**SRINIVASAN COLLEGE OF ARTS & SCIENCE, PERAMBALUR-621 212**

**DEPARTMENT OF BIOTECHNOLOGY**

**CLASS – II B.Sc., BIOTECHNOLOGY SUB CODE :16SCCBT4**

**SUBJECT - IMMUNOLOGY**

UNIT1

ANTIGEN:

Antigen is an any substance that causes your immune systems to produce antibodies against it. This means your immune system does not recognize the substance, and is trying to fight it off. An antigen may be a substance from the environment, such as chemicals ,bacteria,viruses, or pollen. A antigen may also inside from the body.

TYPES OF ANTIGEN ON THE BASIS OF ORDER OF THEIR CLASS :

1. Exogenous Antigens:

These antigens enters the body or system and start circulating in the body fluids and tapped by the APCS ( antigen processing cells such as macrophages, dendritic cells, etc.) The uptakes of these exogenous antigens by APCs are mainly mediated by the phagocytosis.

E.g. : bacteria,viruses, fungi etc.

Some antigens start out as exogenontigens, and later become endogenous ( for example, intracellular viruses).

2. Endogenous antigens:

• These are body's own cells or sub fragments or compounds or the antigenic products that are produced.

The endogenous antigens are processed by the macrophages which are later accepted by the cytotoxic T-cells.

Endogenous antigens include xenogenic (heterologous), autologous (homologous) antigens.

Examples: Blood group antigens ,HLA (histocompatibility leukocyte antigens), etc.

3. Autoantigens:

An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease.

These antigens should not be, under normal conditions, the target of the immune system, but, due mainly to genetic and environmental factors, the normal immunological tolerance for such an antigen has been lost in these patients.

Examples : Nucleoproteins, Nucleic acids, etc.

**Immunogen** :

An Immunogen is any antigen that is capable of inducing humoral and or cell mediated immune response rather than immunological tolerance. This ability is called immunogenicity. Sometimes the term Immunogen is used interchangeably with the term antigen. But only Immunogen can evoke an immune system response.

**Hapten:**

Hapten is an molecule that is incapable , alone, of causing the production of antibodies but which ca do so when fastened to a larger antigenic molecule called a carrier. Some important haptens are Dinitrophenol, Aminobenzene, 0 - aminobenzoic acid, P- aminobenzoic acid.

**Allergen:**

A substance that can cause an allergic reaction. Common allergens include ragweed pollen, animal dander, and mold. Allergen is also an antigen that is capable of stimulating a type-1 hypersensitivity reaction in atopic individuals through immunoglobulin E (igE) responses. Food allergies - some foods such as peanuts, seafood, shellfish. Some drugs also causes the allergies such as penicillin latex, fire ant.

**Tolerogen** :

A foreign antigen suppresses immune response, or produces immune tolerance. In comparison with immunogen that induces an immune response, a tolerogen evokes immune tolerance.

**Super antigens:**

Super antigen is an a class of antigen that result in excessive of the immune system. Specifically it causes non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release.

**Antibody:**

Antibody is also called immunoglobulin, a protective protein produced by the immune system in in response to the presence of a foreign substance , called an antigen. Antibodies recognize and latch on to antigens in order to remove form the body. Antibodies can be triggered by and directed at foreign proteins, microorganism, or toxins.

**Immunoglobulins**

* Immunoglobulins are glycoproteins formed in response to an antigen and react specifically with that antigen.
* It is abbreviated as Ig.
* They are commonly called antibodies (Ab).
* They are synthesized by B lymphocytes and secreted by plasma cells.
* It is Y- shaped.
* Immunoglobulins exist in two forms, namely:
* Soluble immunoglobulins Membrane bound immunoglobulins.
* Immunoglobulin is made up of two pairs of polypeptide chains.
* They are:
* 2 light chains
* 2 heavy chains.
* On end of each chain is called N-terminal end and the other end is called C- terminal end.
* The N-terminal end has the antigen binding site called paratope.
* The four chains are interconnected by intrachain disulfide bonds.
* The two heavy chains are linked by 1 to 13 interchain disulfide bonds.
* Immunoglobulin consists of two regions, namely:
* Constant region (C) Variable region(V).
* The immunoglobulin has two light chain domains and four heavy chain domains.
* The domains of the N-terminal end has CDRs a
* Immunoglobulin can be split at the hinge into two fragments namely:
* Fab - Antigen binding fragment Fc - Crystallizable fragment.
* Five types of immunoglobulins occur. They are:

IgG - Monomeric

IgA- Monomeric or dimeric

IgM – Pentameric

IgD – Monomeric

IgE- Monomeric

* Functions.
* Agglutination of antigens.
* Precipitation of antigens.
* Neutralization of antigens.
* Lysis of the antigens.
* Opsonization.
* Activation of mast cells and basophils.

**Antigenicity** :

Antigenicity is the capable of a chemical structure to bind specifically with a group of certain products that have adaptive immunity: T cell receptors or antibodies.

**Immunogenicity**:

Immunogenicity is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human and other animal. In other words, immunogenicity is the ability to induce a humoral and or cell mediated immune responses.

**Self immunity** :

Self immunity is the reaction of an organisms immune system to self antigens as if they were non self or foreign like alloimmunity, autoimmunity is characterized by the activation of T cells, clonal expansion and antibody production.

**Non self :**

Any substance that is recognized as foreign and is capable of triggering an immune response is called a non self.

**Innate immunity**:

Immunity that is naturally present and is not due to prior sensitization to an antigen from, for example, an infection or vaccination. Since it is not stimulated by specific antigens, innate immunity is generally nonspecific. Also called natural immunity.

* Natural and inherited defense.
* Inherited by birth.
* Non specific.
* Physical factors Skin Mucous membrane Cilia Coughing Peristalsis Tears, saliva and urine
* Biochemical factors – Sweat, HCl in gastric juice, Lactoferrin in milk ,Lysozymes in tears, saliva, Interferons, Complement, Properdin, Bacteriocins ,Spermine.
* Cellular factors Phagocytosis NK cells.
* Genetic factors
* Body temperature
* Inflammation.
* Fever

**Acquired immunity** :

Acquired immunity is also known as Adaptive immunity that develops after exposure to suitable agent ( as by an attack of a disease or by injection of antigens ). The resistance that an individual acquires during life.

* Resistance developed during one's life time.
* Adaptive immunity.
* Not inherited.
* Specific immunity.
* Active or passive.
* Active acquired immunity is the development of resistance due to natural infection or vaccination.
* Active acquired immunity may be natural or artificial.
* Natural active acquired immunity is the resistance developed after an infection. Eg. Resistance developed after measles or mumps.
* Artificial acquired active immunity is the resistance developed due to vaccines. Eg. Polio vaccine.
* The resistance developed by a non-immune individual by receiving antibodies or sensitized lymphocytes from an immune individual is called passive acquired immunity.
* The development of resistance in foetus by the transfer of anti bodies from the mother to the foetus naturally is known as natural passive immunity.
* Eg. Transfer of colostrum through milk from mother to baby.
* The development of resistance in a patient by transfer antibodies or immunized lymphocytes from a donor is known as artificial passive immunity.
* Eg. Treatment of snake bite by the injection of antivenin

There are two types of acquired immunity:

1. Active immunity

2. Passive immunity

**Active immunity** :

Active immunity is a resistance to disease through three creation of antibodies by the immune system.

• Active immunity is the resistance developed by an individual in response to an antigen entering the body either by natural infection or through vaccination.

* It is not inherited.
* It is caused by infections or vaccines.
* Active acquired immunity is of two types, namely natural active acquired immunity and artificial active acquired immunity.
* Natural active acquired immunity is caused by infection.
* Artificial active acquired immunity is caused by vaccine.
* The antigen stimulates the immune system of the host.
* Humoral and cell mediated immune responses are produced.
* Antibodies are produced by B cells.
* Lymphokines are produced by T cells.
* Memory cells are produced.
* Secondary immune response is produced.
* Immunity persists life long and permanent.

**Passive immunity:**

Passive immunity is an protection of one individual conferred by administration of antibody produced in other individual.

* The resistance developed by a non - immune individual by receiving antibodies or sensitized lymphocytes from an immune individual is known as passive immunity.
* Eg. Immunity given by colostrum of milk to the baby.
* Treatment of snake bite by snake venom.
* Passive acquired immunity is of two types, namely natural passive acquired immunity and artificial passive acquired immunity.
* Natural passive acquired immunity is transferred from mother to baby.
* The development of resistance in a patient by transferring antibodies or immunized lymphocytes from a donor is known as artificial passive immunity.
* It is not inherited.
* The host does not produce resistance.
* The immune system of the host is not stimulated.
* There is no primary and secondary immune response.
* Memory cells are not produced.
* Immunity is temporary and persists only for a few days. Protection is immediate.

**Hematopoiesis :**

Hematopoiesis is the term used to describe the differentiation of blood cells from hematopoietic stem cell. This process is continually required to maintain the levels of circulating blood cells in the body. There are three distinct linages of blood cells.

Simply, hematopoiesis is the process through which the body manufactures blood cells. It begins early in the development of an embryo, well before birth, and continues for the life of an individual.

Fast facts of hematopoiesis:

Hematopoiesis begins during the first weeks of embryonic development.

All blood cells and plasma develop from a stem cell that can develop into any other cell.



**hematopoiesis**

Red blood cells transport oxygen through the body.

The blood is made up of more than 10 different cell types. Each of these cell types falls into one of three broad categories:

1. Red blood cells (erythrocytes): These transport oxygen and hemoglobin throughout the body.

2. White blood cells (leukocytes): These support the immune system. There are several different types of white blood cells:

Lymphocytes: Including T cells and B cells, which help fight some viruses and tumors.

Neutrophils: These help fight bacterial and fungal infections.

Eosinophils: These play a role in the inflammatory response, and help fight some parasites.

Basophils: These release the histamines necessary for the inflammatory response.

Macrophages: These engulf and digest debris, including bacteria.

3. Platelets (thrombocytes): These help the blood to

Hematopoiesis occurs in many places:

Hematopoiesis in the embryo provides organs with oxygen.

Sometimes called primitive hematopoiesis, hematopoiesis in the embryo produces only red blood cells that can provide developing organs with oxygen. At this stage in development, the yolk sac, which nourishes the embryo until the placenta is fully developed, controls hematopoiesis.

As the embryo continues to develop, the hematopoiesis process moves to the liver, the spleen, and bone marrow, and begins producing other types of blood cells.

In adults, hematopoiesis of red blood cells and platelets occurs primarily in the bone marrow. In infants and children, it may also continue in the spleen and liver.

The lymph system, particularly the spleen, lymph nodes, and thymus, produces a type of white blood cell called lymphocytes. Tissue in the liver, spleen, lymph nodes and some other organs produce another type of white blood cells, called monocytes.

**The process of hematopoiesis**

The rate of hematopoiesis depends on the body’s needs. The body continually manufactures new blood cells to replace old ones. About 1 percent of the body’s blood cells must be replaced every day.

White blood cells have the shortest life span, sometimes surviving just a few hours to a few days, while red blood cells can last up to 120 days or so.

The process of hematopoiesis begins with an unspecialized stem cell. This stem cell multiplies, and some of these new cells transform into precursor cells. These are cells that are destined to become a particular type of blood cell but are not yet fully developed. However, these immature cells soon divide and mature into blood components, such as red and white blood cells, or platelets.

Although researchers understand the basics of hematopoiesis, there is an-ongoing scientific debate about how the stem cells that play a role in hematopoiesis are formed.

**Organs of immune system:**

The key primary lymphoid organs are thymus, bone marrow. Secondary lymphoid organs are spleen, tonsils, lymph vessels, lymph nodes, adenoids, skin, and liver.

**Lymphoid Organs**

* The lymphocytes are created and matured in the lymphoid or gans.
* They are the army production centres and army camps of the immune system.
* They are of two types, namely:
* Primary lymphoid organ
* Secondary lymphoid organs.
* Primary lymphoid organs are the Army Headquarters.
* Eg. Bone marrow, thymus, bursa of Fabricius.
* In bone marrow, the stem cells of all lymphocytes develop.
* In thymus T cells mature.
* In bursa of Fabricius (birds) B cells develop.
* The immune cells are exposed to the antigen and made func tional in the secondary lymphoid organs.
* Eg. Spleen, lymph nodes, etc.

**Primary Lymphoid Organs**

* The immune cells such as B or T lymphocytes are produced in the primary lymphoid organs.
* B and T cells mature here.
* Antigens do not enter into the primary lymphoid organs.
* They are large at birth and they atrophy with age.
* Primary lymphoid organs are the Army Headquarters of the immune system.
* Eg. Thymus, bone marrow, bursa of Fabricius.
* The army of lymphocytes is created here.
* In bone marrow stem cells, lymphocytes and blood cells are pro duced.
* Thymus is the training centre for T cells.
* Bursa of Fabricius (birds) and bone marrow (mammals) are the training centres for B cells.

**Thymus**

* Thymus is the primary lymphoid organ where T cells develop.
* It resembles a thyme leaf.
* It has two lobes
* It is covered by a capsule.
* Each lobe consists of many lobules separated by septa.
* Each lobe has an outer cortex and inner medulla.
* Thymus is responsible for
* T cell maturation.
* Cell mediated immunity.
* Graft rejection.

**Bone Marrow**

* Bone marrow is the soft tissue located within the bone.
* Bone marrow is of three types. They are:
* Red marrow
* Yellow marrow
* Stroma.
* It is the Army Head Quarter of the immune system.
* The army of lymphocytes is produced here.
* It is the army training centre for B cells.
* Stem cells are produced here.
* All blood cells are made here.
* It functions as both primary and secondary lymphoid organs.

**Secondary Lymphoid Organs**

* Secondary lymphoid organs are the army camps of the immune system.
* Eg. Lymph nodes, Spleen, MALT
* Peyer's patches Tonsils.
* The virgin lymphocytes are exposed to the pathogens here and are trained to identify and fight with them.
* The lymphocytes become functional here.
* They increase in size with age.
* They contain both T and B cells.

**Lymph Nodes**

* Lymph nodes are secondary lymphoid organs.
* They are present along the lymphatic ducts.
* They are bean shaped
* One side of the lymph node has a hilus.
* It is covered by a capsule.
* Capsule penetrates into the lymph node to form septa called tra beculae.
* It is made up of three regions.
* Outer cortex contains B cells.
* Middle paracortex contains T cells and APCs.
* Inner medulla contains B and T cells.
* Cortex and medulla are bursa and B dependent areas.
* Paracortex is the thymus or T dependent area.
* The lymph nodes contain T cells, B cells, dendritic cells and macrophages.
* Lymph nodes function as
* Filters and they filter lymph.
* Important centres of phagocytosis.
* Development of humoral and cell mediated immune response

**Spleen**

* Spleen is the secondary lymphoid organ.
* It is located in the upper part of the abdominal cavity behind the stomach and close to the diaphragm.
* It is a component of lymphatic system.
* . It is deep red in colour.
* It is surrounded by a capsule.
* The capsule penetrates into the tissues as septa called trabeculae.
* Spleen has two regions.
* Red pulp consists of blood filled sinusoids.
* White pulp consists of lymphoid tissues.
* Spleen contains B cells and T cells.
* Functions
* Graveyard for worn out blood cells.
* Formation of RBCs at times of necessity.
* Filters blood.
* It brings about humoral and cell mediated immunity.

**Lymphocytes :**

A small white blood cell that plays a large role in defending the body against disease. Lymphocytes are responsible for immune responses. There are two types of cells such as B-cells and T-cells.

* WBCs circulating in the blood and lymph.
* Mononuclear and nongranular leukocytes.
* Three types T cells B cells Null cells
* Natural killer cells
* Killer cells
* Bring about immune response.
* T cells release cytokines and bring about cell mediated immunity.
* B cells produce antibodies and bring about humoral immunity.

**B Lymphocytes**

* B lymphocytes are WBCs maturing in the bone marrow in mam mals and bursa of Fabricius in birds.
* Mononucleate, nongranular leukocytes.
* Circulate in the blood and lymph.
* B cells contain surface immunoglobulin (Sig) called BCR They bring about humoral immune response.
* **T Lymphocytes**
* T lymphocytes mature in the thymus.
* Mononucleated, nongranular leukocytes.
* Circulate in the blood and spleen.
* T cells contain surface receptors called TCR They bring about cell mediated immune response.

**B Lymphocytes**

* The lymphocyte producing antibodies and bringing about humoral immunity is called B lymphocyte.
* They mature in the bursa of Fabricius or bone marrow.
* It is a type of white blood cell or leukocyte.
* B cells make up 23% of human lymphocytes.
* B cells are mononucleate, nongranular leukocytes.
* They have a large nucleus and a rim of cytoplasm.
* They are found in the blood and lymph.
* They are highly concentrated in the lymph nodes and spleen.
* They are derived from haematopoietic stem cells of bone marrow and mature in the bone marrow itself.
* In birds, B cells are derived from haematopoietic stem cells of bone marrow and mature in the bursa of Fabricius.
* The surface of B cell has B cell receptors. They are antibodies.
* AB cell has about 1,00,000 identical B cell receptors.
* The body produces about 107 or more types, of B cells, each with a unique B cell receptor.
* B cell is activated when BCR binds to the antigen.
* The activated B cell divides into plasma cells and memory B cells.
* Plasma cells produce antibodies.
* Memory B cells produce secondary humoral immune response.
* There are six types of B cells.
* Plasma cells
* Memory B cells, Blcells, B2 cells, MZB cells (Marginal zone B cells) Do, B cells (Follicular B cells).
* B cell has the following surface markers:
* la protein (Immune associated)
* Fc receptor
* CR1 and CR3 receptors
* Slg (surface immunoglobulin).
* Functions
* Secrete antibodies.
* Kill intercellular pathogens.
* Phagocytosis.
* They perform the role of antigen presenting cells.

**T Lymphocytes**

* The leukocyte that matures in the thymus and that brings about cell mediated immunity is called T lymphocyte.
* They mature in the thymus and hence the name.
* It is a type of white blood cell.
* They have a large nucleus and a rim of cytoplasm.
* They are highly concentrated in the blood and spleen.
* They are derived from the haematopoietic stem cells of bone marrow.
* They make up 77% of the lymphocytes and B cells form only 23%.
* There are 8 different types of T cells. They are:
* T helper cells (Th cells) • T cytotoxic cells (Tc cells) or T killer cells (Tk cells) T regulatory cells (Treg) T delayed type hypersensitivity cells (TD cells) Alpha-beta T cells • Gamma-delta T cells Natural killer T cells Memory T' cells.
* cell has the following surface markers:
* Erythrocyte receptor (Tli) T cell receptor (TCR) la protein (Immune associated) IL-1 and IL-2 receptors.
* The surface of the T cell has T cell receptors (TCR).
* The TCR of TH cell and Tc cell recognizes the antigen presented by the antigen presenting cells.
* These T cells are activated.
* The activated T cell secretes cytokines. The cytokines activate the B cells and other types of T cells.
* The activated B cells bring about humoral immune response.
* The activated T cells bring about cell mediated immune response.
* Functions of T Cells Bring about cell mediated immune response.
* Kill infected cells.
* Kill tumour cells.
* Reject grafts.
* Kill bacteria and viruses hidden inside cells.
* T helper cells activate other T cells and B cells.

**Cytokines**

* Cytokines are cell signalling protein molecules secreted hy al cells in response to some stimuli.
* Cytokines secreted by lymphocytes are called lymphokines.
* Cytokines secreted by monocytes and macrophages are called monokines.
* It may be proteins, peptides or glycoproteins.
* It is secreted in large amount during infection.
* They have alpha helical structure.
* Cytokines are classified into seven types. They are:

Lymphokines Monokines

Interleukins

Interferons

Tumour necrosis factors

Leukemia inhibiting factor

Oncostatin M.

* They regulate the intensity and duration of immune response.
* They can stimulate or inhibit the activation, proliferation and differentiation of various cells.
* The cytokines act in the following ways:
* Autocrine action
* Paracrine action
* Endocrine action
* Pleiotropy
* Redundancy
* Synergy
* Antagonism.

Function

* Intercellular messengers.

**Interleukins**

* • Interleukins are cytokine proteins secreted by monocytes or mac rophages or T lymphocytes.
* They are regulatory proteins.
* They are involved in signalling between cells of the immune system
* It is abbreviated as IL.
* It is of several types. They are:
	+ Interleukin ,Interleukin 2 and so on

Functions

* Maturation and proliferation of B cells.
* Activation of NK cells.
* Growth and differentiation of T cells.
* Promote histamine release from mast cells.
* Differentiation of plasma cells.
* Stimulation of antibody production.
* Promote haematopoietic stem cell differentiation.

**Interferon**

* It is a cytokine protein secreted by cells when infected with a virus.
* It triggers a cellular reaction that halts synthesis of viral nucleic acid and consequently disrupts viral life cycle.
* It also inhibits the proliferation of normal and transformed cells.
* Interferons are classified into three types.
* Interferon type-1, Interferon type-2, Interferon type - 3
* • Interferon is used for the treatment of diseases.
* They are used as intramuscular injections.

Functions

* They kill viruses.
* They eradicate tumours.
* They kill taste buds.
* They upregulate MHC molecules.
* They increase immunoproteasome activity.
* They activate macrophages and natural killer cells.

**Lymph**

The lymphatic is the part of the vascular system and an important part of the immune system, composed of a large network of lymphatic vessels that carry a clear fluid called lymph.

**Lymphatic circulation** :

The movement of lymphocytes in the body taked place between the blood and lymphatic system, lymph nodes , spleen and tissues. Less than 10% of the total volume lymphocytes is constantly circulating, while the rest are deposited in the organs and tissues.

**Lymphocyte homing** :

Lymphocyte homing are cells adhesion molecules expressed on lymphocyte cell membranes that recognize addressins on target tissues. Lymphocyte homing is refers to adhesion of the circulating lymphocytes in blood to specialized endothelial cells within lymphoid organs.

**Cell signaling** :

Cell signaling is the process of the cell communicating with other cell within the body, or with the external environment. As a process cell signaling refers to a vast network of communication between, and within, each cell of our body.

**Unit 2**

**Natural Built in Barriers** :

**Skin**

The skin is one of the largest organs in the body in surface area and weight. The skin consists of two layers: The Epidermis and The Dermis.

Beneath the dermis lies the hypodermis or subcutaneous fatty tissue. The skin has three main functions: Protection, Regulation and Sensation.

**Semen**

Semen, also known as Seminal Fluid, is an Organic Fluid that may contain spermatozoa. It is secreted by the Gonads (sexual glands) and other sexual organs of male or and can fertilize female ova.

**Saliva**

Saliva is the watery, produced in Salivary glands, Saliva is 98% water, but it contains many important substances, including Electrolytes, Mucus, Antibacterial Compounds and Various Enzymes.

The digestive functions of saliva include Moistening food, and helping to create a food bolus, so it can be swallowed easily.

Thus, digestion of food occurs within the monster of before food reaches the stomach

**Tears**

Tears are a Clear liquid secreted by the Glands (lacrimal glands/tear gland) found in the eyes of all land mammals (except for goats and rabbits). Their functions include lubricating the eyes (basal tears), removingirritants (reflex tears), and aiding the immune system. Tears also occur as a part of the body's natural pain response.

**Enzymes**

Enzymes are Biological molecules (typically proteins) that significantly speed up the rate of virtually all of the chemical reactions that take place within cells. They are vital for life and serve a wide range of important functions in the body, such as aiding in digestion and metabolism.

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**Complement**

* Complement is a group of larvae Thermolabile enzymatic proteins found in the serum and body fluids and it completes the antigen- antibody reactions, lysis and phagocytosis
* It is represented by the letter C.
* They are B- globulins.
* Antibodies finger' the pathogens; But complements destrow them.
* Complements are activated by protease enzymes.
* They are numbered from Cl to C9 and other components include B, D, P, H and I.

Functions

* Opsonization Chemotaxis
* Killing pathogens Inducing phagocytosis Anaphylactoid reaction
* Coagulation
* Immune adherence.
* Complement components are made active by antigen-antibody complexes, gram negative bacteria, animal viruses, etc.
* . When the complement system is activated, it passes through three distinct pathways. They are:
* Classical pathway
* Alternative pathway
* Lectin pathway.
* Membrane attack complex (MAC) is formed by the activation of complement system. It is deposited on the surface of pathogen to make holes and lysis of the pathogen.
* MAC is the end product of the complement activation.

**Classical Pathway**

* classical pathway is a simple stepwise immunological reaction of complements activated by antigen-antibody comp!
* In the classical pathway 11 components are involved. They are cLq, Cir, Cls, C2, C3, C4, C5, C6, C7,C8, C9.
* It is activated by antigen-antibody complex formed in infection.
* The antibody produced in response to a pathogen, binds to the pathogen to form antigen-antibody complex
* Antigen-antibody complex is recognized by C1 and it binds to the complex.
* Cl activates C4 and C2 to form C3 convertase.
* C3 convertase activates C3 and other complements in a sequence to form MACs (Membrane attack complex).
* The MACs are deposited on the pathogen and they make holes on the pathogen.
* The holes make the lysis of the pathogen.
* Ag-Ab Complex

**Alternative Pathway**

* Alternative pathway is a stepwise immunological reaction of complement activated by properdin.
* Properdin (a normal serum protein) reacts with zymosan (a poly saccharide from yeast cell wall) to form PZ complex.
* In alternative pathway 6 complement components are involved.
* They are C3, C5, C6, C7, C8 and C9.
* PZ complex cleaves the C3 into C3a and C3b.
* C3b is coated on the surface of microbe.
* The factor B binds with C3b to form C3bB complex and it is stabi lized and activated by the factors P and D to form C3 convertase.
* C3 convertase activates more C3 and other complements in a sequence to form MACs (Membrane attack complex).
* The MACS are deposited on the pathogen and they make holes on the pathogen.
* The holes make the lysis of the pathogen.

**Lectin Pathway**

* Lectin pathway is a stepwise immunological reaction of complex ments activated by the lectin.
* . In the lectin pathway 8 components are involved. They are C2,
* C4, C3, C5, C6, C7, C8 and C9.
* Lectin binds with the mannose of pathogen.
* This binding activates MASP-1 which activates MASP-2.
* MASP-2 activates C4 and C2 to form C3 convertase.
* C3 convertase activates C3 and other complements in a sequence to form MACS (Membrane attack complex).
* The MACs are deposited on the pathogen and they make holes on the pathogen.
* The holes make the lysis of the pathogen.

**Tumor Necrosis Factor**

* Tumor necrosis factor (TNF,Cachexin or cachectin; once named as tumor necrosis factor alpha or TNF a) is a cell signalling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction.

**Natural Killer Cells**

* Natural killer cells (also known as NK cells, K cells and Killer Cells) are a type of lymphocyte ( a white blood cell And a component of innate immune system. NK cells play a major role in the host - rejection of both tumours and virally infected cells

**Macrophage**

* Macrophage is a type of white blood cell that ingests foreign material.Macrophages are key players in the immune response to foreign invaders of the body,such as infectious microorganisms. They are normally found in the liver, spleen, and connective tissues of the body.

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**Phagocytosis**

Phagocytosis, or “cell eating”, is the process by which a cell engulfs a particle and digests it. The word phagocytosis comes from the Greek phago-, meaning “devouring”, and -cyte, meaning “cell”. Cells in the immune systems of organisms use phagocytosis to devour bodily intruders such as bacteria, and they also engulf and get rid of cell debris. Some single-celled organisms like amoebas use phagocytosis in order to eat and acquire nutrients.

**Function of Phagocytosis**

The function of phagocytosis is to ingest solid particles into the cell. Phagocytosis is a type of endocytosis, which is when cells ingest molecules via active transport as opposed to molecules passively diffusing through a cell membrane. Only certain small molecules can pass through the cell membrane easily; larger ones have to go through special channels in the cell or be ingested via endocytosis. Other types of endocytosis include pinocytosis, also called “cell drinking”, and receptor-mediated endocytosis, which is when molecules bind to specific receptors on the cell membrane that causes the cell to engulf them.

Phagocytosis is different from pinocytosis because phagocytosis involves the ingestion of solid particles while pinocytosis is the ingestion of liquid droplets. Phagocytosis is also used by cells to take in much larger particles than those that are ingested through pinocytosis. Some single-celled protists, such as amoebae, use phagocytosis to ingest food particles; it is literally how they eat food. Since their entire body consists of one cell, they can ingest food particles through engulfing them, and then digest these particles by connecting with a lysosome. In pinocytosis, the particles that are engulfed do not need to be broken down by a lysosome because they are so small, and instead the vesicle empties its contents directly into the cell.

Steps of Phagocytosis



Step 1:

The cell that will perform phagocytosis is activated. This can be a phagocyte, which is a cell in the immune system that performs phagocytosis, or an organism such as an amoeba, which behaves in a similar way to phagocytes when it carries out phagocytosis. In the case of immune cells, activation occurs when the cells are near bacterial cells or parts of bacterial cells. Receptors on the surface of the cells bind to these molecules and cause the cells to respond.

Step 2:

In the immune system, chemotaxis may occur. Chemotaxis is the movement of phagocytes toward a concentration of molecules. Immune cells pick up chemical signals and migrate toward invading bacteria or damaged cells.

Step 3:

The cell attaches to the particle that it will ingest. Attachment is necessary for ingestion to occur. Some bacteria can resist attachment, making it harder for them to be taken into the cell and destroyed.

Step 4:

The cell ingests the particle, and the particle is enclosed in a vesicle (a sphere of cell membrane with fluid in it) called a phagosome. The phagosome transports the particle into the cell.

Step 5:

A lysosome fuses with the phagosome and the particle is digested. Lysosomes are vesicles that contain hydrolytic enzymes that break down molecules. A phagosome fused with a lysosome is called a phagolysosome.

Step 6:

Cellular waste, such as broken down molecules that the cell cannot reuse, is discharged from the cell by the process of exocytosis. Exocytosis is the opposite of endocytosis; it is when cellular waste products travel in vesicles to the surface of the cell membrane and are released, thereby exiting the cell.

Phagocytosis process

This diagram shows the process of phagocytosis. A cell ingests a particle, breaks it down with the enzymes in lysosomes, and expels waste products through exocytosis.

* **Pinocytosis** A cellular process that permits the active transport of fluid from outside the cell through the membrane surrounding the cell into the inside of the cell.

**Mucosal Associated Lymphoid Tissue (MALT**

Mucosal Associated Lymphoid Tissue (MALT) is scattered along mucosal linings in the human body and constitutes the most extensive component of human lymphoid tissue. These surfaces protect the body from enormous quantity and variety of antigens. The tonsils, the peyer patches within the small intestine and the vermiform appendix are examples of MALT

Gut Associated Lymphoid Tissue (GALT) Gut-associated lymphoid tissue (GALT) is composed of cells residing in the lamina propria, intraepithelial lymphocytes interspersed between epithelial cells, and immune cells located in organized lymphatic tissue (Peyer's patches and mesenteric lymph nodes).

Mucosal Immunity Mucosal immunity is the study of the immune system associated with mucosal sites such as the gut mucosa that comprises Peyer's patches

(PPs), intestinal lamina propria, intestinal intraepithelial, cryptopatches, isolated lymphoid follicles in the gut antimesenteric wall, and the mesenteric lymph nodes

**Unit 3**

**Major Histocompatibility Complex**

* Major histocompatibility complex is a set of surface proteins lo nated on the cell membrane of nucleated cells and is responsible for antigen presentation and lymphocyte recognition.
* It is abbreviated as MHC.
* . The rejection of transplanted graft tissue between genetically non - identical individuals is brought about by the MHC antigens.
* Hence the MHC molecules are called transplantation antigens.
* The MHC of mouse is called H-2.
* MHC of man is called HLA.
* MHC consists of two polypeptide chains namely a chain and B chain.
* It has peptide binding groove or peptide binding cleft on the free end.
* The major role of MHC molecule is to bind with a small peptide fragment of the cell and to present it on the surface of the cell.
* MHC molecules are classified into four classes, namely:

Class I MHC molecules

Class II MHC molecules

Class III MHC molecules

Class IV MHC molecules.

* Class I MHC molecule is present on all nucleated cells.
* Class II MHC molecule is present on the antigen presenting cells and B cells.
* Functions
* Bring protection against cancer.
* Responsible for individual smell of people.
* Bring about defense against infections and disease
* They expose the proteins present inside the cell.
* They help the immune cells to recognize the pathogens hidden inside the cell.
* **HLA Typing**
* Human leukocyte antigen (HLA) typing is a way to tell how closely the tissues of one person match the tissues of another person. It is important in bone marrow and stem cell transplants to know how closely the transplant recipient matches their donor.
* We can determine your HLA type and a potential donor’s type by taking a sample of blood or another body tissue.
* **HLA match**
* Human leukocyte antigens are proteins you inherit from your parents. Together, your HLA proteins, or markers, make up your HLA type. Your immune system uses HLA markers to recognize which cells belong in your body and which do not.
* An HLA match is the number of HLA markers that any two people have in common.
* HLA matching is usually based on either eight or 10 HLA markers.
* The more markers two people share, the better the match.
* A good match means their immune systems will not see each other as foreign and are less likely to attack each other.
* **is likely to be an HLA match**
* The most likely place to find an HLA match is among siblings who have the same mother and father.
* You have a 25-percent chance of inheriting the same HLA markers as your sibling (an HLA-identical match).
* You have a 50-percent chance of inheriting half of the same HLA markers as your sibling (a haploidentical match).
* You have a 25-percent chance of inheriting none of the HLA markers your sibling inherited.
* Two unrelated people can just happen to be a good HLA match, too, although it is less likely.
* **find the best HLA match**
* When a doctor recommends a bone marrow transplant, the patient, their siblings and sometimes their parents will have samples (a blood draw or a swab of the inside of the cheek) collected for HLA typing. These will be tested in a lab. It usually takes about one to two weeks to get the results of typing.
* If a relative is an identical match, the lab will do further testing to be absolutely sure that they are the best match possible.
* If no sibling is a good match, the doctor may ask to test other family members. Your parents and children have the next best chance of being closely matched with you.
* If there are no close matches within the family, the health care team will contact the National Marrow Donor Program to search international registries for an unrelated volunteer donor who is a match.
* If you haven’t found a suitable match, you may be able to have a minimally mismatched, haploidentical or cord blood transplant at Seattle Cancer Care Alliance (SCCA). Learn more about these new options for people seeking a donor match.

**CMI RESPONSE**

**T cell**

A T cell is a type of lymphocyte, which develops in the thymus gland (hence the name) and plays a central role in the immune response. T cells can be distinguished from other lymphocytes by the presence of a T-cell receptor on the cell surface. These immune cells originate as precursor cells, derived from bone marrow, and develop into several distinct types of T cells once they have migrated to the thymus gland. T cell differentiation continues even after they have left the thymus.

Groups of specific, differentiated T cells have an important role in controlling and shaping the immune response by providing a variety of immune-related functions. One of these functions is immune-mediated cell death, and it is carried out by T cells in several ways: CD8+ T cells, also known as "killer cells", are cytotoxic - this means that they are able to directly kill virus-infected cells as well as cancer cells. CD8+ T cells are also able to utilize small signalling proteins, known as cytokines, to recruit other cells when mounting an immune response. A different population of T cells, the CD4+ T cells, function as "helper cells". Unlike CD8+ killer T cells, these CD4+ helper T cells function by indirectly killing cells identified as foreign: they determine if and how other parts of the immune system respond to a specific, perceived threat. Helper T cells also use cytokine signalling to influence regulatory B cells directly, and other cell populations indirectly. Regulatory T cells are yet another distinct population of these cells that provide the critical mechanism of tolerance, whereby immune cells are able to distinguish invading cells from "self" - thus preventing immune cells from inappropriately mounting a response against oneself (which would by definition be an "autoimmune" response). For this reason these regulatory T cells have also been called "suppressor" T cells. These same self-tolerant cells are co-opted by cancer cells to prevent the recognition of, and an immune response against, tumour cells.

Development

Origin, early development and migration to the thymus

All T cells originate from c-kit+Sca1+ haematopoietic stem cells (HSC) which reside in the bone marrow. In some cases, the origin might be the fetal liver during embryonic development. The HSC then differentiate into multipotent progenitors (MPP) which retain the potential to become both myeloid and lymphoid cells. The process of differentiation then proceeds to a common lymphoid progenitor (CLP), which can only differentiate into T, B or NK cells. These CLP cells then migrate via the blood to the thymus, where they engraft. The earliest cells which arrived in the thymus are termed double-negative, as they express neither the CD4 nor CD8 co-receptor. The newly arrived CLP cells are CD4-CD8-CD44+CD25-ckit+ cells, and are termed early thymic progenitors (ETP) cells. These cells will then undergo a round of division and downregulate c-kit and are termed DN1 cells.

**TCR-Beta selection**

At the DN2 stage (CD44+CD25+), cells upregulate the recombination genes RAG1 and RAG2 and re-arrange the TCRβ locus, combining V-D-J and constant region genes in an attempt to create a functional TCRβ chain. As the developing thymocyte progresses through to the DN3 stage (CD44-CD25+), the T cell expresses an invariant α-chain called pre-Tα alongside the TCRβ gene. If the rearranged β-chain successfully pairs with the invariant α-chain, signals are produced which cease rearrangement of the β-chain (and silences the alternate allele). Although these signals require this pre-TCR at the cell surface, they are independent of ligand binding to the pre-TCR. If the pre-TCR forms, then the cell downregulates CD25 and is termed a DN4 cell (CD25-CD44-). These cells then undergo a round of proliferation and begin to re-arrange the TCRα locus.

**Positive selection**

Double-positive thymocytes (CD4+/CD8+) migrate deep into the thymic cortex, where they are presented with self-antigens. These self-antigens are expressed by thymic cortical epithelial cells on MHC molecules on the surface of cortical epithelial cells. Only those thymocytes that interact with MHC-I or MHC-II will receive a vital "survival signal". All that cannot (if they do not interact strongly enough) will die by "death by neglect" (no survival signal). This process ensures that the selected T cells will have an MHC affinity that can serve useful functions in the body (i.e., the cells must be able to interact with MHC and peptide complexes to effect immune responses). The vast majority of developing thymocytes will die during this process. The process of positive selection takes a number of days.

A thymocyte's fate is determined during positive selection. Double-positive cells (CD4+/CD8+) that interact well with MHC class II molecules will eventually become CD4+ cells, whereas thymocytes that interact well with MHC class I molecules mature into CD8+ cells. A T cell becomes a CD4+ cell by down-regulating expression of its CD8 cell surface receptors. If the cell does not lose its signal, it will continue downregulating CD8 and become a CD4+, single positive cell.

This process does not remove thymocytes that may cause autoimmunity. The potentially autoimmune cells are removed by the process of negative selection, which occurs in the thymic medulla (discussed below).

**Negative selection**

Negative selection removes thymocytes that are capable of strongly binding with "self" MHC peptides. Thymocytes that survive positive selection migrate towards the boundary of the cortex and medulla in the thymus. While in the medulla, they are again presented with a self-antigen presented on the MHC complex of medullary thymic epithelial cells (mTECs). mTECs must be AIRE+ to properly express self-antigens from all tissues of the body on their MHC class I peptides. Some mTECs are phagocytosed by thymic dendritic cells; this allows for presentation of self-antigens on MHC class II molecules (positively selected CD4+ cells must interact with MHC class II molecules, thus APCs, which possess MHC class II, must be present for CD4+ T-cell negative selection). Thymocytes that interact too strongly with the self-antigen receive an apoptotic signal that leads to cell death. However, some of these cells are selected to become Treg cells. The remaining cells exit the thymus as mature naïve T cells (also known as recent thymic emigrants). This process is an important component of central tolerance and serves to prevent the formation of self-reactive T cells that are capable of inducing autoimmune diseases in the host.

β-selection is the first checkpoint, where the T cells that are able to form a functional pre-TCR with an invariant alpha chain and a functional beta chain are allowed to continue development in the thymus. Next, positive selection checks that T cells have successfully rearranged their TCRα locus and are capable of recognizing peptide-MHC complexes with appropriate affinity. Negative selection in the medulla then obliterates T cells that bind too strongly to self-antigens expressed on MHC molecules. These selection processes allow for tolerance of self by the immune system. Typical T cells that leave the thymus (via the corticomedullary junction) are self-restricted, self-tolerant, and single positive.

**T Cell Receptor**

* T cell receptor is a surface molecule present on the surface of T cells for recognizing antigens.
* It is abbreviated as TCR.
* It is a protein.
* TCR consists of three domains namely:
* Extracellular domain Transmembrane domain Intracellular domain.
* It is composed of two polypeptide chains called alpha chain and beta chain or gamma chain and delta chains.
* The two chains are linked by disulfide bonds.
* TCR is generated by a set of genes.
* Functions of TCR
* Recognizes the processed peptide fragments deposited on MHC molecule.
* Requires for signal transduction.
* T cell is activated when TCR binds to an antigen.

**Activation**



The T lymphocyte activation pathway: T cells contribute to immune defenses in two major ways; some direct and regulate immune responses; others directly attack infected or cancerous cells.

Activation of CD4+ T cells occurs through the simultaneous engagement of the T-cell receptor and a co-stimulatory molecule (like CD28, or ICOS) on the T cell by the major histocompatibility complex (MHCII) peptide and co-stimulatory molecules on the APC. Both are required for production of an effective immune response; in the absence of co-stimulation, T cell receptor signalling alone results in anergy. The signalling pathways downstream from co-stimulatory molecules usually engages the PI3K pathway generating PIP3 at the plasma membrane and recruiting PH domain containing signaling molecules like PDK1 that are essential for the activation of PKCθ, and eventual IL-2 production. Optimal CD8+ T cell response relies on CD4+ signalling.[33] CD4+ cells are useful in the initial antigenic activation of naïve CD8 T cells, and sustaining memory CD8+ T cells in the aftermath of an acute infection. Therefore, activation of CD4+ T cells can be beneficial to the action of CD8+ T cells.

The first signal is provided by binding of the T cell receptor to its cognate peptide presented on MHCII on an APC. MHCII is restricted to so-called professional antigen-presenting cells, like dendritic cells, B cells, and macrophages, to name a few. The peptides presented to CD8+ T cells by MHC class I molecules are 8–13 amino acids in length; the peptides presented to CD4+ cells by MHC class II molecules are longer, usually 12–25 amino acids in length, as the ends of the binding cleft of the MHC class II molecule are open.

The second signal comes from co-stimulation, in which surface receptors on the APC are induced by a relatively small number of stimuli, usually products of pathogens, but sometimes breakdown products of cells, such as necrotic-bodies or heat shock proteins. The only co-stimulatory receptor expressed constitutively by naïve T cells is CD28, so co-stimulation for these cells comes from the CD80 and CD86 proteins, which together constitute the B7 protein, (B7.1 and B7.2, respectively) on the APC. Other receptors are expressed upon activation of the T cell, such as OX40 and ICOS, but these largely depend upon CD28 for their expression. The second signal licenses the T cell to respond to an antigen. Without it, the T cell becomes anergic, and it becomes more difficult for it to activate in future. This mechanism prevents inappropriate responses to self, as self-peptides will not usually be presented with suitable co-stimulation. Once a T cell has been appropriately activated (i.e. has received signal one and signal two) it alters its cell surface expression of a variety of proteins. Markers of T cell activation include CD69, CD71 and CD25 (also a marker for Treg cells), and HLA-DR (a marker of human T cell activation). CTLA-4 expression is also up-regulated on activated T cells, which in turn outcompetes CD28 for binding to the B7 proteins. This is a checkpoint mechanism to prevent over activation of the T cell. Activated T cells also change their cell surface glycosylation profile.

The T cell receptor exists as a complex of several proteins. The actual T cell receptor is composed of two separate peptide chains, which are produced from the independent T cell receptor alpha and beta (TCRα and TCRβ) genes. The other proteins in the complex are the CD3 proteins: CD3εγ and CD3εδ heterodimers and, most important, a CD3ζ homodimer, which has a total of six ITAM motifs. The ITAM motifs on the CD3ζ can be phosphorylated by Lck and in turn recruit ZAP-70. Lck and/or ZAP-70 can also phosphorylate the tyrosines on many other molecules, not least CD28, LAT and SLP-76, which allows the aggregation of signalling complexes around these proteins.

Phosphorylated LAT recruits SLP-76 to the membrane, where it can then bring in PLC-γ, VAV1, Itk and potentially PI3K. PLC-γ cleaves PI(4,5)P2 on the inner leaflet of the membrane to create the active intermediaries diacylglycerol (DAG), inositol-1,4,5-trisphosphate (IP3); PI3K also acts on PIP2, phosphorylating it to produce phosphatidlyinositol-3,4,5-trisphosphate (PIP3). DAG binds and activates some PKCs. Most important in T cells is PKCθ, critical for activating the transcription factors NF-κB and AP-1. IP3 is released from the membrane by PLC-γ and diffuses rapidly to activate calcium channel receptors on the ER, which induces the release of calcium into the cytosol. Low calcium in the endoplasmic reticulum causes STIM1 clustering on the ER membrane and leads to activation of cell membrane CRAC channels that allows additional calcium to flow into the cytosol from the extracellular space. This aggregated cytosolic calcium binds calmodulin, which can then activate calcineurin. Calcineurin, in turn, activates NFAT, which then translocates to the nucleus. NFAT is a transcription factor that activates the transcription of a pleiotropic set of genes, most notable, IL-2, a cytokine that promotes long-term proliferation of activated T cells.

PLCγ can also initiate the NF-κB pathway. DAG activates PKCθ, which then phosphorylates CARMA1, causing it to unfold and function as a scaffold. The cytosolic domains bind an adapter BCL10 via CARD (Caspase activation and recruitment domains) domains; that then binds TRAF6, which is ubiquitinated at K63.:513–523[39] This form of ubiquitination does not lead to degradation of target proteins. Rather, it serves to recruit NEMO, IKKα and -β, and TAB1-2/ TAK1. TAK 1 phosphorylates IKK-β, which then phosphorylates IκB allowing for K48 ubiquitination: leads to proteasomal degradation. Rel A and p50 can then enter the nucleus and bind the NF-κB response element. This coupled with NFAT signaling allows for complete activation of the IL-2 gene.

While in most cases activation is dependent on TCR recognition of antigen, alternative pathways for activation have been described. For example, cytotoxic T cells have been shown to become activated when targeted by other CD8 T cells leading to tolerization of the latter.

**Endogenous Antigen Processing and Presentation**

* The endogenous antigens are degraded into peptide fragments, coupled with class I MHC molecules and are displayed on the surface of the antigen presenting cells. This is called endogenous antigen processing and presentation.
* Antigens generated inside a cell are called endogenous antigens.
* Endogenous antigens include:
* Viral proteins Cancer cell proteins Worn out proteins, etc.
* It is also called class I MHC pathway.
* As the antigens are processed in the cytosol, it is also called cyto solic pathway.
* The intracellular antigen is degraded with the help of ubiquitin and proteasome into peptide fragments.
* Then the peptide fragment is transferred into the endoplasmic reticulum via TAP.
* Inside the endoplasmic reticulum the peptide fragment is loaded on the class I MHC molecule.
* The class I MHC-peptide complex is moved to the Golgi complex.
* Then the secretory vesicle of Golgi complex deposits the class I MHC-peptide complex on the surface of the cell.
* It is recognized by Tc cells.

**Exogenous Antigen Processing and Presentation**

* The exogenous antigens are degraded into peptide fragments, coupled with class II MHC molecules and are displayed on the surface of the antigen presenting cells. This is called exogenous antigen processing and presentation.
* The antigens entering the cell from outside are called exog enous antigens.
* Exogenous antigens include:
* Viruses Bacteria Carcinogens.
* It is also called class II MHC pathway.
* As the antigens are processed in the endosome, it is also called endocytic pathway.
* The exogenous antigen is taken into the cell by phagocytosis or endocytosis.
* The exogenous antigen is degraded into peptide fragments in the lysosome.
* Then the lysosome fuses with the secretory vesicle containing class II MHC molecule to form lysosome vesicle.
* In the lysosome vesicle the peptide fragment is loaded on the class II MHC molecule.
* The lysosome vesicle deposits the class II MHC-peptide complex on the surface of the cell
* It is recognized by TH cell

**HI RESPONSE**

**B cell**

B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigens (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines. In mammals, B cells mature in the bone marrow, which is at the core of most bones. In birds, B cells mature in the bursa of Fabricius, a lymphoid organ where they were first discovered by Chang and Glick, (B for bursa) and not from bone marrow as commonly believed.



B cells, unlike the other two classes of lymphocytes, T cells and natural killer cells, express B cell receptors (BCRs) on their cell membrane. BCRs allow the B cell to bind to a specific antigen, against which it will initiate an antibody response.

**Development**

B cells develop from hematopoietic stem cells (HSCs) that originate from bone marrow. HSCs first differentiate into multipotent progenitor (MPP) cells, then common lymphoid progenitor (CLP) cells.From here, their development into B cells occurs in several stages (shown in image to the right), each marked by various gene expression patterns and immunoglobulin H chain and L chain gene loci arrangements, the latter due to B cells undergoing V(D)J recombination as they develop.



Early B cell development: from stem cell to immature B cell

B cells undergo two types of selection while developing in the bone marrow to ensure proper development. Positive selection occurs through antigen-independent signaling involving both the pre-BCR and the BCR. If these receptors do not bind to their ligand, B cells do not receive the proper signals and cease to develop. Negative selection occurs through the binding of self-antigen with the BCR; If the BCR can bind strongly to self-antigen, then the B cell undergoes one of four fates: clonal deletion, receptor editing, anergy, or ignorance (B cell ignores signal and continues development). This negative selection process leads to a state of central tolerance, in which the mature B cells don't bind with self antigens present in the bone marrow.

**B Cell Receptors**

* B cell receptor is a surface antibody present on the surface of the B cell for recognizing antigens.
* It is abbreviated as BCR.
* It is an antibody molecule produced by a set of genes.
* Each B cell has about 1,00,000 identical BCR molecules on its surface.
* Human body has 107 types of B cells with specific BCR.
* They are integral membrane proteins.
* BCR consists of three domains namely:
* Extracellular domain Transmembrane domain Intracellular domain.
* It is composed of two polypeptide chains namely, a heavy chain and a light chain.
* The BCR recognizes the antigen directly or with the help of antigen presenting cells.
* When the BCR binds with the antigen, the B cell is activated.
* Functions of BCR
* Binds with the antigen.
* Carries out signal transduction.
* Helps in the endocytosis of the antigen
* Induces changes inside the B cells.

**Activation**



B cell activation: from immature B cell to plasma cell or memory B cell

B cell activation occurs in the secondary lymphoid organs (SLOs), such as the spleen and lymph nodes. After B cells mature in the bone marrow, they migrate through the blood to SLOs, which receive a constant supply of antigen through circulating lymph. At the SLO, B cell activation begins when the B cell binds to an antigen via its BCR. Although the events taking place immediately after activation have yet to be completely determined, it is believed that B cells are activated in accordance with the kinetic segregation model[citation needed], initially determined in T lymphocytes. This model denotes that before antigen stimulation, receptors diffuse through the membrane coming into contact with Lck and CD45 in equal frequency, rendering a net equilibrium of phosphorylation and non-phosphorylation. It is only when the cell comes in contact with an antigen presenting cell that the larger CD45 is displaced due to the close distance between the two membranes. This allows for net phosphorylation of the BCR and the initiation of the signal transduction pathway[citation needed]. Of the three B cell subsets, FO B cells preferentially undergo T cell-dependent activation while MZ B cells and B1 B cells preferentially undergo T cell-independent activation.

B cell activation is enhanced through the activity of CD21, a surface receptor in complex with surface proteins CD19 and CD81 (all three are collectively known as the B cell coreceptor complex). When a BCR binds an antigen tagged with a fragment of the C3 complement protein, CD21 binds the C3 fragment, co-ligates with the bound BCR, and signals are transduced through CD19 and CD81 to lower the activation threshold of the cell.

**T cell-dependent activation**

Antigens that activate B cells with the help of T-cell are known as T cell-dependent (TD) antigens and include foreign proteins. They are named as such because they are unable to induce a humoral response in organisms that lack T cells. B cell responses to these antigens takes multiple days, though antibodies generated have a higher affinity and are more functionally versatile than those generated from T cell-independent activation.



Once a BCR binds a TD antigen, the antigen is taken up into the B cell through receptor-mediated endocytosis, degraded, and presented to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. T helper (TH) cells, typically follicular T helper (TFH) cells recognize and bind these MHC-II-peptide complexes through their T cell receptor (TCR). Following TCR-MHC-II-peptide binding, T cells express the surface protein CD40L as well as cytokines such as IL-4 and IL-21. CD40L serves as a necessary co-stimulatory factor for B cell activation by binding the B cell surface receptor CD40, which promotes B cell proliferation, immunoglobulin class switching, and somatic hypermutation as well as sustains T cell growth and differentiation. T cell-derived cytokines bound by B cell cytokine receptors also promote B cell proliferation, immunoglobulin class switching, and somatic hypermutation as well as guide differentiation. After B cells receive these signals, they are considered activated.

**T-dependent B cell activation**

Once activated, B cells participate in a two-step differentiation process that yields both short-lived plasmablasts for immediate protection and long-lived plasma cells and memory B cells for persistent protection. The first step, known as the extrafollicular response, occurs outside lymphoid follicles but still in the SLO. During this step activated B cells proliferate, may undergo immunoglobulin class switching, and differentiate into plasmablasts that produce early, weak antibodies mostly of class IgM.The second step consists of activated B cells entering a lymphoid follicle and forming a germinal center (GC), which is a specialized microenvironment where B cells undergo extensive proliferation, immunoglobulin class switching, and affinity maturation directed by somatic hypermutation. These processes are facilitated by TFH cells within the GC and generate both high-affinity memory B cells and long-lived plasma cells. Resultant plasma cells secrete large amounts of antibody and either stay within the SLO or, more preferentially, migrate to bone marrow.

**T cell-independent activation**

Antigens that activate B cells without T cell help are known as T cell-independent (TI) antigens and include foreign polysaccharides and unmethylated CpG DNA. They are named as such because they are able to induce a humoral response in organisms that lack T cells. B cell response to these antigens is rapid, though antibodies generated tend to have lower affinity and are less functionally versatile than those generated from T cell-dependent activation.

As with TD antigens, B cells activated by TI antigens need additional signals to complete activation, but instead of receiving them from T cells, they are provided either by recognition and binding of a common microbial constituent to toll-like receptors (TLRs) or by extensive crosslinking of BCRs to repeated epitopes on a bacterial cell. B cells activated by TI antigens go on to proliferate outside lymphoid follicles but still in SLOs (GCs do not form), possibly undergo immunoglobulin class switching, and differentiate into short-lived plasmablasts that produce early, weak antibodies mostly of class IgM, but also some populations of long-lived plasma cells.

**Memory B cell activation**

Memory B cell activation begins with the detection and binding of their target antigen, which is shared by their parent B cell. Some memory B cells can be activated without T cell help, such as certain virus-specific memory B cells, but others need T cell help. Upon antigen binding, the memory B cell takes up the antigen through receptor-mediated endocytosis, degrades it, and presents it to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane. Memory T helper (TH) cells, typically memory follicular T helper (TFH) cells, that were derived from T cells activated with the same antigen recognize and bind these MHC-II-peptide complexes through their TCR. Following TCR-MHC-II-peptide binding and the relay of other signals from the memory TFH cell, the memory B cell is activated and differentiates either into plasmablasts and plasma cells via an extrafollicular response or enter a germinal center reaction where they generate plasma cells and more memory B cells. It is unclear whether the memory B cells undergo further affinity maturation within these secondary GCs.

**Immunoglobulin**

Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen and which function as antibodies. The immunoglobulins derive their name from the finding that they migrate with globular proteins when antibody-containing serum is placed in an electrical field.

**II. GENERAL FUNCTIONS OF IMMUNOGLOBULINS**

**A. Antigen binding**

Immunoglobulins 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. 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.

**B. Effector Functions**

Frequently 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 immunoglobulins mediate 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. Such effector functions include:

**1. Fixation of complement** - This results in lysis of cells and release of biologically active molecules (see chapter two)

2. **Binding to various cell types** - Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins. This binding can activate the cells to perform some function. Some immunoglobulins also bind to receptors on placental trophoblasts, which results in transfer of the immunoglobulin across the placenta. As a result, the transferred maternal antibodies provide immunity to the fetus and newborn

**III. BASIC STRUCTURE OF IMMUNOGLOBULINS**



The basic structure of the immunoglobulins is illustrated . Although different immunoglobulins can differ structurally, they all are built from the same basic units.

**A. Heavy and Light Chains**

All immunoglobulins 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)

**B. Disulfide bonds**

1. Inter-chain disulfide bonds - 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 disulfide binds - Within each of the polypeptide chains there are also intra-chain disulfide bonds.

**C. Variable (V) and Constant (C) Regions**

When 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. These are the:

1. Light Chain - VL (110 amino acids) and CL (110 amino acids

2. Heavy Chain - VH (110 amino acids) and CH (330-440 amino acids)

**D. Hinge Region**

This is the region at which the arms of the antibody molecule forms a Y. It is called the hinge region because there is some flexibility in the molecule at this point.

**E. Domains**

Three dimensional images of the immunoglobulin molecule show that it is not straight as depicted in figure 2A. Rather, it is folded into globular regions each of which contains an intra-chain disulfide bond (figure 2B-D). These regions are called domains.

1. Light Chain Domains - VL and CL

2. Heavy Chain Domains - VH, CH1 - CH3 (or CH4)

F. Oligosaccharides

Carbohydrates are attached to the CH2 domain in most immunoglobulins. However, in some cases carbohydrates may also be attached at other locations.

IV. STRUCTURE OF THE VARIABLE REGION

**A. Hypervariable (HVR) or complementarity determining regions (CDR)**

Comparisons of the amino acid sequences of the variable regions of immunoglobulins show that most of the variability resides in three regions called the hypervariable regions or the complementarity determining regions as illustrated in figure 3. Antibodies with different specificities (i.e. different combining sites) have different complementarity determining regions while antibodies of the exact same specificity have identical complementarity determining regions (i.e. CDR is the antibody combining site). Complementarity determining regions are found in both the H and the L chains.

**B. Framework regions**

The regions between the complementarity determining regions in the variable region are called the framework regions . Based on similarities and differences in the framework regions the immunoglobulin heavy and light chain variable regions can be divided into groups and subgroups. These represent the products of different variable region genes.

**IMMUNOGLOBULIN FRAGMENTS: STRUCTURE/FUNCTION RELATIONSHIPS**

Immunoglobulin fragments produced by proteolytic digestion have proven very useful in elucidating structure/function relationships in immunoglobulins.

**A. Fab**

Digestion with papain breaks the immunoglobulin molecule in the hinge region before the H-H inter-chain disulfide bond Figure 4. This results in the formation of two identical fragments that contain the light chain and the VH and CH1 domains of the heavy chain.

Antigen binding - These fragments were called the Fab fragments because they contained the antigen binding sites of the antibody. Each Fab fragment is monovalent whereas the original molecule was divalent. The combining site of the antibody is created by both VH and VL. An antibody is able to bind a particular antigenic determinant because it has a particular combination of VH and VL. Different combinations of a VH and VL result in antibodies that can bind a different antigenic determinants.

**B. Fc**

Digestion with papain also produces a fragment that contains the remainder of the two heavy chains each containing a CH2 and CH3 domain. This fragment was called Fc because it was easily crystallized.

**Effector functions** - The effector functions of immunoglobulins are mediated by this part of the molecule. Different functions are mediated by the different domains in this fragment . Normally the ability of an antibody to carry out an effector function requires the prior binding of an antigen; however, there are exceptions to this rule.

**C. F(ab')2**

Treatment of immunoglobulins with pepsin results in cleavage of the heavy chain after the H-H inter-chain disulfide bonds resulting in a fragment that contains both antigen binding sites . This fragment was called F(ab')2 because it is divalent. The Fc region of the molecule is digested into small peptides by pepsin. The F(ab')2 binds antigen but it does not mediate the effector functions of antibodies

**Classes of immunoglobulins**

The term constant region is a bit misleading in that these segments are not identical in all immunoglobulins. Rather, they are basically similar among broad groups. All immunoglobulins that have the same basic kinds of constant domains in their H chains are said to belong to the same class. There are five main classes—IgG, IgM, IgA, IgD, and IgE—some of which include a number of distinct subclasses. Each class has its own properties and functions determined by the structural variations of the H chains. In addition, there are two basic kinds of L chains, called lambda and kappa chains, either of which can be associated with any of the H chain classes, thereby increasing still further the enormous diversity of immunoglobulins



The five main classes of antibodies (immunoglobulins): IgG, IgA, IgD, IgE, and IgM.

**IgG**

IgG is the most common class of immunoglobulin. It is present in the largest amounts in blood and tissue fluids. Each IgG molecule consists of the basic four-chain immunoglobulin structure—two identical H chains and two identical L chains (either kappa or lambda)—and thus carries two identical antigen-binding sites. There are four subclasses of IgG, each with minor differences in its H chains but with distinct biological properties. IgG is the only class of immunoglobulin capable of crossing the placenta; consequently, it provides some degree of immune protection to the developing fetus. These molecules also are secreted into the mother’s milk and, once they have been ingested by an infant, can be transported into the blood, where they confer immunity.

**IgM**

IgM is the first class of immunoglobulin made by B cells as they mature, and it is the form most commonly present as the antigen receptor on the B-cell surface. When IgM is secreted from the cells, five of the basic Y-shaped units become joined together to make a large pentamer molecule with 10 antigen-binding sites. This large antibody molecule is particularly effective at attaching to antigenic determinants present on the outer coats of bacteria. When this IgM attachment occurs

**IgA**

IgA is the main class of antibody found in many body secretions, including tears, saliva, respiratory and intestinal secretions, and colostrum (the first milk produced by lactating mothers). Very little IgA is present in the serum. IgA is produced by B cells located in the mucous membranes of the body. Two molecules of IgA are joined together and associated with a special protein that enables the newly formed IgA molecule to be secreted across epithelial cells that line various ducts and organs. Although IgG is the most common class of immunoglobulin, more IgA is synthesized by the body daily than any other class of antibody. However, IgA is not as stable as IgG, and therefore it is present in lower amounts at any given time.

**IgD**

IgD molecules are present on the surface of most, but not all, B cells early in their development, but little IgD is ever released into the circulation. It is not clear what function IgD performs, though it may play a role in determining whether antigens activate the B cells

**IgE**

IgE is made by a small proportion of B cells and is present in the blood in low concentrations. Each molecule of IgE consists of one four-chain unit and so has two antigen-binding sites, like the IgG molecule; however, each of its H chains has an extra constant domain (CH4), which confers on IgE the special property of binding to the surface of basophils and mast cells. When antigens bind to these attached IgE molecules, the cell is stimulated to release chemicals, such as histamines, that are involved in allergic reactions (see immune system disorder: Type I hypersensitivity). IgE antibodies also help protect against parasitic infections.

**Immune Tolerance**

* Tolerance refers to the unresponsiveness of the immune system to an antigen.
* Eg.

Survival of placenta.

Survival of human embryo.

Survival of graft.

* It is an antigen dependent process.
* It has immunological memory.
* Tolerance can be induced.
* Induction of tolerance is easier in T cell than that of B cells
* Tolerance can be broken naturally or artificially.
* Tolerance develops when the antigen comes in contact with the immune system during its foetal life
* tolerance developed to low dose of antigen is called low zone tolerance.
* tolerance developed to high dose of antigen is called high zone tolerance,
* Factors involved in tolerance induction are:
* T Cells
* B cells
* Surface receptors of the cells, etc.
* . Tolerance is classified into eight types. They are:
* Natural tolerance Induced tolerance Central tolerance
* Peripheral tolerance
* Low zone tolerance
* High zone tolerance
* Classical or irreversible tolerance
* Infectious or reversible tolerance.
* Factors causing tolerance are:
* Clonal deletion
* Absence of costimulation Control by regulatory T cells
* Mutation .
* Clonal abortion
* Clonal exhaustion
* Failure of macrophage T suppressor cells Exposure of immature immune system to antigen Soluble antigen
* Monomeric antigen
* Dose of antigen
* Persistence of antigen
* Removal of thymus.
* Significance
* Permits pregnancy.
* Prevents graft rejection.
* Protection from allergy reactions.
* \*Designing treatments for autoimmune diseases.
* recovery from tolerance Elimination of antigen.
* Production of antibodies.
* Addition of fresh T and B cells or immunocompetent cells.

**Suppression**

* Immune suppression, also known as immunosuppression or immunocompromise means your immune system isn't working properly. This includes any or all of the defences that make up your immune system - particularly the white cells in our bloodstream, along with our spleen and lymphnodes.

**Kinetics of immune response**

* Kinetics of immune response and memory Trained narrate immunity. Immunological memory is a distinct characteristic of our immune system, and it relates to its ability to remember antigens from pathogens and mount an immunological response of greater magnitude and with faster kinetics upon reencounter of the same antigens.

**Potentiation**

* the increase in strength of nerve impulses along pathways which have been used previously, either short-term or long – term

**Unit 4**

**Active and passive immunization :**

Active immunization utilizes an immunogen to generate a host response designed to eliminate the malignant cells, whereas in passive immunization preformed antibodies or cells are administered to directly eliminate the transformed cells.

**Live vaccine** :

A live virus vaccine helps the body's immune system recognize and fight infections caused by the non-weakened form of the virus. Examples chickenpox vaccine and (MMR) vaccine. the of live virus vaccines are the measles, mumps, and rubella

**Attenuated vaccine :**

An attenuated vaccine is a vaccine created by reducing the virulence of a pathogen, but still keeping it viable (or "live"). Attenuation takes an infectious agent and alters it so that it becomes harmless or less virulent. These vaccines contrast to those produced by "killing" the virus (inactivated vaccine).

**Plasma derived vaccine :**

The first available hepatitis B vaccines were plasma derived, produced by harvesting hepatitis B surface antigen (HBsAg) from the plasma of persons with chronic HBV infection. The recombinant technology expressed HBsAg in other microorganisms and offered the potential to produce unlimited supplies of vaccine.

**Subunit vaccine:**

A subunit vaccine is a fragment of a pathogen, typically a surface protein, that is used to trigger an immune response and stimulate acquired immunity against the pathogen from which it is derived.

**Recombinant DNA vaccine :**

A Recombinant vaccine is a vaccine produced through recombinant DNA technology. This involves inserting the DNA encoding an antigen (such as a bacterial surface protein) that stimulates an immune response into bacterial or mammalian cells, expressing the antigen in these cells and then purifying it from them.

**Protein based vaccine** :

Protein based subunit vaccines present an antigen to the immune system without viral particles, using a specific, isolated protein of the pathogen. A weakness of this technique is that isolated proteins, if denatured, may bind to different antibodies than the protein of the pathogen.

**Plant based vaccine:**

The plant-based vaccine production method works by isolating a specific antigen protein, one that triggers a human immune response from the targeted virus. A gene from the protein is transferred to bacteria, which are then used to "infect" plant cells.

**Peptide vaccine** :

The plant-based vaccine production method works by isolating a specific antigen protein, one that triggers a human immune response from the targeted virus. A gene from the protein is transferred to bacteria, which are then used to

**Anti idiotypic vaccine** :

Anti-idiotypic vaccines comprise antibodies that have three dimensional immunogenic regions, designated idiotopes, that consist of protein sequences that bind to cell receptors. Idiotopes are aggregated into idiotype specific of their target antigen. In example of anti-idiotype antibody is Racotumomab.

**Conjugate vaccine :**

Conjugate vaccines combine a weak antigen with a strong antigen as a carrier so that the immune system has a stronger response to the weak antigen. In a conjugate vaccine, the weak antigen is covalently attached to a strong antigen, thereby eliciting a stronger immunological response to the weak antigen.

**Combined immunization:**

A combined vaccine is a vaccine that is designed to protect against two or more diseases or against one disease caused by different strains or serotypes of the same organism.

**ISCOMs :**

The structures of ISCOMs are spherical open cage-like Nano particulates that are spontaneously formed when mixing together cholesterol, phospholipids and the immune stimulating saponins under a specific stoichiometry along with the vaccine antigen.

**Adjuvant** :

An adjuvant is a pharmacological or immunological agent that modifies the effect of other agents. Adjuvants may be added to a vaccine to boost the immune response to produce more antibodies and longer-lasting immunity, thus minimizing the dose of antigen needed

**Unit 5**

**IMMUNITY TO INFECTION:**

When the body is exposed to viruses, bacteria, fungi, or parasites through an infection or vaccination the immune system creates antibodies and immune cells that inactivate or destroy the specific infectious organism.

**BACTERIA:**

Bacteria are a type of biological cell. They constitute a large domain of prokaryotic microorganisms. Typically a few micrometres in length, bacteria have a number of shapes, ranging from spheres to rods and spirals.

**VIRUS:**

A virus is a small infectious agent that replicates only inside the living cells of an organism. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria and archaea.

**FUNGI:**

A fungus (plural: fungi) is a kind of living organism: yeasts, moulds and mushrooms are types of fungi. The fungi are a separate kingdom of living things, different from animals and plants. Fungi have cells with nuclei. Their cell walls contain chitin, unlike the cell walls of plants, which contain cellulose.

**PARASITES:**

A parasite is an organism that lives on or in a host organism and gets its food from or at the expense of its host. There are three main classes of parasites that can cause disease in humans: protozoa, helminths, and ectoparasites.

**Hypersensitivity**

* Hypersensitivity is the violent reaction of the immune system leading to severe symptoms and even death in a sensitized animal when it is re-exposed to the same antigen for the second time.
* Hypersensitivity is the allergy.
* The factors causing hypersensitivity are called allergens.
* In hypersensitivity, the cells of the host are killed or the host itself is damaged or killed.

Hypersensitivity is caused by extrinsic factors or intrinsic factors.

* They are the following:
* Drugs Airborne particles Food stuffs Infectious organisms Blood transfusion.
* Hypersensitivity may be:
* Immediate hypersensitivity or Delayed hypersensitivity.
* Based on the different mechanisms of pathogenesis it is classi fied into 5 types:
* Type I : Anaphylactic hypersensitivity
* Type II : Antibody-dependent cytotoxic hypersensitivity
* Type III : Immune complex-mediated hypersensitivity
* Type IV : Cell-mediated hypersensitivity
* Type V : Stimulatory hypersensitivity
* The reactions caused in hypersensitivity may be local reactions or systemic reactions.
* Local reaction is called systemic.
* When the symptoms appear in a restricted area the reaction is called systems of the body,
* The following are the common hypersensitivity reactions and diseases:
* Anaphylaxis Transfusion reactions
* Erythroblastosis fetalis
* Arthus reaction
* Serum sickness
* Mantoux reaction
* Contact dermatitis
* Grave's diseases
* Leprosy
* Small pox
* Measles
* Herpes
* Graft rejection
* Candidiasis
* Leishmaniasis
* Schistosomiasis
* Bacterial endocarditis
* Viral hepatitis
* Systemic lupus
* erythematosus
* Autoimmune haemolytic anaemia
* Autoimmune thrombocytopenic purpura
* Autoimmune thyroiditis
* Autoimmune glomerulonephritis
* Myasthenia gravis.

**Symptoms**

Diarrhoea and vomiting

Atopy

Rashness

Itching

Joint pain

Fever

Malaise

Hypotension

Abdominal pain

Lymphadenopathy

**Type II : Antibody Dependent Cytotoxic Hypersensitivity**

* Type II hypersensitivity is an allergy reaction due to the interactions of antibodies and cell associated antigens.
* When antibodies bind to the antigens located on the surface of cells, the cells become cytotoxic. Hence the name cytotoxic reaction.
* In type II hypersensitivity IgG type antibodies are involved.
* Eg. Agglutination and lysis of blood cells due to mismatched blood group, transfusion.
* Erythroblastosis fetalis, Autoimmune haemolytic anaemia, etc.
* Based upon the type of antigen involved in the reaction, cytotoxic hypersensitivity is classified into two types, namely:
* Isoimmune reactions
* Transfusion reactions Erythroblastosis fetalis Transplant rejection reactions.
* Autoimmune reactions are:
* Autoimmune haemolytic anaemia Autoimmune thrombocytopenic purpura Autoimmune thyroiditis Autoimmune glomerulonephritis.
* Myasthenia gravis.
* In cytotoxic reaction the cell damage occurs in anyone of the fol lowing methods:
* Phagocytosis • Lysis.
* Killing

**Type III : Immune Complex Mediated Hypersensitivity**

* The allergy reaction produced by the antigen-antibody complex is called immune complex mediated hypersensitivity.
* When enormous amount of soluble antigen enters the body, B cells produce large amount of antibodies of the type IgG or IgM.
* The antibodies bind with the antigens to form immune complexes.
* These immune complexes get attached in and around minute capil laries. They cause tissue damage leading to hypersensitivity.
* It is caused by repeated infections of a microorganism or repeated contact with environmental agents and autoimmunity antibodies.
* Examples for immune complex mediated immunity are Arthus reaction, serum sickness, etc.
* Symptoms Itching Joint pain Fever Abdominal pain Oedema Gangrene, etc.

Treatment Corticosteroids Plasmapheresis Antihistamines, etc.

**Type IV : Cell-Mediated Delayed Hypersensitivity**

* Type IV hypersensitivity is caused by the interaction between anti gens and sensitized T cells. As T cells are involved in this reaction, it is called cell-mediated hypersensitivity.
* The symptoms on the skin appear only after 24 to 72 hours. As the reaction appears well later it is also called delayed type hypersen sitivity.
* It is caused by infectious pathogens like bacteria, viruses, fungi and parasites.
* It is also caused by contact to certain chemicals like nickel salts formed from jewellery, neomycin ointment, etc.
* In type IV hypersensitivity TD cells are involved.
* Examples for type IV hypersensitivity are:
* Tuberculin reaction Contact dermatitis Leprosy Small pox Measles Herpes Candidiasis, etc.
* When the antigen enters the sensitized body, it is picked up by an antigen presenting cells like macrophages.
* They activate the TD cell by peptide-class II MHC complex.
* The activated TD cell secretes cytokines and chemokines such as:
* IFN-Y MCF MIF, etc.
* These secretions activate macrophages and Tc cells. These cells are made to migrate towards the antigen and surround the antigen and the antigen is destroyed.

**Autoimmune Diseases**

* Autoimmune diseases are a group of disorders caused by immune response to self antigens.
* Antigens present in one's own cells are called autoantigens or self antigens.
* Antibodies produced by the autoantigens are called autoantibody ies.
* Immune response caused by autoantigens is called autoimmunity.
* Autoimmunity is of two types, namely:

Humoral autoimmunity

Cell mediated autoimmunity.

* Autoimmune diseases are caused by:
* Sequestered antigens ,Neoantigens ,Cross-reactive antigens, Cessation of tolerance
* Loss of immunoregulation.
* Autoimmune diseases are classified in two ways:
* Based on the type of tissues and organs involved.

Haemolytic autoimmune diseases

Localised autoimmune diseases

Systemic autoimmune diseases.

* Based on the type of immune response.

Antibody mediated autoimmune diseases

Immune complex mediated autoimmune diseases

Cell mediated autoimmune diseases.

* Common autoimmune diseases are:
* Pernicious anaemia
* Thrombocytopenia
* Rheumatoid arthritis
* Lupus erythematosus Graves disease - Thyrotoxicosis
* Myasthenia gravis
* Hashimoto's thyroiditis.
* Autoimmune diseases are diagnosed by:
* Immunofluorescent antibody test Antiglobulin reaction Haemagglutination, etc.
* Autoimmune diseases can be treated by the following methods.
* Antithyroid drugs • Vitamin B12 • Anti Inflammatory drugs Antimitotic drugs such as corticosteroid, cyclophosphamide and azathioprine.

**Transplantation Immunology**

* Transplantation immunology refers to the study of the response of the immune system when a graft is implanted on an animal.
* Transplantation refers to the implantation of a tissue from one individual to another.
* The implanted tissue is called graft or transplant.
* Cells or tissues or organs are transplanted.
* The grafts are classified into four types. They are:
* Autograft or allogeneic graft
* Syngraft or syngeneic graft
* Allograft or allogeneic graft
* Xenograft or xenogeneic graft.
* When the graft tissue remains alive, it is said to be accepted and the process is called graft acceptance.
* When the graft tissue dies, the graft is said to be rejected and the process is called graft rejection.
* Graft rejection may be two types. They are:
* Graft reaction
* Host reaction.

**Host-Versus Graft Reaction**

* In host-versus graft reaction, the host produces immune response to the graft. Eg. Kidney transplantation.
* Allograft is the transfer of tissue between two genetically distinct members of the same species.
* Allograft rejection is of four types. They are:
* Acute rejection
* Early acute rejection
* Late acute rejection
* Hyperacute rejection
* Insidious rejection
* Chronic rejection.
* Mechanism of allograft rejection involves the following events:
* Immunological contact Production of sensitized T cells and cytotoxic antibodies
* First set rejection Second set rejection
* Cell mediated cytotoxic reaction Antibody mediated cytotoxic reaction.
* The facilitating effect of antibodies on the growth of allograft is called immunological enhancement.

**Graft-Versus Host Reaction**

* In graft-versus host immune reaction the graft produces immune response to the host. Eg. Bone marrow transplantation.
* It brings about damage to the host and host cells.
* During reaction, the graft-lymphocytes aggregate in the host lymphoid organs.
* The stimulated lymphocytes of graft, produce lymphokines.
* Symptoms
* Skin rash
* Emaciation
* Splenomegaly Inflammation

Gastrointestinal problems

**Tumour Immunology**

* Tumour is an independent, autonomous, uncontrolled growth of a tissue containing a mass of abnormal cells.
* It is also called cancer.
* Tumours are classified into six types. They are:
* Malignant tumour Benign or non-malignant tumour Carcinoma • Sarcoma • Lymphoma • Leukemia.
* Malignant tumour grows rapidly and spreads from one place to another. It gives pain.
* Benign tumour grows slowly and it does not spread from one place to another.
* Tumour cells grow and multiply rapidly.
* They originate from differentiated cells by dedifferentiation.
* They evade the immune system.
* They loose their contact inhibition.
* Tumours are caused by:
* Viruses Chemicals Oncogenes, etc.
* The antigens developed by tumour cells are called tumour antigens.
* Tumour antigens are of three types. They are:

Foetal antigens

Tumour specific antigens

Tumour associated antigens.

* The tumour cells escape from the action of immune system by the following mechanisms.
* Immunological enhancement of tumour growth.
* Modulation of tumour antigens.
* Shedding class-I MHC molecules from tumour cells.
* Inhibition of complement activation.
* Phagocytosis of MAC.
* Cell mediated immune response and humoral immune re spouse fight tumour cells.

**Immune Response to Tumour**

* The protective action of immune system against tumour cells called tumour immunity.
* Factors involved in tumour immunity are:
* Cytotoxic T cells
* T helper cells
* B cells
* Plasma cells
* Dendritic cells
* NK cells
* Macrophages
* Complements.
* Tumour is fought by

Innate immunity

Adaptive immunity.

* Adaptive immunity is the acquired immunity.
* There are two types of adaptive immune responses. They are:
* Humoral immune response Cell mediated immune response.
* Humoral immune response is B cell and antibody mediated.
* B cells destroy tumour cells in three different ways, namely:
* Complement mediated lysis
* Antibody dependent cell mediated cytotoxicity Opsonization.
* In cell mediated immune response immune cells kill tumour cells.
* The immune cells involved in tumour killing are the following:
* Dendritic cells
* NK cells
* Macrophages
* Tc cells
* Down regulation of TSA and killing of tumour cells.
* B cells, macrophages and dendritic cells identify the tumour cells and kill them by phagocytosis.
* The B cells are activated by tumour antigens and the activated B cells produce antibodies. The antibodies function as opsonin and bind to tumour cell.
* The opsonized tumour cells are swallowed by macrophages.
* The antibody combines with tumour antigen to form antigen-an tibody complex. The antigen-antibody complex activates comple ments.
* The activated complements produce MAC (membrane attack com plex on the tumour cell and the tumour cell is killed.
* The Tc cell recognizes tumour cells and kills them by secreting perforin, granzyme and granulysin.
* NK cells identify the tumour cells when the tumour cells shed their class I MHC molecule. NK cells kill them by secreting perforin and tumour necrosis factor (TNF).

**Immunodeficiency Diseases**

* The disease caused by the defects in the immune system is called immunodeficiency diseases.
* Immunodeficiency is classified into two types, namely:
* Primary immunodeficiency
* Stem cell deficiency
* B cell deficiency
* T cell deficiency
* Combined B and T cell deficiency
* Phagocyte cell deficiency
* Complement deficiency
* Secondary immunodeficiency.
* The defect of the immune system caused by the defective genes is called primary immunodeficiency.
* Primary immunodeficiency diseases are the following:

Reticular dysgenesis Bruton's agammaglobulinemia

Di- George syndrome

Severe combined immunodeficiency disorders Hereditary neutropenia

Lazy leukocytes Chediak- Higashi diseases.

* Secondary immunodeficiency refers to the depression of the immune response caused by many factors other than genetic.
* Secondary immunodeficiency is caused by the following agents:
* Drugs
* Malnutrition
* X-rays
* Malignancies
* Ageing Viral infections
* Corticosteroids.
* AIDS is the secondary immunodeficiency disease

**AIDS**

* AIDS is an epidemic viral disease of human population. It is called acquired immune deficiency syndrome.
* It is caused by the infection of an RNA virus on TH cells. This leads to the suppression of the immune system.
* As the initial infection of virus, paves way for the development of a complex of diseases, it is called a syndrome.
* AIDS is caused by Human Immunodeficiency Virus (HIV).
* HIV is transmitted in the following ways:

Sexual contact

Blood transfusion

Mother to foetus through the placenta Tissue transplantation Injection with unsterile syringes and needles.

* AIDS patients show the following symptoms:
* Rash
* Headache
* Weight loss
* WBC count is reduced Pulmonary infection, etc.
* AIDS is diagnosed by the following tests.
* CD4 T cell test CD8 T cell test Viral load test.
* AIDS can be treated by the following methods:
* Antiretroviral therapy
* Prevention of viral replication
* Inactivation of reverse transcriptase Stimulation of immune system Grafting of bone marrow Convergent combination therapy.