CHAPTER 4: ADAPTIVE IMMUNITY

Unlike innate immunity, adaptive (acquired) immunity is highly specific and depends on exposure to foreign (non-self) material. It depends on the actions of T and B lymphocytes (i.e., T cells and B cells) activated by exposure to specific antigens (Ag).

Antigen= any substance that is recognized by an antibody or the antigen receptor of a T or B cell. Only antigenic material that is "foreign" should trigger an immune response, although "self-antigens" can trigger autoimmune responses. Adaptive Immunity is the immunity that our body gains after exposure to the pathogen. It produces antibodies and effector cell, and memory cell that neutralize the harmful pathogens and/or its toxins. Its major cells are T lymphocytes and B lymphocytes. It is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules (i.e., foreign antigens). Its responses are not the same in all members of a species. It is not independent of innate immunity. It displays four unique characteristic attributes:

- ☑ **Antigenic specificity**: it permits to distinguish subtle differences among antigens.
- ☑ **Diversity**: the immune system is capable of generating tremendous diversity in its recognition molecules, allowing it to recognize billions of unique structures on foreign antigens.
- ☑ **Immunologic memory**: once the immune system has recognized and responded to an antigen, it exhibits immunologic memory; that is, may stay life-long and during second encounter with the same antigen induces a heightened state of immune reactivity.
- ☑ **Self/non-self-recognition**: distinguish self from non-self and respond, but there may be inappropriate response to self-molecules can be fatal.

Specificity of the Adaptive Immune Response

Specificity on the adaptive immune response resides in the antigen receptors on T and B cells, the TCR and BCR respectively, which is unique for a particular antigenic determinant and there are different antigen receptors on both B and T cells. Two basic hypotheses were proposed to explain the generation of these receptors: the instructionist (template) and the clonal selection hypothesis.

1. Instructionist hypothesis: It states there is only one common receptor encoded in the germ line and that different receptors are generated using the antigen as a template. Each antigen would cause the one common receptor to be folded to fit the antigen. This hypothesis did not

account for self/non-self-discrimination and could not explain why the one common receptor did not fold around self-antigens.

2. <u>Clonal selection hypothesis</u>: It states that the germ-line encodes many different antigen receptors one for each antigenic determinant to which an individual will be capable of mounting an immune response. Antigen selects those clones of cells that have the appropriate receptor. The four basic principles of the clonal selection hypothesis are:

- Each lymphocyte bears a single type of receptor with a unique specificity.
- Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with a high affinity leads to lymphocyte activation.
- The differentiated effector cells derived from an activated lymphocyte will bear receptors of an identical specificity to those of the parental cell from which that lymphocyte was derived.
- Lymphocytes bearing receptors for self-molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes.

The clonal selection hypothesis is now generally accepted as the correct hypothesis to explain how the adaptive immune system operates. It explains many of the features of the immune response:

1) The specificity of the response
2) The signal required for activation of the response (i.e. antigen)
3) The lag in the adaptive immune response (time is required to activate cells and to expand the clones of cells) and
4) Self/non-self-discrimination

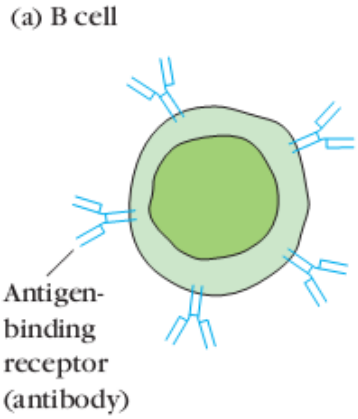
4.1. The Lymphatic System

Within the body, there are two circulatory systems, the blood and the lymph. Lymphatic system use for balancing of body fluid and defends the body against infections. The extracellular fluid, fluid out of the blood circulation, returns to the blood by draining into a network of vessels called lymphatics, the tissue called lymph nodes. The lymph carries antigen from the tissues to the lymph nodes where immune responses are initiated. Lymph organs include the bone marrow (produces both B and T lymphocytes), lymph nodes, spleen, and thymus. Lymph nodes are areas of concentrated lymphocytes and macrophages. Lymphocytes produce and display antigen-

binding cell-surface receptors, so play role in specificity, diversity, memory, and self/non self-recognition.

4.1.1. B lymphocytes and humoral immunity

B-Lymphocytes: B lymphocytes produced and mature within the bone marrow, after maturation it expresses a unique antigen-binding receptor on its membrane, i.e. membrane-bound antibody molecule, can recognize antigen alone without any APC. When a naive B cell first encounters antigen, divide rapidly into memory B cells and effector B cells called plasma cells, which produce the antibody, the major effector molecules of humoral immunity. Memory B cells provide long-lasting immunity to reinfection.



Humoral immunity (antibody-mediated system) is mediated by secreted Ab, complements proteins and certain antimicrobial peptides and also involves humors or body fluids (cell-free bodily fluid or serum). It works based on the interaction of B cells (Ab) with Ag. Humoral immunity functions (functions of Ab) include pathogen/toxin neutralization, classical complement activation, and opsonization or phagocytosis and pathogen elimination.

4.1.2. Antigen and antibody recognition

To fight the wide range of pathogens the immune system has to recognize a great variety of different antigens from bacteria, viruses, and other disease-causing organisms. The antigen-recognition molecules of B cells are the immunoglobulins (Ig) known as the B-cell receptor (BCR). The antibody molecule has two separate functions:

1. Bind specifically to molecules from the pathogen that elicited the immune response;
2. Recruit other cells and molecules to destroy the pathogen once the antibody is bound to it.

The antigen-recognition molecules of T cells are made solely as membrane-bound proteins and only function to signal T cells for activation. These T-cell receptors (TCRs) does not recognize and bind antigen directly, but instead recognizes short peptide fragments of pathogen protein antigens, which are bound to MHC molecules on the surfaces of other cells, this is known as MHC restriction, because any given TCR is specific not simply for a foreign peptide antigen, but for a unique combination of a peptide and a particular MHC molecule. TCRs recognize features both of the peptide antigen and of the MHC molecule to which it is bound.

Nature of antigen-antibody reactions

Lock and Key Concept: Ag-Ab interactions shows, Ag (the Key) fit into Ab (the lock) at the combining site of the Ab.

Non-covalent Bonds: The bonds that hold the Ag to the Ab combining site are all non-covalent. These include hydrogen bonds, electrostatic bonds, Van der Waals forces and hydrophobic bonds.

Reversibility: Since Ag-Ab reactions occur via non-covalent bonds, they are by their nature reversible

Strength of Antigen-Antibody Interactions (Affinity and Avidity)

A. Affinity

The combined strength of the non-covalent interactions between a single antigen-binding site on an antibody and a single epitope is the affinity of the antibody for that epitope. It is the sum of the attractive and repulsive forces operating between the antigenic determinant and the combining site of the antibody. Affinity is the equilibrium constant that describes the antigen-antibody reaction. Most antibodies have a high affinity for their antigens. Low-affinity antibodies bind antigen weakly and tend to dissociate readily, whereas high-affinity antibodies bind antigen more tightly and remain bound longer. The higher the affinity of the antibody for the antigen, the more stable will be the interaction. The association between binding sites on an antibody (Ab) with a monovalent antigen (Ag) can be described by the equation

$$\mathrm{Ag} + \mathrm{Ab} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Ag\text{-}Ab}$$

Where k_1 is the forward (association) rate constant and k-1 is the reverse (dissociation) rate constant. The ratio k1/k-1 is the association constant Ka (i.e., k1/k-1=Ka), a measure of affinity.

$$K_a = \frac{[\text{Ag-Ab}]}{[\text{Ab}][\text{Ag}]}$$

$$\text{Ag-Ab} \rightleftharpoons \text{Ab} + \text{Ag}$$

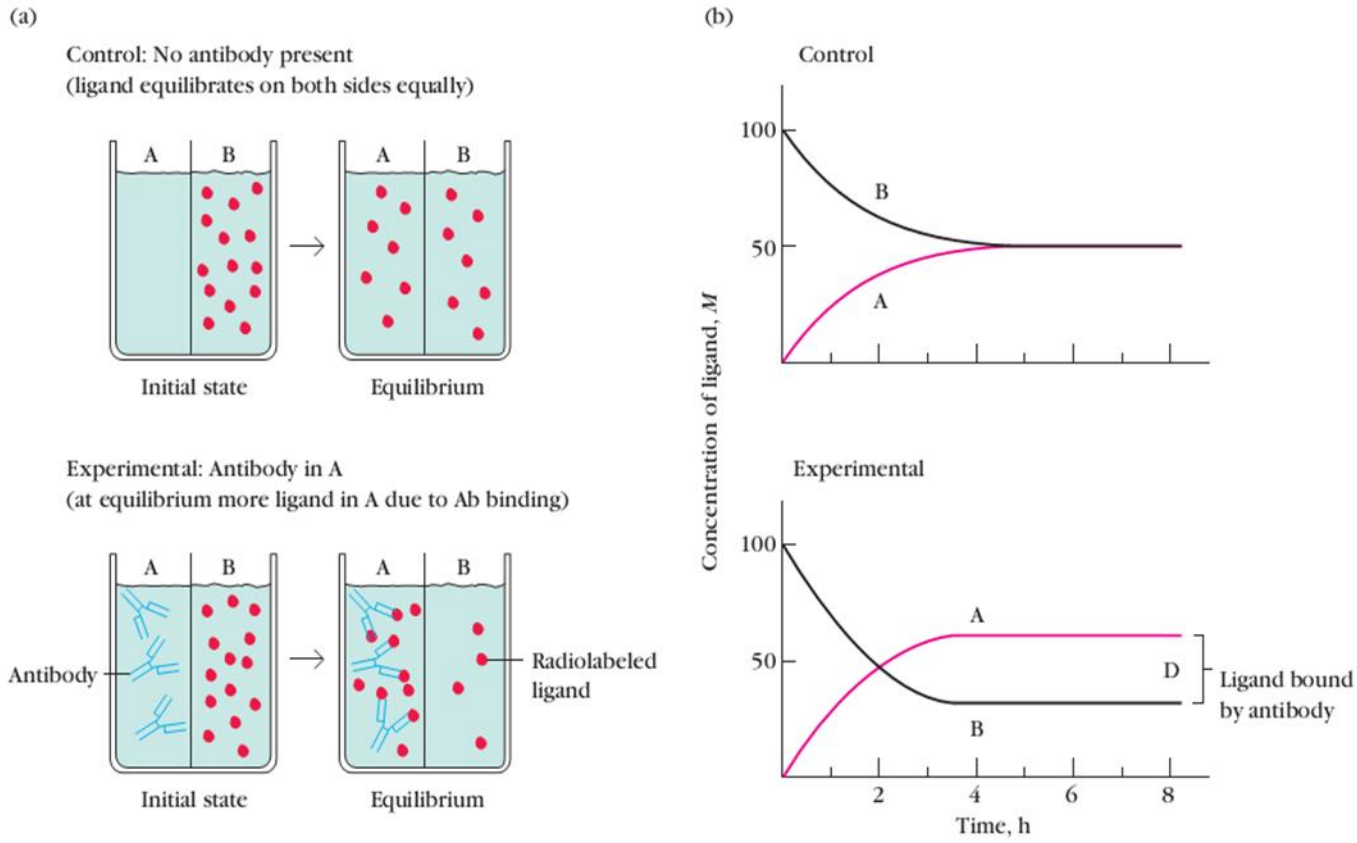
$$K_d = [\text{Ab}][\text{Ag}]/[\text{Ab-Ag}] = 1/K_a$$

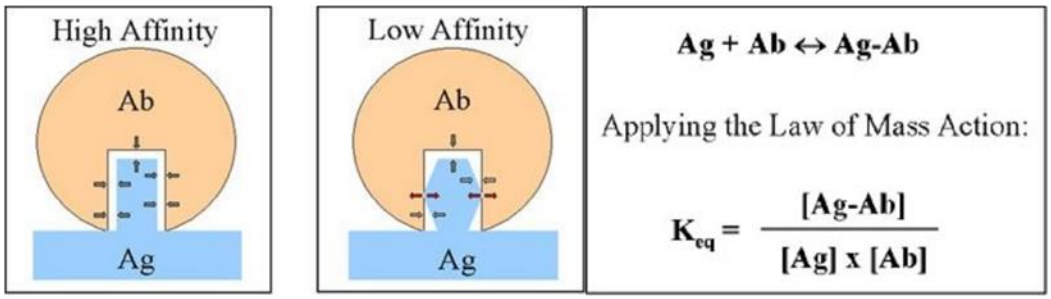
The dissociation of the antigen-antibody complex is:

The dissociation constant for that reaction is Kd, the reciprocal of Ka.

This is a quantitative indicator of the stability of an Ag-Ab complex; very stable complexes have very low values of Kd, and less stable ones have higher values.

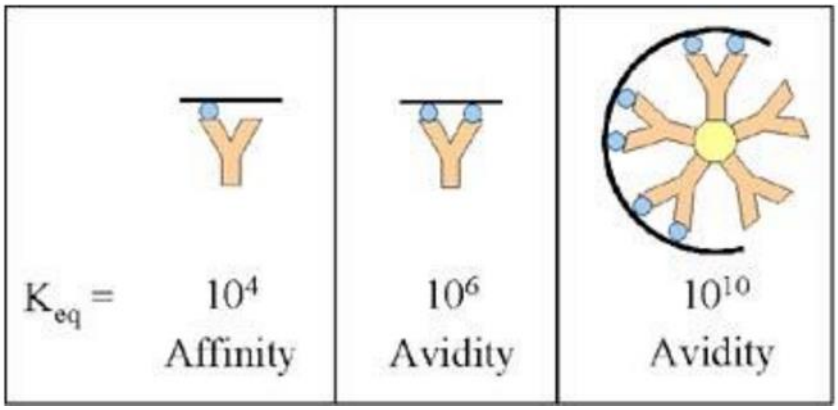
The affinity constant, Ka, can be determined by equilibrium dialysis or by various newer methods. This procedure uses a dialysis chamber containing two equal compartments separated by a semipermeable membrane. Antibody is placed in one compartment, and a radioactively labeled ligand that is small enough to pass through the semipermeable membrane is placed in the other compartment. Suitable ligands include haptens, oligosaccharides, and oligo-peptides. In the absence of antibody, ligand added to compartment B will equilibrate on both sides of the membrane. In the presence of antibody, however, part of the labeled ligand will be bound to the antibody at equilibrium, trapping the ligand on the antibody side of the vessel, whereas unbound ligand will be equally distributed in both compartments. Thus the total concentration of ligand will be greater in the compartment containing antibody. The difference in the ligand concentration in the two compartments represents the concentration of ligand bound to the antibody (i.e., the concentration of Ag-Ab complex). The higher the affinity of the antibody, the more ligand is bound. Since the total concentration of antibody in the equilibrium dialysis chamber is known, the equilibrium equation can be rewritten as:





Avidity: Avidity is a measure of the overall strength of binding of an Ag with many antigenic determinants and multivalent Abs. Avidity is more than the sum of the individual affinities and it refers to the overall strength of binding between multivalent Ags and Abs. Reactions between multivalent Ags and multivalent Abs are more stable and thus easier to detect. It is dependent on three major parameters:

- Affinity of the Ab for the epitope
- Valency of both the Ab and Ag
- Structural arrangement of the parts that interact

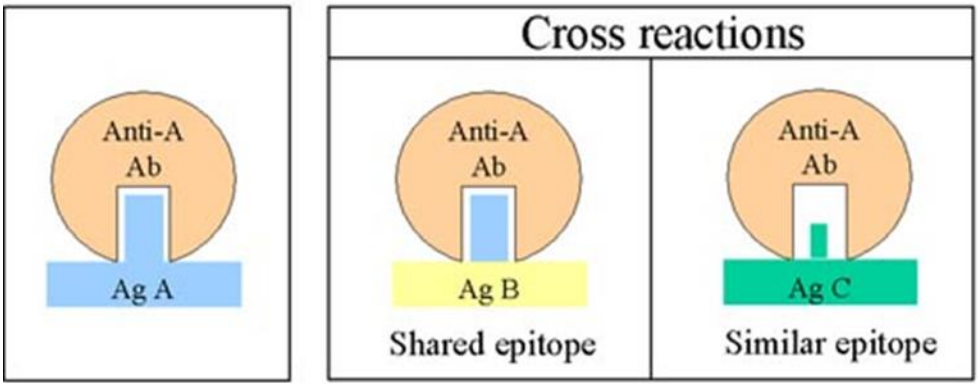


Specificity and cross reactivity

Specificity: the ability of an individual Ab combining site to react with only one antigenic determinant or the ability of a population of Ab molecules to react with only one Ag.

Cross reactivity: the ability of an individual Ab combining site to react with more than one antigenic determinant or the ability of a population of Ab molecules to react with more than one Ag. Cross reactions arise because

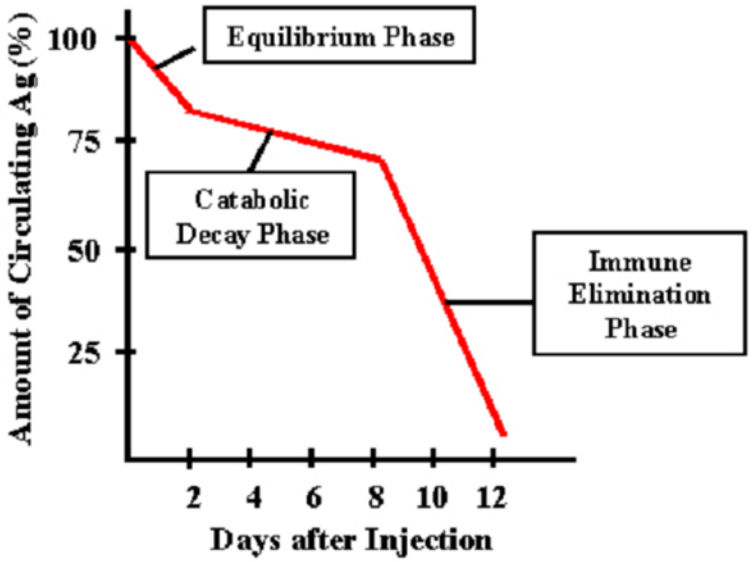
- The cross reacting antigen shares an epitope in common with the immunizing antigen or
- It has an epitope which is structurally similar to one on the immunizing Ag (multi-specificity)



Events during Immunogene Clearance

1. Clearance after primary injection

- ✓ **Equilibrium phase**: the Ag equilibrates between the vascular and extravascular compartments by diffusion. Since particulate Ags don't diffuse, they do not show this phase.
- ✓ **Catabolic decay phase**: The host's cells and enzymes metabolize the Ag with macrophages and other phagocytic cells.
- ✓ **Immune elimination phase**: newly synthesized antibody form Ag-Ab complexes which are phagocytosed and degraded. Antibody appears in the serum only after this phase is over.



2. Clearance after secondary injection: If there is circulating antibody in the serum injection of the antigen for a second time results rapid immune elimination. But, if there is no circulating antibody, all three phases occur but the onset of the immune elimination phase is accelerated.

Kinetics of antibody responses to Antigen

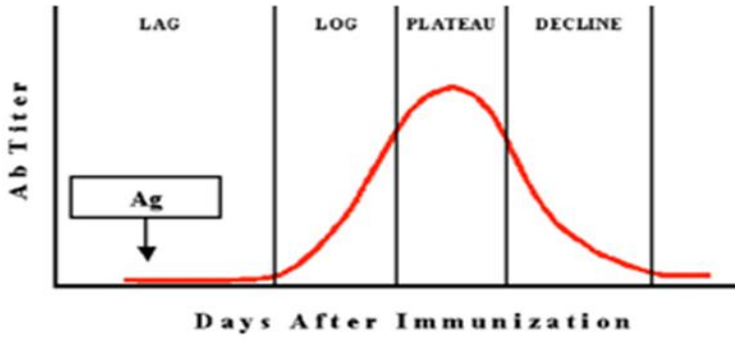
- **Primary (1^{o}) Antibody response**

a. Inductive, latent or lag phase: the antigen is recognized as foreign and the cells begin to proliferate and differentiate in response to the antigen. The duration is usually 5 to 7 days.

b. Log or Exponential Phase: the antibody concentration increases exponentially as the B cells that were stimulated by the antigen differentiate into plasma cells which secrete antibody.

c. **Plateau or steady-state phase**: Ab synthesis is balanced by Ab decay so that there is no net increase in Ab concentration.

d. Decline or decay phase: the rate of antibody degradation exceeds that of antibody synthesis and the level of antibody falls. Eventually the level of antibody may reach base line levels.



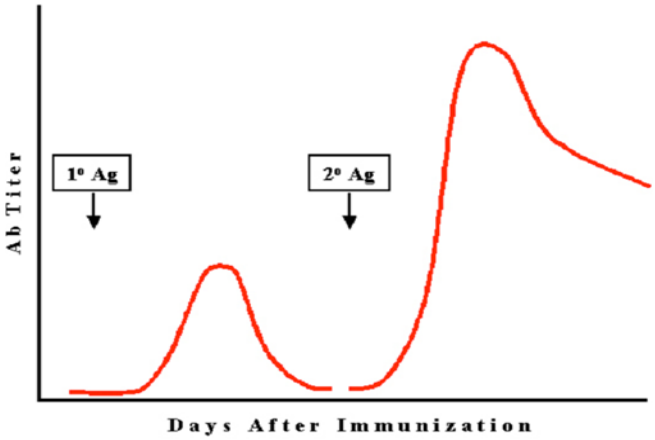
❖ **Secondary (2^o), memory or anamnestic response**

a. Lag phase: shorter

b. Log phase: is more rapid and higher Ab levels are achieved

c. Steady state phase: rapid

d. Decline phase: is not as rapid and Ab may persist for months, years or even a lifetime.



Ways of defending pathogens at different site

There are two main sites where pathogens may reside: extracellularly in tissue spaces or intracellularly

Extracellular pathogens: primary defenses are antibodies by three major ways:

i. Neutralization: By binding to the pathogen or foreign substance, Abs can block the association of the pathogen with their targets. E.g., Abs to bacterial toxins can prevent the binding of the toxin to host cells thereby rendering the toxin ineffective. Similarly, Ab binding to a virus or bacterial pathogen can block the attachment of the pathogen to its target cell thereby preventing infection or colonization.

ii. **Opsonization**: Ab binding to a pathogen or foreign substance can opsonize the material and facilitate its uptake and destruction by phagocytic cells. The Fc region of the antibody interacts with Fc receptors on phagocytic cells rendering the pathogen more readily phagocytosed. The antigen-antibody complex is eventually scavenged and degraded by macrophages.

iii. **Complement activation**: Activation of the complement cascade by antibody can result in lysis of certain bacteria and viruses. In addition, some components of the complement cascade (e.g. C3b) opsonize pathogens and facilitate their uptake via complement receptors on phagocytic cells.

4.1.3. Antibody structure

Are glycoprotein molecules which are produced by plasma cells in response to an immunogen. Its termed as immunoglobulin. General Functions of antibody:

Ag binding: - Immunoglobulin bind specifically to one or a few closely related antigens. Each immunoglobulin actually binds to a specific antigenic determinant. Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host.

Valency:- The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind. The valency of all antibodies is at least two and in some instances more.

Effector Functions: - Often the binding of an antibody to an antigen has no direct biological effect. Rather, the significant biological effects are a consequence of secondary "effector functions" of antibodies. The immunoglobulin mediates a variety of these effector functions.

Usually the ability to carry out a particular effector function requires that the antibody bind to its antigen. Not every immunoglobulin will mediate all effector functions.

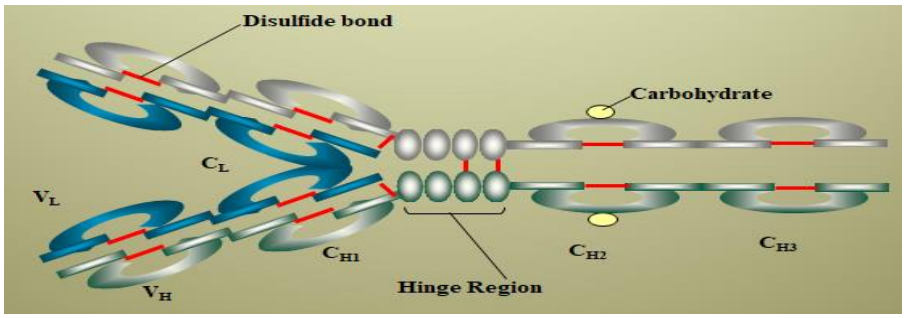


Figure 4: General structure of antibody

Heavy and Light Chains: - All immunoglobulin have a four chain structure as their basic unit. They are composed of:

- ✓ Two identical light chains (23Kd) and
- ✓ Two identical heavy chains (50-70Kd)

Disulfide bonds:-

1. Inter-chain:- The heavy and light chains and the two heavy chains are held together by inter-chain disulfide bonds and by non-covalent interactions. The number of inter-chain disulfide bonds varies among different immunoglobulin molecules.

2. Intra-chain: - Within each of the polypeptide chains there are also intra-chain disulfide bonds.

Variable (V) and Constant (C) Regions:- After the amino acid sequences of many different heavy chains and light chains were compared, it became clear that both the heavy and light chain could be divided into two regions based on variability in the amino acid sequences.

- ✓ Light Chain:- V L (110 aa) and C L (110 aa)
- ✓ Heavy Chain: - V H (110 aa) and C H (330-440 aa)

Hinge Region: - The region at which the arm of the antibody molecule forms a Y is called the hinge region because there is some flexibility in the molecule at this point.

Domains: - The 3D images of the immunoglobulin molecule shows that it is not straight as depicted in Figure. Rather, it is folded into globular regions each of which contains an intra-chain disulfide bond. These regions are called domains.

- ✓ Light Chain Domains - V L and C L
- ✓ Heavy Chain Domains - V H, C H1 - C H3 (or CH4)

Oligosaccharides: - Carbohydrates are attached to the C H2 domain in most immunoglobulin. However, in some cases carbohydrates may also be attached at other locations.

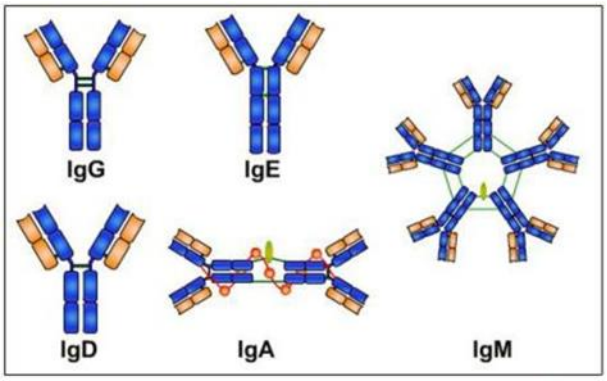
Fab (fragment, Ag binding) region: Ab arms that contain two specific foreign Ag binding sites. It is composed of one constant and one variable domain from each heavy and light chain of the Ab.

Fc (Fragment, crystallizable) region: the base of the Ab that plays a role in modulating immune cell activity. It is composed of two heavy chains that contribute two or three constant domains depending on the class of the Ab. It ensures that each Ab generates an appropriate immune response for a given Ag, by binding to a specific class of Fc receptors, and other immune molecules, such as complement proteins, phagocytic and killer cells.

4.1.4. Classes of immunoglobulin

Different immunoglobulin molecules can have different antigen binding properties because of different V H and V L regions. Based on differences in the amino acid sequences in the constant region of the heavy chains there are five classes of Igs.

1. IgG- gamma heavy chain
2. IgM-miu heavy chain
3. IgA- alpha heavy chain
4. IgD- delta heavy chain
5. IgE- epsilon heavy chain.



In each class of Ig small differences in the constant regions of the heavy chain still occur, leading to subclasses of the Igs e.g. IgG1,IgG2,IgG3 etc.

1. IgG

All IgG are monomers, subtypes and subclasses differ in number of disulphide bonds and lengths of hinge region.

Properties

1. It is the most versatile Ig and can carry out all functions of Ig molecules.
2. It is the major Ig in serum
3. It is also found/ the major Ig in extravascular spaces.
4. It is the only Ig that crosses the placenta.
5. It fixes complement although not all subclasses do this well.
6. It binds to cells and is a good poisoning(substance that enhances phagocytosis)

2. IgM

It normally exists as a pen tamer in serum but can also occur as a monomer. It has an extra domain on the mui chain (CH4) and another protein covalently bound via S-S Called J-chain. This chain helps it to polymerize to the pentamer form.

Properties

1. It is the first Ig to be made by fetus in most species and new B cells when stimulated by Ags.
2. It is the 3rd most abundant Ig in serum.
3. It is a good complement fixing Ig leading to lyses of microorganisms

4. It is also a good agglutinating Ig, hence clumping microorganisms for eventual elimination from the body.

5. It is also able to bind some cells via Fc receptors.

6. B cells have surface IgMs , which exists as monomers and lacks J chain but have an extra 20amino acid at the C-terminal that anchors it to the cell membrane.

3. IgA

Serum IgA is monomeric, but IgA found in secretions is a dimer having a J chain. Secretory IgA also contains a protein called secretory piece or T- piece; this is made in epithelial cells and added to the IgA as it passes into secretions helping the IgA to move across mucosa without degradation in secretions

Properties

1. It is the second most abundant Ig in serum

2. It is the major class of Ig in secretions- tears, saliva, colostrums, mucus, and is important in mucosal immunity.

3. It binds to some cells- PMN cells and lymphocytes

4. It does not normally fix complement.

4. IgD

It exists as monomers.

Properties

1. It is found in low levels in serum and its role in serum is uncertain

2. It is found primarily on B cells surface and serves as a receptor for Ag.

3. It does not fix complement.

5. IgE

It occurs as a monomer and has an extra domain in the constant region.

Properties

1. It is the least common serum Ig, but it binds very tightly to Fc receptors on basophils and mast cells even before interacting with Ags.

2. It is involved in allergic reactions because it binds to basophils and mast cells.

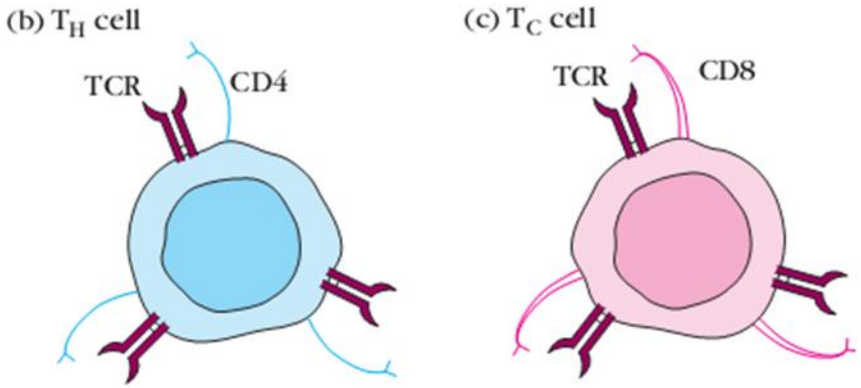
3. It plays a role in parasitic helminthic diseases. Serum levels rise in these diseases. Eosinophils have Fc receptors for IgEs and when eosinophoils bind to IgEs coated helminthes death of the parasite results.

4.2. T-lymphocytes (T-cells) and CMI

T-Lymphocytes: T lymphocytes produced in the bone marrow but mature in thymus. T cell express antigen-binding molecule called the T-cell receptor, which recognize only antigen that is bound to APC like major histocompatibility complex (MHC). When a naive T cell encounters antigen combined with a MHC molecule on a cell, the T cell proliferates and differentiates into memory T cells and various effector T cells. There are two subpopulations of T cells: T-helper (TH) and T cytotoxic (TC) cells. Th and Tc cells express membrane glycoproteins CD4 and CD8 on their surfaces as receptor.

Cell-mediated immunity: immune response that involves activation of phagocytes, Ag-specific cytotoxic T-lymphocytes (CTLs), and the release of various cytokines in response to an Ag. Both activated TH cells and CTLs serve as effector cells in cell-mediated immune reactions. Cytokines secreted by TH cells can activate various phagocytic cells. Cellular immunity protects the body by:

1. Activating antigen-specific CTLs that are able to induce apoptosis of virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
2. Activating macrophages and natural killer cells to destroy pathogens; and
3. Stimulate cytokines secretion
4. Participates in defending fungi, protozoans, cancers, intracellular bacteria and transplant rejection.



After a TH cell recognizes and interacts with an antigen–MHC, it secretes cytokines. This cytokines activate B cells, TC cells and macrophages. Activated TC-cell recognizes an antigen–MHC and then proliferates and differentiates into an effector cell called a cytotoxic T lymphocyte (CTL), which has a cell-killing or cytotoxic activity. The CTL has a vital function in monitoring the cells of the body and eliminating any that display antigen, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft. Cells that display foreign antigen complexed with a class I MHC molecules are called altered self-cells; these are targets of CTLs.

Antigen Presenting Cells (APCs)

The three main types of APCs are dendritic cells, macrophages and B cells. APCs first internalize antigen, either by phagocytosis or by endocytosis, and then display part of that Ag on their membrane.

- Dendritic cells is specialized APC which are found in skin and other tissues, ingest antigens by pinocytosis and present antigens to naïve T cells. Furthermore, they can present internalized antigens in association with either class I or class II MHC molecules (cross presentation).
- The 2nd types of APC is the macrophage and ingests Ag by phagocytosis or pinocytosis but are not as effective in presenting Ag to naïve T cells but they are very good in activating memory T cells.
- The 3rd type of APC is B cell. These cells bind Ag via their surface immunoglobulin and ingest it by pinocytosis. Like macrophages these cells are not as effective as dendritic cells in presenting Ag to naïve T cells but effective in presenting to memory T cells, especially when the Ag concentration is low because surface immunoglobulin on the B cells binds Ag with a high affinity.

To ensure carefully regulated activation of TH cells, antigens should be expressed with APCs. APCs are distinguished by two properties:

1) They express class II MHC molecules on their membranes, and
2) They are able to deliver a co-stimulatory signal that is necessary for TH-cell activation.

Major histocompatibility complex (MHC)

Cell-cell interactions of the adaptive immune response are critically important in protection from pathogens. The major function of the T cell antigen receptor (TCR) is to recognize antigen in the correct context of MHC molecule and to transmit an excitatory signal to the interior of the cell.

MHC genes are important in rejection of transplanted tissues, and also involved in controlling both humoral and cell-mediated immune responses. Due to strains difference in one or more of the genes in the MHC, some strains could respond to a particular antigen but other strains could not. There are two kinds of molecules encoded by the MHC Class I and class II molecules which are recognized by different classes of T cells. Class I molecules were found on all nucleated cells (not red blood cells) whereas class II molecules were found only on APCs which included dendritic cells, macrophages, B cells and a few other types. The TCR recognize antigenic peptides in association with MHC molecules. Tc recognizes peptides bound to class I MHC molecules and Th recognizes peptides bound to class II MHC molecules.

Important Aspects of MHC

- There is a high degree of polymorphism for a species in class I and class II MHC
- Each MHC molecule has only one binding site. Different Ag bind to the same site, but only one at a time.
- Because each MHC molecule can bind many different peptides, binding is termed degenerate.
- MHC molecules are membrane-bound; recognition by T cells requires cell-cell contact.
- Polymorphism in MHC is important for survival of the species.

4.2.1. Cytokines and their role in CMI

In response to microbes, macrophages and other cells secrete proteins called cytokines (soluble proteins) that mediate cellular immunity, inflammatory reactions and communications between leukocytes. Cytokines are a diverse group of non-antibody proteins that act as mediators between cells. There are different kinds of cytokines. These include:

- ☑ Monokines: cytokines produced by mononuclear phagocytic cells
- ☑ Lymphokines: cytokines produced by activated lymphocytes, especially Th cells
- ☑ Interleukins: cytokines that act as mediators between leukocytes
- ☑ Chemokines: small cytokines primarily responsible for leukocyte migration

Cytokine signaling is very flexible and can induce both protective and damaging responses. They are involved in both the innate and adaptive immune response, and bind to specific receptors on target cells with high affinity and the cells that respond to a cytokine are either:

- ➢ The same cell that secreted cytokine (autocrine)

- A nearby cell (paracrine)
- A distant cell reached through the circulation (endocrine).

Categories of Cytokines

Cytokines can be grouped into different categories based on their functions or their source

Mediators of natural immunity (innate immunity): Cytokines that play a major role in the innate immune include: TNF-α, IL-1, IL-10, IL-12, type I interferons (IFN-α & -β), IFN-γ, and chemokines.

- ☑ TNF-α: Tumor necrosis factor alpha is produced by activated macrophages in response to microbes, e.g., Gram negative bacteria. It also initiates fever.
- ☑ IL-1: Interleukin 1 is another inflammatory cytokine produced by activated macrophages. Its effects are similar to that of TNF-α and it also helps to activate T cells.
- ☑ IL-10: is produced by activated macrophages and Th2 cells and it is an inhibitory cytokine. It inhibits production of IFN-γ by Th1 cells and shifts immune responses toward a Th2 type.
- ☑ IL-12: produced by activated macrophages and dendritic cells. Stimulates the production of IFN-γ.
- ☑ Type I interferon (IFN-α & -β): are produced by many cell types and inhibit viral replication in cells

Mediators of adaptive immunity: Cytokines that play a major role in the adaptive immune system include: IL-2, IL-4, IL-5, TGF-β, IL-10 and IFN-γ.

- ☑ IL-2: produced by Th cells and the major growth factor for T and B cells and activate NK cells and monocytes.
- ☑ IL-4: produced by macrophages and Th2 cells. It stimulates the development of Th2 cells from naïve Th cells and promotes the growth of differentiated Th2 cells resulting in the production of an antibody response.
- ☑ IL-5: is produced by Th2 cells and functions to promote the growth and differentiation of B cells and eosinophiles.
- ☑ TGF-β: Transforming growth factor beta is produced by T cells and many other cell types. It is primarily an inhibitory cytokine.