IMMUNE SYSTEM

Introduction and overview of the immune System

Introduction

The term immunity comes from the Latin word immunitas, means protection from legal prosecution. Immunity refers to protection from disease and other pathogens. The cells and molecules responsible for immunity are called immune system and their efforts in regards to any etiological agent are called immune responses. Normally the immune responses are elicited against the foreign substances but occasionally to the self molecules and are referred as autoimmune responses. Immunology is a branch of life- science which deals with the cellular and molecular events occurring in the body after encounters of micro-organisms and other foreign substances.

The history of immunology is quite old. In ancient China, people often used skin lesions of patients recovered from small pox to cure small pox in young children. The first successful record of vaccination came from the work of Edward Jenner's efficacious vaccination against smallpox. Jenner observed that milkmaid who had recovered from cowpox never showed any symptom of smallpox. Following this observation he inoculated the cowpox pustules into the arm of a young boy who later did not show full progressive smallpox symptoms. Small pox was the first disease that was eradicated worldwide by vaccination.

Recently the science of immunology has grown up by the advent of new molecular biology tools. Our current understanding of the human and animal immune system and its functions has remarkably improved. Advances such as recombinant DNA technology, immunohistochemistry, monoclonal antibody production and x-ray crystallography have changed the immunology to a broader area. The development of techniques to produce transgenic and knockout mice has also played a great role to understand many complex immunological pathways.

Overview of the Immune Response

Humans and other mammals live in a world that is heavily populated by both pathogenic and non-pathogenic microbes, and that contains a vast array of toxic or allergenic substances that threaten normal homeostasis. The community of microbes includes both obligate pathogens, and beneficial, commensal organisms, which the host must tolerate and hold in check in order to support normal tissue and organ function. Pathogenic microbes possess a diverse collection of mechanisms by which they replicate, spread and threaten normal host functions. At the same time that the immune system is eliminating pathological microbes and toxic or allergenic proteins, it must avoid responses that produce excessive damage of self-tissues or that might eliminate beneficial, commensal microbes. Our environment contains a huge range of pathogenic microbes and toxic substances that challenge the host by a very broad selection of pathogenic mechanisms. It is not surprising, therefore, that the immune system uses a complex array of protective mechanisms to control and usually eliminate these organisms and toxins. A general feature of the immune system is that these mechanisms rely on detecting structural features of the pathogen or toxin that mark it as distinct from host cells. Such host-pathogen or host-toxin discrimination is essential to permit the host to eliminate the threat without damaging its own tissues.

The mechanisms permitting recognition of microbial, toxic, or allergenic structures can be broken down into two general categories: i) hard-wired responses that are encoded by genes in the host's germ line and that recognize molecular patterns shared both by many microbes and toxins that are not present in the mammalian host; and ii) responses that are encoded by gene elements that somatically rearrange to assemble antigen-binding molecules with exquisite specificity for individual unique foreign structures. The first set of responses constitutes the innate immune response. Because the recognition molecules used by the innate system are expressed broadly on a large number of cells, this system is poised to act rapidly after an invading pathogen or toxin is encountered and thus constitutes the initial host response. The second set of responses constitutes the adaptive immune response. Because the adaptive system is composed of small numbers of cells with specificity for any individual pathogen, toxin or allergen, the responding cells must proliferate after encountering the antigen in order to attain sufficient numbers to mount an effective response against the microbe or the toxin. Thus, the adaptive response generally expresses itself temporally after the innate response in host defense. A key feature of the adaptive response is that it produces long-lived cells that persist in an apparently dormant state, but that can re-express effector functions rapidly after another encounter with their specific antigen. This provides the adaptive response with the ability to manifest immune memory, permitting it to contribute prominently to a more effective host response against specific pathogens or toxins when they are encountered a second time, even decades after the initial sensitizing encounter.

The **lymphatic system** is part of the circulatory system and a vital part of the immune system, comprising a network of lymphatic vessels that carry a clear fluid called lymph (from Latin *lympha* meaning *water*) directionally towards the heart. The lymphatic system was first described in the seventeenth century independently by Olaus Rudbeck and Thomas Bartholin. Unlike the cardiovascular system, the lymphatic system is not a closed system. The human circulatory system processes an average of 20 litres of blood per day through capillary filtration, which removes plasma while leaving the blood cells. Roughly 17 litres of the filtered plasma are reabsorbed directly into the blood vessels, while the remaining three litres remain in the interstitial fluid. One of the main functions of the lymph system is to provide an accessory return route to the blood for the surplus three litres.

The other main function is that of defense in the immune system. Lymph is very similar to blood plasma: it contains lymphocytes and other white blood cells. It also contains waste products and debris of cells together with bacteria and protein. Associated organs composed of **lymphoid tissue** are the sites of lymphocyte production. Lymphocytes are concentrated in the lymph nodes. The spleen and the thymus are also lymphoid organs of the immune system. The tonsils are lymphoid organs that are also associated with the digestive system. Lymphoid tissues contain lymphocytes, and also contain other types of cells for support.The system also includes all the structures dedicated to the circulation and production of lymphocytes (the primary cellular component of lymph), which also includes the bone marrow, and the lymphoid tissue associated with the digestive system.

The blood does not come into direct contact with the parenchymal cells and tissues in the body (except in case of an injury causing rupture of one or more blood vessels), but constituents of the blood first exit the microvascular exchange blood vessels to become interstitial fluid, which comes into contact with the parenchymal cells of the body. Lymph is the fluid that is formed when interstitial fluid enters the initial lymphatic vessels of the lymphatic system. The lymph is then moved along the lymphatic vessel network by either intrinsic contractions of the lymphatic passages or by extrinsic compression of the lymphatic vessels via external tissue forces (e.g., the contractions of skeletal muscles), or by lymph hearts in some animals. The organization of lymph nodes and drainage follows the organization of the body into external and internal regions; therefore, the lymphatic drainage of the head, limbs, and body cavity walls follows an external route, and the lymphatic drainage of the thorax, abdomen, and pelvic cavities follows an internal route.[5] Eventually, the lymph vessels empty into the lymphatic ducts, which drain into one of the two subclavian veins, near their junction with the internal jugular veins.

Structure

The lymphatic system consists of lymphatic organs, a conducting network of lymphatic vessels, and the circulating lymph.

The thymus and the bone marrow constitute the primary lymphoid organs involved in the production and early clonal selection of lymphocyte tissues. Bone marrow is responsible for both the creation of T cells and the production and maturation of B cells. From the bone marrow, B cells immediately join the circulatory system and travel to secondary lymphoid organs in search of pathogens. T cells, on the other hand, travel from the bone marrow to the thymus, where they develop further. Mature T cells join B cells in search of pathogens. The other 95% of T cells begin a process of apoptosis (programmed cell death).

The **central** or **primary lymphoid organs** generate lymphocytes from immature progenitor cells.

Secondary or **peripheral lymphoid organs**, which include lymph nodes and the spleen, maintain mature naive lymphocytes and initiate an adaptive immune response. The peripheral lymphoid organs are the sites of lymphocyte activation by antigens. Activation leads to clonal expansion and affinity maturation. Mature lymphocytes recirculate between the blood and the peripheral lymphoid organs until they encounter their specific antigen.

Secondary lymphoid tissue provides the environment for the foreign or altered native molecules (antigens) to interact with the lymphocytes. It is exemplified by the lymph nodes, and the lymphoid follicles in tonsils, Peyer's patches, spleen, adenoids, skin, etc. that are associated with the mucosa-associated lymphoid tissue (MALT).

In the gastrointestinal wall the appendix has mucosa resembling that of the colon, but here it is heavily infiltrated with lymphocytes.

The **tertiary lymphoid tissue** typically contains far fewer lymphocytes, and assumes an immune role only when challenged with antigens that result in inflammation. It achieves this by importing the lymphocytes from blood and lymph.)

Thymus

The thymus is a primary lymphoid organ and the site of maturation for T cells, the lymphocytes of the adaptive immune system. The thymus increases in size from birth in response to postnatal antigen stimulation, then to puberty and regresses thereafter. The loss or lack of the thymus results in severe immunodeficiency and subsequent high susceptibility to infection. In most species, thymus consists of lobules divided by septa which are made up of epithelium and therefore is an epithelial organ. T cells mature from thymocyte, proliferate and undergo selection process in the thymic cortex before entering the medulla to interact with epithelial cells.

Spleen

The main functions of the spleen are:

1. to produce immune response against blood-borne antigens
2. to remove particulate matter and aged blood cells, mainly erythrocytes
3. to produce blood cells during fetal life

The spleen synthesizes antibodies in its white pulp and removes antibody-coated bacteria and antibody-coated blood cells by way of blood and lymph node circulation. A study published in 2009 using mice found that the spleen contains, in its reserve, half of the body's monocytes within the red pulp.These monocytes, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages while promoting tissue healing. The spleen is a center of activity of the mononuclear phagocyte system and can be considered analogous to a large lymph node, as its absence causes a predisposition to certain infections.

Like the thymus, the spleen has only efferent lymphatic vessels. Both the short gastric arteries and the splenic artery supply it with blood.

The germinal centers are supplied by arterioles called *penicilliary radicles*.

Up to the fifth month of prenatal development the spleen creates red blood cells. After birth the bone marrow is solely responsible for hematopoiesis. As a major lymphoid organ and a central player in the reticuloendothelial system, the spleen retains the ability to produce lymphocytes. The spleen stores red blood cells and lymphocytes. It can store enough blood cells to help in an emergency. Up to 25% of lymphocytes can be stored at any one time.

Lymph nodes

A lymph node is an organized collection of lymphoid tissue, through which the lymph passes on its way back to the blood. Lymph nodes are located at intervals along the lymphatic system. Several afferent lymph vessels bring in lymph, which percolates through the substance of the lymph node, and is then drained out by an efferent lymph vessel. There are between five and six hundred lymph nodes in the human body, many of which are grouped in clusters in different regions as in the underarm and abdominal areas. Lymph node clusters are commonly found at the base of limbs (groin, armpits) and in the neck, where lymph is collected from regions of the body likely to sustain pathogen contamination from injuries.

The substance of a lymph node consists of lymphoid follicles in an outer portion called the cortex. The inner portion of the node is called the medulla, which is surrounded by the cortex on all sides except for a portion known as the hilum. The hilum presents as a depression on the surface of the lymph node, causing the otherwise spherical lymph node to be bean-shaped or ovoid. The efferent lymph vessel directly emerges from the lymph node at the hilum. The arteries and veins supplying the lymph node with blood enter and exit through the hilum.

The region of the lymph node called the paracortex immediately surrounds the medulla. Unlike the cortex, which has mostly immature T cells, or thymocytes, the paracortex has a mixture of immature and mature T cells. Lymphocytes enter the lymph nodes through specialised high endothelial venules found in the paracortex.

A lymph follicle is a dense collection of lymphocytes, the number, size and configuration of which change in accordance with the functional state of the lymph node. For example, the follicles expand significantly when encountering a foreign antigen. The selection of B cells, or *B lymphocytes*, occurs in the germinal center of the lymph nodes.

Lymph nodes are particularly numerous in the mediastinum in the chest, neck, pelvis, axilla, inguinal region, and in association with the blood vessels of the intestines.

Other lymphoid tissue

Lymphoid tissue associated with the lymphatic system is concerned with immune functions in defending the body against infections and the spread of tumors. It consists of connective tissue formed of reticular fibers, with various types of leukocytes, (white blood cells), mostly lymphocytes enmeshed in it, through which the lymph passes. Regions of the lymphoid tissue that are densely packed with lymphocytes are known as *lymphoid follicles*. Lymphoid tissue can either be structurally well organized as lymph nodes or may consist of loosely organized lymphoid follicles known as the mucosa-associated lymphoid tissue.

The lymphatic vessels, also called lymph vessels, conduct lymph between different parts of the body. They include the tubular vessels of the lymph capillaries, and the larger collecting vessels– the right lymphatic duct and the thoracic duct (the left lymphatic duct). The lymph capillaries are mainly responsible for the absorption of interstitial fluid from the tissues, while lymph vessels propel the absorbed fluid forward into the larger collecting ducts, where it ultimately returns to the

bloodstream via one of the subclavian veins. These vessels are also called the lymphatic channels or simply *lymphatics*.

The lymphatics are responsible for maintaining the balance of the body fluids. Its network of capillaries and collecting lymphatic vessels work to efficiently drain and transport extravasated fluid, along with proteins and antigens, back to the circulatory system. Numerous intraluminal valves in the vessels ensure a unidirectional flow of lymph without reflux. Two valve systems are used to achieve this one directional flow—a primary and a secondary valve system.The capillaries are blind-ended, and the valves at the ends of capillaries use specialised junctions together with anchoring filaments to allow a unidirectional flow to the primary vessels. The collecting lymphatics, however, act to propel the lymph by the combined actions of the intraluminal valves and lymphatic muscle cells.

Function

The lymphatic system has multiple interrelated functions:

- It is responsible for the removal of interstitial fluid from tissues
- It absorbs and transports fatty acids and fats as chyle from the digestive system
- It transports white blood cells to and from the lymph nodes into the bones
- The lymph transports antigen-presenting cells (APCs), such as dendritic cells, to the lymph nodes where an immune response is stimulated.

Clinical significance

The study of lymphatic drainage of various organs is important in diagnosis, prognosis, and treatment of cancer. The lymphatic system, because of its physical proximity to many tissues of the body, is responsible for carrying cancerous cells between the various parts of the body in a process called metastasis. The intervening lymph nodes can trap the cancer cells. If they are not successful in destroying the cancer cells the nodes may become sites of secondary tumors.

CELLS AND ORGANS OF IMMUNE SYSTEM

Specific as well as non-specific immunity is maintained in the body the lymphoreticular system that is a complex organization of cells of diverse morphology and distributed widely in different parts of the body. Lymphoreticular cells include reticuloendothelial cells and lymphoid cells.

Reticuloendothelial system:

The reticuloendothelial system mainly comprise of phagocytic cells whose function is to engulf microbes, immune complex from blood and tissues and participate in inflammation. This way they contribute to non-specific immunity. These cells also participate in specific immunity by way of antigen presentation and cytokine secretions. The role of phagocytes was highlighted by Elie Metchnikoff. The deficiency of phagocytic system can lead to disorders such as Chronic Granulomatous Disease.

The major phagocytic cells are:

• Polymorphonuclear leucocytes (PMNLs), also called neutrophils, microphages

• Blood and tissue monocytes.

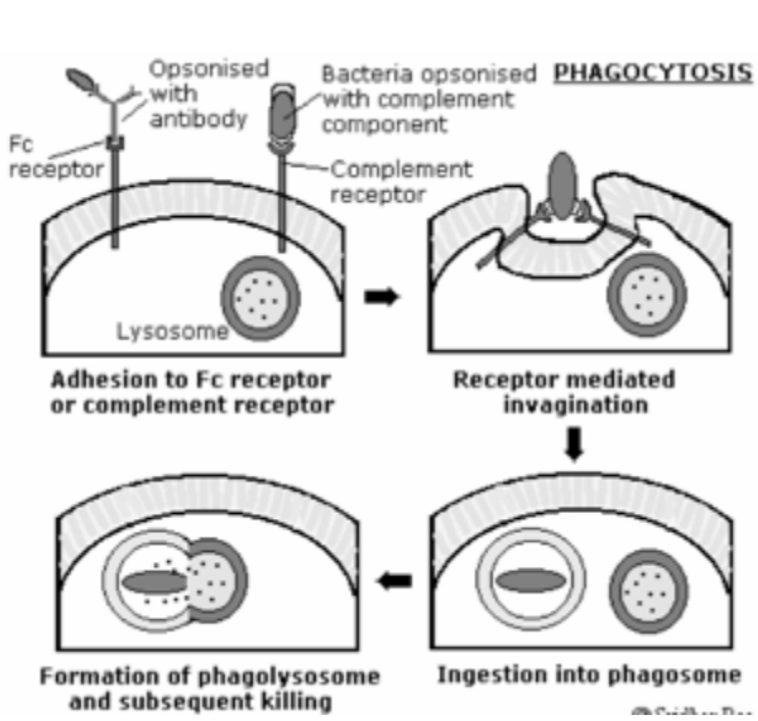
They both are derived form the bone marrow during hematopoiesis.

Neutrophils have short life span. They circulate in the blood for 6-7 hours, then migrate through the endothelial cell junctions and reside in tissue spaces where they live only for few days and do not multiply. Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. An adult typically has 3,000-7,500 neutrophils/mm3 of blood but the number may increase two- to three-fold during active infections. Adult body usually produces 1011 neutrophils

per day. Some neutrophils may remain attached to endothelial lining of large veins and can be mobilised during inflammation. The nucleus of a neutrophil is segmented into 3-5 connected lobes, hence the name polymorphonuclear leukocyte. They are called neutrophils because their granules stain poorly with the mixture of dyes used in staining leukocytes. Because of the granules, they are considered as one of the granulocytes. There are two types of granules, the specific granules and azurophilic granules. Specific granules are present in abundance and contain proteolytic enzymes such as lysozyme, collagenase and elastase. They stain neither with acidic nor basic dyes. The azurophilic granules are actually lysosomes.

Monocytes have rounded or kidney-shaped nuclei with finely granular cytoplasm, measure 12-15 µm and have half-life of 3 days in circulation. Monocytes normally make up 2-8% of the WBCs (100-500/mm3 of blood). Once monocytes leave circulation and enter tissue, they are called macrophages. There are two types of macrophages, one that wander in the tissue spaces and the other that are fixed to vascular endothelium of liver, spleen, lymph node and other tissue. Tissue macrophages survive for months and can multiply. Macrophages present in different organs have been given different names. They are Histiocytes (in tissue), Kupffer cells (in liver), Alveolar macrophages (in lungs), Peritoneal macrophages (in peritoneum), Microglial cells (in brain), Mesangial cells (in kidneys) and Osteoclasts (in bone). Some macrophages develop abundant cytoplasm and are called epitheloid cells. Macrophages can fuse to form multi-nucleated giant cells. Some mononuclear cells differentiate into dendritic cells. Functions of macrophage include killing of microbes, infected cells, tumor cells, secretion of immunomodulatory cytokines, antigen processing and presentation to T cells. Macrophages respond to infections as quickly as neutrophils but persist much longer; hence they are dominant effector cells in the later stage of infection.

Microbial killing by phagocytes:



Phagocytosis involves two steps namely attachment and ingestion. Following attachment of the organism, invagination of the phagocyte results in the formation of a phagosome. Some capsulated bacteria don't attach to the phagocyte, but they can still be phagocytosed if they are coated with opsonins such as IgG and complement component (C3b). The engulfed bacteria are held inside a vacuole called phagosome. The formation of phagosome triggers respiratory bursts and fusion of lysosome with phagosome to form phagolysosome.

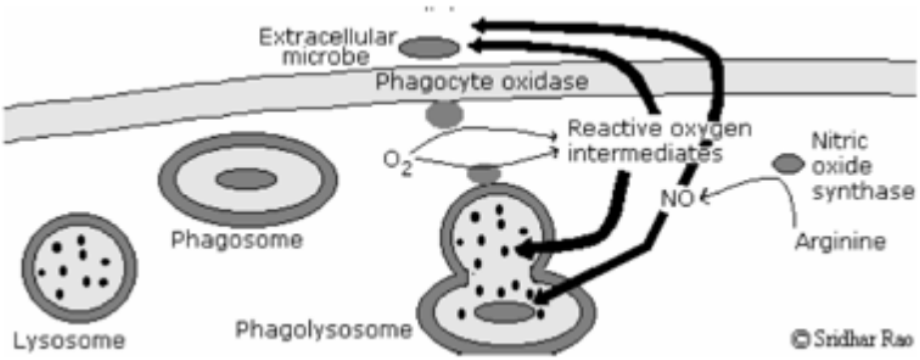
The phagocytes appear to kill engulfed bacteria by two pathways, oxygen independent pathway and oxygen dependent pathway. The microbicidal mechanisms of the respiratory burst are termed oxygen dependent and phagolysosome formations are termed oxygen independent.

Oxygen dependent mechanism involves catalytic conversion of molecular oxygen to oxyhalide free radicals, which are highly reactive oxidizing agents. The phagocyte oxidase present in the plasma membrane and phagolysosome reduce oxygen into reactive oxygen intermediates such as superoxide radicals. Superoxide is converted to H2O2, which is used by enzyme myeloperoxidase to convert unreactive halide ions to reactive hypohalous acids that are toxic to bacteria.

Oxygen independent mechanism involves release of lysosomal contents into phagolysosomes. The content of lysosome includes lactoferrin, cathepsin G, lysozyme and defensins etc.

In addition to the phagocyte oxidase system, macrophages have free-radical generating system, namely inducible nitric oxide synthase. This cytosolic enzyme is absent in resting macrophages but can be induced in response to bacterial

lipopolysaccharides and IFN-γ. This enzyme catalyses the conversion of arginine to citrulline, and in the process releases nitric oxide gas. Nitric oxide may then combine with H2O2 or superoxide to form highly reactive peroxynitrite radicals that kill the microbes.



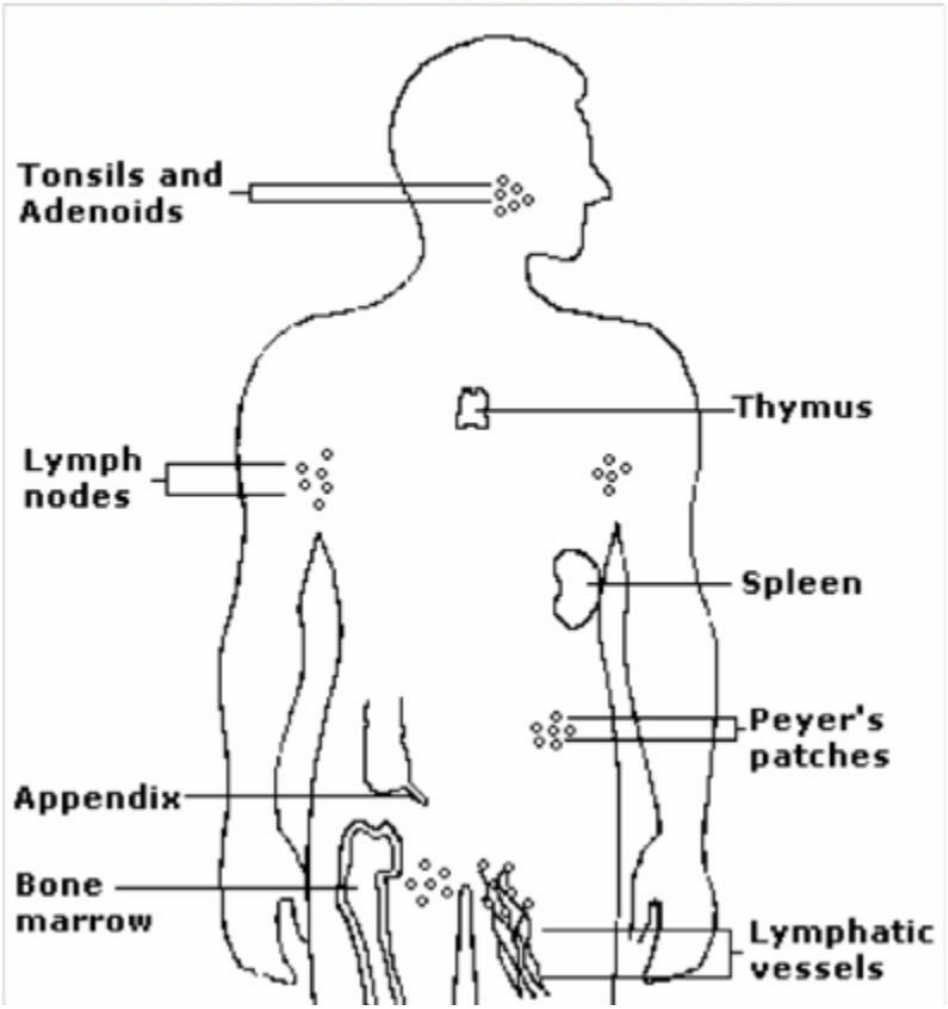
Dendritic cells:

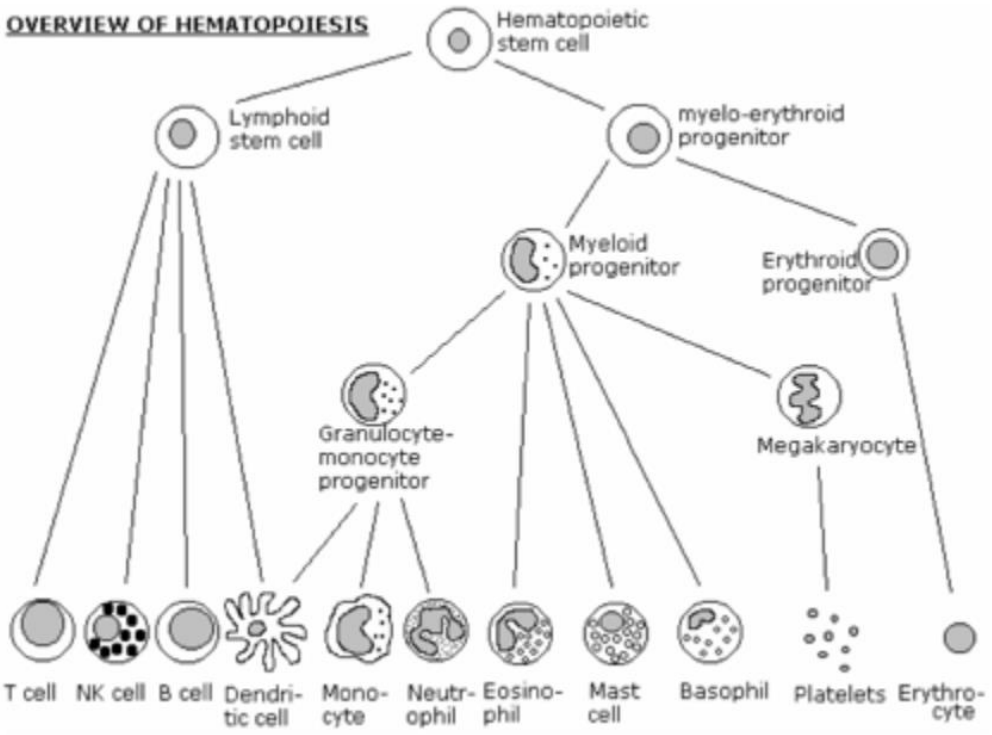
These cells are derived from myeloid progenitor in the bone marrow and are morphologically identified by spiny membranous projection on their surfaces. Immature dendritic cells are located in epithelia of skin, gastrointestinal tract and respiratory tract and are called langerhan cells. They express low levels of MHC proteins on their surface and their main function is to capture and transport protein antigen to the draining lymph node. During their migration to the lymph node, dendritic cells mature into excellent antigen presenting cells (APC). Mature dendritic cells reside in the T cell area (paracortex) of the lymph node. Here, they are referred as interdigitating dendritic cells. These cells are distinct from the dendritic cells that occur in the germinal centers of lymphoid follicles (follicular dendritic cells) in lymph node, spleen and MALT. The follicular dendritic cells are not derived from the bone marrow and their role is to present antigen-antibody complex and complement products to B cell.

Lymphoid system:

Lymphoid organs are stationed throughout the body and are concerned with the growth, development and deployment of lymphocytes. These structurally and functionally diverse lymphoid organs and tissues are interconnected by the blood vessels and lymphatic vessels through which lymphocytes circulate. The organs involved in specific as well as non-specific immunity are classified as primary (central) lymphoid organs and secondary (peripheral) lymphoid organs. The blood and lymphatic vessels that carry lymphocytes to and from the other structures can also be considered lymphoid organs. Recently, it has become accepted that the liver is also a hematopoietic organ, giving rise to all leukocyte lineages.

OVERVIEW OF LYMPHATIC SYSTEM





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