CHAPTER 5: ADVERSE IMMUNE REACTIONS

The immune systems, in addition to defending the host against infection, are themselves capable of causing tissue injury and disease. Disorders that are caused by immune responses are called Hypersensitivity diseases. Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) response or reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. This disease may be caused by two types of abnormal immune responses.

- First =>Uncontrolled or unregulated response against foreign Ags, resulting in tissue injury.
- Second => Response against self (autologous) antigens due to failure of self-tolerance.

Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

5.1. Type I hypersensitivity- Allergic reactions

It also called as immediate or anaphylactic hypersensitivity. The reaction may involve skin, eyes (conjunctivitis), nasopharynx, bronchopulmonary tissues (asthma) and gastrointestinal tract. It is induced by allergens. E.g., Protein, vaccine, foods (nuts, eggs, milk…), plant pollens, insect venom, drugs (penicillin), mold, spores. Allergens are non-specific antigens capable of stimulating type I hypersensitivity reaction. This reaction mostly occur on mucosal surface to allergens enter by inhalation or ingestion. The clinical manifestation ranges from fatal condition (systemic anaphylaxis and asthma) to minor local reaction (hay fever). The reaction usually takes 15-30 minutes after exposure to the antigen, although sometimes it may have a delayed onset (10-12 hours). Allergenicity most importantly appears by the genetic appearance of the recipient, and additionally by complex interaction, dose, entrance route and/or adjuvant.

Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity is the mast cell and blood basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. A biopsy of the reaction site demonstrates mainly mast cells and eosinophils. The mechanism of reaction involves preferential production of IgE, and IgE has very high affinity for its receptor (CD23) on mast cells and basophils. Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests and measurement of total IgE and specific IgE antibodies against the suspected allergens. Increased IgE levels are

indicative of an atopic condition. The first step in controlling type I is to avoid contact with known allergens.

- ❖ Skin test: small amount of potential allergens are introduced at specific skin sites either by intradermal injection or superficial scratching, if person is allergic the local mast cell accumulate and release histamine this results with production of a weal and flare within 30 minutes.

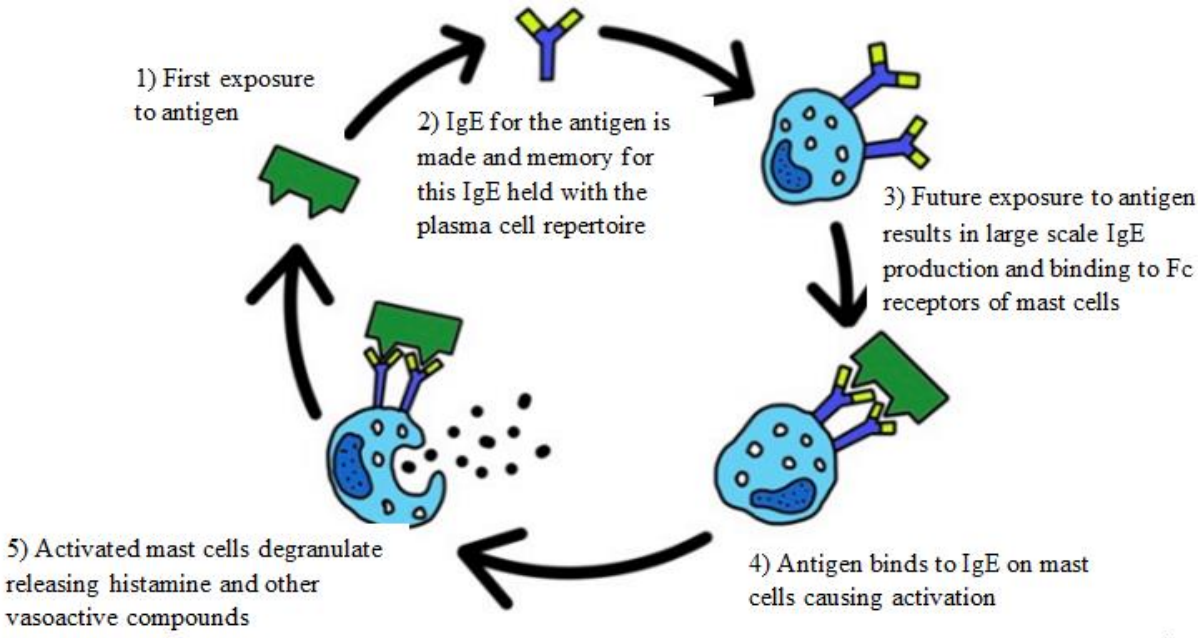

Figure 5.1: Diagrammatic representation of type I hypersensitivity reactions

5.2. Type II hypersensitivity – Autoimmune reactions

Also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. It is Ab-mediated destruction of cells. Antibodies bind to the foreign and mediate opsonization, phagocytosis, complement activation and/or cell-mediated immunity. The antigens are normally endogenous or exogenous chemicals (haptens) including few drugs. The reaction time is minutes to hours. It is primarily mediated by IgM or IgG, and Phagocytes also play a role. The lesion contains antibody, complement and neutrophils. Diagnostic tests include detection of circulating antibody against the tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence. Treatment involves anti-inflammatory and immunosuppressive agents.

- Blood transfusion incompatibility is type II. RBCs have different protein and glycoprotein encoding genes. These genes differences are considered as foreign between two individuals. Antibody against blood type antigen are called iso-hemagglutinis of the IgM class
- Hemolytic disease of new born develops when maternal IgG antibody specific for fetal blood-group antigen cross the placenta and destroy fetal RBCs. This is when Rh^+ fetus express Rh antigen on its blood cells that the Rh^- mother does not express.
- Some drugs (E.g., Penicillin) can adsorb nonspecific proteins on RBCs that leads to formation of Ab against to this RBCs and mediate lysis that result with anemia. But the anemia disappears when the drugs withdrawn.

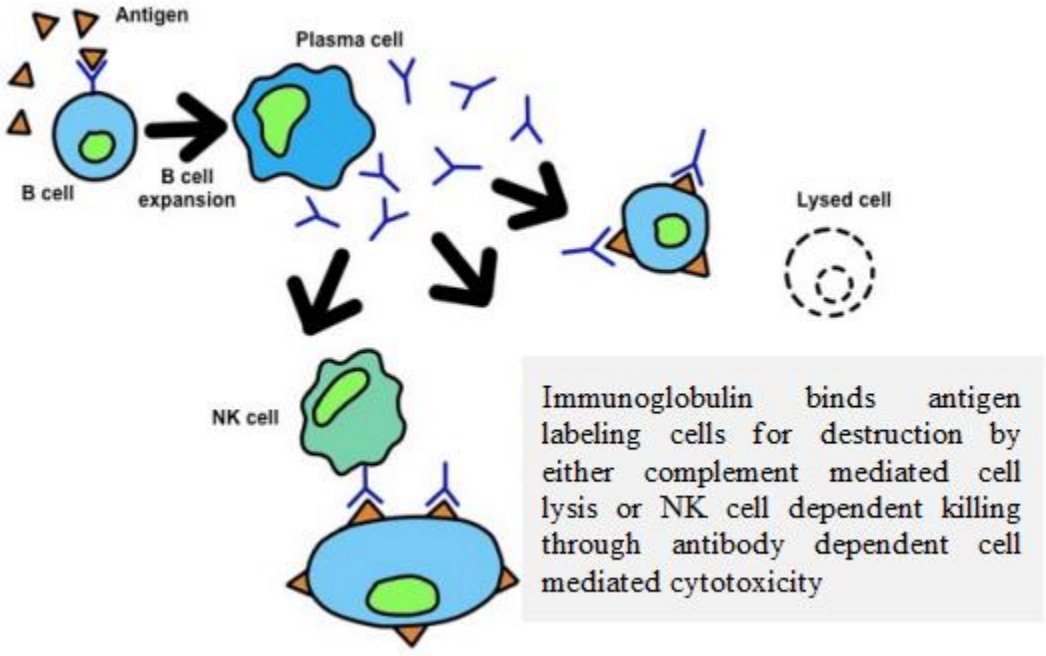

Figure 5.2: Type II Hypersensitivity reactions. The Presence of antigen stimulates specific B-cells. The B-cell undergoes clonal expansion and produces large amounts of immunoglobulin against the antigen. By binding antigen, the immunoglobulin labels the cell for destruction by NK cells or complement.

5.3. Type III hypersensitivity- Immune complexes

It also called as immune complex hypersensitivity. The reaction may be general (e.g., serum sickness) or may involve individual organs including skin, kidneys, lungs, blood vessels, joints or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms. The reaction may take 3-10 hours after exposure to the antigen. It is mediated

by soluble immune complexes. They are mostly of the IgG and IgM. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity). The antigen is soluble and not attached to the organ involved. The damage is caused by platelets and neutrophils. The lesion contains primarily neutrophils, immune complexes and complement.

Diagnosis involves examination of tissue biopsies for deposits of immunoglobulin and complement by immunofluorescence microscopy. Treatment includes anti-inflammatory agents.

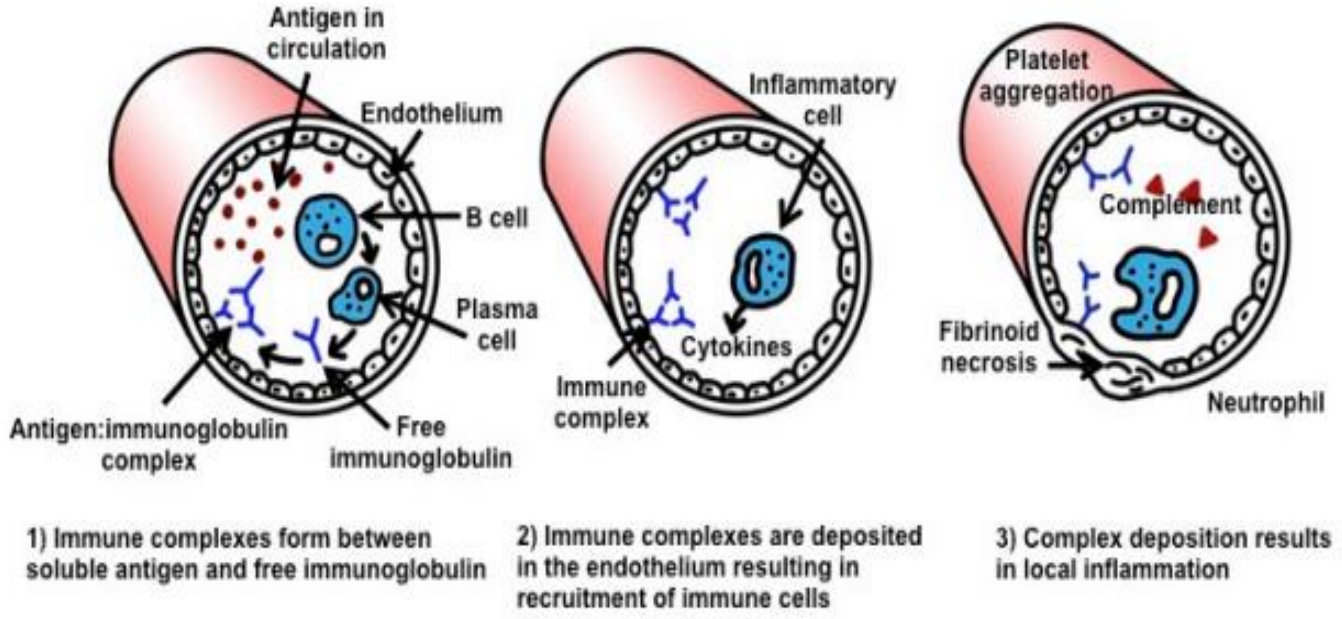

Figure 5.3: Pathogenesis of type III hypersensitivity

5.4. Type IV hypersensitivity – Delayed type

It also called as cell-mediated or delayed type hypersensitivity. The lesion is characterized by in duration and erythema. It is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison chemicals, heavy metals, etc.). Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation.

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. The delayed hypersensitivity lesions mainly contain monocytes and a few T cells. Diagnostic tests *In-vivo* includes delayed cutaneous reaction and patch test (for contact

dermatitis) and also *In vitro* tests. Corticosteroids and other immunosuppressive agents are used in treatment.

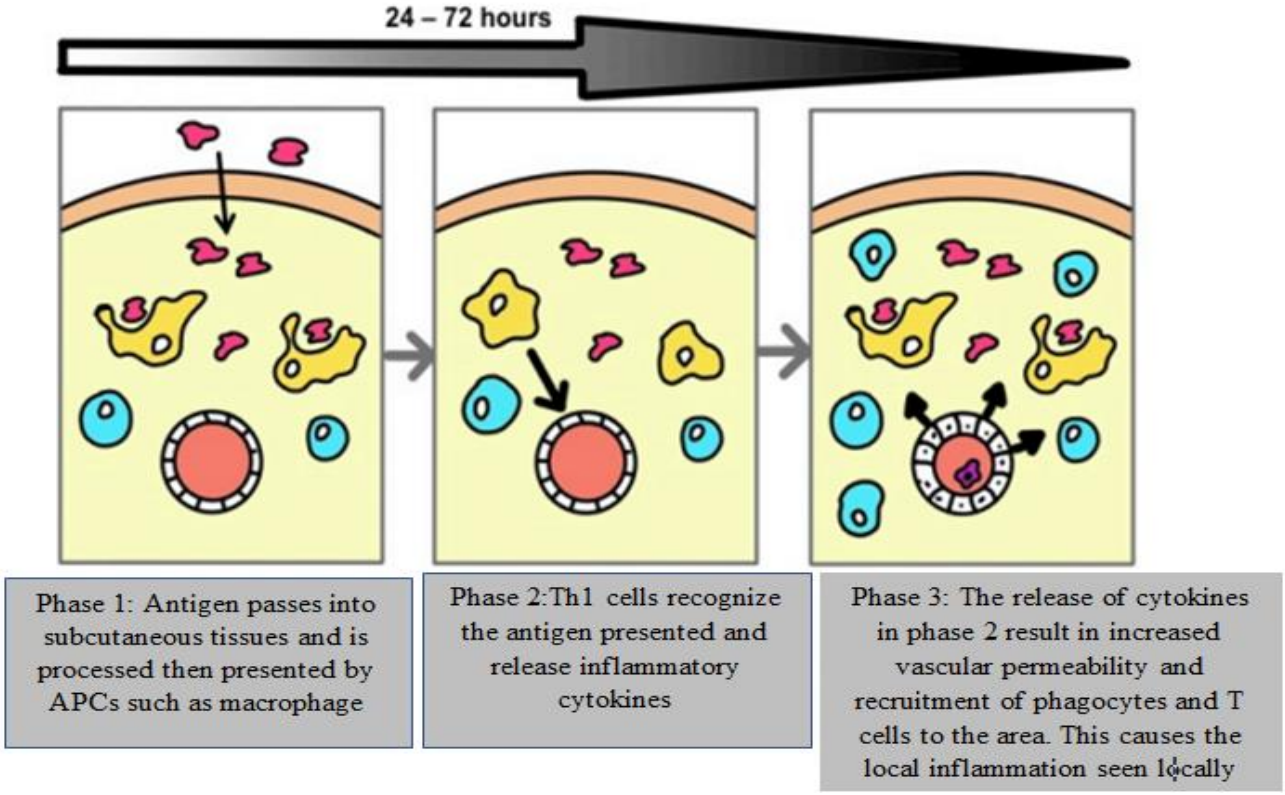

Figure 5.4: Pathology of cutaneous type IV hypersensitivity

Table 5.1: Comparison between types of hypersensitivity

Characteristic	Type-I	Type-II	Type-III	Type-IV
Antibody	IgE	IgG,IgM	IgG,IgM	none
Antigen	Exogenous	Cell surface	Soluble	Intracellular
Response time	15-30min	Min-hrs	3-8hrs	48-72hrs or longer
Appearance	Weal & flare	Lysis & necrosis	Erythema & Edema	Erythema & induration
Histology	Basophils & Eosinophils	Ab & complement	PMN & complement	Monocytes & Lyphocytes
Transfer with	Antibody	Antibody	Antibody	T-cells
Example	Hay fever, asthma	Pemphigus, Good pasture	Farmers lung, SLE	TB test, poison ivy, granuloma