Structure and Function of Immune System:

The lymphoreticular system: is a complex organization of cells of diverse morphology, distributed widely in different organs and tissues of the human body, and is responsible for immunity.

It consists of **lymphoid** and **reticuloendothelial components** and is responsible for immune response of the host.

Lymphoid Tissues and Organs: The specific immune response to antigen is of two types:

(*a*) humoral or antibody-mediated immunity, mediated by antibodies produced by plasma cells.

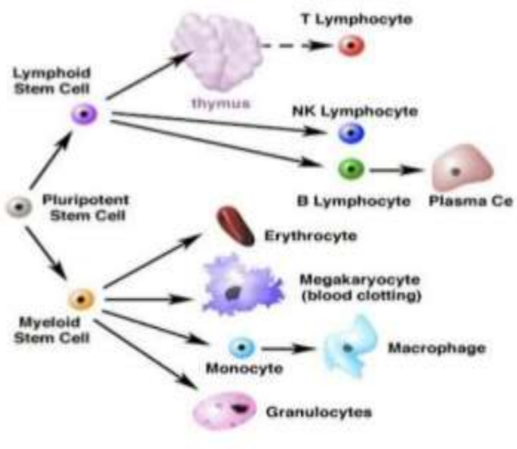
(*b*) cell-mediated immunity, mediated by sensitized lymphocytes.

The immune system is organized into several special tissues, which are collectively termed **lymphoid** or **immune tissues**. The tissues that have evolved to a high degree of specificity of function are termed **lymphoid organs**.

Lymphoid organs: include the gut-associated lymphoid tissues—tonsils, Peyer's patches, and appendix—as well as aggregates of lymphoid tissue in the submucosal spaces of the respiratory and genitourinary tracts. The lymphoid organs,based on their function, are classified into central (primary) and peripheral (secondary) lymphoid organs.

Central (Primary) Lymphoid Organs:

Central or primary lymphoid organs are the major sites for lymphopoiesis. These organs have the ability to produce progenitor cells of the lymphocytic lineage. These are the organs in which precursor lymphocytes proliferate, develop, and differentiate from lymphoid stem cells to become immunologically competent cells. The primary lymphoid organs include thymus and bone marrow. In mammals, T cells mature in thymus and B cells in fetal liver and bone marrow. After acquiring immunological competency, the lymphocytes migrate to secondary lymphoid organs to induce appropriate immune response on exposure to antigens.



Thymus:

Thymus is the first lymphoid organ to develop. It reaches its maximal size at puberty and then atrophies, with a significant decrease in both cortical and medullary cells and an increase in the total fat content of the organ. The thymus is a flat, bilobed organ situated above the heart. Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae. Each lobule is organized into two compartments: cortex and medulla. The stroma of the organ is composed of dendritic cells, epithelial cells, and macrophages.

■ **Cortex:** It consists mainly of (*a*) cortical thymocytes, the immunologically immature T lymphocytes, and (*b*) a small number of macrophages and plasma cells.

■ **Medulla:** It contains predominantly mature T lymphocytes and has a larger epithelial cell-to-lymphocyte ratio than the cortex.

Functions of the thymus: It has many functions:

1- Production of thymic lymphocytes is the primary function of the thymus. It is a major organ for proliferation of lymphocytes in the body.

2- It is believed to play a key role in determining the differentiation of T lymphocytes.

3- The T lymphocytes are primarily responsible for cell mediated immunity (CMI).

Bone marrow:

Some lymphoid cells develop and mature within the bone marrow and are referred to as **B cells** (B for **bursa of Fabricius**, or bone marrow). The function of bursa of Fabricius in birds is played by bone marrow in humans. Bone marrow is the site for proliferation of stem cells and for the origin of pre-B cells and their maturation to become immunoglobulin-producing lymphocytes.

Peripheral (Secondary) Lymphoid Organs:

Peripheral or secondary lymphoid organs consist of

(1) lymph nodes

(2) spleen

(3)nonencapsulated structures, such as mucosa-associated lymphoid tissues (MALT).

1- Lymph nodes:

The lymph nodes are extremely numerous and disseminated all over the body. They play a very important and dynamic role in the initial or inductive states of the immune response. The lymph node has two main parts: cortex and medulla.

Cortex: The cortex and the deep cortex, also known as paracortical area, are densely populated by lymphocytes. Roughly spherical areas containing densely packed lymphocytes, termed primary lymphoid follicles or nodules, are found in the cortex. B and T lymphocytes are found in different areas in the cortex.

The primary lymphoid follicles predominately contain B lymphocytes. They also contain macrophages, dendritic cells, and some T lymphocytes. T lymphocytes are found predominantly in the deep cortex or paracortical area; for this reason, the paracortical area is designated as T-dependent. Interdigitating cells are also present in this area, where they present antigen to T lymphocytes.

Medulla: It is less densely populated and is composed mainly of medullary cords. These cords are elongated branching bands of the lymphocytes, plasma cells, and macrophages. They drain into the hilar efferent lymphatic vessels. Plasma cells are also found in the medullary cords.

Functions of the lymph nodes: Lymph nodes serve the following functions:

1- They act as filter for the lymph, the fluid, and cellular content of the lymphocytic circulatory system.

2- They also provide sites for mingling of lymphocytes, monocytes, and dendritic cells for initiation of immune responses.

3- They phagocytose microbial pathogens and other foreign substances.

Spleen

The spleen is the largest lymphoid organ. It is a large, ovoid secondary lymphoid organ situated high in the left abdominal cavity.

The spleen parenchyma is heterogeneous and is composed of the white and the red pulp. It is surrounded by a capsule made up of connective tissue.

Functions of the spleen: The spleen plays a major role in:

1- Mounting immune responses to antigens in the blood stream. The circulating antigens are trapped by the macrophages present in the marginal zone. These macrophages then process the antigen, migrate deeper into the white pulp, and initiate the immune response by interacting with T and B lymphocytes.

2- Filtering or clearing of (*a*) infectious organisms (*b*) aged or defectively formed elements (e.g., spherocytes, ovalocytes) and (*c*) particulate matter from the peripheral blood.

3-Mucosa-associated lymphoid tissues

Mucosa-associated lymphoid tissues (MALT) consist of the lymphoid tissues of the intestinal tract, genitourinary tract,tracheobronchial tree, and mammary glands. All of the MALT are noncapsulated and contain both T and B lymphocytes, and the latter predominate. Structurally, these tissues include clusters of lymphoid cells in the lamina propria of intestinal villi,tonsils, appendix, and Peyer's patches.

Tonsils: These are present in the oropharynx and are predominantly populated by B lymphocytes. These are the sites of intense antigenic stimulation, as shown by the presence of numerous secondary follicles with germinal centers in the tonsillar crypts.

Peyer's patches: These are lymphoid structures that are found within the submucosal layer of the intestinal lining.The follicles of the Peyer's patches are extremely rich in B cells, which differentiate into IgA-producing plasma cells.

MALTs play an important role in defense system of the human host. This is demonstrated by large population of antibody-producing plasma cells in MALT, whose number far exceeds that of plasma cells in the spleen, lymph nodes, and bone marrow, when combined together.

Cells of the Lymphoreticular System

It is essential for the immune system to distinguish its own molecules, cells, and organs (self) from those of foreign origin (nonself). The innate immunity does this by expressing germline-encoded pattern recognition receptors on the surface of its cells, receptors that recognize structures on potentially invasive microorganisms. The adaptive immunity, on the other hand, makes use of somatically generated epitope-specific T-cell receptors (TCRs) and B-cell receptors (BCRs). These receptors are produced randomly and fresh within each individual T and B lymphocytes by gene recombination prior to encounter with antigens.

The cells involved in the adaptive immune responses are (*a*) lymphocytes, (*b*) antigen-presenting cells (APCs), and (*c*) effector cells that function to eliminate antigens.

Lymphocytes: The lymphocytes occupy a very special place among the leukocytes.

■ They participate in immune reactions due to their ability to interact specifically with antigenic substances and to react to nonself antigenic determinants.

■ They also contribute to the memory of the immune system.

The lymphocytes consist of heterogeneous populations of cells that differ greatly from each other in terms of origin,lifespan, preferred areas of settlement within the lymphoid organs, surface structure, and function. They differentiate from stem cells in the fetal liver, bone marrow, and thymus into two main functional classes: B cells and T cells.They are found in the peripheral blood and in all lymphoid tissues.

The lymphocytes are classified depending upon where they undergo their development and proliferation: (*a*) T lymphocytes or T cells undergoing development in the thymus or (*b*) B lymphocytes, or B cells undergoing development in the bone marrow.

Antigen-presenting cells

Antigen presenting cells (APCs) include (*a*) macrophages and (*b*) dendritic cells.

Macrophages:The mononuclear phagocytic system consists of monocytes circulating in the blood and macrophages in the tissues. The monocyte is considered a leukocyte in transit through the blood, which becomes a macrophage when fixed in a tissue. Monocytes and macrophages as well as granulocytes are able to ingest particulate matter (microorganisms, cells, inert particles) and for this reason are said to have phagocytic functions. The phagocytic activity is greater in macrophages, particularly after activation by soluble mediators released during immune responses, than in

monocytes. Differentiation of a monocyte into a tissue macrophage involves a number of changes as follows:

1. The cell enlarges 5–10 folds.

2. Its intracellular organelles increase in number and complexity.

3. It acquires increased phagocytic ability.

4. It produces higher levels of hydrolytic enzymes.

5. It begins to secrete a variety of soluble factors.

Macrophage-like cells serve different functions in different tissues and are named according to their tissue location. Examples include

(*a*) alveolar macrophages in the lung (*b*) histiocytes in connective tissues (*c*) Kupffer cells in the liver (*d*) mesangial cells in the kidney (*e*) microglial cells in the brain, and (*f*) osteoclasts in the bone.

For their participation in the immune reaction, the macrophages need to be stimulated and reach an “activated state.”

■ Macrophages can be activated by various cytokines, components of the bacterial cell wall, and mediators of the inflammatory response.

■ Gamma interferon produced by helper T cells is a potent activator of macrophages and is secreted by various cells in response to appropriate stimuli. Bacterial lipopolysaccharides (endotoxin), bacterial peptidoglycan, and bacterial DNA are the substances that also activate macrophages.

■ Activated macrophages are more potent than normal macrophages in many ways, such as having greater phagocytic ability and increased ability to kill ingested microbes. They are better APCs, and they activate T-cell response in a more effective manner. By secreting various cytotoxic proteins, they help in eliminating a broad range of pathogens, including virus-infected cells, tumor cells, and intracellular bacteria.

Functions of macrophages: Macrophages perform three main functions: (*a*) phagocytosis, (*b*) antigen presentation, and (*c*) cytokine production.

Dendritic cells: Dendritic cells are so named because of their many long, narrow processes that resemble neuronal dendrites, which make them very efficient at making contacts with foreign materials.

They are primarily present in the skin (e.g., Langerhans cells) and the mucosa, from where they migrate to local lymph nodes for presentation of antigen to helper T cells.

■ Dendritic cells are very important for presentation of the antigen to T cells during primary immune response.

■ They are bone marrow-derived cells that express class II MHC proteins and present antigen to CD4+ T cells.

■ They have little or no phagocytic activity.

■ They also serve as professional APCs, although macrophages and B cells are the major APCs.

Plasma cells: Plasma cells originate from terminally differentiated B cells.

Plasma cells are oval or egg-shaped structures characterized by a stellate (star-like pattern) nucleus, nonstaining Golgi, and basophilic cytoplasm.

■ The main function of the plasma cells is to produce and secrete all the classes of immunoglobulins into the fluids around the cells.

■ They secrete thousands of antibody molecules per second, which are specific for the epitope of the antigen for a few days and then die.

■ They do not express membrane immunoglobulins.

■ They divide very poorly, if at all, and are usually found in the bone marrow and in the perimucosal lymphoid tissues.

■ They have a short lifespan of 30 days during which they produce large quantities of immunoglobulins.

Natural killer cells: Natural killer (NK) cells are morphologically described as large granular lymphocytes. These cells are called natural killer cells due to their ability to kill certain virally infected cells and tumor cells without prior sensitization. Their activities are not enhanced by exposure and are not specific for any virus.

Functions of natural killer cells

1. Kill virus-infected cells and tumor cells.

2. Nonspecific killing of virus-infected cells and tumor cells.

3. Killing is independent of antigen presentation by MHC proteins.

4. Mechanism of killing is by perforins and granzymes, which cause apoptosis of target cell.

5. Killing is activated by failure of a cell to present antigen with class I MHC or by reduction of class I MHC proteins on the cell surface.