

DISEASES OF IMMUNITY

CHAPTER

3

LEARNING OBJECTIVES

After the completion of this chapter, you should be able to,

- ◆ *Explain the various organs of immune system*
- ◆ *Describe the different types of major histocompatibility complex (MHC) molecules*
- ◆ *Outline the types, mechanisms and factors influencing induction of immune tolerance*
- ◆ *Elaborate the various types of hypersensitivity reactions*
- ◆ *Provide a note on allergy due to food, drug and chemicals*
- ◆ *Elucidate briefly about mechanism and prevention of transplant rejection*
- ◆ *Discuss the aetiology and pathophysiology of AIDS and amyloidosis.*

1. INTRODUCTION

Immune system is a fluid network present inside our body comprising of many interdependent types of cells and is designed to protect us from millions of microbes, toxins and parasites. Immunity is a state of resistance from infectious diseases. It may be categorized into three types.

1. Innate (Natural) Immunity

Innate immunity is a type of general protection that we all have. It includes external barriers of the body like skin and mucous membranes lining the nose, throat and gastrointestinal tract. It is a non-specific defence mechanism. It can recognize few highly conserved structures present in many different microorganisms. The structures recognized are lipopolysaccharides from Gram-negative cell wall, peptidoglycan, lipotechoic acids from Gram-positive cell wall, sugar mannose (common in microbial glycolipids and glycoproteins), bacterial DNA, N-formylmethionine found in bacterial proteins, RNA from viruses, glucans from fungal cell walls etc.

Example: Fowls are resistant to plague, while human are highly susceptible. Though whites are highly sensitive to yellow fever but blacks are resistant.

2. Adaptive (Active or Acquired) Immunity

This type of immunity develops throughout our lives. It involves lymphocytes. This type of immunity develops as the children and adults are exposed to diseases or immunized against diseases through vaccination.

Adaptive immunity is further categorized into two types.

(a) Humoral Immunity

It refers to the production of antibody in response to an antigen, mediated by B-cells.

(b) Cell-mediated Immunity

It refers to the production of cytotoxic T-lymphocytes (CTLs), macrophages, activated natural killer (NK) cells and cytokines in response to antigens, mediated by T-lymphocytes.

3. Passive Immunity

This type of immunity is meant for a short time, especially when the antibodies in the mother's breast milk provide an infant with temporary immunity to diseases that the mother has been exposed to, thus providing protection to the infant against infection during early years of childhood.

2. STRUCTURE OF IMMUNE SYSTEM 5

2.1 ORGANS OF IMMUNE SYSTEM

Based on the functions of various organs of the immune system, they are broadly categorized as follows.

1. Primary (Central) Lymphoid Organs

(a) Thymus

Thymus is located in the chest between the breast bone and heart. The immature thymocytes (prothymocytes) are produced in the bone marrow, which then migrate via the blood stream to the thymus and mature there. The mature T-cells are released into the circulatory system.

(b) Bone Marrow

Bone marrow is the site of origin of all the cells of the immune system by the process of haematopoiesis. It produces red blood cells, platelets, B-cells, natural killer cells, granulocytes and immature thymocytes.

Haematopoiesis is the formation and development of blood cells. The blood cell population is maintained constant by the production of new cells and destruction of old cells.

2. Secondary (Peripheral) Lymphoid Organs

(a) Spleen

This gland is located above the stomach, on the left side under the ribs. It serves as immunologic filter of the blood. It has B-cells, T-cells, macrophages, dendritic cells, natural killer (NK) cells and red blood cells. The spleen looks for foreign materials (antigens) from the blood passing through it. The macrophages and dendritic cells present the antigen to B or T-cells. The B-cells get activated and produce a large amount of antibody. The old red blood cells are destroyed in this organ.

(b) Lymph Nodes

Lymph nodes are small clusters of cells, surrounded by a capsule, present throughout the body, mainly found in neck region, under the arms and in the groin. They filter out and trap bacteria, viruses, cancer cells and other unwanted substances. Then they safely eliminate these from the body.

The cells in the lymph nodes are of two types,

(i) Lymphocytes: These cells produce antibodies (protein particles that bind to the foreign substances including infectious particles).

(ii) Macrophages: These cells digest the debris.

(c) Tonsils

Tonsils are found as three groups,

(i) Lingual tonsils located at the base of the tongue

(ii) Palatine tonsils located at the sides of the back of the mouth

(iii) Pharyngeal tonsils located at the roof of the nasopharynx.

All these groups defend the body against antigens that may gain entry through the nasal and oral epithelial routes.

3. Tertiary Lymphoid Organs

Skin is an impervious external barrier for the entry of pathogens. Specialized epithelial cells called as *keratinocytes* located in the epidermal layer of the skin secrete cytokines that provide primary defense.

E.g: Cutaneous Associated Lymphoid Tissue

2.2 CELLS OF IMMUNE SYSTEM

White blood cells (WBCs) also termed as leucocytes form the defense system of our body. They protect our body against foreign substances, viruses, bacteria as well as abnormal cells that originate within our body. The number of leucocytes in a healthy human adult varies from 5,000 - 10,000/ μ l ($5 - 10 \times 10^9$ /litre or 5,000,000,000 - 10,000,000,000/litre). These cells are nucleated and act like independent, living single cell organisms. They are divided into two main types viz granulocytes and agranulocytes.

1. Granulocytes/Polymorphonuclear Leucocytes (PMNs)

They are so named because these cells contain cytoplasmic granules containing chemicals that are capable of damaging the invading pathogens. They are further divided as follows.

(a) Eosinophils

They comprise about 3% of circulating WBCs. Their number increases during invasion of parasites and during allergic attacks.

(b) Basophils

They comprise about 0.5% of circulating WBCs. They play a role in acute allergic reactions.

(c) Neutrophils

They are the most common form of WBCs with a life span of less than a day. Their number increases during injury, infections, inflammatory diseases, metabolic changes, blood loss etc.

2. Agranulocytes

They have a large nuclei with no distinct granules in their cytoplasm. They include monocytes and lymphocytes.

(a) Monocytes/Macrophages

Monocytes are young cells that possess migratory, chemotactic, pinocytic and phagocytic activities. They migrate to tissues and undergo further differentiation to form multifunctional tissue macrophages. Thus, it can be said that monocytes are immature macrophages or precursors to macrophages.

Macrophages are also referred as scavengers or antigen presenting cells (APC). Their job is to pick up and ingest foreign material and present these antigens to T-cells and B-cells.

(b) Lymphocytes

These are also known as immunocytes i.e., cells that create immunity. Lymphocytes are an important part of immune system. These cells are manufactured in the bone marrow and characterized by a single large nuclei. Their number ranges from $1.5 - 4.0 \times 10^9$ per litre of blood in a healthy individual. They are further differentiated into T-lymphocytes, B-lymphocytes and natural killer cells. T-lymphocytes (helper, killer and suppressor) are responsible for cell-mediated immunity, while B-lymphocytes are involved in antibody production and provide antibody mediated immunity.

(i) T-lymphocytes

T-lymphocytes (helper, killer and suppressor) are responsible for cell-mediated immunity. They account for 75-80% of lymphocytes. These cells are processed by the thymus gland, an organ located between the heart and the sternum. Thymosin hormone secreted by the gland aids in the processing of T-lymphocytes to form mature, functional T-lymphocytes. Mature T-lymphocytes can identify only one type of antigen and cannot react with any other antigen.

An immature T-cell has a T-cell receptor associated with a signal transduction module made up of different polypeptide chains (CD3 protein). In the thymus, the cells develop both CD4 and CD8 markers. These cells are referred to as double positive). An immature T-cell lacking CD4 and CD8 are referred as double negatives (DN). Then the cells lose one of the markers (either CD4 or CD8) to form one of the functional cells. Those cells which retain a CD4 marker are called helper T-cells (T_H cells), while those with CD8 are called cytotoxic T-cells (T_C cells). Both T_H and T_C cells have a T-cell receptor with different functions in the immune system.

Besides the markers, T-cells also carry a receptor for identifying MHC molecules. T-cell receptor is the antigen receptor molecule on the surface of T-cells. It comprises of two different polypeptide chains viz α and β chains, as shown in the diagram given below. A small population of T-cells have δ and γ chains.

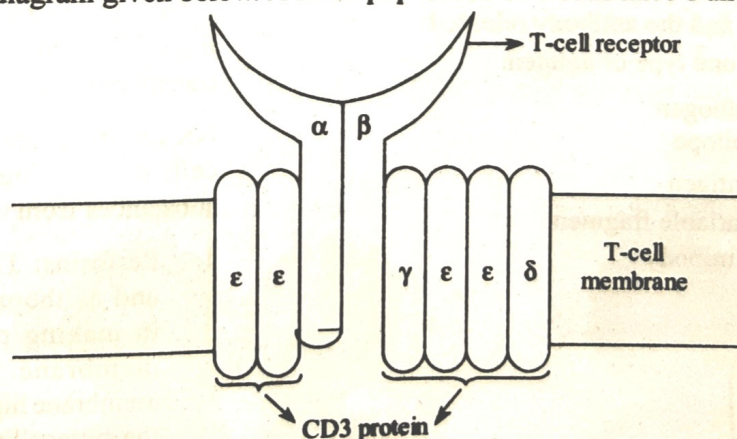


Figure: Diagrammatic Representation of T-Cell Receptor

Clonal Expansion of T-lymphocytes

When an antigen presenting cell (APC) i.e., monocytes, macrophages, dendritic cells presents a foreign antigen on its cell surface to a T-lymphocyte, the T-cells are processed to target that particular antigen. T-lymphocytes proliferate by mitosis to multiply into a large number of identical cells called as clone. Each member of the clone would carry the same antigen receptor. This is referred to as clonal expansion of T-lymphocytes.

During such clonal expansion of T-lymphocytes, three types of specialized cells against the original antigen are produced.

1. **Memory T-cells:** These cells are long-lived and provide immunity to the antigen.
2. **Cytotoxic T-cells (T_C -cells):** These destroy abnormal cells by releasing powerful toxins. Since they suppress the immune response, they are also called suppressor T-cells (T_S -cells). They carry CD8 moiety on their surface hence are called $CD8^+$ cells. They are mainly involved in destroying cells infected with foreign cells, tumour cells and viruses.
3. **Helper T-cells (T_H - cells):** These increase the number of cytokines to support or activate T-cells, B-cells and phagocytic cells. They carry CD4 molecules on their surface and hence are called $CD4^+$ cells. The normal ratio of $CD4^+ : CD8^+$ is 2:1. Depending on the type of cytokine increased, they are T_H1 (Augments IL-2 and IFN- γ) and T_H2 (Augments IL4, IL-5 IL-6 IL-10).

(ii) B-lymphocytes

B-lymphocytes are processed in the bone marrow. They account for 10-15% of lymphocytes. These cells are involved in antibody production and provide antibody mediated (humoral) immunity. Like T-lymphocytes, B-lymphocytes can also target one type of antigen and the antibody released can react with only one type of antigen.

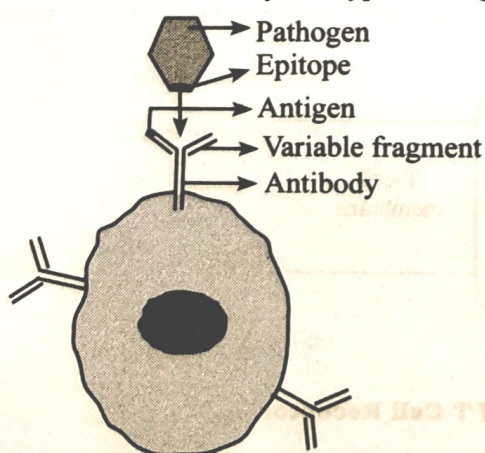


Figure: B-Lymphocyte

Clonal Expansion of B-lymphocytes

When an antigen presenting cell (APC) presents a foreign antigen on its cell surface to a B-cell, the B-cell is signalled to proliferate and produce antibodies that specifically bind to that

antigen. This is referred to as clonal expansion of B-lymphocytes. Binding of antibodies to antigens on bacteria or parasites acts as a signal for the macrophages to phagocytose and kill them.

B-cells are of two main types,

1. **Plasma cells:** These produce antibodies which are released into blood, lymph, lining of lungs and gut.
2. **Memory cells:** These remain in circulation. Whenever there is a second infection, they divide and produce more plasma and memory cells.

(iii) Natural Killer (NK) Cells

Natural killer cells are the type of lymphocytes that freely circulate in the blood and are also found in lymphatic organs like spleen and lymph nodes as well as in the red bone marrow. These derive their name from the fact that they are non-specific in their action and bring about the lysis of various virus-infected cells and tumour cells. The characteristic aspect of these cells is that they do not require any activation by the immune system, but act on their own. All the normal body cells possess class I MHC proteins on their plasma membranes, the complementary receptors of which are located on these NK cells. These cells bring about the destruction of only those cells which either completely lack or exhibit reduced amounts of these MHC proteins. E.g.s: Virus-infected, tumour cells or organ transplants etc.

NK cells bring about the lysis of these abnormal cells by releasing the following two types of substances from their granules.

1. **Perforins:** These are basically proteins and as the name suggests are involved in making perforations in the plasma membrane. This renders the plasma membrane highly porous thereby allowing the extracellular fluid to accumulate in the cell, ultimately resulting in its bursting.
2. **Granzymes:** Basically, these are enzymes that catalyze the process of proteolysis i.e., breakdown of proteins. Therefore, the abnormal cell is ultimately stimulated to undergo self-destruction or apoptosis (programmed cell death), thereby resulting in cell death. However, no damage is effected to the microbes invading the cell.

3. MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) PROTEINS 5 marks

Histocompatibility molecules are essentially glycoproteins expressed on the surface of all vertebrate cells. All the cells have thousands of such molecules present in their plasma membrane. These are responsible for the compatibility between genetically different individuals. No two individuals will have a similar set of histocompatibility molecules (with the exception of monozygotic (identical) twins). That is the reason why a graft of tissue of one human into another will provoke an immune response. The histocompatibility molecules of one human act as antigens (called as histocompatibility antigens/transplantation antigens) when introduced into a different individual, thus causing rejection of transplant. However, this is accomplished by suppressing the immune system.

In case of humans, histocompatibility molecules are called as human leucocyte antigens (HLA) because the molecules were first studied in leucocytes. These proteins are encoded by the HLA genes located on short arm of chromosome number 6.

Types of MHC Molecules

Histocompatibility molecules are categorized into two, class-I and class-II.

1. Class-I Histocompatibility Molecules

These are transmembrane proteins expressed on the surface of all nucleated cells (except red blood cells and cells of the central nervous system). These molecules are made up of two polypeptide chains. A heavy chain of 346 amino acids and a light chain of 99 amino acids. The heavy chain has five main domains that includes, three extracellular domains, one transmembrane domain and a cytoplasmic domain.

Another protein molecule called as beta-2-microglobulin (β_2 M) lies adjacent and attached to the heavy chain by a number of noncovalent interactions.

Class I molecules in humans are of three different types,

- (a) HLA - A
- (b) HLA - B
- (c) HLA - C.

2. Class-II Histocompatibility Molecules

Human class-II histocompatibility molecules are called HLA-D and are encoded by genes located in the major histocompatibility complex (MHC). Class-II molecules are glycoproteins containing two transmembrane polypeptides (an alpha (α) chain and a beta (β) chain having MW of 33,000 and 28,000). These molecules are expressed on only certain types of cells like macrophages, B-lymphocytes, dendritic cells of the spleen and Langerhans cells of the skin.

Here, it is to be remembered that class-I and class-II present their antigens to different subsets of cells. The T-cells may be distinguished into two types based on the presence of surface glycoproteins as CD4 and CD8. Those T-cells that have CD4 surface glycoproteins are called CD4⁺ T-cells, while those that have CD8 surface glycoprotein are designated CD8⁺ T-cells. Both CD4⁺ and CD8⁺ T-cells have antigen receptors called as T-cell receptors (TCR) that look for peptides nestled in histocompatibility molecules. CD8 molecules of CD8⁺ T-cells can bind only to class-I histocompatibility molecules, while CD4 molecules of CD4⁺ T-cells can bind only to class-II histocompatibility molecules.

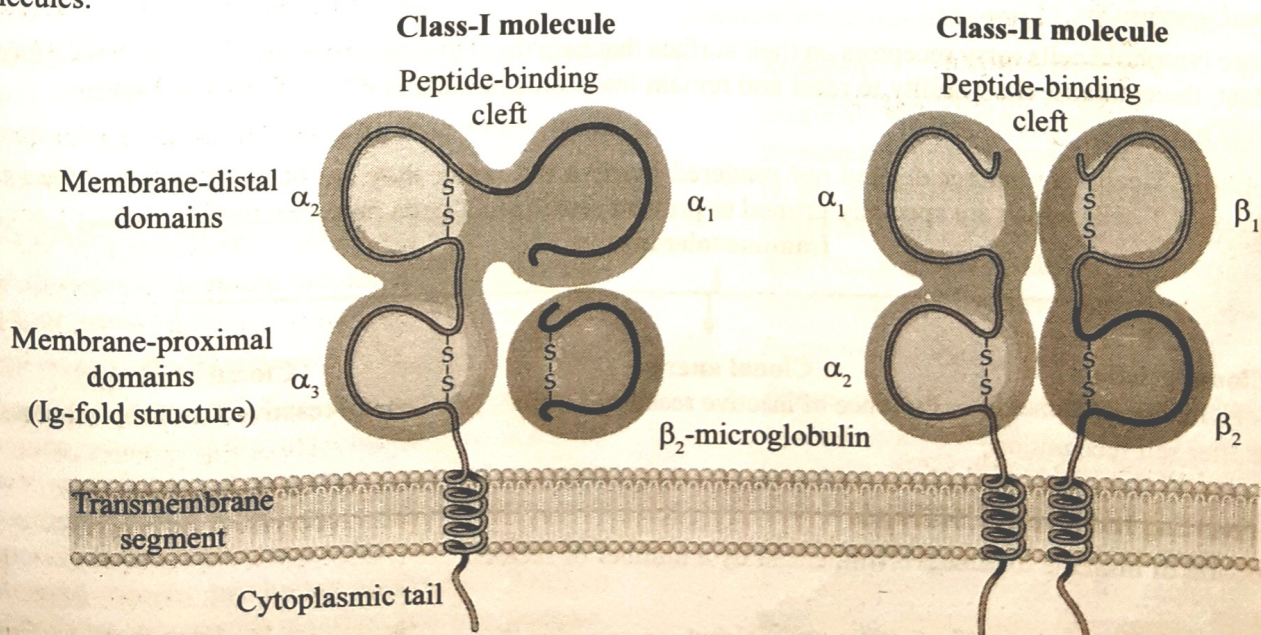


Figure: Major Histocompatibility Complex (MHC) Molecules

Role of MHC Proteins

MHC proteins are significant in various ways.

1. *Organ Transplantation*

When a damaged tissue or organ is removed and replaced with a new weak performing tissue or organ of different person, the immune system either accepts or rejects it. MHC antigens causes a very strong immune response and are known to play a vital role in transplant rejection.

2. *Regulation of the Immune System*

Class I and class II MHC antigens play a pivotal role in regulating both cellular and humoral immunity. Functioning of cytotoxic T-cells is regulated by class I MHC antigens while the functioning of helper T-cells is controlled by class II MHC antigens.

3. *MHC Associated Diseases*

Diseases that have been found to be associated with the MHC include autoimmune diseases, inflammatory diseases and inherited metabolic diseases.

4. IMMUNE TOLERANCE *to marker*

Immune system functions to provide protection to the body against foreign agents (non-self). Immune tolerance is a state of unresponsiveness to body's own cells, tissues, antigens and organs (i.e., self).

Types of Tolerance

Immune tolerance appears in the following two forms.

1. *Central Tolerance*

Immature lymphocytes that identify self-antigens in central lymphoid organs (i.e., thymus and bone marrow) are destroyed by apoptosis (i.e., programmed cell death).

2. *Peripheral Tolerance*

Mature self reactive lymphocytes that identify self-antigens in peripheral tissues are killed, rendered inactive or turned off by regulatory T-cells.

Mechanisms of Tolerance

One or more of the following mechanisms operate to ensure that immune system remains tolerant to self antigens and react only to foreign antigens.

1. *Clonal Deletion*

During embryonic life, mature T-cells and B-cells form colonies (clones). These clones upon activation by antigens or macrophages respond against body's own antigens and tissues. Hence such lymphoid cells are selectively deleted or sequestered so that no clones are available. Consequently, a state of immune tolerance develops.

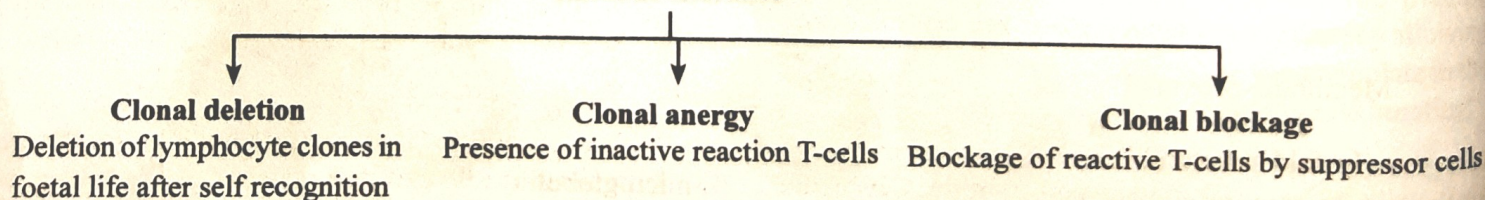
2. *Clonal Anergy*

Mature lymphoid cells carry receptors on their surface that help them to identify antigens. When the surface receptors are lost, the cells lose their ability to react and remain inactive. The state is referred as clonal anergy.

3. *Clonal Blockage*

Lymphoid T-cells are neither deleted nor rendered inactive but rather they are blocked by other forces source of suppressor T-cells which are specially primed to prevent sensitized T-cells from reacting.

Immune tolerance



Factors Influencing Induction of Tolerance

Induction of immune tolerance is influenced by a number of factors.

1. *Species*

Induction of immune tolerance differs from species to species. For instance, chicken and guinea pigs are rendered tolerant less rapidly than rabbits and mice.

2. **Immunological Competency and Age of Host**
Immunological competency is related to age of the host. Higher the immunological competency, more difficult is the induction of tolerance. For example, induction of tolerance is easier in new borns and embryos as their immune system is immature and less competent.
3. **Antigen**
Following characteristics of antigen influences the induction of tolerance.
 - (a) **Physical Nature of Antigen:** Aggregated antigens easily undergo phagocytization by the macrophages and are then presented to antibody forming cells. Hence they are highly immunogenic whereas in free state (i.e., soluble form) antigens are not phagocytized and therefore are tolerogenic.
 - (b) **Administrative Route:** Induction of tolerance is also influenced by route of administration of antigen. Even when antigens are administered through i.v route in large doses it leads to tolerance due to suppression by T-cells.
4. **Dose**
In moderate doses, antigen is immunogenic while in small doses given repeatedly, the same antigen is immuno tolerant.

Importance of Tolerance

The concept of immune tolerance demonstrates why immune system does not reacts to body's own cells and antigens which further explains the breakdown of immune tolerance leading to development of autoimmune diseases. Autoimmune diseases are multi-system disorders that are difficult to detect as well as treat. Breakdown of immune tolerance and development of autoimmune disorders indicate an abnormal and autonomous or improper functioning of immune system as it gains access to self antigens and cells.

Methods for inducing tolerance are helpful for treating allergic and autoimmune disorders and for preventing immune responses in stem cell and gene therapy and graft rejection.

5. DISEASES OF IMMUNE SYSTEM

The diseases of immune system are classified into following four groups.

1. **Hypersensitivity Reactions**
Hypersensitivity or allergy is an inappropriate immune response to the invading antigens. It occurs due to sensitization of the person upon first exposure to antigen acting as allergen. Upon subsequent exposure to the same antigen, immune system gets activated thereby producing antibodies. Antigen antibody reaction results in rashes, pruritus, oedema, wheezing etc.

2. **Autoimmune Diseases**
Autoimmune diseases arise as a result of failure of immune tolerance.
E.g: Systemic lupus erythematosus (SLE)
3. **Immunodeficiency Disorders**
These group of disorders are characterized by deficient cellular and humoral immune functions.
E.g: AIDS
4. **Possible Immune Disorders**
Immunologic mechanisms are believed to be involved in possible immune disorders.
E.g: Amyloidosis

5.1 HYPERSENSITIVITY REACTIONS 10 marks

Hypersensitivity or allergy refers to inappropriate immune response by the normal immune system to antigens invading the body. Hypersensitive reactions are classified into the following four types.

1. Type-I or IgE Mediated Hypersensitivity

Type-I hypersensitivity response is also referred as immediate/anaphylactic hypersensitive response. When certain types of allergens attack the body, a humoral antibody response is induced resulting in the production of antibody secreting plasma cells and memory cells.

The tissue mast cells and basophils contain F_C receptors on the cell surface to which IgE binds with high affinity. A second exposure to the same allergen causes cross-linking between the membrane bound IgE molecules resulting in degranulation of mast cells and basophils.

Inflammatory mediators released by the degranulation of these cells diffuse into the surrounding tissue and act upon them resulting in increased Ca^{++} influx, causing vasodilation and smooth muscle contraction.

Components Involved in Type-I Hypersensitivity

- (a) **Allergens**
Some of the common allergens causing type I hypersensitive response include plant pollen, drugs (E.g.s: Penicillins, sulphonamides, anaesthetics, salicylates etc), foods (E.g.s: Sea foods, eggs, milk, nuts etc.), insect products (E.g.s: Bee venom, dust, mites etc), mold spores, animal hair and dander.
- (b) **Reaginic Antibody**
These are IgE class of immunoglobulins formed against an allergen. IgE consists of two heavy and two light chains with molecular weight of 190,000. The high molecular weight of IgE is due to the presence of additional constant region domain that alters the conformation of the molecule in order to bind to the glycoprotein receptors on the membranes of basophils and mast cells.

(c) *Mast Cells and Basophils*

IgE binds to the tissue mast cells and blood basophils with greater affinity. The cytoplasmic membrane bound granules of basophils contain histamine (an inflammatory agent), heparin (an anticoagulant) and other substances that are released in response to allergies. Cytoplasmic granules of mast cells also contain heparin, histamine and serotonin which are released during inflammation and allergic responses.

(d) *F_C Receptors*

F_C portion of IgE antibody binds to the receptors on the surface of basophils and mast cells with high affinity. Two types of F_C receptors are F_CRI (high affinity receptors) and F_CRII (low affinity receptors). Degranulation is initiated by the crosslinking of IgE class of immunoglobulins.

Certain biochemical events followed by such crosslinking results in the following,

- (i) Increase in the fluidity of membrane
- (ii) Formation of Ca⁺⁺ channels
- (iii) Increase in Ca⁺⁺ ions due to uptake of extracellular calcium ions as well as its release from intracellular storage depots
- (iv) Increase in Ca⁺⁺ ions results in arachidonic acid formation, conversion of arachidonic acid to leukotrienes and prostaglandins
- (v) Release of inflammatory mediators.

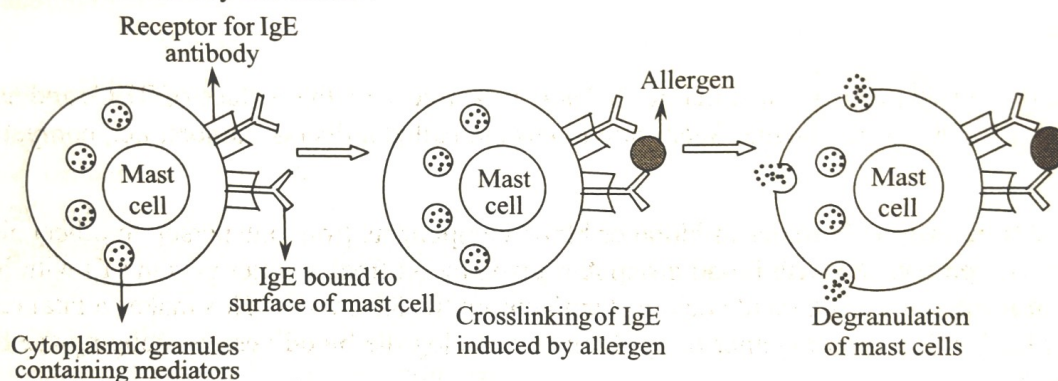


Figure: Diagrammatic Representation of Immediate (Type-I) Hypersensitivity

The inflammatory mediators have been classified into two types.

1. *Primary Mediators*

These substances are produced before degranulation and are stored in cytoplasmic granules.

E.g.s: Histamine, proteases, eosinophil chemotactic factor, neutrophil chemotactic factor and heparin.

2. *Secondary Mediators*

These substances are produced after target cell activation or released during the breakdown of membrane phospholipids.

E.g.s: Platelet activating factor, leukotrienes, prostaglandins, bradykinins and cytokines.

Anaphylactic Reactions and their Treatment

The effect of inflammatory mediators is anaphylaxis, an emergency condition resulting from an abnormal and immediate allergic response to a substance to which the body has become intensely sensitized. This results in flushing, itching, nausea, vomiting, swelling of mouth and tongue and airways to cause obstruction, wheezing, sudden drop in blood pressure and may even prove to be fatal. Anaphylactic reactions are treated by administering drugs that counteract the action of these mediators. They include epinephrine (adrenaline), antihistamines, corticosteroids, cromolyn sodium etc.

- (a) Prednisone (corticosteroid) is effective in the treatment of asthma.
- (b) Aminophylline administered to asthmatic and chronic bronchitis patients relaxes the smooth muscles, dilates the air passages and stimulates respiration.
- (c) Asthma can be reverted by using leukotriene receptor inhibitor (montelukast) and cromolyn sodium.
- (d) Antihistamines are given to patients with allergic rhinitis and allergic conjunctivitis.

2. **Type-II or Antibody Mediated Hypersensitivity**

It is also known as cytotoxic hypersensitivity and is mediated by IgM or IgG class of antibodies and complement system. Some examples of type-II hypersensitivity are ABO transfusion reactions, Rh haemolytic disease and drug induced haemolytic anaemia.

ABO Transfusion Reactions

Blood typing and transfusions are based on the alloantigens of human erythrocytes. The term alloantigen refers to antigens that differ among individual members of a species. Such differences in blood is due to the presence or absence of antigens on the surface of the red blood cells (RBCs) and antibodies in the blood plasma. Humans exhibit four different kinds of blood types A, B, AB and O.

Blood Group A

Individuals with blood group A have 'A' antigen on the surface of RBCs and 'B' antibodies circulating in the blood plasma.

Blood Group B

Individuals with blood group B have 'B' antigen on the surface of RBCs and 'A' antibodies circulating in the blood plasma.

Blood Group AB

Individual with blood group AB have both 'A' and 'B' antigens on the surface of the red blood cells (RBCs) and no antibodies circulating in the blood plasma. Such individuals are called universal recipients i.e., can receive blood of any group.

Blood Group O

Individuals with blood group O have neither 'A' nor 'B' antigens on the surface of RBCs and have both 'A' and 'B' antibodies circulating in the blood plasma. Such individuals are called universal donors, i.e., compatible with any blood group.

During blood transfusions (transfer of blood or blood components from one person to other) blood matching must be accurately done. If a person (X) with blood group A is given blood from another person (Y) with blood group B, then the 'B' antibodies in the plasma of (X) will stick to B antigens on the RBCs of Y. This makes a fatal reaction whereby the RBCs of donated blood will clump together or agglutinate and clog the blood vessels stopping the blood circulation to various parts of the body.

Table: Compatibility of Blood Transfusions Between Different Blood Groups

Blood Group	Antigens present on RBCs	Antibodies present in serum	Can donate blood to	Can receive blood from
O	Nil	A and B	A, B, AB and O (all groups)	O
A	A	B	A and AB	A and O
B	B	A	B and AB	B and O
AB	A and B	Nil	AB	A, B, AB and O (all groups)

Additional antigens present on the surface of the RBCs are called 'Rh' factors. Those who have Rh factor are called Rh⁺, while those who do not have Rh factor are called Rh⁻.

'Rh' antibodies are naturally not present in a person with Rh⁻ blood but when a Rh⁻ person receives blood from Rh⁺ person, 'Rh' antigen of Rh⁺ blood triggers the production of 'Rh' antibodies. A person with Rh⁺ blood can safely receive blood from a Rh⁻ person.

Based on the above explanation, a person can belong to either of the following eight blood groups.

O Rh ⁺	A Rh ⁺	B Rh ⁺	AB Rh ⁺
O Rh ⁻	A Rh ⁻	B Rh ⁻	AB Rh ⁻

Blood Typing

Blood typing is done by mixing the person's blood separately with three reagents namely, antiserum against 'A' antigen, antiserum against 'B' antigen and 'Rh' antibodies. If agglutination occurs, then it is an indication that the blood has reacted with certain antibody. In simpler sense, if agglutination occurs with 'A' antiserum, blood group is A.

Rh Incompatibility

Rh blood type is important in case of pregnant women. Problem arises when an Rh^{-ve} woman becomes pregnant with a baby (foetus) that has Rh^{+ve} blood (the gene for 'Rh' factor being inherited from the father). This is referred to as Rh incompatibility.

Rh incompatibility can trigger the production of antibodies. This can happen when the Rh^{+ve} RBCs of the foetus mixes with the blood of Rh^{-ve} mother, during pregnancy or delivery. This type of antibody response is called 'Rh' sensitization. The immune system of the mother identifies the Rh^{+ve} RBC of the foetus as 'foreign' and starts producing antibodies. The mother is now said to be "Rh sensitized". This affects the future pregnancy. If the second or third baby's blood type is Rh^{+ve}, then the antibodies in the mother's immune system attacks the foreign cells (baby's cells) and destroy them resulting in severe problems called as Rh disease or haemolytic disease of the new born (HDN) or erythroblastosis foetalis.

Babies born to such mothers are anaemic, due to which the newborn's body starts making RBCs at a faster rate than normal in bone marrow, liver and spleen leading to enlargement of these organs. Immature erythroblasts formed cannot perform the function of mature red blood cells. Thus, babies are unable to get rid of bilirubin formed as a breakdown product of the blood pigment (haemoglobin), resulting in its accumulation in the blood, other tissues and fluids of the baby's body. This is referred to as hyperbilirubinemia and may lead to jaundice (yellowing of the baby's skin and tissues).

Prevention of Hemolytic Disease, Erythroblastosis Foetalis or Rh Disease

Recent advancement in prenatal care can help to prevent the HDN. Rh^{-ve} mothers are usually given 'Rh' immunoglobulin (RhIg), also known as Rho GAM at 28 weeks of gestation and a second dose of the drug within 72 hours after the baby has been delivered. The drug helps in preventing the antibodies of Rh^{-ve} mother to react with Rh^{+ve} cells of the foetus, thus preventing activation of B-cells and formation of memory cells.

3. Type-III or Immune-Complex Mediated Hypersensitivity

Immune complexes formed as a result of interaction between antigen and antibody are normally removed by the reticuloendothelial system. At certain

times, they are retained in the body and are deposited in tissues causing immune-complex diseases. A few of these have been mentioned below.

(a) Arthus Reaction

Deposition of immune complexes in the tissues leads to inflammation. Inhalation of microorganisms (bacteria or fungi) causes occupation related hypersensitivity pneumonitis like cheese-worker's lung, wood-worker's lung, wheat-miller's lung, farmer's lung and pigeon-fancier's disease.

(b) Serum Sickness

When a foreign antigen is injected, it binds with the antibodies to form larger particles (immune complexes) that are deposited in various tissues causing inflammation and various other symptoms. Serum sickness is characterized by fever, urticaria (nettle rash or hives), arthralgia (shooting pain in the joints), lymphadenopathy and splenomegaly (enlargement of the spleen), eosinophilia etc.

Some other drugs associated with this type of reaction are allopurinol, barbiturates, captopril, cephalosporins, griseofulvin, phenytoin, procainamide, quinidine, and sulphonamides.

(c) Glomerulonephritis (Glomerular nephritis)

It is a type of kidney disease characterized by the inflammation of glomeruli of the kidneys. This leads to impairment in the kidney's ability to filter urine.

(d) Rheumatoid Arthritis

It is an autoimmune disease characterized by the presence of rheumatoid factor, IgM and IgG antibodies bound to F_C region of the normal human IgG in their serum and synovial fluid.

The binding of antigen and antibody forms immune complexes that deposit on synovial membrane causing inflammation. These immune complexes activate the complement system and cause damage to the tissues. Treatment involves non-steroidal anti-inflammatory drugs like aspirin, immunosuppressive drugs or corticosteroids.

(e) Systemic Lupus Erythematosus

It is an autoimmune disease wherein antibodies are formed against DNA, histones and nucleolar proteins. Immune complexes are formed by the binding of DNA and anti-DNA antibodies that get deposited on the synovial membrane or on the basement membrane of the kidney.

4. Type-IV or Delayed Type Hypersensitivity

It is the only type of hypersensitive response stimulated by antigen specific T-cells. As the name suggests, the response is often delayed. The antigen presenting cells (APC) ingest the antigen, process it and display the epitope part on their surface close to class II MHC protein. The T-helper cell binds to the APC, gets activated and begins to produce cytokines.

(a) Contact Hypersensitivity

Exposure of certain individuals to simple chemicals like nickel, nitrophenol, formaldehyde, turpentine, drugs like sulphonamides, neomycin, cosmetics and soaps results in contact hypersensitivity. All these molecules penetrate the skin and act as haptens. The APC in the epidermal layers of skin and macrophages take up the antigens and are carried to the lymph nodes for activation of T-cells. Upon second exposure to the antigen, cytotoxic T-cells (T_C cells) secrete cytokines that result in erythema (flushing of the skin due to dilation of blood capillaries), itching, eczema or necrosis of the skin.

(b) Tuberculin Type Hypersensitivity

Another familiar example of delayed type hypersensitivity is tuberculosis. The bacterial protein, tuberculin is injected intradermally and acts as an antigen. The protein is derived from the cell wall of the tubercle bacterium, *Mycobacterium tuberculosis*.

Patients suffering from tuberculosis or those who have recovered from infection develop reddish swollen skin lesions at the site of injection caused by the infiltration of macrophages.

Allergy Due to Food, Drugs and Chemicals**1. Food Allergy**

Food allergies are non-toxic, immune-mediated IgE or non-IgE hypersensitivity reactions. The food we consume contains various complex particles like carbohydrates, proteins, fats, lipids etc. These food particles upon ingestion get converted to simple digestible particles by catalytic reactions.

Under normal conditions, several tissue barriers prevent the entry to these particles into the tissues of gut. However, occasionally the unbroken proteins enter into gut tissues by absorption through GI tract and evoke an immunological response when they are presented to T-cells i.e., the activation of Th1 or Th2 cells induces non-IgE mediated or IgE mediated immune response respectively.

In IgE mediated allergic response, the unbroken food proteins (antigens) enters the gastric mucosa and gets engulfed by antigen presenting cells (dendrite cells).

The activated Th2 cells causes stimulation of B-cells for production of IgE food-specific antibodies to the antigens that comes across the tissue.

The IgE antibodies undergo sensitisation by binding with mast cells (tissue binding) and/or basophils (cellular binding) and remains in tissue awaiting for the upcoming allergen (antigen or protein) for subsequent binding. When the next allergen enters, the specific IgE antibody identifies it and binds to epitope (a specific area on protein) to release histamine, bradykinin, leukotrienes, prostaglandins etc., by degranulation of cells. The release of these mediators result in inflammation.

In non-IgE-mediated food allergic reaction, when the allergen enters GI tract, the already sensitised T-cells binds to the allergen resulting in release of cytokines and finally leads to chronic inflammation.

Symptoms

The symptoms of food allergy can be seen in various organ systems like cutaneous, gastrointestinal, respiratory and other systems. Various symptoms of food hypersensitivity allergic reactions are listed in the table below.

Types of hypersensitivity		Characteristics	Symptoms
1.	Type I	IgE mediated	Urticaria, angioedema, anaphylaxis
2.	Cell mediated food hypersensitivity	Non-IgE mediated	Food-protein induced proctocolitis, FPI enterocolitis, FPI enteropathy and coeliac disease

2. Allergy Due to Chemicals and Drugs

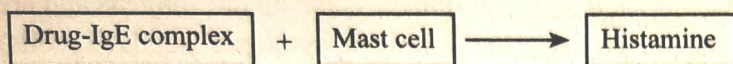
Drugs and chemical allergy reactions are the true hypersensitivity reactions ranging from 5 to 10% of the total drugs reactions. They result due to interaction among the pharmacological agent and immunological response triggered by IgE (immunoglobulin E).

These IgE mediated drug reactions fall under type-I hypersensitivity reactions and their mechanism is clearly evident in contrast with other hypersensitivity reactions.

The adverse reactions which are often non-immune mediated but resembles immune mediated allergic reactions are often termed as pseudo allergy reactions since they exhibit specific immunological resemblance.

Mechanism of Action

The drug IgE-complex binds with mast cells to release histamine.

**Clinical Symptoms**

The symptoms include urticaria (skin lesion), angioedema, bronchospasm, pruritis, anaphylaxis, vomiting and diarrhoea.

Time of Onset

After a few minutes or hours of drug administration.

Treatment

1. Termination of medicament causing allergy and its substitution with similar chemical entity.
2. Usage of corticosteroids and oral histamine for monitoring of the symptoms like urticaria, angioedema etc.
3. Performance of penicillin skin test before administration of β -lactam antibiotics like cephalosporin to the patients with serious penicillin allergy.

Such patients should avoid the use of carbapenems due to adverse reaction between β -lactam ring and penicillin.

5.2 AUTOIMMUNE DISEASES *10 marks*

When the immune system fails to differentiate self-antigens from foreign, effective and specific immune responses are directed towards the body's own cells and tissues (i.e., self) as a result of which pathological autoimmune diseases arise. In other words, break down of immune tolerance leads to autoimmune diseases.

E.g: Systemic lupus erythematosus (SLE).

Generally, whenever an injury occurs to cells or the cell dies by apoptotic mechanism or any other mechanisms, its antigens are released into the circulation. These antigens associate with bacteria, virus and even drugs and eventually get metabolized. Immune system and the antigens so released do not react with each other but when the immune system fails to function properly, it reacts against body's own antigens and thereby induces autoimmune diseases. This type of immune response is known as autoimmunity.

Types of Autoimmune Diseases

Depending upon whether the autoimmune response is directed against a particular tissue or against widespread antigens, autoimmune diseases are classified into organ specific and non-organ specific diseases respectively.

1. Organ Specific Diseases

In these type of diseases, autoantibodies formed react with antigens in a specific tissue or organ and thereby causes its chronic inflammatory destruction.

2. Organ Non-Specific Diseases

In these diseases, autoantibodies formed react with antigens in many tissues or organs and thus cause systemic lesions.

Mechanism

Various possible mechanisms that underline the development of autoimmune diseases includes,

1. Reappearance of forbidden deleted lymphocyte clones that are capable of reacting against self-antigens.
2. Defects in the functioning of helper T-cells that can escape suppressor T-cells.
3. Decreases in the level of suppressor T-cells that regulate self primed lymphocytes.
4. Immune paralysis due to development of abnormal antigenic properties in self cells caused by injury or infections.
 - (a) Foreign antigens complex with self-antigens so that the latter also gets destroyed by the antibodies while destroying the former. This mechanism is evident in many drug-induced autoimmune diseases.
 - (b) When the infecting agents contain antigens similar to that of the body's own antigens, the antibodies produced against the infecting organism also attacks the body cells. This is known as *antigenic mimicry* and such antibodies that reacts against self antigens when produced for reacting against foreign antigens are called *cross reacting antibodies*. This mechanism is evident in rheumatic heart disease and polyarteritis nodosa.

The mechanisms demonstrated above are resolved into 3 theories.

1. Defects in Immune System

- (a) Cell Based Defects
 - (i) Emergence of forbidden or deleted clones of lymphocytes
 - (ii) Inactivation or loss of suppressor T-cells
 - (iii) Emergence of clones of abnormal helper T-cells
 - (iv) Abnormal antigen processing and cell to cell interactions.
- (b) Development of cross reacting antibodies.
- (c) Defects in MHC system (genetic defects).

2. Defect in Somatic System

These include production of abnormal antigens in normal cells due to cell injury or infection induced antigenic mimicry.

3. Combined Immune and Somatic Defects

In this case, autoimmune diseases arise as a result of defects of both autoantigens and abnormal immune reactivity.

Transplant Rejection 10 marks

Transplantation is the process of replacing improper or non-functioning cells, tissues or organs with functional ones from other sites or regions of either the same or different individual or species.

Transplant rejection is the phenomenon wherein the immune system of body recognizes the transplanted organ called *graft* as a foreign body and triggers certain cell-mediated or humoral immunologic reactions which leads to the rejection of the transplant (graft). For example, in case of rejection of kidney transplant, the transplanted kidney initially becomes thickened and scarred and renal grafts exhibit glomerulonephritis (inflamed glomerulus). To avoid such rejections, HLA compatibility between donor and recipient should be checked prior to the transplantation. The intensity or severity of immune response depends partially on the genetic differences between the host and the recipient.

Types of Tissue Transplantations

Based on the genetic differences between donor and recipient, transplantation of tissues is classified into the following four types.

1. Autografts

These are the grafts wherein donor and recipient are same i.e., the graft is harvested from one site of an individual and transplanted to another site of the same individual. Since genetic differences are nil, graft does not get rejected.

2. Isografts

These are the grafts wherein donor and recipient are derived from different individuals who are genetically identical i.e., share same genotype such as monozygotic twins. The graft does not get rejected since no genetic differences exist.

3. Allografts

Allografts are the most common type of grafts wherein donor and recipient are of same species but are genetically non-identical i.e., are of different genotypes. Due to genetic differences, grafts are bound to undergo rejection, the severity of which depends on the degree of similarity or histocompatibility between the donor and recipient.

4. Xenografts

These are the grafts in which the donor and the recipient belong to different species. Since they exhibit maximum genetic differences, the degree of immune response is also very high leading to instant graft rejection.

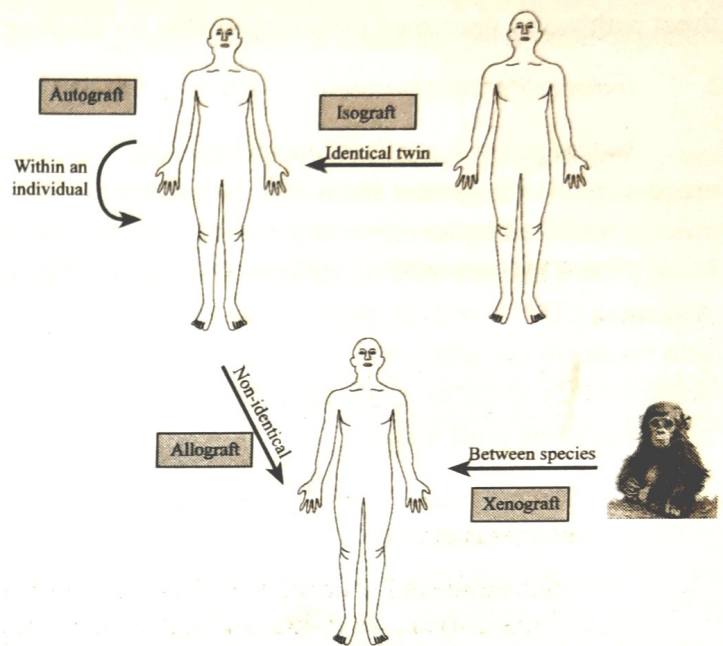


Figure: Types of Tissue Transplantations

Mechanism of Allograft Rejection

As explained previously, allografts and xenografts get rejected due to genetic differences between the donor and the recipient. Allografts can survive rejection by using immunosuppressive drugs. Allograft rejection involves mechanisms mediated by cellular (lymphocyte mediated) and humoral (antibody mediated) systems wherein T-lymphocytes and antibodies destroy the grafts.

Cell-mediated immune reactions are mediated by T and B-lymphocytes. Difference in HLA alleles of donor and recipient induce the rejection of allografts. After transplantation, alloantigens presenting cells of donor graft are recognized as foreign by two pathways.

1. Direct Pathway

In this pathway, CD8 and CD4 T-cells of the recipient recognize the alloantigenic MHC molecules on the antigen presenting cells (APCs) of the graft via their T-cell receptors. Recognition of an antigen requires the association of T-cell receptors with the MHC molecules and the presence of costimulatory molecules. Dendritic cells are assumed to play an important role in the graft rejection reaction because they express both class I and II MHC molecules as well as costimulatory molecules. Dendritic cells of the graft are recognized by the T-cells of the host either in the graft or when these dendritic cells have reached the lymph nodes.

Class I MHC antigens on the APCs of the graft are recognized by the CD8⁺ cytotoxic T-cells of the host and differentiate into active CTLs. Activated CTLs so formed damage the graft cells. Class II MHC antigens on the surface of APCs of the graft are recognized by the CD4⁺ T-cells which undergo proliferation and result in the production of cytokines like IFN- γ which initiate a local inflammatory response in the graft which include increased vascular permeability, accumulation of macrophages and lymphocytes in the tissue and eventually damage of the graft tissue by activated macrophages. Thus, direct pathway is presumed to be responsible for eliciting early immune response.

2. Indirect Pathway

In this pathway, antigen presenting cells (APCs) of the host pick up the allogenic MHC molecules from the graft, process them and present them to T lymphocytes. This pathway of graft rejection resembles the normal physiological process involved in the presentation of antigen. It generates CD4⁺ T-cells which gain access to the graft. In the graft these CD4⁺ T-cells interact with the antigens presented by the APCs of the host. This initiates a delayed hypersensitivity reaction. Activated CD4⁺ T-cells in turn stimulate the B lymphocytes which generate antibodies against the graft. Indirect pathway also results in the generation of CD8⁺ T-cells which by themselves are not able to recognize the graft cells but require the help of APCs of the host, which present the antigens to them. Hence, CD8⁺ T-cells generated by the indirect pathway do not damage the graft tissue.

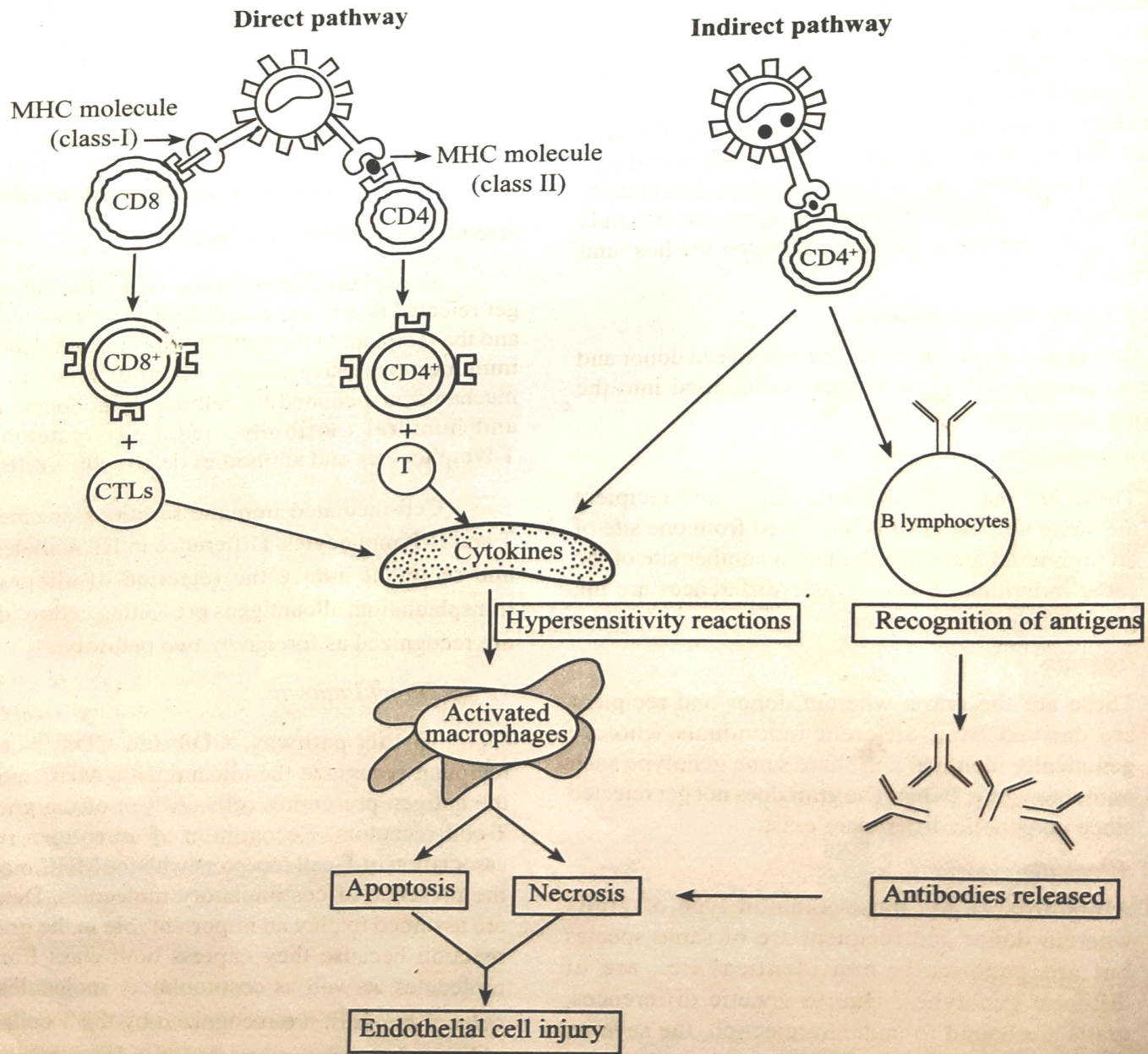


Figure: Mechanism of Allograft Rejection by Direct and Indirect Pathways

Types of Rejection Reactions

These reaction are of the following three types.

1. Hyperacute Rejection

Hyperacute rejection is the phenomenon of graft rejection which get initiated almost immediately after transplantation due to the presence of preformed antidonor antibodies in the blood of recipients. Examples of people who exhibit hyperacute rejection include multiparous women (who develop antibodies against paternal antigens), previous transplant rejectors and people with a history of blood transfusion. To prevent this reaction, recipient's serum is tested for the present of antibodies against donor's cells, by the process called cross-matching.

2. Acute Rejection

It refers to the rejection of a graft due to the production of antidonor antibodies formed after transplantation process due to exposure to the class I and II HLA antigens. People who have not been sensitized previously to transplantation antigens shows this reaction. These antigen in turn induce the production of antibodies in the recipient. These antibodies induce complement dependent cytotoxicity, inflammation and antibody dependent cell mediated cytotoxicity causing injury and damage to the vasculature of the graft.

3. Chronic Rejection

This type of rejection reaction may arise either due to repeated episodes of acute reaction or may arise insidiously. In this type of rejection reaction, antibodies remain unidentified in graft but are found in circulation and cause damage to the vascular components.

Prevention of Graft Rejection

Graft rejection can be prevented by using immunosuppressive drugs. Steroids (which reduce inflammation), tacrolimus (phosphatase calcineurin inhibitor) and mycophenolate mofetil (which inhibits lymphocyte proliferation) are the drugs currently used to prevent graft rejection. Other drugs used to reduce inflammation include intravenous Ig G (IVIG) and T-cell and B-cell depleting antibodies, whose mechanism of action is yet to be understood. Another method of preventing rejection reaction is by interrupting the interaction between B7 molecules of dendritic cells of donor and CD28 receptors of host T-cells thereby preventing host T-cells from receiving co-stimulatory signals.

However, the major drawback of using immunosuppressive agents is the drastic reduction in the immunity of the host thereby making him susceptible to opportunistic infections. In most cases, decreased immunotolerance of the host results in the reactivation of latent viral infections, the most common being polyoma virus which infects the renal tubules, lower genitourinary tract and causes graft failure. Other probable complications that might occur in immunocompromised patients include EBr-induced lymphomas, Kaposi's sarcoma and human papillomavirus induced squamous cell carcinoma. Injecting regulatory T-cells, blocking costimulatory signals needed for lymphocyte activation and giving donor T-cells to recipients to induce donor specific tolerance (mixed chimerism) may help in avoiding the above mentioned complications and infections.

5.3 IMMUNODEFICIENCY DISORDER

Acquired Immuno Deficiency Syndrome (AIDS)

AIDs is caused by a lentivirus i.e., humans immunodeficiency virus (HIV). It has the following characteristics,

1. Opportunistic infections lead to suppression of the immune system
2. Secondary tumours and neurological manifestations are seen.

Aetiology

The causative agent of AIDs is a retrovirus called Human immunodeficiency virus (HIV) which belongs to the family Retroviridae. HIV-1 and HIV-2 cause the disease with same properties and antigens, but differ only in genetic terms. HIV-1 is common in Europe, United States and Central Africa whereas HIV-2 is found in West Africa and India.

The features of both the forms include,

1. Incubation period which is followed by slow fatal outcome
2. Tropism for haematopoietic and nervous system
3. Suppression of immunity.

Routes of Transmission

1. By sexual contact.
2. Parenteral transmission i.e., use of contaminated needles during blood transfusion.
3. Transplacental transmission from infected mother to foetus (during pregnancy or during parturition through amniotic fluid).

Symptoms

Individuals may not show any symptoms initially but in severe cases, there may be weight loss, diarrhoea, fever, night sweats, oral candidiasis (fungal infection), skin rashes, flaky skin, short term memory loss, severe pain or numbness in hands and feet.

Structure of HIV

Retrovirus (HIV) is spherical in shape with size ranging in between of 100 - 140 nm. It contains an electron dense core surrounded by a lipid membrane. The core is made up of two RNA strands, reverse transcriptase enzyme and core proteins (p24 and p18). The core is surrounded by a lipid bilayer which is studded with two viral glycoproteins (gp120 and gp41). These glycoproteins are important for HIV infection. HIV-1 genome contains genes namely *gag*, *pol*, *env* and *tat*.

1. *gag* for the production of core proteins (p24 and p18).
2. *pol* for reverse transcriptase enzyme.
3. *env* for envelope or lipid proteins (gp120 and gp41).

The above genes act as markers for diagnosis in laboratory.

4. *tat* gene (transactivator) is responsible for carrying out the functions of viral amplification, budding and replication.

Pathophysiology

The two major systems affected by HIV are immune system (T-cells and B-cells) and central nervous system.

1. Pathogenesis of the Immune System

Immune system is made up of T-cells (cell mediated immunity) and B-cells (antigen-antibody mediated immunity).

(a) T-cells

HIV mainly affects the cell mediated immunity. The normal function of T-cells is recognition and binding to specific T-cell receptors. T-cells express a variety of molecular protein complexes like CD3, CD4, CD8, CD11_A and CD2. Of all these protein complexes, CD4⁺ T-cells (60% T-cells) and CD8⁺ T-cells (30% T-cells) are expressed as mutually exclusive subsets. CD4⁺ T-cells have the following functions.

- (i) They are the master regulator of the immune system.
- (ii) Secrete some soluble factors like cytokines which influence other T-cells of the immune system. Hence, if CD4⁺ T-cells count are less, then it indicates that the regulation of immune system is not proper. The intensity of the disease is measured by counts of CD4 and CD8 cells.

Pathogenesis of Destruction of Immunity by HIV

HIV enters the human body and exhibits selective tropism for CD4 cells (acts as a receptor). It also enters monocytes and macrophages. The initial step is binding of HIV to CD4 cells through gp120. This binding is followed by fusion of HIV with T-cell, after which HIV enters the membrane of T-cell. This is known as *internalization*. The virus lacks DNA (which is necessary for cell multiplication), hence reverse transcriptase produces c-DNA (complementary DNA - a proviral DNA which helps in multiplication) through reverse transcription process. The state of the T-cell also plays an important role during viral replication. If the T-cell remains in a crescent state, then the virus remains in the T-cell for many years without dividing. But, if the T-cells are active, then the virus divides. During division of T-cell, the c-DNA enters the T-cell and integrates into the host genome of T-cell by budding. Such type of infection is known as *productive infection*. Initiation of proviral DNA transcription occurs when the infected cell is activated by exposure to antigen.

Macrophages and monocytes are also infected by HIV. Majority of macrophages infected by HIV are found in tissues and not in blood. Macrophages also express CD4⁺ T-cells (but in low quantities) which aids in the binding of HIV to macrophages. Budding and multiplication of infected macrophages occur in a slow manner when compared to infected T-cells.

The infected macrophages act as, reservoir for the viral particles, safe vehicle for the transportation of virus from one part of the body to another.

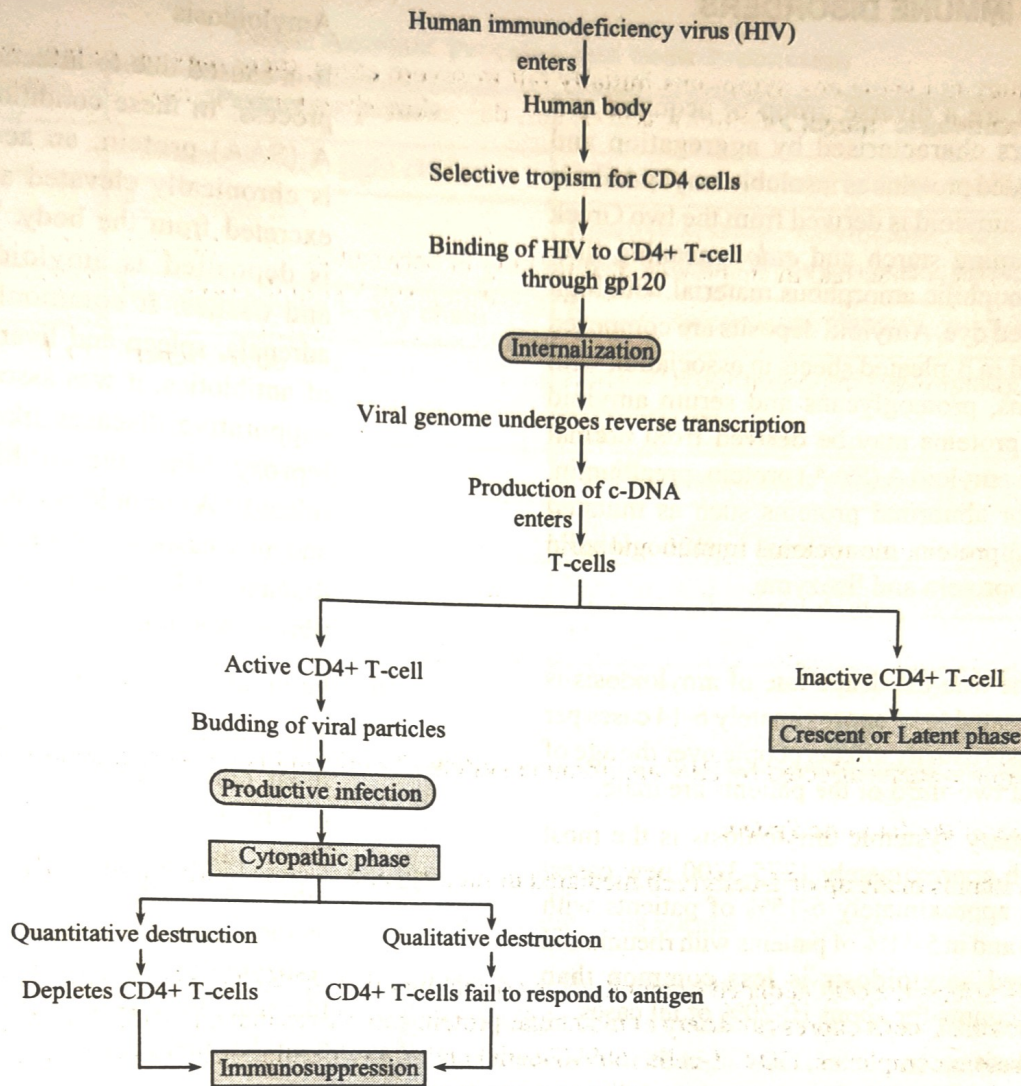


Figure: Sequence of Events of HIV Infection in CD4⁺ T-cells

(b) *B-cells*

B-cells are destroyed by glycoprotein (gp120) of HIV. The cell mediated immunity (by T-cells) is relatively affected than antigen-antibody mediated immunity (by B-cells).

2. *Pathogenesis of the Central Nervous System*

After the attack of the immune system, monocytes and macrophages are targeted. The HIV infected macrophages produce cytokines which are highly toxic to the neuronal cells.

Phases of HIV Infection

1. *Early/Acute Phase*

It represents the initial response of the body to virus. Non-specific symptoms like sore throat, rashes occur which subside after 2-3 weeks.

2. *Middle/Chronic Phase*

It is a period of clinical latency as no signs and symptoms are observed. The immune system is intact and HIV replication occurs slowly (confined only to lymphatic system). Latent phase lasts for 7 to 10 days.

3. *Final/Crisis Phase*

During this phase the patient is diagnosed, when the immune system is at total risk. The symptoms are,

- (a) Long lasting fever
- (b) Severe weight loss
- (c) Persistent diarrhoea
- (d) Fatigue
- (e) Reduced CD4⁺ T-cell count
- (f) High risk of developing infections
- (g) Oral candidiasis.

5.4 POSSIBLE IMMUNE DISORDERS

Amyloidosis

Amyloidosis are a diverse group of acquired and hereditary disorders characterised by aggregation and deposition of misfolded proteins as insoluble amyloid fibrils in tissues. The term amyloid is derived from the two Greek words, *amylos* meaning starch and *eidos* meaning like. Amyloid is an eosinophilic amorphous material with high affinity for Congo red dye. Amyloid deposits are composed of proteins arranged in β -pleated sheets in association with glycosaminoglycans, proteoglycans and serum amyloid P(SAP). Amyloid proteins may be derived from normal proteins like serum amyloid A (SAA) protein, prealbumin, β_2 microglobulin or abnormal proteins such as mutated transthyretin (TTR) protein, monoclonal immunoglobulin light chain, apolipoprotein and lysozyme.

Epidemiology

Although the true incidence rate of amyloidosis is unknown, it is estimated to be approximately 6-14 cases per million. Amyloidosis usually affects people over the age of 40 years and about two-third of the patients are male.

In US, primary systemic amyloidosis is the most common type with approximately 1275-3200 new cases/year. It occurs in approximately 6-15% of patients with multiple myeloma and in 5-11% of patients with rheumatoid arthritis. Localised amyloidosis is less common than systemic and it accounts for about 10-20% of all cases.

Types of Amyloidosis

Amyloid syndromes are classified based on the distribution of deposits or the responsible protein.

1. Based on Distribution of Amyloid Deposits

The protein accumulation is either systemic or localised.

(a) Systemic Amyloidosis

The amyloid fibril protein is secreted into the circulation and deposited at multiple sites. It is classified into primary, secondary, hereditary/familial types etc.

(i) Primary Systemic (AL) Amyloidosis

It is usually associated with plasma cell dyscrasia or myeloma. It involves heart, liver, GIT, peripheral nerve tissue and skin.

Skin involvement occurs in approximately one-third of patients with primary systemic amyloidosis. It occurs when bone marrow produces proteins that can't be broken down. The amyloid fibrils in this type of amyloidosis are composed of immunoglobulin light chain proteins (lambda or kappa) either whole or in fragments.

(ii) Secondary (Reactive) Systemic (AA) Amyloidosis

It is caused due to infection or inflammatory process. In these conditions, serum amyloid A (SAA) protein, an acute phase reactant is chronically elevated and is inadequately excreted from the body. The excess protein is deposited as amyloid fibrils in organs and tissues. It commonly affects kidneys, adrenals, spleen and liver. Before the advent of antibiotics, it was associated with chronic suppurative diseases like tuberculosis, and leprosy. Since the antibiotic era, infection related AA amyloidosis is much less common and most cases are now related to inflammatory diseases like rheumatoid arthritis, cystic fibrosis and inflammatory bowel disease.

(iii) Familial or Hereditary Amyloidosis

There are several types of familial amyloidosis, most common of which is caused due to genetic defects in transthyretin (TTR) protein. They mostly have autosomal dominant inheritance. Others are caused due to mutations in apolipoprotein (I or II), gelsolin, cystatin C, lysozyme or fibrinogen α -A. Specific organs like heart, liver, kidney, eye and nervous system are often involved.

(iv) Senile Systemic Amyloidosis

It is caused due to deposition of normal transthyretin (a transporter protein) in tissues. It is an important cause of heart disease in elderly people (> 70 years).

(v) β_2 -microglobulin (Haemodialysis Associated) Amyloidosis

β_2 -Microglobulin is generally associated with long term dialysis and is primarily excreted by kidneys. In patients with renal failure, it is inadequately cleared from the body. The excess β_2 -microglobulin is processed to amyloid which deposits in joints and tendons causing pain, stiffness and carpal tunnel syndrome.

(b) Localised Amyloidosis

In this form, the amyloid fibril protein is deposited at or near the site of synthesis. It typically affects laryngo-tracheo bronchial tree, skin, eye or urinary bladder. It is caused due to local production of immunoglobulin light chains not originating in the bone marrow. They rarely become systemic.

2. **Based on the Responsible Protein****Table: Amyloid Proteins and their Precursors**

Amyloid protein		Precursor protein	Clinical syndrome
1.	AL	Immunoglobulin light chain	Primary systemic amyloidosis, multiple myeloma
2.	AA	Apo-serum AA	Reactive systemic amyloidosis, familial mediterranean fever, Muckle-Wells syndrome (MWS)
3.	AH	Immunoglobulin heavy chain	Primary systemic amyloidosis, multiple myeloma
4.	ATTR	Transthyretin	Familial amyloidotic polyneuropathy, senile systemic amyloidosis
5.	AApo-AL	Apolipoprotein AI	Familial amyloidotic polyneuropathy
6.	A β_2 M	β_2 -Microglobulin	Chronic haemodialysis
7.	AGel	Gelsolin	Familial amyloidotic polyneuropathy
8.	A β	β -precursor protein	Alzheimer's disease
9.	ACal	Calcitonin	Medullary carcinoma of thyroid
10.	AIAPP	Islet amyloid polypeptide	Insulinoma, type-2 diabetes mellitus

Aetiology

In general, amyloidosis is caused by protein misfolding. These misfolded proteins infiltrate, aggregate and form insoluble fibrils that deposit in any tissue(s) or organ(s) and affects its normal functioning.

The specific cause of amyloidosis depends on its form. The exact cause for primary amyloidosis is unknown but it is believed to be related to the presence of immunoglobulin light chain circulating in the blood. The secondary amyloidosis is caused due to infection or inflammatory diseases. It is associated with high levels of serum amyloid A protein. Genetic factor may be associated as some case are familial. Other causes include long term dialysis.

Pathophysiology

Amyloidosis occurs due to misfolding of proteins which assume a β -pleated sheet conformation, aggregate, polymerise and finally deposit as insoluble amyloid fibrils in extracellular tissues. Under normal circumstances, these misfolded or abnormal proteins are degraded intracellularly by proteosomes and extracellularly by macrophages. In amyloidosis, these control mechanisms fail as a result of which abnormal proteins accumulate and deposit as fibrils. The deposition of these inert amyloid fibrils in the organs causes pressure atrophy which eventually interferes with the normal functioning of the organ. Amyloid is formed from proteins under two circumstances.

1. When large numbers of normal proteins having an inherent tendency to form amyloid are produced.
E.g: AA protein
2. When normal amounts of mutant proteins that are prone to misfolding and aggregation are produced.
E.g: Mutated transthyretin (TTR) protein

So far 18 different forms of amyloid fibril proteins and their precursors have been identified. Each condition is associated with a specific precursor protein. Local concentration of amyloid proteins, environmental factors (like temperature, pH, oxidation, ions, osmolytes etc.) and extracellular matrix play a vital role in formation of amyloid fibrils.

Signs and Symptoms

Symptoms of amyloidosis depend on the type of amyloidosis and the organ systems involved. General symptoms of amyloidosis include fatigue, weight loss, swelling, changes in skin color, anaemia, clay-colored stools, shortness of breath, tingling and numbness in legs and feet, joint pain and feeling of fullness in the stomach.