotypes IgG2a, IgG2b, and IgG3. IL-6 seems to be required for B-cell differentiation of some but not all mucosal IgA responses (420,421). On the other hand, mice expressing IL-6 transgenically from an Ig enhancer have hyperactive B cells that independently class-switch and these mice develop IgG1 plasmacytomas, suggesting a role for IL-6 in malignant transformation (422–425). Perhaps the most dramatic action of IL-6 is its induction of synthesis and secretion of acute-phase proteins from hepatocytes (426–430). It is the most potent known regulator of acute-phase proteins, inducing elevated serum levels of fibrinogen, C-reactive protein, α_1-antitrypsin, α_1-antichymotrypsin, serum amyloid A, and haptoglobulin and reducing levels of albumin, fibronectin, and transferrin. IL-6 also has an important role in regulating neutrophil activity (431,432).

Receptor. The IL-6R is constructed of an 80-kDa IL-6-specific ligand-binding α chain and a 130-kDa chain (gp130), which is required for signal transduction but has no

detectable affinity for IL-6. IL-6Rα contains the membrane-proximal WSXWS motif characteristic of its family of receptors. Binding of IL-6 to IL-6Rα stimulates disulfide-linked dimerization with gp130, and initiates tyrosine phosphorylation activity (433). Although it does not appear to bind gp130, two regions of IL-6 have been found important in gp130 triggering (434–436). gp130 is expressed in most tissues (437) and is a common receptor component found in oncostatin M (OSM), ciliary neutrotrophic factor (CNTF), leukemia inhibitory factor (LIF), and IL-11 (438) receptor complexes. IL-6Rα has a more limited distribution, being restricted to PBMC, mature T cells, activated and Peyer's patch B cells (439–442). To facilitate the role of IL-6 in acute-phase responses, the receptor is also expressed in hepatocytes (443–445). Both mice and humans express a soluble form of IL-6Rα, which retains the ability to bind IL-6 and to deliver signals through gp130 (446,447).

7.2.2. Interleukin 7

IL-7 supplied by bone marrow stromal cells (448,449) induces the proliferation of progenitor B cells and is required for normal B-cell development (450–455). IL-7 also supports the growth of immature (452,456–458) and mature T-cell populations (459,460). An important source of IL-7 is epithelial goblet cells in the gut, where it may be involved in regulating intestinal mucosal lymphocytes (461). Analysis of IL-7 actions in fetal thymic cultures indicates that the cytokine can maintain expression of the RAG1 gene and promote rearrangement of TCR Vβ genes (458). Nude mice expressing an IL-7 transgene have significant numbers of normal thymocytes and $CD4^+/CD8^+$ peripheral T cells (462). The situation is different for B cells, where IL-7 appears to regulate downregulation of RAG1 and RAG2 (462). Administration of IL-7 after irradiation enhances lymphocyte reconstitution (463), whereas antibody blocking or gene-targeted IL-7 deficiency undermines both lymphopoiesis (464–466) and myelopoiesis (463,467,468). IL-7 treatment of normal mice also induces T-cell lymphopoiesis (469,470) similar to that seen in IL-7-transgenic mice (471). IL-7 has been reported to enhance the generation of cytotoxic T cells, NK cells, and monocytes (472,473). IL-7 administration during leishmania infection has been shown to exacerbate disease (474).

Transgenic mice expressing IL-7 from an MHC class II Eα promoter develop lymphoid tumors and generate large numbers of bipotent cells capable of differentiating B-cell or macrophagelike function (475). The number of progenitor B cells in these mice is significantly increased in bone marrow, from where they appear to "spill over" into blood, spleen, and lymph nodes of adult animals (476). Thymic profiles in the IL-7-transgenic mice do not reveal any significant phenotypic changes and there is no apparent defect in T-cell maturation, although hyperplasia of peripheral lymphoid organs and elevated numbers of peripheral $CD8^+$ and $CD4^+CD8^+$ T cells are observed (477). Other transgenic mouse lines have also been found to have abnormal thymic profiles with a significant incidence of T-cell tumors (478,479). IL-7 has also been reported to mobilize pluripotent stem cells with long-term repopulating activity from the bone marrow to the peripheral blood (480).

Receptor. IL-7 mediates its activity via a high-affinity heterodimeric receptor composed of a 90kDa IL-7-specific α chain and a common γ subunit (γ_c) (481–483). The α chain has no intrinsic enzymatic activity and is a member of the hematopoietic growth factor receptor family (481). IL-7 receptors are expressed on pro-B and pre-B cells (481,484). A single tyrosyl mutation in the α-chain cytoplasmic domain blocks progenitor

B-cell proliferation but permits Ig heavy chain gene rearrangement, suggesting a capacity for differential signaling in B cells (485). The α chain is also expressed on resting T cells (486,487) and forms a high-affinity $\alpha\gamma_c$ heterodimer on activated T cells (488). Receptor expression is critical for proliferation of thymocytes before TCR gene rearrangement in the thymus (489).

Tyrosine phosphorylation of multiple targets ensues after receptor engagement (487,490–493). A chimeric CD8-IL-7Rα chain has been shown to associate with $p59^{fyn}$ in a murine cell line (494), and IL-7Rα constitutively associates with $p56^{lck}$ and $p59^{fyn}$ in primary human T cells (493). $p59^{fyn}$-deficient mice do not have defects in lymphopoiesis associated with an IL-7/IL-7R blockade (495), suggesting that its role in mediating biological responses through IL-7R is not critical and/or is redundant during lymphoid development. Phosphatidylinositol 3-kinase associates with the α chain and mediates signaling (496). IL-7 has been shown to induce JAK1 and JAK3 kinases and the transcription factor STAT 5 (497–499). Interestingly, mice with gene-targeted mutations for the IL-7R have a block in γδ T-cell development (500,501).

7.2.3. Interleukin 10

IL-10 has a complex role in the regulation of the immune response. It is secreted by B and T lymphocytes (502–505), monocytes/macrophages (506–508), and keratinocytes (509). IL-10 upregulates class II expression on B cells and supports their growth and Ig production (510–512); it supports the growth and differentiation of thymocytes and mature T cells (513–515); it enhances mast cell proliferation in culture (516), induces protease production, and downregulates TNFα and GM-CSF secretion in mast cells (517). IL-10 appears to interfere with T-cell synthesis of cytokines that are in part regulated by NF-κB/Rel, which includes IL-1, IL-2, IL-2Rα, IL-6, GM-CSF, and TNFα (518–521), and downregulates synthesis of IL-1, IL-6, IL-8, GM-CSF, and TNFα in macrophages (522–527). IgE-mediated induction of nitricoxide synthase and cytokine secretion in keratinocytes is also inhibited by IL-10 (528). However, IL-10 can potentiate IL-15 expression in activated murine macrophages (325), which in light of its negative regulatory effect on IL-2 (i.e., effect on Th1-type response) suggests a paradoxical support for cell-mediated immune responses (see Section 7.1.7). IL-10 differentially modulates B7-1 and B7-2 expression on APC (529–531) and plays an important role in regulating their efficiency of antigen presentation (518,532–534). Thus, IL-10 can intervene in T-cell activation both directly through paracrine regulation of cytokine secretion (535) and indirectly via reducing APC function. Its direct effects may involve interfering in the proximal evens of TCR signaling (536–538).

IL-10 protects against endotoxin-induced relapses in experimental autoimmune encephalomyelitis (539). Considerable evidence supports the notion that IL-10 plays an active role in driving a Th2-type immune response important in clearing parasitic infections. IL-10-deficient mice succumb to chronic inflammatory bowel disease that appears to be mediated by hyperactive $CD4^+$ T cells (540,541). These hyperactive T cells may in part be explained by the normal function of IL-10 to tolerize peripheral $CD4^+$ T cells (538). EBV encodes an IL-10 homologue that is expressed during infection and that may facilitate chronic infection (519,542,543). IL-10 is also important in protecting against endotoxic shock (544,545).

Receptor. IL-10R is expressed on the same cells from which the cytokine is derived, although it is also upregulated on fibroblasts after stimulation with LPS (546). IL-10R

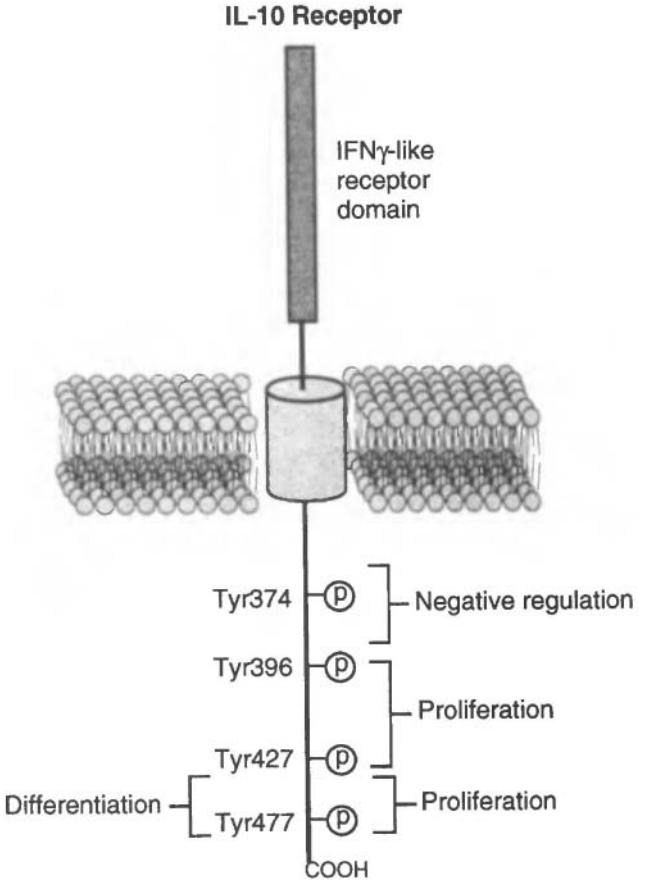

Figure 7.6. IL-10R is a 100-kDa member of the family of interferon receptor-like molecules (1009). The cytoplasmic tail of IL-10R can be dissected into regions that contain phosphotyrosine residues that mediate specific signaling functions. Used with permission, *Molecular and Cellular Biology*, Ho *et al.*, **15**:5043–5053, 1995 [Ref. 1010].

induces phosphorylation of the tyrosine kinases STAT1 and STAT3 (547,548). However, recent studies of STAT1-deficient mice show no apparent defects in IL-10 responses (398,399). JAK1 and TYK2 are also phosphorylated after IL-10R perturbation (548). There are four key tyrosine residues in the cytoplasmic tail each of which appears to mediate unique biological responses through the receptor (Figure 7.6).

7.2.4. Interleukin 11

IL-11 is a stromal cell-derived cytokine that is an important component of the bone marrow microenvironment (549,550), where it induces growth and differentiation of a variety of hematopoietic cells. IL-11 acts to promote megakaryopoiesis and thrombopoiesis in both mice and humans (551–556), stimulates erythropoiesis (557,558) and myelopoiesis (559–561), and may induce stem cell differentiation to committed progenitors (562). IL-11 has also been reported to enhance the growth of T and B lymphocytes

(563–565). Treatment of animals with IL-11 does not have dramatic effects on hematopoiesis, although it does result in marked megakaryopoiesis with elevated numbers of platelets in the blood (554,566) and increased numbers of CFU-GM, BFU-E, and CFU-GEMM (567). In addition to its effects on hemostasis, IL-11 exerts its activity on cells of nonhematopoietic lineages, inducing acute-phase proteins in cultured hepatocytes (568), although it may not have a significant role in the induction of acute-phase proteins *in vivo* (569). IL-11 has been shown to block adipogenesis in cultured cell lines (570,571), and to regulate the expression of metalloproteinase inhibitor in connective tissue cells, where IL-11 is expressed in chondrocytes and synoviocytes (572). IL-11 is also expressed in brain and testes (573) and osteoblasts (574). It protects crypt stem cells in the gut and accelerates recovery of intestinal mucosa after treatment with chemotherapeutic agents (575–578) and enhances (mainly neutrophil) hematopoiesis after bone marrow transplantation or chemotherapy-induced cytopenia (579,580).

Receptor. The IL-11 receptor is composed of a 151-kDa IL-11-specific α chain and the gp130 signal-transducing subunit of IL-6R (see Section 7.2.1) (581–583). The IL-11 receptor can exist in membrane and soluble forms. Both forms of the receptor are capable of mediating activation signals, which involve STAT1 and STAT3 proteins in human cell lines (584). The α-chain gene has only recently been cloned and shown to contain the WSXWS extracellular motif characteristic of other hematopoietin receptors (585). Murine and human α chains exhibit 84% sequence identity. Osteoblasts and osteoclasts have been found to express IL-11Rα, suggesting a role for the cytokine in the maintenance of bone (574).

7.2.5. Interleukin 12

IL-12 is a 75-kDa disulfide-linked heterodimeric glycoprotein, composed of p35 and p40 chains (586,587). It was originally identified by its ability to enhance IL-2 activity in supporting cytotoxic T and NK cell responses (588–590). It is a potent stimulator of NK cell cytotoxicity (32,591–593) and induces proliferation and cytotoxicity in T cells (594–598). IL-12 also stimulates B-cell growth in an IFNγ-dependent manner (599), and it has significant potency *in vivo* for stimulating mobilization of hematopoietic progenitors and extramedullary hematopoiesis (600). Biologically active IL-12 requires both subunits (601), expressed by different genes that are independently regulated (602). p35 is expressed in most cells whereas p40 is upregulated in monocytes, macrophages, and B cells in response to infection or stimulus with LPS (603–605). p40 expression is also upregulated in macrophages in response to NO (606). T cells appear to drive monocyte expression of IL-12 by cognate interactions between CD40 and CD40L (607). Murine p40–p40 homodimers exist that bind the IL-12 receptor without inducing a response and thus antagonize IL-12 activity *in vitro* (608,609). *In situ* hybridization reveals that p35 and p40 expression are differentially expressed in different regions of the spleen (610). IL-12 is also expressed in small amounts by keratinocytes (611) and dendritic cells (612,613), where it appears to enhance APC activity. IL-12 acts on its own (344,614), and synergizes with the recently discovered interferon-γ inducing factor (IGIF) (tentatively named IL-18), to enhance IFNγ production by T cells (615).

IL-12 synthesis early in response to infection is thought to induce and/or augment IFNγ upregulation (592,615), thereby activating phagocytes to establish a front-line defense (616) and driving a Th1-type cell-mediated immune response (617–620) (Figure 7.7). Administration of IL-12 has been shown to prevent graft-versus-host disease in a

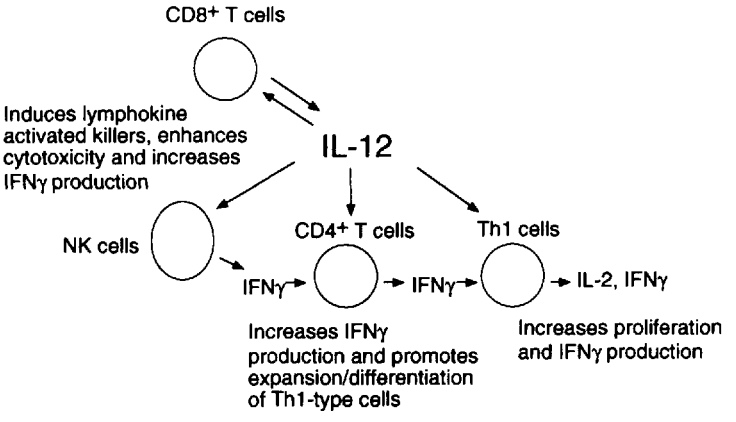

Figure 7.7. IL-12 is a potent inducer of IFNγ production and cell-mediated responses.

murine model (621) and anti-IL-12 antibodies have been shown to block Th1 responses by preventing proper APC function (622). IL-12-deficient mice have reduced capacity to produce IFNγ and fail to develop normal Th1-type immune responses (623,624). Natural susceptibility of mice to infection with *Leishmania* may also reflect genetically programmed IL-12 responses to infection (625,626), supported by the observation that IL-12 administration can cure systemic infection (627–629). IL-12 is also critical for mediating resistance against *Trypanosoma cruzi* infection (630). These effects have led to the suggestion that IL-12 might be an effective adjuvant during immunization to induce Th1-type immunity (629,631).

IL-12 has been shown to inhibit hypersensitivity reactions and may be an important influence in a cytokine balancing act that prevents Th2-mediated atopic disorders (632–634). IL-12 administration to mice or rats induces B cells to preferentially synthesize IgG subclasses to antigen (635,636). IL-12 administration also sensitizes mice to lethal shock induced by TNF (637). The synthesis of IL-12 is deficient during HIV infection, and IL-12 treatment can enhance antigen-specific immune responses and prevent apoptosis of $CD4^+$ T cells from HIV-infected patients (638–641). IL-12 is also beneficial in MAIDS infections (642). Anti-IL-12 antibodies alleviate experimental colitis (643), suggesting that the cytokine may play a role in autoimmune disease (600,644).

Receptor. A high-affinity IL-12R is expressed on activated T and NK cells but is absent from B cells. An IL-12R subunit (IL-12Rβ) has been cloned and found to exhibit significant homology to gp130 but demonstrates no IL-2 signaling when expressed in cell lines (645–647). More recently, monoclonal antibodies directed against different epitopes on the IL-12Rβ chain blocked IL-12 activity and detected IL-12Rβ on cell lines of T, NK, and B lineages, but not on nonlymphoid cell lines (648). Resting PBMC also express IL-12Rβ without demonstrable IL-12 binding, indicating that the high-affinity IL-12R may include an additional subunit(s) for which expression is differentially regulated with the IL-12Rβ chain. Despite a lack of characterization of the IL-12R, an important signaling pathway has been identified. Splenocytes from mice with gene-targeted deletions in the gene encoding the transcription factor STAT4 do not proliferate in response to IL-12, do not differentiate Th1 cytokine production, and do not respond with Th1 immunity to *Listeria monocytogenes* infection (649,650). Thus, STAT4 appears to have a nonredundant and specific role in mediating IL-12 responses.

7.2.6. Interferons α and β (Type I Interferons)

The interferons were identified 40 years ago for their ability to *interfere* with viral replication *in vitro* (339). The IFN nomenclature initially was assigned based on their source, with IFNα and IFNβ identified as products of leukocytes and fibroblasts, respectively. Type I interferons also include IFNω and IFNτ, although IFNω is not found in mice and IFNτ appears only in embryonic tissues of ruminants. There are 14 functional IFNα genes and a single gene each for IFNβ and IFNω clustered on chromosome 9 in humans, encoding related proteins of 165–172 amino acids (651–655). IFNα and β are synthesized as proproteins and subject to proteolytic processing. Significant amounts of IFNα are produced from activated T cells and macrophages, as are low levels of IFNβ. Infectious agents induce secretion of both interferons from T and B cells, macrophages, fibroblasts, and endothelial cells. IFNα/β expression is upregulated by double-stranded RNA, CSF, and PDGF (656,657). IFNα mRNA is constitutively expressed in spleen, kidney, liver, and peripheral blood leukocytes in humans (658). IFNα/β have extensive direct antiviral effects, which include activating cellular RNase and inhibiting protein synthesis (659). IFNα/β upregulate class II expression and enhance macrophage APC function and bactericidal activity (660) and sensitize macrophages to LPS-induced apoptosis (661). Class I expression on neuronal cells as a result of measles virus infection is regulated by IFNβ (662). IFNα induces IL-10 secretion from $CD4^+$ T cells and monocytes (663), although it has been reported that IFNα may also help direct Th1-type immune responses by enhancing IL-12-induced inhibition of IL-4 synthesis from T cells (664). The latter observation is consistent with the report that allergen-specific T-cell clones derived in the absence of IFNα produce IL-4 and IL-5 but not IFNγ (i.e., Th2-like cells), whereas clones generated in the presence of IFNα produce IFNγ and only limited amounts of IL-4 or IL-5 (e.g., Th1- or Th0-like cells) (665). Neutralization of IFNα/β also shows specific effects on NK cell responses to viral infection (666).

Antigen-stimulated histamine release is decreased in IFNα/β-treated peritoneal mast cells, whereas release is potentiated in those isolated from intestinal mucosa (667). IFNα/β also appear to regulate TNFα and FcεR expression in mast cells (373,667). In bone marrow cells, IFNα blocks the upregulation of IL-11 synthesis in response to IL-1 (668).

IFNα/β appear to be a critical component of host antiviral defense systems (669–671). Murine resistance to MAIDS is strain dependent and may involve strain-specific differences in IFNα/β expression (672). In Newcastle virus infection, IFNβ has been found to inhibit replication through blocking viral expression of hemagglutinin-neuraminidase (HN) (673). Moreover, IFNα induction of mRNA-degrading enzyme activity, while beneficial in blocking viral replication, can also be detrimental to the host, as it induces this activity specifically in β-islet cells (as opposed to nonislet cells) of the pancreas, suggesting that early expression of IFNα there during pancreatic leukocytic infiltration may partially mediate β-islet-cell-specific autoimmune destruction and diabetes (674). IFNα/β enhance the tolerizing effects of orally administered myelin antigen and reduce relapses or progression in EAE (675–677), an effect that may in part be mediated by IFN-induced production of IL-4, IL-10, and TGFβ (678). Type I interferons are currently used for treating a number of disorders including chronic hepatitis B and C infections and cancer therapy.

Receptor. A single 63-kDa receptor chain (IFNAR) has been identified that appears to bind and transduce signals from the various signals from the various α and β IFNs

(654,679). Although by itself IFNAR binds IFNs, it appears to cooperate with other proteins to form a functional receptor complex (680–682) that is capable of differentially transducing IFNα or IFNβ signals (683,684). IFNAR has a large (408 amino acid) extracellular domain with twofold symmetry and 15 potential sites for N-linked glycosylation (685). IFNα stimulation results in phosphorylation of JAK1, STAT1α, STAT2, STAT3, and TYK2 (686). IFNα induces tyrosine phosphorylation of STAT3 and DNA-binding activity. IFNα stimulation also results in STAT3 association with IFNAR, which may involve an SH2 domain of STAT3 and the phosphorylated cytoplasmic tail of the receptor (687). IFNα has been found to induce the tyrosine kinase TYK2, which may link receptor stimulation to activation of genes containing ISGF-3-binding, IFN-stimulated response elements (ISRE) (688), although ISGF-3-independent mechanisms of gene activation also exist in response to IFNα stimulation (689).

7.3. β-TREFOIL [INTERLEUKIN 1 (IL-1α, IL-1β, IL-1ra)]

IL-1 activity is represented by two separate glycoproteins, IL-1α and IL-1β, that are transcribed from two different genes. The genes for human IL-1α, IL-1β, and IL-1ra (IL-1 receptor antagonist), in addition to the IL-1R1 and IL-1R2 receptors, occupy a 430-kb stretch of DNA on the long arm of human chromosome 2 (690). Most known biological activities of IL-1 are common to the acidic IL-1α and neutral IL-1β isoforms (691), which appear to have distinct binding sites on the IL-1R (692–696). Both genes are translated into 31-kDa proproteins that lack leader sequences and are subject to proteolytic processing by IL-1β-converting enzyme (ICE), although IL-1α is also active in its pro-form (697). Regulation of IL-1 expression is in part achieved through tissue-specific regulation of ICE (698,699).

There are numerous immunological roles for IL-1. IL-1α is expressed in the thymus and supports thymocyte maturation and development (700) and is a potent upregulator of endothelial adhesion molecules, inducing P-selectin, E-selectin, ICAM-1, and VCAM-1 expression (701–707). IL-1 is secreted by dividing $CD34^{+}CD45RA^{lo}CD71^{lo}$ progenitor cells purified from human umbilical cord blood (708) and has an important role in hematopoiesis by inducing the production of growth factors such as G-CSF, and IL-3 (709). It also stimulates hematopoiesis after radiation or myeloablative drugs (710–713), although it blocks erythroid production by interfering with CFU-E formation (714,715). IL-1β-deficient mice have normal responses to LPS but do not develop normal fevers or acute-phase responses to infections (716). Nevertheless, they do not appear to have significant defects in their immune response to pathogens nor in other hematological parameters. This contrasts the observation that immunocompromised mice are protected from lethal challenge with pathogen if injected with low amounts of IL-1 one day prior to infection (717).

IL-1 may at times be involved in exacerbation and pathogenesis of disease. A role for IL-1 in skin diseases and hypersensitivity has been forwarded (718–721), consistent with the recent observation that IL-1β-deficient mice have impaired contact hypersensitivity (722). Elevated levels of IL-1 have been observed during malignant hematological disorders (723,724), in systemic sclerosis (725), rheumatoid arthritis (726), and during graft-versus-host disease (727). IL-1 also has a true receptor antagonist, IL-1ra, defined as having no known function other than to bind IL-1 receptors in the absence of any signal transducing activity (728–732). However, for a complete block of IL-1 function, IL-1ra

must be present in a 100-fold excess over IL-1 (733). Thus, although it appears that the role of IL-1ra *in vivo* is more likely to modulate IL-1 activity rather than to abolish it, pharmacological dosages could prove effective in blocking inflammatory effects of IL-1. IL-1ra may in part regulate hematopoiesis (712).

Receptor. The IL-RII-receptor is an 80-kDa glycoprotein that solely mediates the biological effects of IL-1, binding IL-1α and IL-1β (734–736). The receptors are expressed or are upregulated on most cells and can be triggered to induce physiologically relevant signals by the binding of as few as few as 10 IL-1 molecules on the cell surface (737). Binding of IL-1 to IL-RI results in the formation of a high-affinity complex (IL-1R-AcP) that includes a transmembrane accessory protein (AcP) (738). IL-1 binds an additional receptor, IL-1R2, a 68-kDa protein expressed on epithelial cells (739,740) and on hematopoietic lineages including B cells (741,742). Interestingly, IL-1R2 has no role in signaling and exists merely as a decoy receptor that can sequester IL-1 on the membrane or be secreted and bind soluble IL-1 (743,744). Vaccinia and cowpox virus encode an IL-1R2 gene, which they express in infected cells ostensibly to reduce the strength of the ensuing IL-1 mediated inflammatory responses (745,746). IL-1-induced signaling involves activation of NF-κB in a variety of cells including T cells (747–752). In common with other cytokines, IL-1 also appears to involve the JAK–STAT kinase cascade (753). A number of transcription factors have been identified that are activated and/or upregulated by IL-1, such as C/EBP (754), EGR-1 (755), FOS (756,757), JUN (758–760), MYB and MYC (761), and NFIL6 (762).

7.4. β-JELLY ROLL (TRIMERS)

7.4.1. Tumor Necrosis Factor (TNFα)

TNF was first identified because of its ability (as its name suggests) to induce hemorrhagic necrosis of tumors in mice (763). TNF or TNFα has many overlapping biological activities and is closely linked to the gene for lymphotoxin α (LTα), also known as TNFβ, which are located in the HLA and MHC regions of humans and mice, respectively (764–767). TNF molecules are synthesized as 226-amino-acid proproteins that are proteolytically processed to produce mature 157-amino-acid subunits that assemble into homotrimeric complexes (768,769). TNF can also exist as a transmembrane surface glycoprotein and is capable of delivering differential signals, compared with the soluble form, through the TNF receptor (770). The three-fold axis symmetry and bell-shaped β-jelly-role structure of the TNF homotrimer are similar to several viral coat proteins, such as found in the satellite tobacco necrosis virus (771).

The list of cells that secrete TNF is large, including a variety of hematopoietic cells such as T and B cells, NK cells, granulocytes and mast cells, and cells of other lineages such as astrocytes, epidermal cells, hepatocytes, fibroblasts, smooth muscle, and ovarian cells (772). However, monocytes and macrophages are an important source of TNF (773–775). Mast cells also secrete large amounts of TNF stored in granules (776,777), recently reported to play a critical role in host protection against acute bacterial peritonitis induced by cecum ligation and puncture (778); they may also be an important source of TNF in facilitating neutrophil influx and clearance of enterobacteria infections (779). Thymic stromal cells produce small amounts of TNF that may regulate thymocyte cell death and development (700,780). TNF also mediates apoptotic cell death in mature $CD8^+$ T cells, overlapping with the FAS/FASL system (781). The killing of tumor targets by macro-

phages and NK cells may be mediated in part by TNF (773,774, 782,783), although a recent study has suggested an inhibitory role for TNF on NK cell tumor clearance *in vivo* (784).

TNF has long been known for its ability to mediate systemic effects such as fever (785), induction of acute-phase response proteins (786), endotoxic shock (787), and cachexia (788). Recent data suggest that it also induces angiogenesis (789). Depletion of TNFα or receptor deficiency results in susceptibility to *Mycobacterium tuberculosis* and *Listeria monocytogenes* infections (616,787,790), which may reflect the requirement for TNF-dependent reactive nitrogen production in macrophages during host defense (790). TNFRp55-deficient mice also have a defect in TNF-induced infiltration of neutrophils and mononuclear cells into lung, liver, and kidney, observed in concordance with reduced levels of expression of the adhesion molecules VCAM-1 and E-selectin (791). TNFα and IL-3 have been found to synergize to stimulate the development of human dendritic/Langerhans cells from progenitor cells (792). TNF also upregulates class I MHC expression on vascular endothelial cells, fibroblasts, and neuronal cells (793–796) and has intrinsic antiviral activity (797). IL-1 induces TNF expression in PBMC, and TNF in turn induces IL-1 upregulation (798,799). Interestingly, signaling through CD28 appears to upregulate TNF synthesis (800) and mice deficient for the T-cell costimulatory molecule CD28 are no longer susceptible to exotoxin-induced toxic shock, apparently the result of a complete loss of production of TNF and a 90% decrease in IFNγ secretion (801).

Receptor. TNFα and LTα share the receptors TNFR p55 (CD120a) and TNFR p75 (CD120b), both of which are expressed on most cells in mice and humans (802). Binding of the TNF receptors by either of the structurally related molecules mediates a number of similar biological activities and it has been suggested that they may be redundant molecules (803–805). TNF receptor expression is differentially regulated on various cell types: Activated T cells upregulate both p55 and p75 (806–808), whereas B-cell activation results in the upregulation of p75 but does not influence expression of p55 (809). TNF receptors also exist in soluble form, and these too are secreted differentially depending on stimuli and cell type, whereas serum levels can be indicative of either normal or pathological immune responses (810–812). The soluble receptors appear under different circumstances to be capable of either enhancing or downmodulating TNF activity (812–815). Despite evidence for the role of TNF in thymic development and apoptosis, TNF receptor-deficient mice have normal T-cell development (816). Not surprisingly, however, they are protected against toxic shock. TNFR deficiency does result in a breakdown in germinal center formation in peripheral lymphoid organs (817).

p55 and p75 are members of a larger TNFR superfamily of molecules, involved in a broad range of biological activities such as acute-phase responses, apoptosis and activation of lymphocytes, and tumor cell growth (818–820). At least part of the pleiotropy of the TNFRs reflects the fact that they bind and mediate the effects of both TNF and LTα. LTα homotrimers bind both the p55 and p75 TNFRs (821) (Figure 7.8A), although it is not clear if the TNFRs can mediate specific signals via interactions with TNF or LTα (822,823). However, cells expressing a high ratio of TNFR p75/p55 are unresponsive to LTα, and the high levels of p75 receptor appear to inhibit the effects of LTα (805).

There have been a great many studies aimed at elucidating the signaling pathways resulting from the activation of TNFRs, and the picture that emerges is complex. TNFR-family-associated factors (TRAFs) (824–828) and a recently described TANK protein (829) have been implicated in NF-κB activation. A number of additional molecules involved in transducing apoptotic signals through the TNFR include FADD (830,831),

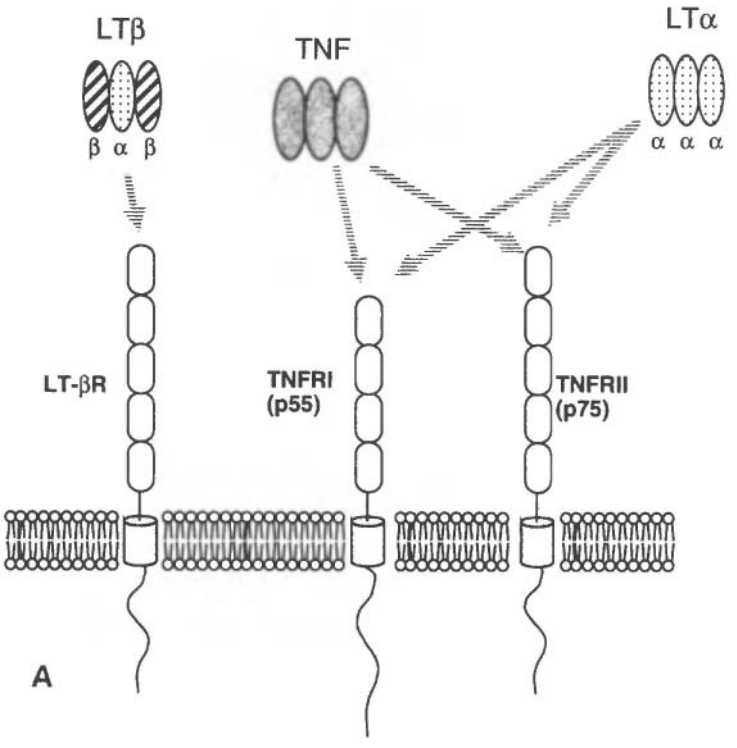

Figure 7.8. (A) Lymphotoxin α (LTα) and TNF are both ligands for the p55 and p75 TNFRs. Recent evidence suggests that p75 may act as a decoy for LTα, thereby reducing its activity through interactions with the p55 receptor (1011). LTβ contains a single LTα and two LTβ-specific subunits, and the heterotrimer has its own specific receptor, LT-βR.

FLICE (832), MACH (833), RIP (834) and TRADD (835–837). These so-called death domain proteins appear to "cross talk," allowing intracellular communication between apoptosis-inducing and NF-κB activating signals. These signals can be induced through receptor–ligand interactions involving both TNF and FAS (838) (Figure 7.8B).

7.4.2. Lymphotoxins α (TNFβ) and β

The lymphotoxins α (LTα) and β (LTβ) are members of the TNF superfamily of molecules (839). LTα is also commonly referred to as TNFβ, which highlights the fact that the two cytokines have overlapping biological activity and share the same receptor (see Section 7.4.1). LTα is composed of three α-chain subunits whereas the predominate form of LTβ has two β-chain subunits and a single α chain ($LT\alpha_1\beta_2$), although an $LT\alpha_2\beta_1$ complex also exists (840). LTα is secreted but is also expressed on the surface of lymphocytes via a transmembrane region of the molecule. LTβ is not secreted and exists as a type II integral membrane protein in association with an LTα subunit (803,841). Surface expression of the $LT\alpha_1\beta_2$ complex appears to be essential for the normal development of peripheral lymph nodes and for the establishment of splenic architecture (842,843). Mice deficient for LTα have been generated, revealing a similarly crucial role for the cytokine in the development of lymphoid organs; deficient mice lack lymph nodes, do not form germinal centers, and lack organized architecture of follicular marginal zones

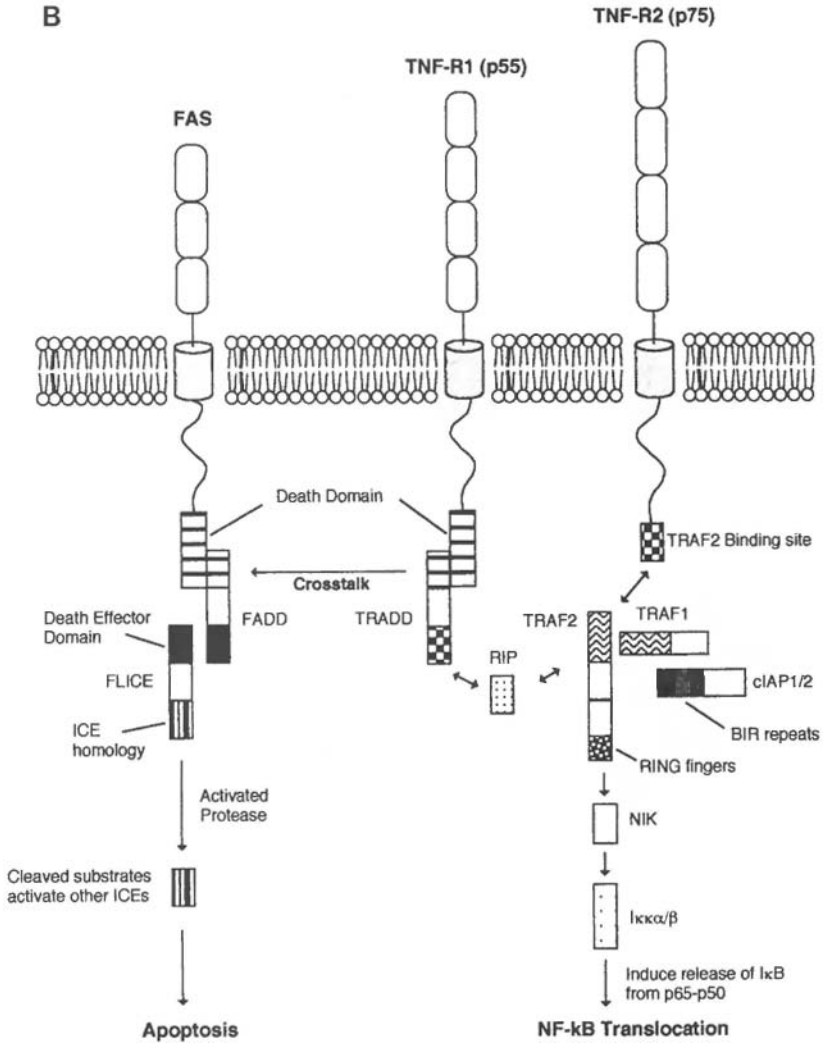

Figure 7.8. (B) TNFR signaling involves the TRAF family of molecules. Signaling through TNFR p55 or p75 can induce NF-κB activation via the TRAF transducers. The p55 receptor binds TRADD, which initiates the TRAF pathway. TRADD can also bind FADD, providing a means by which signaling through p55 can "cross talk" with the FADD/FLICE cascade for the induction of ICE-mediated apoptosis (1012). Figure provided by Wen Chen Yeh.

(844–846). Interestingly, overexpression of LTα in mice using a rat insulin promoter transgene results in vascular changes that mimic the development and organization of peripheral lymphoid organs, suggesting LTα may play a fundamental role in directing lymphoid organogenesis (847).

Receptor. LTα binds both the p55 and p75 receptors of TNF (see above). The X-ray crystal structure of a p55–LTα complex has been elucidated and suggests that trimerization of the receptor may be involved in the generation of a signaling complex (848). On the other hand, LTβ has a unique receptor that appears not to be expressed on lymphoid cells, but is found on a wide range of nonlymphoid cells. The murine LTβR has a single

transmembrane region and is 415 amino acids in length with 76% identity to its human counterpart (849). Signal transduction through the LTβR involves TRAF-5 and NF-κB activation (821,850,851). Recent evidence also suggests that the cytoplasmic tail of LTβR can bind the hepatitus C proteins, which may provide a means by which the virus can manipulate host immune response (852).

7.5. CYSTEINE KNOT [TRANSFORMING GROWTH FACTOR-β (TGFβ1, -β2, -β3)]

TGFβ is a homodimeric complex assembled from one of three polypeptide isomers, β1, β2, and β3, that exhibit 75–80% primary sequence homology and that are transcribed from separate genes (853). The three genes are uniquely regulated, with β1 showing strong immune induction and hematopoietic expression, and all three are under differential control and expressed in numerous different tissues during fetal development (854,855). The majority of TGFβ is secreted as an inactive complex that includes a latent TGFβ binding protein disulfide-linked to the N-terminus of a TGFβ propeptide (856–858). TGFβ is expressed in T and B cells, NK cells, macrophages, platelets, bone marrow, and thymic stromal cells (859,860). Glucocorticoids may be an important regulator of TGFβ production in T cells (861). TGFβ is constitutively expressed in NK cells where it is upregulated through interactions with stromal cells (862,863). TGFβ has been shown to have immunosuppressive effects on cell-mediated immunity, reducing CTL and NK activity (864,865) and inhibiting T-cell proliferation. TGFβ has also been shown to downregulate B-cell Ig synthesis (866) and to induce apoptosis in B cells (867–869), and at the same time it also appears to promote IgA class switching in some B cells (870,871). TGFβ1 inhibits DNA synthesis in $CD56^+$ NK cells and downregulates expression of IFNγ and TNFα, although it does not block activation by IL-2 or IL-12 (862). TGFβ downregulates a number of cytokines including IL-1, IL-2, IL-6, IFNγ and TNFα in various cells (872–875) and interferes with class II expression (874,876). TGFβ regulates NO synthesis in macrophages by a mechanism that involves the regulation of iNOS mRNA stability and the induction of arginase activity (877–879). TGFβ inhibits T-cell homing and adhesion to endothelial cells (880) but can also act as a potent chemoattractant for neutrophils (881–883), monocytes, and T cells (884). The chemotherapeutic agent bleomycin upregulates TGFβ synthesis from pulmonary macrophages and eosinophils, which, in turn, induces collagen synthesis from fibroblasts and is thus a clinically important cause of lung fibrosis (885–888). Triple-negative ($CD3/4^-CD3/4$ $CD8^-$) thymocytes express TGFβ (889), which has been shown to induce an accumulation of $CD4^-CD8^-$ cells in fetal thymic organ cultures (890). TGFβ blocks growth of bone marrow progenitor cells (891) by a mechanism that appears to involve the regulation of steel factor (kit ligand) and c-kit (892–894).

Taken together, these observations indicate a critical immunoregulatory role for TGFβ. The induction of oral tolerance in experimental autoimmune disease in mice has been associated with TGFβ expression (895–897). A number of studies have found that TGFβ1-deficient mice suffer from spontaneous disease characterized by profound lymphocytic and myelocytic infiltration and inflammation in various organs, including heart, lung, liver, intestines, and pancreas with death occurring by about 4 weeks of age (898–901). Interestingly, trypanosomes must induce the TGFβ signaling pathway for successful infection (902). Other infectious agents such as tuberculosis may rely on TNFβ effects in

order to avoid cell-mediated destruction (903,904). The suppression of Th1-type immune responses may indeed be a critical but in some cases paradoxical aspect to the immunoregulatory role of TGFβ (905,906). The importance of TGFβ as a pivotal immunoregulatory agent appears to vary according to genetic background (907).

Receptor. There are three principal TGFβ receptors of 55, 80, and 280 kDa, type I, II, and III receptors, respectively (908,909). There is also a TGFβ-binding protein, endoglin, expressed on endothelial cells, macrophages, and hematopoietic progenitors, that exhibits significant sequence similarity to the intracellular portion of the type III receptor (910–913) and is deficient in the inherited disease hemorrhagic telangiectasia (914). TGFβ signaling involves the formation of a heteromeric complex of type I and II chains, which are expressed on most TGFβ-producing cells and during embryonic development (915). Chimeric receptors have been used to show that heteromeric association occurs between both extracellular and intracellular domains. A glycine- and serine-rich region adjacent to the kinase domain of the type I receptor, known as the GS domain, plays a critical role in interactions and signaling (916). Coexpression of cytoplasmic domains of type I and II receptors or a linked type I–II cytoplasmic domain results in ligand-independent TGF-like activation, and it appears that both type I and type II receptors are involved in mediating TGFβ signals (917–921). Unlike most other surface receptors, the type I and II chains have intrinsic serine/threonine kinase activity (922,923), with a substrate that includes the associated WD-domain protein, TRIP (924). Signal transduction through the type I and II receptors has recently been shown to also involve the MAD family of tumor-suppressor proteins (925–927). The type III receptor has both transmembrane and soluble isoforms, exhibits less affinity for TGFβ than the other receptors, and is expressed from endothelial cells and some hematopoietic lineages (912,928,929). The type III receptor appears to modulate signaling through the type I and II receptors and may be involved in TGFβ binding to type I and II chains (912,930).

7.6. α-CHEMOKINES (C-X-C; INTERLEUKIN 8)

IL-8 was originally identified because of its chemoattractant activity on neutrophils (931,932). It is now the best-characterized chemokine of the α-chemokine group, which includes melanoma growth-related oncogene α (GROα) (933–935), neutrophil-activating peptide-2 (NAP-2) (936–938), platelet factor-4 (PF-4) (939–941), β thromboglobulin, and epithelial neutrophil activating peptide-78 (942,943). The α-chemokines have been grouped because of their similar chemoattractant activities, receptor usage, genomic location in humans (4q12–21), and the common presence of four cysteine residues that form two disulfide bridges, with the first two cysteines being separated by a single amino acid (Cys-X-Cys or C-X-C). The molecules all share considerable primary sequence homology and are translated as proproteins that undergo proteolytic processing and are eventually secreted as dimers or tetramers (944,945).

IL-8 is produced from a variety of cells including T cells (946,947), monocytes (948–951), neutrophils (952–955), endothelial cells (956,957), eosinophils (958), granulocytes (959), mesangial cells (960), and tumor cells (961,962) in addition to fibroblasts and keratinocytes (963). Numerous agents can upregulate IL-8 in these cells, such as infectious agents, endotoxin, lectins, IL-1, and TNFα. IL-8 induces $CD4^+$ and $CD8^+$ T-cell migration to sites of lesions (946,964). It also induces neutrophils to express β_2 integrins and extravasate across vascular endothelium (965), which is critical for early host de-

fenses but which can also result in neutrophil-mediated pathology (966–970). IL-8 also induces respiratory burst and degranulation in neutrophils (950,951). In addition, it is a potent activator and inducer of transendothelial migration for basophils (971,972). Residues important for IL-8 binding have recently been mapped and appear to involve a hydrophobic "pocket" (973,974).

Receptor. Two IL-8 receptors, IL-8RA and IL-8RB, have been identified that share significant sequence homology (975,976) but differ in their ability to bind multiple chemokine ligands. A third promiscuous receptor with broad chemokine binding capacity has been identified on erythrocytes (977). The IL-8RA and IL-8RB, cloned from neutrophil-lineage cells, are both G_i-coupled glycoproteins with seven membrane-spanning regions and intracellular C- and extracellular N-termini (975,976). IL-8RA binds IL-8 with high affinity and has a limited binding capacity for other chemokines (975,978,979). On the other hand, while IL-8RB binds IL-8 with high affinity, it also binds additional C-X-C cytokines such as GROα and NAP-2 with varying affinities (978,979). Divergent residues between the two receptors are clustered in the N-terminus and this region appears largely to determine receptor specificity (973,978–981). More recently, multiple domains in the receptors have been found to regulate receptor affinities (982).

7.7. OTHERS

7.7.1. Interleukin 14 [High-MW B-Cell Growth Factor (BCGF1)]

IL-14 was isolated from supernatants of T cells and T- and B-cell lines and lymphoid tumor cells (983). It is secreted by activated T cells, mRNA levels being upregulated about 8 hr after stimulation with phytohemagglutinin (984). IL-14 activity results in proliferation of activated B cells but blocks their ability to differentiate antibody production (985). B cells from patients with hematopoietic malignancies have in some cases been found to proliferate in response to IL-14 (986–989). IL-14 is secreted by some B-cell lymphomas and may be present in effusion fluids from patients with large tumor burdens (990). Although resting B cells do not respond to IL-14 treatment, B cells are the only identified source of binding sites for IL-14 (991,992).

7.7.2. Interleukin 16 (Lymphocyte Chemoattractant Factor)

IL-16 was originally described for it ability to act as a specific chemoattractant on T cells (993). It has no primary sequence homology with other cytokines and appears to function as a 56-kDa tetradimeric complex, composed of four identical 14-kDa chains. It was found to act only on T cells of $CD4^+$ lineages, where in addition to chemotaxis it enhances growth competency, upregulates IL-2R, and stimulates migration of $CD4^+$ monocytes (994,995). It has also been found to act as a chemoattractant for $CD4^+$ eosinophils but otherwise appears to have little effect on these cells (996). IL-16 is secreted from activated $CD8^+$ T cells, where it appears to be released from granules, as secretion is not accompanied by mRNA synthesis or translation (997,998).

Receptor. Unique among the cytokine families, IL-16 does not have a specific receptor. Rather it appears to bind the CD4 coreceptor on T cells and CD4 expressed on eosinophils and monocytes (996,999). Hybridoma cells transfected with a CD4 mutant protein lacking LCK binding sites do not respond to IL-16, suggesting an LCK-mediated activation pathway (1000). Interaction between IL-16 and CD4 results in increased intra-

cytoplasmic calcium and inositol trisphosphate and translocation of protein kinase C to the membrane (67).

7.7.3. Interleukin 17 [Cytotoxic T-Lymphocyte-Associated Antigen 8 (CTLA8)]

IL-17 was identified and cloned from a subtracted murine cDNA library derived from T cells (1001). It was mapped to a single site on mouse chromosome 1A and human chromosome 2q3. Human IL-17 has been cloned and its immunological features investigated (1002,1003). IL-17 is a homodimer composed of 155-amino-acid subunits. It is secreted by activated $CD4^+$ T cells and stimulates endothelial, epithelial, and fibroblast cells to produce a variety of cytokines, including IL-6, IL-8, G-CSF, and prostaglandin E_2 (1002,1003). IL-17 also upregulates expression of intracellular adhesion molecule 1 (ICAM-1) on human fibroblasts (1003) and supports hematopoietic progenitor cell proliferation and differentiation into neutrophils (1002). IL-17 exhibits 57% amino acid sequence identity with the predicted protein encoded in the 13th ORF of the T-lymphotropic virus *Herpesvirus saimiri* (1001).

7.7.4. Interleukin 18 [Interferon-γ Inducing Factor (IGIF)]

IL-18 activity was identified from tissue extracts of mice infected with heat-killed bacterium and mitogen, which resulted in the induction of high levels of IFNγ production (1004,1005). IL-18 was purified and found to potentiate proliferation and IFNγ production from nonadherent spleen cells in the presence of IL-2, anti-CD3 antibody, or concanavalin A (1006). IL-18 has been cloned and sequenced and found to be synthesized as a 192-amino-acid proprotein that is processed into a mature 157-amino-acid molecule (1007). IL-18 mRNA is upregulated in Kupffer cells and stimulated macrophages (1007,1008). Recombinant IL-18 was found to markedly induce IFNγ production from $CD4^+$ T cells treated with anti-CD3 antibody and to induce NK cell cytotoxicity (1007,1008). Human and murine IL-18 exhibit 65% conservation of the protein sequences.

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8

Leukocyte Cluster of Differentiation Antigens

The list of cluster designation (CD) (differentiation) antigens is constantly expanding as new molecules and monospecific antibodies are identified. The table below is updated for all of the differentiation antigens officially designated from the 6th International Workshop in Human Leukocyte Differentiation Antigens, held in November 1996 in Japan*. This Workshop resulted in the addition of 41 new CD clusters or subclusters, which represent cytokine receptor chains, the CD30/CD40 ligands, NK receptors, important ectoenzymes among many other both well-characterized and recently identified molecules. We have attempted to provide a brief overview of some of the important structural and biological features of the CD antigens, including some referencing that should have utility for an initial investigation of these molecules.

*Kishimoto, T., Goyert, S., Kikutani, H., Mason, D., Miyasaka, M., Moretta, L., Ohno, T., Okumura, K., Shaw, S., Springer, T. A., Sugamura, K., Sugawara, H., von dem Borne, A. E. G. K., Zola, H., eds. 1997 *Leukocyte Typing VI: White Cell Differentiation Antigens*, New York, Garland Publishers (in press).

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
$CD1_{a-e}$	T6	45 kDa	Cortical thymocytes, B cells, dendritic cells, intestinal epithelial	CD1 molecules have some homology to the MHC class I α3 domain and the β2 domain of class II (1). CD1 also associates with β_2-microglobulin and presents antigens on the cell surface in a TAP-independent manner (2,3). Complex alternative splicing of CD1 genes results in tissue-specific forms of the protein, which can be located intracellularly, membrane bound, or secreted (4,5). Surface CD1 molecules present longer peptides than those normally found on class I molecules. Peptide-specific $CD8^+$ αβ T-cell responses have been generated to targets bearing CD1 molecules (6–11).
CD2	T11, leukocyte function antigen (LFA-2)	51 kDa	Expressed in murine during early B-cell development (12), where the majority of IgM^-, $B220^+$ cells are $CD2^+$. Most T cells, immature thymocytes	CD2 is a monomer with two extracellular Ig-like domains and a long proline-rich cytoplasmic tail. Ligand is CD58 (LFA-3). CD2 acts as an adhesion molecule between effectors and targets, thymocytes and other cells of the microenvironment, or T cells and antigen-presenting cells (13). CD2 can transduce activation signals in T cells probably in association with CD3 and p59fyn (14). IL-5, IL-6, and IL-10 expression is induced by CD2 cross-linking (15). CD45 activity is required for CD2-induced tyrosine kinase activity, PLCγ1 activation, and IL-2 induction (16,17). CD2 engagement may play a role regulating Th1–Th2 differentiation (18,19).
CD3 γ, δ, ε, ζ, and η	T-cell receptor invariant chain	26 kDa 20 kDa 20 kDa 16 kDa 22 kDa	Thymocytes and mature T cells	The CD3 chains associate noncovalently with either αβ or γδ T-cell receptors. CD3 includes γ, δ, ε, η, and ζ chains. CD3 may also associate with the γ chain of the Fcε receptor I (FcεRIγ), as part of a TCR complex or as an Ig receptor. CD3 subunits are arranged as homo- and heterodimers, including CD3γε and CD3δε hetero-

				dimers, and a disulfide-linked heterodimer consisting of a ζ subunit and one of either ζ, η, or FcεRIγ-chain subunits (20,21). Cytoplasmic regions of CD3 chains interact with signaling kinases such as ZAP70 to mediate antigen receptor signaling.
CD4	T4, L3T4, TCR co-receptor	55 kDa	Thymocytes and mature T-helper cells. In humans also expressed on monocytes and macrophages	CD4 contains four extracellular Ig-like domains. The $CD4^+$ T-cell subset is MHC class II restricted, and subserves T-helper cell functions. CD4 interacts via its N-terminal Ig-like domain with nonpolymorphic α2 and β2 domains of MHC class II molecules (22,23). The N-terminus of CD4 also acts as a high-affinity receptor, the HIV envelope glycoprotein gp120 (22,24), providing an attachment point for viral entry (25,26).
CD5	T1, Leu-1, Ly-1	67 kDa	Thymocytes and mature T cells. May also be present on B cells, such as the autoantigen-producing B-1 B cells (27)	Contains three extracellular cysteine-rich domains and multiple cytoplasmic phosphorylation sites. About 50% of human fetal B cells are $CD5^+$, whereas only 3% are $CD5^+$ in adult lymph nodes (28). Almost all cases of chronic lymphocytic leukemia are $CD5^+$. $CD5^+$ B cells have been implicated in numerous autoimmune conditions (29). CD5 associates with TCR and BCR complexes and is phosphorylated in responses to antigen receptor stimulation (30,31). CD72 on B cells is a natural ligand for CD5 (27). Anti-CD5 antibodies potentiate T-cell proliferation, IL-2 secretion, and IL-2R (CD25) expression (32,33). IL-5-deficient mice have dramatic reductions in $CD5^+$ B-cell populations (34).
CD6	T12	115 kDa	Thymocytes, pan-T-cell marker, chronic B-cell leukemias, and brain	CD6 is a monomeric glycoprotein with potential N- and O-linked glycosylation sites (35). It contains an extracellular membrane-proximal cysteine-rich domain, simi-

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
				lar to that found for CD5 (36). Variable cytoplasmic domains can be generated through alternate splicing of CD6 transcripts (37). CD6 cross-linking induces T-cell proliferation and receptor phosphorylation (38,39). Antibody-blocking studies have shown CD6 involvement in thymocyte interactions with thymic epithelial cells (40). CD6 binds the activated leukocyte cell-adhesion molecule (ALCAM) expressed on activated leukocytes (41).
CD7	gp40	40 kDa	T cells, NK cells, T-cell progenitors in fetal liver, thymus, and bone marrow, hematopoietic stem cells (42)	CD7 is a homodimeric glycoprotein that associates with the TCR complex (43). Cross-linking studies suggest that CD7 may be involved in regulating phosphoinositide levels important to antigen receptor signaling (44). CD45 and CD3 coimmunoprecipitate with CD7, suggesting an association with the antigen receptor complex (43). Signaling via CD7 molecules has been described on human NK cells, inducing tyrosine phosphorylation and β_1 integrin-mediated adhesion to fibronectin (45). CD7 overexpressed in transgenic mice does not cause obvious hematological disturbance (46).
CD8	T8, Lyt2/3, TCR coreceptor	α/β 38 kDa 33 kDa	Thymocytes, mature (cytotoxic) T cells	CD8 is a transmembrane heterodimer expressed as a coreceptor on class I-restricted T cells. CD8 heterodimers are expressed on virtually all class I-restricted T cells excluding intestinal intraepithelial lymphocytes (IEL), which express a CD8α homodimer (47). CD8 is required for thymic selection processes (48,49) and class I-restricted T-cell cytotoxic responses (49).
CD9	None	25 kDa	Endothelium, platelets, activated T cells, B cells, eosinophils and basophils, megakaryocytes, stromal cells	Contains two extracellular loops, protruding from four transmembrane regions (50). Belongs to the tetraspan family of molecules, which includes CD19, CD21, CD53, TAPA-1, and R2/C33. Involved in platelet aggregation (51). In cats, a CD9 homologue has been

				identified as a feline immunodeficiency virus receptor (52,53). CD9 has also been reported as a pre-B-cell adhesion molecule, possibly important during B-cell ontogeny (54). CD9 is also involved in cell motility, perhaps through integrin regulation (55), and may regulate hematopoiesis (56).
CD10	Common aculte lymphoblastic leukemia antigen (CALLA), enkephalinase, gp100	100 kDa	Pre-B cells, thymocytes, neutrophils, granulocytes, bone marrow stromal cells, epithelial cells, kidney cells, and malignant cells (57,58).	CD10 is a zinc metalloproteinase/neutral peptidase (59). It cleaves a number of biologically important molecules such as: enkephalins, angiotensins, neurotensin, and substance P (60). CD10 is upregulated by C5a-stimulated leukocytes (61). CD10 may regulate B lymphopoiesis, as its inhibition promotes maturation of spenic B cells, perhaps by cleaving a peptide substrate responsible for B-cell proliferation or maturation (62,63). May also have a role in thymocyte development (58). CD10 degradation of IL-1β in bone marrow microenvironment may regulate its levels there (64). CD10 also regulates neutrophil activities (65,66).
CD11a	LFA-1, LeuCAM, integrin a^L subunit	180 kDa	Present on neutrophils, monocytes, macrophages, and lymphocytes	CD11a contains 12 potential sites for N-linked glycosylation and may possess other O-linked oligosaccharides. CD11a is a β_2 integrin and exists only as a heterodimer with CD18. Ligands for CD11a/CD18 heterodimers include ICAM-1, ICAM-2, and ICAM-3, which are present on both activated and resting endothelial cells. The CD11 family is important for effective leukocyte recirculation, adherence and diapedesis, phagocytosis, and antitumor responses (67–69).
CD11b	MAC-1, Mo-1, CR3, OKM-1, LeuCAMb, integrin a^M subunit	170 kDa	Present on neutrophils, monocytes and macrophages, NK cells	CD11b is an integrin family member and exists as a heterodimer with CD18 (CD11b/CD18). CD11b/CD18 contains binding sites for complement iC3b and is therefore important to particle recognition and phagocytosis (70). CD11b/CD18 also binds coagulation factor X, fibrinogen, heparin, and LPS (71–74), in addition to ICAM-1 (CD54) (75) and FcεR (CD23) (76).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD11c	p150, p150, 95, LeuCAMc, integrin a^X subunit	150 kDa	Neutrophils and monocytes, NK cells, activated B and T cells (77)	A member of the β_2 integrin family and exists only as a heterodimer with CD18. As with CD11b, CD11c is an important receptor for iC3b, fibrinogen, LPS (77–79), ICAM-1 (CD54), and FcεR (CD23) (76,80). Like other family members, cross-linking also induces homotypic aggregation of T cells (80). Platelet-expressed fibrinogen induces oxidative burst in neutrophils through CD11c (81).
CD12		90–120 kDa	Monocytes, granulocytes, platelets	IFNγ induces expression on thymic epithelium (82).
CD13	gp150, neutral aminopeptidase	160 kDa	Neutrophils, basophils, monocytes, eosinophils, and myeloid leukemias. Numerous other cells also express, such as fibroblasts, osteoclasts, synaptic membranes of the CNS, and gut epithelium	CD13 has a single transmembrane portion with its N-terminus located intracellularly (i.e., type II membrane protein). The external –COOH region functions enzymatically to hydrolyze terminal amino groups from peptides. It may function to inactivate or activate peptides, or regulate duration of peptide-mediated signals (83). It can perform peptidase activity on peptides that are bound to class II molecules on the surface of antigen-presenting cells (84). There is high CD13 activity on stromal cells that bind $CD4^+CD8^+$ thymocytes, suggesting a role during T-cell development (85). Anti-CD13 antibody recognizes an epitope on cytomegalovirus (86,87). Present on malignant cells and may play a role in metastasis (88).
CD14	None	55 kDa	Monocytes, macrophages, uterus, adipose tissue (89)	CD15 lacks a transmembrane region and is bound to the cell membrane by a GPI anchor. CD14 also exists in soluble forms (90,91). It associates with the complement receptor CR3 on some cells (92) and is critical for recognition of lipopolysaccharide by the LPS recep-

				tor complex (93) and is important to innate responses against gram-negative and -positive bacteria (94). CD14 is important in mediating endotoxic shock (95). Mice with gene-targeted mutations at the CD14 locus are resistant to endotoxic shock and to gram-negative bacteria (96).
CD15	Lewis X, Le^x	Carbohydrate	Neutrophils, monocytes, and eosinophils. Also associated with myeloid leukemia and Reed–Sternberg cells	CD15 is not a protein. It represents a pentasaccharide that can be found linked to various lipid or protein backbones (97). The carbohydrate structure participates in adhesion and activation processes of neutrophils and other granulocytes (98). Thus, CD15 mAbs inhibit neutrophil adhesion-dependent functions (99). A CD15-associated structure is a ligand for CD2 (100).
CD16	FcγRIII (FcγRIIIa, FcγRIIIb)	60 kDa	Polymorphonuclear neutrophils, NK cells, macrophages	CD16 contains two extracellular Ig-like domains and five sites for N-linked glycosylation. There are two forms of CD16, FcγRIIIa and FcγRIIIb, that exhibit structural differences and are products of separate but adjacent genes (101). FcγRIIIb lacks cytoplasmic and transmembrane domains and is GPI-anchored to the membrane. Both forms of CD16 are low-affinity receptors for the Fc portion of IgG and mediate phagocytosis and ADCC.
CD17	Lactosyl-ceramide (IacCer)	Galβ1-4Glcβ1-1Cer	Neutrophils, basophils, leukemic cells (102,103)	CD17 is a phosphatidylinositol-anchored surface antigen synthesized in Golgi bodies and abundantly expressed on neutrophils (104,105). Cross-linking with anti-CD17 mAbs results in calcium flux and upregulation of other surface molecules, such as CD11b and CD67 (104,106). CD17 can act as a mitogen to induce proliferation of vascular smooth muscle cells, mimicking a process of atherosclerosis (107).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD18	Integrin β subunit	90 kDa	Neutrophils, monocytes, macrophages, leukocytes	CD18 is a β_2 integrin family member. CD11/CD18 heterodimers are involved in important adhesion processes between cells and matrix proteins. A hereditary mutation in CD18 results in a reduction or lack of a functional CD11a/CD18 (LFA-1), CD11b/CD18, and CD11c/CD18 heterodimers. Individuals affected by this lymphocyte adhesion deficiency (LAD) suffer from lethal susceptibility to bacterial and fungal infections (108–110).
CD19	B4	95 kDa	B-cell-specific marker (111)	CD19 has two extracellular Ig-like domains with five sites for N-linked glycosylation, and a long cytoplasmic tail with 9 Tyr residues and SH2- and SH3-binding domains (112–114). Anti-CD19 mAbs result in calcium flux and endocytosis of the CD19–mAb complex (115). Anti-Ig-, IL-2-, and IL-4-induced activation of human B cells is blocked by mAb to CD19, whereas stimulation of CD19 can also enhance B-cell response to stimuli (116,117). CD19 may act as a coreceptor in enhancing B-cell antigen receptor signaling (118).
CD20	B1, Bp35	33 kDa 35 kDa 57 kDa	B cells, but not on plasma cells	There are three splice variants for CD20 (119). Both C- and N-termini of the nonglycosylated CD20 are located intracellularly. Four membrane-spanning domains form a structure similar to known ion channel molecules. CD20 appears to be involved in the regulation of calcium flux across the cell membrane (120,121). Anti-CD20 antibodies can interfere with cell cycle progression and block B-cell differentiation (122–124).
CD21	CR2, EBV receptor, C3δγ receptor	145 kDa	B cells, dendritic cells, epithelial cells, thymocytes, peripheral T cells	CD21 contains numerous sites for N-linked glycosylation and at least 15 complement control protein (CCP) modules, otherwise known as short consensus repeats (SCRs). Functions as recetor for C3d complement frag-

				ment and Epstein–Barr virus (125). Through its interactions with CD23 (126), it may be involved in the regulation of IgE production (and B-cell activation) and play a role in allergic reactions (127). EBV proteins bind CD21 and upregulate B-cell IL-6 and CD21 expression (128,129).
CD22	BL-CAM	130 kDa 140 kDa	IgM^+ and IgM^+IgD^+ B cells but not on plasma B cells	CD22 splice variants CD22a and CD22b contain at least 10 sites for N-linked glycosylation and 5 and 7 extracellular Ig-like domains, respectively (130,131). CD22 mediates homotypic and heterotypic adhesions through interactions with various N-linked sialoglycoproteins (130–132). CD22 may regulate B-cell activation after stimulation through the antigen receptor (132–134). CD22 may bind the sialoglycoprotein CD45 on T cells (135).
CD23	FcεRII, BLAST-2	45 kDa	Monocytes, macrophages, eosinophils, platelets, and lymphocytes	CD23 exists as two alternate splice variants, with FcεRIIa being expressed on B cells and FcεRIIb on monocytes and eosinophils (136,137). CD23 is a low-affinity receptor for the Fc portion of IgE. CD23 may be involved in regulating IgE synthesis (138) via interactions with CD21 on B cells (127), although CD23-deficient mice produce normal levels of IgE (139). CD23 triggering may be an important stimulator of NO production and IL-10 synthesis from macrophages and monocytes (140,141).
CD24	Homologue in mouse called heat-stable antigen (HSA), nectadrin	40 kDa	Immature B and T cells, granulocytes. Activated T cells. Expression declines on mature cells and is not found on plasma cells	CD24 is a small protein core (33 amino acids) with heavy glycosylation, attached to the membrane via a GPI anchor. CD24 costimulates activation of T-helper cells (142) and may be involved in thymocyte selection (143). CD24 binds P-selectin (144,145) and is tran-

(continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
				siently upregulated on activated T cells where it may function as costimulatory molecule (142). CD24 may function in B-cell development, supported by the observation that CD24-deficient mice have reduced numbers of immature B cells in bone marrow (146,147).
CD25	Interleukin-2 receptor α (IL-2Rα)	55 kDa	Activated T, B, and NK cells, monocytes. Thymocytes	There are three IL-2 receptor chains, α (CD25), β (CD122), and γ. Low-affinity CD25 has small cytoplasmic chain and two extracellular complement control protein modules (CCP). CD25 is required for IL-2 signaling, is absent from most cells but upregulated after activation (148). CD25 gene-targeted deletions result in hyperactive immune systems, lymphadenopathy, and autoimmunity (149). CD25 is expressed on thymocytes (150) and immature B cells in the bone marrow (151), although CD25-deficient mice have normal T- and B-cell development.
CD26	Dipeptidyl peptidase IV (DPPIV or DP IV)	110 kDa	T cells, some B cells, macrophages, epithelial cells	CD26 is a type II membrane glycoprotein that associates with adenosine deaminase on T cells (152,153). CD26 ectoenzyme-proline-specific peptidase activity mediates cell migration across endothelial barriers. CD26 may also provide a CD3-dependent (154) alternate activation pathway for T cells (155–157). HIV Tat protein binding to CD26 has been shown to inhibit cell activation (158). CD26 is also a controversial cofactor necessary for HIV entry into T cells (159,160).
CD27	None	120 kDa	Most T cells, B cells, and NK cells. Induced on T cells after TcR stimulation	CD27 is a disulfide-linked homodimer with some homology with the TNF/NGF receptor family. Involved in T-cell activation as a result of various stimuli, such as anti-CD2, PHA, and tetanus toxoid, and may be involved in T–B-cell interactions (161). Through binding

				of its ligand CD70 (162), CD27 regulates NK-cell cytotoxicity (163), B-cell activation and synthesis of Igs (164), T-cell activation and development of immature thymocytes (165–167). CD27 is also a marker for memory T cells (168,169).
CD28	Tp44	90 kDa	$CD4^+$ T cells, 50% of murine $CD8^+$ T cells (in mice a pan-$CD8^+$ T-cell marker)	CD28 is a disulfide-linked homodimer, each subunit containing a single extracellular Ig-like domain. $CD4^+CD8^+$ thymocytes express CD28 (170,171) and mature T cells upregulate the molecule after activation (172). CD28 binds two ligands, CD80 (B7/B7-1) (173) and CD86 (B70/B7-2) expressed on APC. CD28 costimulation supports T-cell proliferation, cytokine production, and effector function (174,175) by inducing activation and secretion of IL-2 (176,177), as well as IFNγ, IL-1, TNF, IL-4, and IL-5 (178–180). An absence of CD28 signaling during T-cell activation can induce T-cell unresponsiveness, or anergy (181,182).
CD29	Integrin β_1 subunit, very late activation antigen (VLA)	130 kDa	Leukocytes, macrophages, memory marker on T cells	CD29 (β_1 subunit) exists as heterodimer associated with various α-integrin ($CD49_{a-f}$) subunits, forming the VLA molecules (see CD49). The heterodimers mediate cell–cell and cell–matrix adhesive interactions. VLA molecules are implicated in numerous biological roles such as leukocyte transendothelial migration (183–185). Adhesion between T and B lymphocytes may involve VLA molecules (186).
CD30	Ki-1, Ber-H2 antigen	112 kDa	Activated T cells ($CD45RO^+$) (187) and B cells	CD30 is a type I transmembrane glycoprotein that also exists in some situations in a soluble 84-kDa form (188,189). Extracellular domain shares similarity with other TNF/NGF receptor superfamily members, includ-

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
				ing TNF receptors, NGF receptor, 4-1BB, OX-40, CD27, CD40 and CD95 (190). Expressed on malignant cells including Hodgkin's and Reed–Sternberg cells (191,192). In addition, CD30 has been detected on $CD8^+$ and $CD4^+$ T cells from patients with HIV, and on $CD4^+$ T cells from allergic patients (193–196). CD30 is expressed in the thymic medulla (197) and appears to function in mediating thymocyte death (198). A ligand (CD30L) for CD30 is expressed on activated T cells and macrophages (199,200).
CD31	PECAM-1 (platelet endothelial cell adhesion molecule-1)	130 kDa	Platelets, endothelial cells, granulocytes, monocytes	CD31 has six extracellular Ig-like domains and nine sites for N-linked glycosylation. Membrane-bound and soluble forms of CD31 are produced by differential splicing (201,202). CD31 is involved in leukocyte–endothelial adhesion and in activation of T-cell integrins (203,204). CD31 homophilic interactions mediate leukocyte extravasation, including T cells, NK cells, and monocytes, across vasculature walls in response to inflammatory cytokines (205–208).
CD32	FcγRII	40 kDa	B cells, neutrophils, monocytes, T cells (209,210)	CD32 has two extracellular Ig-like domains and exists in various isoforms as a low-affinity receptor for the Fc portion of IgG (211). CD32 mediates myriad functions as Fc receptors for IgG immune complexes. Various isoforms appear capable of mediating different functions, such as B-cell activation or inactivation (212), enhance antigen capture and class II presentation (213), cytokine synthesis by mast cells/NK cells (214). CD32 gene-targeted mice have enhanced sensitivity to IgG-triggered degranulation and exaggerated cutaneous anaphylaxis responses, which appear to result from reduced threshold for mast cell activation through FcγRIII (CD16) (215).

CD33		67 kDa	Early myeloid progenitors and leukemic cells, mRNA detected in bone marrow, spleen, thymus, brain, and liver	CD33 contains two extracellular Ig-like domains and five sites for N-linked glycosylation. The gene for CD33 has recently been cloned in mice: there is 61% amino acid identity in the human and mouse Ig-like domains, but significant differences between cytoplasmic domains. There are two CD33 isoforms (216), both members of the sialoadhesin family, which includes CD22 and MAG, with sialic acid-dependent cell adhesion properties (217). CD33 is expressed in a number of myeloid and B-cell neoplasms (218,219).
CD34		105–120 kDa	About 3% of bone marrow cells, hematopoietic progenitor cells	CD34 expression is widely used in the identification and purification of hematopoietic stem and progenitor cells (220–222). CD34 is expressed on early progenitor cells with hematopoietic reconstitution potential (223,224). However, in mice, stem cells have also been found that are $CD34^{low\text{-}negative}$ (225). $CD34^{+}$ progenitor cells have been used to generate human T cells and dendritic cells *in vitro* (226,227). CD34 may be involved in hematopoietic cell adhesion to stroma. CD34 expressed transgenically in thymocytes or in cell lines increases adhesion to bone marrow stromal cells via an unidentified ligand (228).
CD35	Complement receptor 1, CR1, C3b/C4b receptor	250 kDa	Present on all cells in the peripheral blood excluding platelets. On T-cell subsets, B cells, monocytes, neutrophils eosinophils, follicular dendritic cells	CD35 has 20 sites for N-linked glycosylation and short consensus repeats (SCRs) or complement control protein (CCP) modules, three of which contain binding sites for C3b and/or C4b (229,230). CD35 molecule is polymorphic, with large variations in molecular mass. CD35 mediates phagocytosis of particles coated with C3b or C4b, immune adherence, immune complex clearance, and C3b/C4b regulation. It may be involved in anti-tumor cell cytotoxicity by neutrophils (231).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Mol. mass	Tissue distribution	Structure/function	
CD36	Platelet glycoprotein IV, OKM5 antigen	88 kDa	Monocytes, platelets, adipocytes, and some endothelial and epithelial cells	CD36 has 10 sites for N-linked glycosylation and interacts with a broad range of ligands such as thrombospondin, malaria-infected erythrocytes, platelet-agglutinating protein, long-chain fatty acids, and collagen types I/IV (232–234). CD36 mediates phagocytosis by macrophages (235). Expression of CD36 is regulated both developmentally and in response to activation, and its genetic regulatory elements have been investigated (236). Ligand specificity has been reported to depend on phosphorylation of an ectodomain (237). CD36 may also play a role in wound healing (238).
CD37		40–52 kDa	Mature B cells, but absent from pre-B or plasma cells. Low expression on myeloid and T cells (239)	CD37 has three sites for N-linked glycosylation and belongs to a tetraspan family of molecules that includes CD19, CD21, and CD53 (240). The function of CD37 is not known.
CD38	T10	45 kDa	T- and B-cell subsets, such as mitogen-activated T cells, pre-B and germinal center B cells, Ig^+ plasma cells, platelets, hematopoietic progenitors (241,242)	CD38 is a cell-surface enzyme (ectoenzyme) that utilizes NAD^+ and has ADP-ribosylating activity (243–245). Posttranslational modification of CD38 alters its catalytic properties (246). Anti-CD38 antibodies potentiate biological lymphocyte activation, including the induction of B-cell proliferation. Other functions of CD38 have been described, such as signal transduction and cell adhesion (247), and it may mediate selectin-type adhesion between lymphoid cells and HUVECs (248). CD38 also regulates apoptosis in geminal B cells (249) and induces the upregulation of CD125 (IL-5Rα) (250).
CD39		70–100 kDa	Activation lymphocytes (251)	CD39 has six potential N-linked glycosylation sites, 11 Cys residues, and two possible transmembrane regions (252). Primary amino acid sequence of CD39 is similar to those of several newly identified nucleotide triphosphatases, and CD39 has ecto-apyrase activity (253). It may define a subset of activated $CD8^+$ T cells (251).

CD40		50 kDa	Splenic B cells, some pre-B cells, 5–10% of splenic $CD4^+$ and $CD8^+$ T cells (254), dendritic cells	CD40 has four cysteine-rich repeats in its extracellular region and shares significant homology with TNF/NGF receptor family. CD40 is involved in B-cell stimulation of T-helper cells, through its ligand CD40L (254). Cross-linking of CD40 strongly induces B cells to proliferate and facilitates B-cell isotype switching *in vitro*. CD40 plays a critical role in cognate interactions between T and B cells, to facilitate T-cell-dependent B-cell activation (255,256). Preventing interactions between CD40 and its ligand CD40L blocks lymphocyte activation *in vivo* and blocks autoimmunity (257,258). Mice that lack either CD40 or CD40L do not mount IgG, IgA, or IgE antibody responses, do not form germinal centers, and have blocked activation of T-cell responses (259,260). Blocking both CD28 and CD40 promotes survival of allografts (261).
CD41a,b	GPIIb, a^{IIb} integrin	125 kDa/22 kDa	Megakaryocytes and platelets	CD41 exists as a noncovalently linked heterodimer with CD6. CD41 is itself composed of two disulfide-linked subunits, formed from posttranslational cleavage of a 125-kDa molecule (262). The CD41 heterodimer is expressed on adherent/activated platelets, where it binds fibrinogen and von Willebrand factor and is important in platelet aggregation and blood clotting (263–266).
$CD42_{a-d}$	GPIX, GPIbα, GPIbβ, GPV	23 135,23 22 85 kDa	Megakaryocytes and platelets	CD42 binds von Willebrand factor that has adhered to collagen on subendothelium (267,268). Interaction prevents platelet detachment from vessel wall and thus helps facilitate aggregation (266).
CD43	Leukosialin, sialophorin	35–115 kDa	Mature T cells and thymocytes, activated B-cell subsets, plasma cells, monocytes, macrophages, granulocytes, NK, plate	One third of CD43's extracellular residues are O-glycosylated, with sugars comprising about 50% of its molecular mass. CD434 has little secondary or tertiary structure. Sialic residues impart a negative charge on the molecule and may be important in its function. ICAM-1

(*continued*)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
			lets, and 30% of bone marrow cells	has been reported as a ligand (269). CD43 signaling pathway has been reported to be defective in peripheral blood mononuclear cells in Wiskott–Aldrich syndrome (270).
CD44	PgP-1, Lt-24 (mouse), Hutch-1, Hermes antigen	80–95 kDa, 130 kDa	T cells, B cells, monocytes, granulocytes, and medullary thymocytes and erythrocytes	CD44 has seven sites for N-linked glycosylation and O-linked sugars vary among the 20 known isoforms (271), which arise from alternative splicing, and may contain several chondroitin sulfate moieties. CD44 expression is inducible with TNFα (256) and is transiently upregulated on T cells during immune responses (272). CD44 mediates T-cell integrin-independent adhesion, by interacting with hyaluronic acid (273,274), an interaction important for diverse functions such as lymphocyte extravasation at HEV and inflammatory responses in asthma. CD44 may mediate lymphocyte rolling (275). Different CD44 isoforms may be involved in tumor metastasis (276). CD44 gene-targeted deletions in mice reveal a role for CD44 in hematopoietic progenitor distribution, regulation of granuloma responses, and tumor growth.
CD45	Leukocyte common antigen (LCA), Ly-5, B220, T2000	180–220 kDa	On all leukocytes and hematopoietic progenitors	CD45 has 11–16 sites for N-linked glycosylation and abundant O-linked sites on isoforms A, B, and C. Different CD45 isoforms have been used as markers for T-cell subsets and B cells. Phosphorylase activity of CD45 is essential for antigen receptor-induced signaling (277–280).
CD46	Membrane cofactor protein, complement regulator protein	51–58 kDa, 59–68 kDa	Immature and mature T cells, B cells, monocytes, NK cells, granulocytes, platelets, endothelial and epithelial cells	CD46 has three sites for N-linked glycosylation and several sites for O-linked sugars, depending on alternatively spliced form. Contains four extracellular CCP modules (see CD21,CD55). Binds C3b or C4b and permits their enzymatic breakdown. Presence on surface of

				cell prevents lysis of autologous cells by activated complement, thereby present on cells bathed by extracellular fluids (276). Various isoforms act as receptors for measles virus (281,282). CD46 mediates virus-induced suppression of IL-12 synthesis from monocytes (283).
CD47	Integrin-associated protein (IAP)	50 kDa	Present on most cells of hematopoietic origin, epithelial, endothelial, fibroblasts, sperm, and some tumor cell lines	CD47 has a single extracellular Ig-like domain, five membrane-spanning regions, a short cytoplasmic tail, and exists as several alternate-splice variants (284,285). The molecule is believed to mediate calcium flux in response to binding of cell adhesion molecules to ligand structures, and to mediate neutrophil migration across endothelium (286–288). Anti-CD47 antibodies can induce oxidative burst in neutrophils.
CD48	CD2 ligand, sgp60 murine (289)	45 kDa	T and B cells, macrophages, eosinophils, some epithelial and endothelial cells	CD48 has two Ig-like domains and is anchored to the membrane via a GPI moiety. Anti-CD48 antibodies are reported to enhance graft survival (290). Cross-linking CD48 induces aggregation of B cells (291). Associated with multimolecular complexes that contain kinase activity such as lck and fyn (292,293). CD48, a natural ligand for CD2, can costimulate T cells and enhance antitumor cytotoxic responses (294,295).
$CD49_{a-f}$	Very late antigens 1–6, α_1 β_1 integrins	120–210 kDa	Pan-leukocyte expression	VLA molecules contain a CD29 subunit and one of the VLA subunits $CD49_{a-f}$. The CD29/CD49 heterodimers bind extracellular matrix, such as laminin, collagen, fibronectin, and epilegrin (296,297). VLA4 and VLA5 are expressed on thymocytes (298). VLA molecules enhance signaling through T-cell antigen receptor (297,299).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD50	Intercellular adhesion molecule 3 (ICAM-3)	130 kDa	T cells, B cells, thymocytes, monocytes, and granulocytes	CD50 is a counterreceptor for CD11a/CD18 (LFA-1) (300). CD50 is involved in adhesion events during the initial phase of the immune response, and costimulates T-cell activation (301–303). CD50 is probably important to cellular interactions between APC and T cells (304,305). Cross-linking CD50 induces calcium flux and protein tyrosine kinase activity and coimmunoprecipitates with p56lck and p59fyn (306,307).
CD51	α^{v} integrin, alpha v vitronectin receptor	150 kDa	Erythroid or megakaryocyte progenitors (308), monocytes, platelets and megakaryocytes, umbilical endothelial cells	CD51 has 13 sites for N-linked glycosylation and exists as a heterodimer in noncovalent association with CD61, CD51 is expressed as 150-kDa molecule which is posttranslationally cleaved into 125- and 24-kDa subunits, which are disulfide-linked CD51 dimer (309). CD51/CD61 is a receptor for vitronectin, thrombospondin, fibrinogen, and von Willebrand factor. The receptor is involved in monocyte adhesion to endothelium (310). Stimulation of CD51/CD61 induces tyrosine phosphorylation in T cells (311) and may regulate NK cell activation (312). CD51 may be involved in tumor metastasis (313,314).
CD52	CAMPATH-1 antigen	21–28 kDa	T cells, B cells, thymocytes, monocytes, neutrophils, granulocytes, and eosinophils	Very small GPI-anchored receptor with a single site for N-linked glycosylation (315). Cross-linking induces calcium flux and oxidative burst (316), but in monocytes decreases their functional activity such as superoxide production and PMA response (317). CD52 triggering can also activate T cells (318). Anti-CD52 antibodies used therapeutically for GVHD and to improve engraftment (319), in addition to their use in the treatment of some forms of leukemia (320).

CD53	MRC-OX44	35–42 kDa	B cells, monocytes, T cells, thymocytes, platelets, osteoblasts and osteoclasts, granulocytes	CD53 belongs to a family of membrane molecules that have four membrane-spanning regions and associated with tyrosine phosphatase activity (321). Cross-linking causes increased intracellular inositol phosphates and diacylglycerol, calcium flux, and release of nitric oxide in macrophages (322), oxidative burst in monocytes (323), and activation of B cells (324). CD53 is upregulated on T cells after TCR engagement (325,326). CD53 associates with class II MHC (327).
CD54	ICAM-1	85–110 kDa	Hematopoietic cells, upregulated on activated T and B cells and monocytes	CD54 has five Ig-like domains and eight sites for N-linked glycosylation. It mediates cell adhesion through binding of β_2 integrins, such as CD11a/CD18 and CD11b/CD18, which results in T-cell activation (328). Cross-linking augments IL-2 receptor expression and effects of CD40 ligation on B cells (329). CD54-deficient mice have impaired inflammatory responses, such as loss in neutrophil emigration, and do not function as stimulators in a mixed lymphocyte reaction (330). CD54 is believed to play a role in virulence of *Plasmodium falciparum* (malaria) infections (331).
CD55	Decay accelerating factor (DAF)	60–70 kDa	Present on most if not all cells exposed to serum	CD55 has a single site for N-linked glycosylation and numerous O-linked sites. Contains four CCP modules (see CD46, CD21) and has a GPI membrane anchor. CD55 can exist as a dimer (332). CD55 proteolytic activity blocks C3 convertase assembly to prevent formation of membrane attack complex, which protects cells from complement-mediated destruction. CD55 is a receptor for echovirus (333). Patients with paroxysmal nocturnal hemoglobinuria are deficient for CD55 on RBCs (334).

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A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD56	NKH-1, Leu-19, neural cell adhesion molecules (N-CAM)	175–185 kDa	NK cells, nervous tissues	CD56 has five Ig-like regions, six sites for N-linked glycosylation, and two fibronectin type III domains. CD56 is involved in cell–cell interactions during development of the nervous system (335), and various isoforms are present on differentiated nerve cells. CD56 is also a marker for NK cells, where it mediates adhesion. NK cells can be identified by the phenotype $CD56^+/CD16^+/CD3^-$.
CD57	HNK-1 (Leu-7)		NK cells, small proportion of peripheral T cells	Number of $CD57^+CD8^+$ T lymphocytes is elevated during HIV and human cytomegalovirus (HCMV) infection and after allogeneic transplant (336–339). CD57 may identify a suppressor subset of $CD8^+$ T cells (340–343).
CD58	Leukocyte function-associated antigen-3 (LFA-3)	55–70 kDa	Hematopoietic and non-hematopoietic cells. T cells, germinal B cells, macrophages, endothelium	CD58 has two extracellular Ig-like domains with six sites for N-linked glycosylation. Both transmembrane- and GPI-anchored splice variants exist. CD58 transduces CD40-independent signals in B cells to induce isotype switching (344). CD58 binds CD2 (345,346) (as does CD48 and CD59), an interaction that may enhance T-cell adhesion with APC (347). A soluble form of CD58 exists in humans (348). A recombinant molecule that blocks CD58/CD2 interactions is reported to abrogate T-cell responses (349).
CD59	Membrane attack complex inhibitory factor, protectin	19 kDa	Most cells of hematopoietic origin, vascular endothelium, epithelial cells, nervous tissue. Coexpressed on $CD34^+$ stem cells (350)	CD59, a GPI-anchored inhibitor of the C9 component of the C5b–9 membrane attack complex (MAC), thereby protecting cells from species-specific complement-mediated lysis (351). CD59 (together with CD58 and CD48) is a ligand for CD2 and can mediate Ag-independent T-cell activation (352–354). Soluble GPI-free forms of CD59 can block complement-induced hemolysis (355,356). Species-specific transgene expression of CD59 in grafts can enhance survival of xeno-

				transplants (357–359). Defects in biosynthesis of GPI anchors, and concomitant lack of CD59, are observed in the hematological disorder paroxysmal nocturnal hemoglobinuria (360). CD59 may be incorporated into viral envelopes to protect them from complement-mediated destruction (361,362).
CD60		Carbohydrate	Marker for a reported $CD8^+$ T-helper subset (363). Granulocytes, some thymocytes, B cells, and monocytes. Nonlymphoid cells in synovium and vascular endothelium (364,365).	CD60 has been described as a marker for T-cell subsets and is expressed on the surface for most T lymphocytes in synovial tissue and fluid and on a smaller proportion of peripheral T cells (364,365). CD60 cross-linking costimulates T cells (364), while CD60 is upregulated by triggering LFA-3 (19). Activation of T lymphocytes can be triggered through CD60. Functional $CD8^+$ T-cell subsets have been identified according to CD60 expression (363).
CD61	GPIIIa, integrin β_3 subunit, vitronectin receptor β chain	110 kDa	Macrophages, megakaryocytes, platelets, and nonhematopoietic cells	CD61 has six sites for N-linked glycosylation. CD61 exists as a heterodimer in noncovalent association with CD41 or CD51 to form the adhesion molecules known as $a^{IIb}b_3$ integrin (GPIII5-IIa complex) and $a^{V}b_3$ integrin (vitronectin receptor), respectively. A putative binding site responsible for $a^{IIb}b_3$ integrin binding to ligands has been located on the loop domain of CD61 (366). The CD61 heterodimers play important roles in platelet aggregation and adhesion (see CD41, CD51).
CD62	P selectin, GMP 140, PADGEM	140 kDa	Activated platelets, megakaryocytes, and endothelial cells	CD62 has 12 sites for N-linked glycosylation and contains an extracellular N-terminal C-type lectin domain, an EGF domain, and nine-repeat CCP molecules. CD62 is a member of the selectin family, which includes E-, L-, and P-selectin (CD62). All bind sialyl Lewis X *in vitro* (367). CD62 is important in leukocyte rolling (368,369) and platelet adherence to monocytes and neutrophils. CD62 is involved in activation of neutrophils (370) and

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
				eosinophil accumulation at sites of allergic inflammation (371). CD62-deficient mice bleed excessively from wounds (372), and CD62/E-selectin double-mutants also have high susceptibility to infections (373). CD62 is upregulated on endothelial cells by the cytokines IL-3, IL-4, and oncostatin M (OSM) (374,375). CD62 binding and leukocyte rolling *in vivo* are mediated by P-selectin glycoprotein ligand-1 (PSGL-1) (376,377). CD62 is required for normal T-cell recruitment and homing (373,378).
CD63	Melanoma marker ME491, MLA1, PTLGP40	53 kDa	Activated platelets, monocytes, megakaryocyte cell lines, macrophages, and weakly on granulocytes, T cells, and B cells. Marker for melanoma	CD63 is a four-transmembrane-region glycoprotein, and a member of the TM4 superfamily that includes CD9, CD37, and CD53. CD63 is found together with von Willebrand factor and P-selectin in secretory granules of endothelial cells, and is likely to be rapidly exocytosed in response to agonists such as thrombin (379). Transfection into melanoma cells inhibits tumorigenicity (380). CD63 associates with VLA (CD29/CD49) heterodimers and CD9 and CD81 (381,382).
CD64	FcγRI	72 kDa	Macrophages, monocytes, neutrophils	CD64 has three Ig-like extracellular domains with 50% protein sequence identity with CD32 and CD16. CD64, which has the highest affinity among the three Fcγ receptors for IgG, induces phagocytosis (383–385), ADCC (386,387), and is transferred across the placenta (388,389). IgG also binds soluble FcγR (390,391). Affinities for various Fcγ receptors are attributed to sequence variations encoded in the C3 domains (392–395). Mice deficient for FcγR are resistant to autoimmune disease (396). CD64 signaling is associated with CD45 phosphatase (397).

CD65	Ceramide dodecasaccharide (VIM-2)	18-residue sugar moiety	Myeloid lineages, granulocytes, and some monocytes	Cross-linking of CD65 induces calcium flux, oxidative burst, and granule-associated proteins CD11b and CD67 (316). Probably involved in phagocyte activation. CD65 surface expression varies with extent of differentiation. Antibody VIM-2 identifies two gangliosides representing CD65, a ceramide dodecasaccharide and a ceramide decasaccharide (398).
$CD66_{a-e}$	a: biliary glycoprotein (BGP-1) c: nonspecific cross-reacting antigen (NCA-95, NCA-50/90) b: carcinoembryonic antigen (CEA)	170–200 kDa	Neutrophils, granulocytes, small proportion of myeloid progenitor cells and colon epithelial cells. A granulocyte-specific activation marker, upregulated on neutrophils (399)	CD66 has four extracellular Ig-like domains and 20 sites for N-linked glycosylation. Eight known splice variants exist, members of the CEA family of adhesion molecules. CD66 mediates homotypic and heterotypic adhesion, and binds to endothelial E-selectin (400). The N-terminal IgV-like domain of CD66 has been shown to mediate adhesion (401,402). CD66 can induce activation and respiratory burst in neutrophils (403,404), and regulate neutrophil adhesion (405). CD66 binds bacterial cell wall constituents and may be important in innate responses to infection (406,407).
CD67	CGM6	100–110 kDa	Like CD66, an activation marker found on granulocytes and neutrophils	CD67 has three Ig-like domains, 11 sites for N-linked glycosylation, and is membrane-bound via a GPI anchor. CD66, expressed together with CD67 in granules (408), is absent from granules in patients with paroxysmal nocturnal hemoglobinuria, a condition related to a defect in GPI synthesis (409). CD67 may be involved in similar adhesion processes as CD66 (398).
CD68	Macrosialin	87–115 kDa	Macrophages, monocytes, and dendritic cells. Larger blasting B cells (lymphomas). Giant cells, some stromal cells and osteoclasts (410)	CD68 has heavy O-glycosylation and nine sites for N-linked glycosylation. Two distinct extracellular domains of CD68 are separated by a proline-rich hinge. CD68 is a macrophage marker and has significant homology with the lysosomal acidic glycoprotein family (LAMP/LGP) (411–413). Associated with cells exhibiting phagocytic or autophagy function.

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A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD69	Lymphocyte activation inducer molecule (AIM), EA 1, MLR-3, Leu-23	33- and 28-kDa homodimer	Platelets. Present also on thymocytes, germinal T cells, and activated lymphocytes	CD69 contains an extracellular C-type lectin domain (414) and exists as a homodimer. It is among the first glycoprotein to be detected on lymphocytes after activation, whereas cross-linking on platelets results in aggregation and release of mediators. CD69 expression inversely correlates with RAG-1 expression during thymocyte selection (415,416), and p21ras may mediate upregulation in T cells (417,418). Signaling through CD69 has been reported to regulate IL-2 expression (419). CD69 may regulate cell death in eosinophils (420).
CD70	CD27 ligand (CD27L)	29 kDa	Found on activated T and B cells	CD70 is a member of the TNFR and NGFR families (162,421). CD70 is a natural ligand for CD27 (422). CD70 engagement by CD27 is important for T-cell activation and T-cell-dependent IgG synthesis (161,423). (See CD27)
CD71	Transferrin receptor	90–95 kDa	Not present on resting lymphocytes but upregulated on most cells (including nonhematopoietic) during proliferation	CD71 has a 671-residue extracellular region and is a homodimer linked via two disulfide bonds. CD71 binds the iron-transport protein transferrin in serum, which it takes up via endocytosis (424). CD71 is present on early committed progenitors and leukemic cells, but not on stem cells, thus it is a good target for *in vitro* purging (425). Hepatitis B virus binds transferrin to facilitate entry via CD71-mediated uptake into cells (426). CD71 is present on proliferating cells including thymocytes (427), a process that requires iron. Expression of CD71 is downregulated by TNFβ (428). CD71 may be associated with CD3 subunits (429).

CD72	Lyb-2	42 kDa	B-cell marker, but absent from plasma cells. Little expression on macrophages	CD72 is a disulfide-linked homodimer with an extracellular C-type lectin domain (430). Three alternative-splice variants for CD72 have been described with specific distributions in murine splenic B cells (431).
CD73	Ecto-5′-nucleotidase	69 kDa	Thymocytes and subsets of mature lymphocytes (432), particularly $CD8^+$ T cells and B cells	CD73 is membrane bound by a GPI anchor. CD73 is an ectoenzyme, catalyzing the 5′ dephosphorylation of purine and pyrimidine (deoxy)ribonucleosides, facilitating their uptake through the membrane. CD73-mediated signaling occurs in response to cross-linking and PMA (433). NK cells have a conspicuous lack of CD73 activity (434).
CD74	MHC II invariant chain (Ii)	31 kDa, 41 kDa	B cells, antigen-presenting cells	The invariant chain (Ii) (CD74) is a transmembrane glycoprotein found in intracellular compartments in association with class II molecules. Splice variants of CD74 result in p31 and p41 isoforms, both of which support class II antigen presentation. In the endosome of B cells, CD74 is cleaved into two fragments, the leupeptin-induced (12 kDa) (LIP) and small-leupeptin-induced proteins (22 kDa) (SLIP), which associate with the class II molecule (435). CD74 is critical for normal class II antigen presentation (436–438).
CD75	HB-6	53 and 87 kDa	Lymphocyte subsets	CD75 is a carbohydrate antigen produced by α2,6-sialyltransferase, an enzyme also responsible for producing CD76. The 2,6-linked sialic acid residue is a critical component of these carbohydrate antigens (439), which are recognized by the mAb HB-6 (440).
CD76		85, 67 kDa	Mature B cells, T-cell subsets	Antibodies to CD76 recognize a carbohydrate antigen synthesized by an α2,6-sialyltransferase (439). mAb directed against this antigen recognizes the carbohydrate epitope irrespective of the carrier molecule (441).

(*continued*)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD77	Burkitt's lymphoma antigen, Gb3		Germinal center B lymphocytes and Burkitt's lymphoma cells	CD77 binds lectins found on pili of *E. coli* It has been shown to bind CD19, which is highly homologous to the verotoxin β subunit (442). CD19/CD77 binding may facilitate important adhesion and signaling in B-cell development, and may be involved in the formation of germinal centers (443). Expression of CD77 is modulated by EBV-encoded antigens (444).
CD78	Ba, Leu21, LO-panB-a			The anti-human CDw78 mAb appears to recognize a determinant on the MHC class II molecule (445).
CD79a,b	Igα/Igβ	42 and 37 kDa	Both genes are expressed early in B-cell ontogeny and in all nonplasma B cells; CD79b is expressed in plasma cells (446)	The B-cell antigen receptor incorporates a transmembrane heterodimer, the disulfide-linked glycoproteins CD79a (Igα) and CD79b (Igβ), respective products of mb-1 and B-29 genes (447–449). Cytoplasmic tails of the heterodimer are phosphorylated immediately after BCR cross-linking at Ty residues in antigen-recognition homology 1 (ARH1) motifs (450,451). CD79 are key signaling components of the BCR complex. SRC kinases constitutively associate with the chains via cytoplasmic ARH1 motifs (452).
CD80	B7, B7-1, BB-1	60 kDa	B cells (highly inducible), macrophages, dendritic cells, and T cells	CD80 has two extracellular Ig-like domains and eight sites for N-linked glycosylation. CD80 is a ligand for CD28 or CTLA-4, providing T cells with costimulatory signals. Expression on B cells is induced by CD40L engagement (453). Transgenic expression of B7 can break tolerance to tissue-specific antigens (454), whereas blocking B7 interactions can prevent autoimmune disease (455). CD80 is 26% identical to CD86 (B7-2),

CD81	Target of anti-proliferative antibody (TAPA-1)	26 kDa	B cells and cells of non-hematopoietic origin	CD81 has four transmembrane domains, with both N- and C-termini being cytoplasmic. CD81 exists as a complex with CD19, CD21, and MHC II (327,457). The complex reportedly functions to amplify B-cell signals, enhancing responses to low antigen concentrations (458,459). Anti-CD81 antibodies cause homotypic aggregation of cells and growth inhibition, and block the development of αβ T cells in fetal organ cultures, suggesting a role for the molecule in lineage-specific T-cell development (460).
CD82	IA-4	28 kDa	Monocytes (461,462), activated T cells	CD82 is a member of the tetraspan family of surface receptors that includes CD9, CD37, CD53, CD63, and CD81 (463). CD82 may associate with $p56^{lck}$ non-associated CD4 of T cells (464). CD82 cross-linking is reported to costimulate activation and IL-2 secretion of a T-cell line (465) and activation of a monocyte cell line (461).
CD83	HB15	45 kDa	Langerhans cells, dendritic cells, mitogen-activated lymphocytes (466,467), germinal center lymphocytes (468)	CD83 has a single V-type Ig domain (466,469). CD83 may be important to antigen presentation or cellular interactions that follow lymphocyte activation (466). It provides a marker for a subset of human blood dendritic cells (468,470).
CDw84	GR6	73 kDa	Mature B cells and on pre-B and B-cell lines, monocytes, platelets, tissue macrophages, activated T cells (471)	Function is unknown.
CD85	GR4	120, 83 kDa	Monocytes and B cells (471)	Function is unknown.
CD86	B70, B7-2	80 kDa	Professional antigen-presenting cells: dendritic cells (472–474), monocytes, activated B cells (456,475)	CD86 is a second costimulatory ligand for the T-cell ligands CD28 (456) and CTLA-4 (475,476). CD86 ligand interactions stimulate T-cell cytokine production, and may support Th2 differentiation (477).

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A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD87	Urokinase plasminogen activator receptor (uPAR), Mo3	50–65 kDa	Mononuclear phagocytes (478–480)	CD87 functions to localize uPA on the cell surface. uPA converts plasminogen to the broad-specificity protease, plasmin. CD87 regulation of protease activity facilitates monocyte penetration/invasion into stromal tissue (481) and is required for monocyte and PMN chemotaxis (482,483). CD87 may play a role in tissue invasion and tumor metastasis (481,484).
CD88	Complement receptor for C5a (C5aR)	40 kDa	Polymorphonuclear leukocytes, macrophages, basophils, mast cells (485). Nonmyeloid cells: bronchial and alveolar epithelial cells, hepatocytes, astrocytes, and vascular endothelial cells (486)	CD88 is a seven-transmembrane-region protein that belongs to a family of G-protein-coupled receptors. CD88 was only recently cloned and characterized (487,488). CD88 mediates proinflammatory actions of the complement anaphylatoxin C5a, stimulates chemotaxis, contact sensitivity, granule enzyme release, and superoxide anion production. CD88 has 34% protein sequence identity with the N-formylpeptide receptor (488). Gene-targeted deficiency shows that CD88 is critical for mucosal immune responses in the lung (489).
CD89	IgA Fc receptor (FcαR)	50–75 kDa	Monocytes, neutrophils, macrophages, polymorphonuclear leukocytes (490,491)	CD89 has two extracellular Ig-like domains and six sites for N-linked glycosylation (492). CD89 splice variants are differentially expressed on leukocytes (493). There are different Binding of FcαR triggers phagocytosis, ADCC, superoxide production, and release of inflammatory mediators (494,495). FcαR associates with the FcRγ chain (496) and is critical for FcRγ-mediated responses (497).
CD90	Thy-1	18 kDa	Thymocytes, T cells, hematopoietic progenitors (498)	CD90 is a GPI-anchored cell-surface molecule. It plays a role in T-cell adhesion (499–501) and cross-linking may stimulate T cells (502). Mice expressing CD90

				from an IgE enhancer develop lymphoid hyperplasia (503). CD90 may play a role in regulating growth of hematopoietic cells (504).
CD91	α_2-macroglobulin receptor (α2MR), low-density lipoprotein receptor-related protein (LRP)	600 kDa	Monocytes, lymphokine-activated killer cells (505)	α2MR is a large surface receptor consisting of a 515-kDa heavy chain and an 85-kDa light chain, derived via proteolysis of a 600-kDa precursor. α2MR regulates platelet-derived growth factor-BB-induced proliferation of fibroblasts (506), mediates internalization of prourokinase (507,508) and thrombospondin (509). CD91 may be involved in tumor metastasis (510).
CD92	GR9	70 kDa	Neutrophils, monocytes, platelets, endothelium	Function is unknown.
CD93	GR11	120 kDa	Neutrophils, monocytes, and endothelium	Function is unknown.
CD94	KP43	43 kDa	T cells, NK cells, $\gamma\delta$ T cells (511)	CD94 is a type II membrane protein encoded by a unique gene of the C-type lectin superfamily with some homology to NKR-P1 and NKG2 (512). CD94 is a putative NK immune receptor and may be involved in NK recognition of class I molecules (513–516). Activation through CD94 induces IFNγ, TNFα, and GM-CSF expression from NK cells (517). May also function as an accessory molecule on $\gamma\delta$ T cells (511).
CD95	FAS	200 kDa	T cells, B cells (518)	CD95 is a member of the TNF-R family of molecules, which include CD30, CD40, CD120, and 4-1BB (519). Engagement of CD95 by its ligand FASL may play an important role in peripheral-induced T-cell tolerance (520–523) and immune privilege (524). B cells also upregulate CD95 and become susceptible to apoptosis (525,526). CD95 is defective in autoimmune lpr/gld mice (527,528).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD96	TACTILE	160 kDa	Peripheral T cells, activated B cells	CD96 has three Ig domains, is likely subject to extensive O-glycosylation, and exhibits homology with *Drosophila* amalgam, the melanoma Ag MUC-18, the poliovirus receptor, and the neural cell adhesion molecule (CD96). CD96 is upregulated after activation on T cells and NK cells and may be involved in adhesive interactions of activated T and NK cells during late phases of the immune response (529).
CD97		75–85 kDa	Activated leukocytes	CD97 is a seven-transmembrane-region molecule dubbed "secretins," a peptide hormone receptor with similarities to calcitonin. CD97 is, however, unique because of its extended extracellular region of 433 amino acids, containing three N-terminal epidermal growth factor-like domains, two of which incorporate a calcium-binding site, and a single Arg-Gly-Asp (RGD) motif (530). Recently, lymphocytes and erythrocytes were shown to adhere to CD97-transfected cells via interactions with CD55 (531).
CD98	CAF7, 4F2, fusion regulatory protein-1 (FRP-1)	80, 40 kDa	Hematopoietic progenitors, lymphocytes, and myeloid and erythroid lineages	Antibodies against CD98 induce homotypic aggregation of lymphoid progenitor cells and inhibit the generation of lymphoid, myeloid, and erythroid lineage cells. CD98 thus appears to be a cell membrane receptor involved in survival/growth of hematopoietic progenitor cells (532). Recently, CD98 and FRP-1 were suggested to be identical entities (533).

CD99	MIC2, E2, 12E7	32 kDa	T cells, thymocytes	CD99 is expressed from an X-linked gene that unusually has a Y chromosome homologue (534). CD99 is isomorphic, having two epitopes that are differentially expressed by T cells and thymocytes, and is involved in homotypic adhesion (535,536). E2 mAbs induce surface expression of phosphatidylserine on thymocytes but not on mature T cells and homotypic aggregation of $CD4^+CD8^+$ human thymocytes in an integrin-independent manner (537).
CD100	BB18	150 kDa	T cells (538), Langerhans cells	Cross-linking of the homodimeric CD100 molecule can potentiate CD2- or CD3-induced proliferation of T cells or synergize with submitogenic concentrations of phorbol myristate acetate (538,539). May be involved in germinal center formation (540).
CD101		140 kDa	Langerhans and dendritic cells	Accessory molecule for APC stimulation of T cells (541).
CD102	ICAM-2	60 kDa	Hematopoietic cells, NK cells, dendritic cells (542), endothelial, and Langerhans cells	The natural ligands for LFA-1 (CD11a/CD18) are ICAM-1 (CD54), ICAM-2 (CD102), and ICAM-3 (CD50). CD102 adhesion mediates interactions between T lymphocytes and endothelial tissues (543), and plays a role in NK cell migration (300,543,544). LFA-1/CD102 interactions play a part in cell death after SEB rechallenge (545). (See CD11a/CD18.)
CD103	alpha-E beta-7 integrin, HML-1, α6, M290	150, 25 kDa	γδ T cells (95 and 40% of intestinal epithelial and lamina propria lymphocytes, respectively), cervical T cells, small proportion of peripheral blood lymphocytes, stimulated macrophages (546) and mast cells (547)	CD103 exists as a noncovalent αβ heterodimer, binds Mn^{2+}, and has cysteine-rich repeats. CD103 is expressed on resident T cells of gut and skin epithelia and is upregulated on activated T cells (548,549). It binds E-cadherin expressed on epithelial cells (550) and appears to be involved in homing of epithelial trophic T cells (551,552). TGFβ has been shown to induce CD103 expression on lymphocytes but it does not appear to be sufficient to facilitate homing to mucosal tissue (553).

(*continued*)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
				TGFβ or IgE-mediated cross-linking of FcεRI upregulates CD103 on mast cells (547). It also has an accessory role in the activation of γδ T cells (554). CD103 is expressed on malignant cells of hematological origin (552,555).
CD104	β_4 integrin	200 kDa	Epithelial cells (in complexes called hemidesmosomes), i.e., keratinocytes	There are eight β-integrins in the integrin receptor family of αβ heterodimers. The β_4 integrin is unique among the β-integrin chains: it has a large (~1000 amino acid) cytoplasmic tail that contains a tyrosine-based activation motif (TAM) (556). CD104 may be involved in signaling cell-cycle regulation and apoptosis (557). CD104 is localized on the surface of basal cells in hemidesmosomes, subcellular structures involved in attachment of epithelial cells to the extracellular matrix (558). Mutations in CD104 are associated with a rare inherited disorder characterized by pyloric stenosis and skin blisters (559).
CD106	Endoglin, TGFβ receptor	95 kDa	Endothelial cells, macrophages (560), bone marrow stromal cells (561,562)	CD106 is a homodimeric membrane glycoprotein that binds the cytokines TGFβ1 and TGFβ3, and forms part of a heteromeric TGFβ receptor complex (563,564). It has significant sequence homology in its cytoplasmic domain with the type II TGFβ receptor, but little similarity in the extracellular regions (565,566). CD106 expression is upregulated on myeloid cells on differentiation to macrophages. The human disease, hereditary hemorrhagic telangiectasia, is the result of mutations at the CD106 locus (567,568).
CD107a,b	Lysosomal-associated membrane proteins (LAMP1/LAMP2)	110 kDa 120 kDa	Neutrophils (569)	CD107 is a type I transmembrane glycoprotein localized primarily in lysosomes and endosomes, with only a minor portion being found on the plasma membrane, although surface levels may be elevated during autoim-

				mune disease (570,571). CD107 endosomal sorting signals may be useful for directing antigen traffic into class II pathway for antigen presentation (572). CD107a on neutrophils may be a bacterial receptor (573). There are several splice variants of CD107b.
CDw108	JMH (John Milton Hagen)	76–80 kDa	Erythrocyte blood group antigen	CD108 is a GPI-anchored protein that is commonly found on red blood cells, known as the blood group antigen JMH (574–576). CD108 is absent from erythrocytes of patients with paroxysmal nocturnal hemoglobinuria, where cells are incapable of generating GPI links.
CD109		175 kDa	Activated T cells (577), hematopoietic progenitors (578), platelets (579), vascular endothelial (577)	CD109 is a GPI-linked membrane glycoprotein. It is upregulated on activated T cells and highly expressed on vascular endothelium. However, its function is unknown.
CD110–CD113 reserved				
CD114	HG-CSFR, G-CSFR	115 kDa	Myeloid lineages, immature B cells, hematopoietic progenitor cells	CD114 is a member of the hematopoietic growth factor receptor family and thus contains the WSXWS extracellular motif and has a signal transducing cytoplasmic tail that lacks intrinsic kinase activity. Granulocyte colony-stimulating factor (G-CSF) induces CD114 dimerization and regulates cell growth and differentiation. Mutational analysis suggests that membrane-proximal and -distal regions of the cytoplasmic tail mediate proliferation and differentiation signals, respectively (580,581). In addition to stimulating gorwth of granulocytes (582,583), it may also be involved in B-cell development (584) and in embryogenesis (585).

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Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD115	M-CSF receptor, c-FMS	150 kDa	Some B cells (586), myeloid progenitors, monocytes, macrophages, osteoclasts, and embryonic cells	CD115 binds M-CSF and is a member of the type III tyrosine kinase growth factor receptors, which includes CSF-1R, PDGFR, FLK-1, -2, and FLT-1, -4 (587–589). CD115 promotes growth, survival, and differentiation of hematopoietic cells (590,591) and adhesion to bone marrow stroma (592). CD115 is identical to the oncogene c-FMS (593,594). M-CSF-deficient mice are toothless and have osteopetrosis, associated with a lack of osteoclasts, and resident macrophage populations are selectively absent (595,596).
CD116	GM-CSFRα	75–58 kDa	Eosinophils, erythroid progenitors, megakaryocyte progenitors, macrophages, neutrophils	The high-affinity GM-CSF receptor is composed of a cytokine-specific α chain (CD116) and a common β chain shared with receptors for IL-3 and IL-5. CD116 contains the common hematopoietic receptor motif WSXWS in its membrane-proximal region and is expressed in two alternative splice forms (597–599). There is only 35% homology between mouse and human CD116. Stimulation by its ligand GM-CSF induces the formation of granulocyte and macrophage colonies from bone marrow progenitor cells, increased numbers of eosinophils, neutrophils, and hematopoietic progenitor cells (600,601).
CD117	c-KIT, stem cell factor, or steel factor receptor	145–160 kDa	Hematopoietic progenitor cells, mast cells, nervous tissue (602–604)	CD117 has five Ig-like extracellular domains and is a member of the type III tyrosine kinase growth factor receptors, which includes CSF-1R, PDGFR, FLK-1, -2, and FLT-1, -4 (587,588). Mutations at the CD117 locus occur in mice, which are characterized by hematopoietic deficits resulting in anemia, inadequate development of gonads and concomitant sterility, and blocked differentiation of melanocytes.

CD118	IFNα/β receptor	63 kDa	Most cells	CD118 has a 409-amino-acid extracellular domain with twofold symmetry and 15 potential sites for N-linked glycosylation (605). CD118 mediates biological responses to α and β IFNs (606), binds IFNs directly, and cooperates with other surface molecules to form a functional receptor complex (607,608).
CD119	IFNγR	90 kDa	Most cells	IFNγR consists of α and β subunits which associate in respopnse to IFNγ binding (609,610). The high-affinity α chain mediates specificity of the receptor and is required for signaling (611,612). IFNγ induction of antiviral signaling depends on both JAK2 and STAT1 activation (613,614). STAT1-deficient mice have a complete block in response to IFNγ (615).
CD120a,b	TNFR1, TNFRII	55 kDa 75 kDa	T cells, B cells, upregulated on most other cells	CD120a (TNFRp55) and CD120b (TNFRp75) are shared receptors for TNFα, TNFβ, and lymphotoxin-α (616). CD120a/b exist in soluble forms which can up- or downregulate TNF activity (617). CD120 deficiency protects against endotoxic shock (618) and results in defective germinal center formation (619). CD120 is a member of the TNF-receptor superfamily of molecules.
CD121a,b	IL-1R type I, IL-1R type II	80 kDa 68 kDa	On most cells	CD121a (IL-1R1) binds IL-1α and IL-1β and mediates biological activity in association with a high-affinity complex that includes a transmembrane accessory protein (AcP) (620). IL-1 also binds CD121b (IL-1R2) which has no role in signaling and exists merely as a decoy (621). Vaccinia and cowpox virus encode an IL-1R2 gene (622,623).

(*continued*)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD122	IL-2Rβ	75 kDa	Constitutively expressed on most mature lymphocytes	There are three IL-2 receptor chains: α (CD25), β (CD122), and γ. CD122 and γ chain form a functional low-affinity signaling receptor (624,625) whereas addition of the α chain results in high binding affinity for IL-2. CD122 is required for T- and B-lymphocyte immunoregulation, as gene-targeted deletions result in hyperactive lymphoid compartments and severe autoimmunity (626).
CD123	IL-3Rα	41 kDa	Subset of peripheral B cells (627), hematopoietic progenitors, myeloid-lineages (628)	The IL-3 receptor consists of α (CD123) and β chains. The β chain is common for the cytokines GM-CSF, IL-5, and IL-3 whereas CD123 probably mediates cytokine-specific signals (629). CD123 exhibits low-affinity IL-3 binding capacity (630).
CD124	IL-4R	140 kDa	T cells, B cells, hematopoietic progenitors	The IL-4 receptor is a heterodimer that consists of an IL-4-specific α chain (CD124) and a common γ chain (631,632). CD124 is a member of the hematopoietin superfamily of receptors and contains a WSXWS motif in its membrane-proximal extracellular domain (633). STAT6 is required for mediating IL-4 responsiveness and for the development of Th2 cells (634).
CD125	IL-5Rα	45.5 kDa	Basophils, eosinophils (635)	The IL-5 receptor is a heterodimer composed of an IL-5-specific α chain (CD125) and a shared β subunit (βc), which is found in receptors for IL-3 and GM-CSF. CD125 independently binds IL-5 but has no capacity to transduce signals (636,637). Soluble CD125 isoforms are expressed from eosinophils that can antagonize IL-5 activity (638). CD38 ligation on B cells upregulates surface expression of CD125 (639).

CD126	IL-6Rα	80 kDa	Mature T cells, peripheral blood mononuclear cells, activated and Peyer's patch B cells	The IL-6R is composed of an IL-6-specific α chain (CD126) and a 130-kDa β chain (gp130). CD126 contains the membrane-proximal WSXWS motif characteristic of hematopoietin receptors. Binding of IL-6 to CD126 results in disulfide-linked dimerization with gp130 (640). Both mice and humans express a soluble CD126, which retains the ability to bind IL-6 and to deliver signals through gp130 (641,642).
CD127	IL-7Rα	75 kDa	Pro-B and pre-B cells, thymocytes	IL-7 receptor is a heterodimer composed of an IL-7-specific α chain (CD127) and a common γ subunit (γ_c) (643,644). CD127, a member of the hematopoietic growth factor receptors (643), is critical for proliferation of thymocytes before TCR gene rearrangement in the thymus (645,646). Mice with gene-targeted mutations in CD127 have a specific block in γδ T-cell development (647,648).
CD128	IL-8Rα	58–67 kDa	Lymphocytes, neutrophils, monocytes, fibroblasts	Two IL-8 receptors, IL-8Rα (CD128) and IL-8Rβ, have been identified that share significant sequence homology (649,650) but differ in their ability to bind multiple chemokines. CD128 binds IL-8 with high affinity and has restricted binding capacity for other chemokines (649).
CD129 reserved				
CD130	IL-6Rβ, IL-11Rβ, OSMRβ, LIFRβ, gp130	130 kDa	Expressed on most cell types (651)	CD130 (gp130) is a common receptor chain for IL-6 (IL-6Rβ), IL-11 (IL-11Rβ), oncostatin-M (OSMRβ), leukemia inhibitory factor (LIFRβ), and ciliary neurotrophic factor (CNTFRβ) (652). CD130 contains an extracellular Ig-like domain and three fibronectin type II domains, in addition to the WSXWS motif characteristic of hematopoietin receptors. CD130 has no binding affinity for cytokines but facilitates signal transduction through complexing with its respective receptor subunits (640,653).

(continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD131	IL-3Rβ_c (GM-CSFRβ, IL-5Rβ)	120 kDa	Hematopoietic progenitors, myelomonocytic lineages	CD131 is the common β chain (β_c) for GM-CSF, IL-5, and IL-3 receptors (654,655). It is a member of the hematopoietin receptor superfamily, containing the WSXWS motif and facilitating signaling without apparent intracellular catalytic domain. CD131 does not bind cytokines for which it forms a receptor complex (630). CD131 is upregulated in response to IL-1, TNFα, and IFNγ (656). GM-CSF also induces CD131 expression on neutrophils (657).
CD132	IL-2Rγ_c	40 kDa	T cells, B cells, NK cells	CD132 (common γ chain) is a subunit for the IL-2, IL-4, and IL-7 receptor complexes (658–660). It is a member of the hematopoietin family for receptors, containing an SRC-homology region in its cytoplasmic tail but no catalytic kinase activity. CD132 is constitutively expressed on most mature lymphocytes (661–663). CD132 is defective in X-linked severe combined immunodeficiency (X-linked SCID) (664).
CD133 reserved				
CD134	OX40	28 kDa	Activated $CD4^+/CD8^+$ T cells, B cells	OX40 is a member of the TNF superfamily of molecules. It is expressed on activated $CD4^+/CD8^+$ T-cell subsets particularly in PALS. CD134 has a natural ligand (OX40L) (665), a molecule with significant homology with the cytokine tumor necrosis factor (TNF). CD134 mediates adhesion of activated T cells to endothelium (666). Cross-linking of OX40L on B cells by CD134 induces proliferation and Ig secretion (667,668). CD134–ligand interactions are important for secondary immune responses and B-cell differentiation and Ig responses. OX40 expression is regulated by HTLV-1 genes (669).

CD135	FLT3, FLK2	130 kDa	Hematopoietic progenitors	The FLT3 receptor tyrosine kinase (RTK) belongs to the class III subfamily of tyrosine kinase receptors which includes platelet-derived growth factor (PDGFR), colony-stimulating factor-1 (CSF1), and steel factor (SF) receptors (217,670). FLT3 controls growth and differentiation of early human hematopoietic cells and in combination with other growth factors, stimulates the proliferation and mobilization of hematopoietic ($CD34^+CD38^-$) progenitors of both lymphoid and myeloid lineages (671–674). FLT3-deficient mice have a specific defect in B-lymphoid development (675).
CD136	Macrophage stimulating protein receptor (MSP-R), STK, RON	47 kDa, 22 kDa	Peritoneal macrophages, megakaryocytes, osteoclasts	CD136 is composed of a two-chain disulfide-linked structure. CD136 is a member of the met/hepatocyte protein tyrosine kinase receptor family (676,677). It enhances peritoneal macrophage differentiation (678) and responses to chemoattractants and complement (679,680). It also induces growth and migration of keratinocytes, and may play a role in wound healing (681). CD136 regulates megakaryopoiesis (682). Signaling through CD136 also inhibits the effects of CFU-GM formation in response to cytokines (683). CD136 mediates reorganization of osteoclast cytoskeleton and bone resorption (684).
CD137	4-1BB	30-kDa monomer, 55-kDa homodimer	Peripheral T cells, activated thymocytes, IEL, B cells, and monocytes	CD137 is a member of the TNF receptor superfamily. Alternate splice variants (685) produce soluble form (686). CD137 is upregulated on activated T cells (687–690) where it costimulates proliferative responses (691,692). Its costimulatory effect is independent but additive with CTLA-4 and CD28 (692). Ligand for CD137 is expressed on B cells and macrophages and has TNFR homology (693–695).

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A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD138	Syndecan-1, B-B4	160 kDa, 110 kDa	Pre-B cells and plasma cells	A member of a family of transmembrane heparin sulfate glycoproteins, and binds extracellular matrix proteins and regulates cell morphology (696–698). Two splice variants exist (699), and expression is potently down-regulated by TNFα (700) and IL-6 (701). CD138 has a highly conserved noncatalytic cytoplasmic domain involved in microfilament association (702,703). Loss of CD138 may be involved in cell metastasis (704).
CD139	B-031			No data.
CD140a,b	Platelet-derived growth factor receptors, PDGFRα/β	120 kDa 121 kDa	CD140a: fibroblasts, smooth muscle cells, mesothelial cells, and liver endothelial. CD140b: neurons, meningeal cells, capillary endothelial cells, fibroblasts, smooth muscle	CD140a/b are receptor-type tyrosine kinases with five extracellular Ig-like domains, members of a family of PDGFR/CSF1R receptors that include FLT3 (CD135). CD140a/b mediates ligand (PDGF)-induced chemotaxis of fibroblasts and smooth muscle cells and cell growth (705). However, CD140a can act as a negative regulator of chemotaxis. The receptors play a role in wound healing and fetal development. CD140a is located near KIT (706,707) and one or both genes may be deleted in congenital disorders in humans (i.e., piebaldism) or mice (708,709).
CD141	Thrombomodulin	57 kDa	Endothelial cells	CD141 is a cell-surface glycoprotein containing six tandem epidermal growth factor (EGF)-like structures. It is a powerful anticoagulant blocking the action of thrombin. Embryonic lethality of CD141-deficient mice has indicated an essential role in murine development (710). CD141 is released into blood in a soluble form (TM) during inflammatory responses, such as those caused by autoimmune disease (711–716), and is a disease marker. A ligand for thrombomodulin is thrombin, an enzyme that induces clot formation and platelet activation. Ligand binding prevents thrombin from being able to clot fibrinogen or to activate platelets (717).

CD142	Tissue factor	37 kDa	Endothelial cells, monocytes	CD142 is a glycoprotein with extracellular Ig-like and fibronectin type III-like domains (718,719). Absence of the WSXWS motif characteristic of the hematopoietic cytokine receptors is replaced by a similar secondary structure having a polyproline helical conformation (719). CD142 is the cellular receptor for the serine proteinase coagulation factor VI/VIIa, enhancing the latter's catalytic function and acting as the primary physiological initiator of blood coagulation. CD142 is an embryonic lethal mutation in mice, where it appears to have a critical role in blood vessel development (720–722). TNF induction of coagulation may be the result of its effect to upregulate CD142 expression (723).
CD143	Angiotensin converting enzyme (ACE)	184 kDa	Vascular endothelium, testes	Both CD143 isoforms are transmembrane molecules with extensive N-linked glycosylation. The larger isoform has two similar cytoplasmic domains each with a putative catalytic site, whereas the smaller isoform has a single catalytic site. Soluble CD143 is found in plasma and other body fluids and is derived via posttranslational modification of membrane forms. CD143 has peptidase or endopeptidase activity and is involved in the regulation of the specific maturation or degradation of a number of bioactive peptides. CD143 plays a critical role in the regulation of blood pressure and a number of specific inhibitors have been developed (724,725).
CD144	Vascular endothelial (VE) cadherin/ cadherin-5	120 kDa	Endothelial tissue at intercellular junctions	An adhesion molecule. CD144 negatively regulates cell growth through homotypic and heterotypic interactions. Negative growth regulation requires the extracellular adhesive domain and its cytoplasmic tail, which associates with the catenin family of proteins (726,727). It may function in establishing the architecture of vascular structures (728).

(continued)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD145				No data
CD146	MUC18, S-endo	113 kDa		CD146 is a melanoma-associated cell adhesion molecule with five Ig-like extracellular domains. It has protein sequence similarity to neural cell adhesion molecules such as N-CAM (729), for which it also shows similar gene structure (i.e., 2 exons per Ig domain) (730). It likely plays a role in tumor growth and metastasis (731).
CD147	Neurothelin, basoglin, HT7, OX-47	41 kDa		CD147 is a cell-surface glycoprotein with two extracellular C2-type Ig domains and is specifically expressed on endothelial cells forming the tight junctions of the blood–brain barrier (BBB) (732,733). It is speculated that CD147 is involved in the transport of low-molecular weight compounds into the neural environment (734).
CD148	HPTP-η, p260	260 kDa		CD148 is a transmembrane protein tyrosine phosphatase. It contains type III fibronectin repeats in the extracellular domain and a single PTPase domain in its cytoplasmic tail (735). Its function is obscure at this time, although the CD148 gene is often deleted in malignant cells, suggesting tumor suppressor function (736).
CD149	MEM-133			No data.
CD150	SLAM, IPO-3	42 kDa	Activated B cells, T cells, thymocytes	CD150 is a monomeric N-glycosylated surface protein with intrinsic kinase activity. It is upregulated on resting B cells within 16 hr after BCR ligation or activation through other surface molecules (737). Expression is also induced on T cells after CD3 cross-linking.

CD151	PETA-3	27 kDa	RNA expressed in most tissues	CD151 is a member of the tetraspan family of proteins, which have in common four conserved putative transmembrane domains and a large divergent extracellular loop between the third and fourth membrane-spanning regions. CD151 also contains a consensus sequence for N-linked glycosylation located in this extracellular loop (738). Antibodies against CD151 induce platelet activation (739). CD151 may form a subunit of the FcγRII signal-transducing complex in platelets (739).
CD152	CTLA-4		T cells	CD152 has a single Ig-like extracellular domain and an overall high sequence similarity with CD28 (740), the genes perhaps arising from a duplication event (741–743). The cytoplasmic region exhibits 100% sequence conservation between human, mouse, and rat, suggesting an important signaling function. Functional studies on CD152 have shown both positive and negative lymphocyte activation via the molecule (744,745). CD28 and CD152 shares the counterreceptors, B7-1, B7-2, and B7-3. Mice deficient for CD152 have a profound hyperactivation of lymphocytes and autoimmune disease, suggesting a role for CD152 in negative immunoregulation (746).
CD153	CD30L		T cells, B cells, macrophages, neutrophils	CD153 (CD30L) is a type II transmembrane glycoprotein and a member of the tumor necrosis factor ligand superfamily. In concert with cytokines, CD153 signaling can enhance B-cell proliferation and Ig secretion and may play a role in cognate T–B-cell interactions (747,748). CD153 has been shown to induce the proliferation of CD30-expressing malignant cells (i.e., Hodgkin's and Reed–Sternberg) (749). On the other hand, CD153 downmodulates proliferation and viability of $CD30^+$ large-cell anaplastic lymphoma cell lines (200). A clear understanding of CD153 function is yet to be established.

(continued)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD154	CD40L	39 kDa	T cells, basophils, mast cells, and eosinophils	CD154 is the major contact-dependent signal that supports B-cell activation and Ig heavy chain switching (750–752). In addition to its function on B cells, CD154 can stimulate monocytes and T cells. CD154 interaction with its ligand CD40 is also crucial for *in vivo* priming of T cells, via its effects on stimulating IL-12 secretion by APC (753). CD154 is required for normal antiviral humoral immune responses, and for the induction of $CD8^+$ CTL memory (754). CD40L is defective in X-linked hyper-IgM syndrome (755).
CD155	Poliovirus receptor (PVR)	57 kDa	Monocytes	CD155 has three Ig-like extracellular domains. Virus attachment occurs via the first Ig-like domain of CD155, which binds a depression on the surface of the viral capsid (756,757). Despite the widespread pattern of PVR expression, poliovirus infection in TgPVR mice is restricted to only a few sites, supporting observations in human cells that poliovirus tropism does not merely reflect receptor expression (758–761). Although the function of CD155 is unknown, its upregulation on monocytes during an immune response suggests a role in monocyte function.
CD156	ADAM8	89 kDa	Macrophages, monocytes	CD156 has five putative extracellular N-glycosylation sites and a cysteine-rich domain, and a proline-rich cytoplasmic region similar to CD2 (762). A mutant truncated version of CD156 has been expressed transgenically in mice without any profound hematological consequence (763).

CD157	Bone marrow stromal cell antigen (BST-1), MO-5		Bone marrow stromal cells, pancreatic α/β islet cells, thymus	CD157 is a GPI-anchored ectoenzyme with homology with CD38 and Aplysia ADP-ribosyl cyclase (764,765). CD157 has both ADP-ribosyl cyclase and cADPR hydrolase activities and likely regulates Ca^{2+} release from intracellular pools (766). CD157 may be involved in stromal cell support of B-cell growth (767–769).
CD158a,b	Class I-specific NK receptors, p58.1, p58.2	58 kDa	NK cells	Human NK cells express inhibitory receptors that are specific for different groups of HLA-C or HLA-B alleles. The majority of these receptors belong to the Ig superfamily and are characterized by two or three extracellular Ig-like domains. The HLA-C-specific receptors are represented by two highly homologous proteins/genes.
CD159 reserved				
CD160 reserved				
CD161	HKRP1			No data.
CD162	P-selectin glycoprotein ligand-1 (PSGL-1)	120 kDa	αβ T cells, subsets of γδ T cells, B cells, myeloid cells, eosinophils, neutrophils	CD162 is a disulfide-bonded homodimeric mucinlike glycoprotein with an N-terminal lectin domain, an EGF domain, and at least nine consensus repeats (CRs). On myeloid and lymphoid cells (770,771), CD162 interacts with both P- and E-selectin to mediate leukocyte rolling on P-selectin expressed by activated platelets or endothelial cells. PSGL-1 contains unique tyrosine sulfate and O-linked glycans that are predicted to be critical for high-affinity interactions between PSGL-1 and selectins (772,773). PSGL-1 on mouse myeloid cells is critical for high-affinity binding to P-selectin but not E-selectin.
CD163	GHI/61, M130, KiM8, Ber-Mac3, SM4	130 kDa	Macrophages	CD163 contains a large (1003 residue) extracellular portion possessing nine repeating elements with homology to the scavenger receptor superfamily (774).

(continued)

A Reference Table for Cluster of Differentiation (CD) Antigens (Continued)

Cluster designation	Common names	Mol. mass	Tissue distribution	Structure/function
CD164	MGC-24	24 kDa	Colon, small intestine, and thyroid tissues	CD164 is a peanut-agglutinin-binding protein that contains extensive hydroxyl and cysteine residues. It has no known function (775).
CD165	Epidermal growth factor receptor (EGFR), A108	170 kDa	Widely expressed but absent from hematopoietic cells	CD165 is a receptor tyrosine kinase that mediates mitogenic signals in response to the structurally related ligands epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) (776,777). CD165 plays important roles during embryogenesis (778). Mice deficient for CD165 die perinatally from impaired epithelial development in organs such as lung and gastrointestinal tract (779).
CD166	Activated leukocyte cell adhesion molecule (ALCAM)		Activated leukocytes, thymic epithelium	CD166 has five extracellular Ig-like domains and may exist in both monomeric and dimeric forms (780). CD6 is a natural ligand for CD166 (36,41), interacting via its N-terminal Ig-like domain with the third membrane-proximal scavenger receptor cysteine-rich (SRCR) domain of CR6 (781). CD6–CD166 interactions may play a role in mediating thymocyte binding to thymic epithelial cells and of T cells to activated leukocytes. These interactions may regulate the proliferative capacity of T cells (782).

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