Lymphoid Tissues and Organs;

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***. The lymphoid organs, based on their function, are classified into **central (primary) and peripheral (secondary) lymphoid organs .**

A-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.

I-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. 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. Thymus is the site where a large diversity of T cells is produced and so they can recognize and act against a myriad number of antigen–MHCs (major histocompatibility complexes). The thymus induces the death of those T cells that cannot recognize antigen–MHCs. It also induces death of those T cells that react with self-antigen MHC and pose

a danger of causing autoimmune disease. More than 95% of all thymocytes die by apoptosis in the thymus without ever reaching maturity.

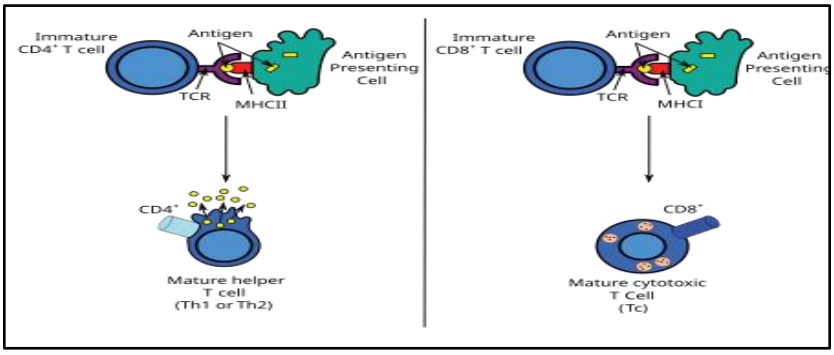
Development of T-cell:

All T cells originate from haematopoietic stem cells (HSC) which reside in the bone marrow. In some cases, the origin might be the fetal liver during embryonic development. 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, they are known as thymocytes, the immature stage of a T cell.

The earliest cells which arrived in the thymus are commonly termed *double-negative*, as they express neither the CD4 nor CD8 co-receptor. Expression of both CD4 and CD8 makes them *double positive*, and matures into either CD4+ or CD8+ cells. A critical step in T cell maturation is making a functional T cell receptor (TCR). Each mature T cell will ultimately contain a unique TCR .The thymocytes must undergo multiple stages as well as positive selection and negative selection..

Positive selection

The process of positive selection takes 3 to 4 days and occurs in the thymic cortex. 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, which reside on the surface of cortical epithelial cells. Only thymocytes that interact well with MHC-I or MHC-II will receive a vital "survival signal", while those that cannot interact strongly enough will receive no signal and die. This process ensures that the surviving thymocytes will have an 'MHC affinity' that means they can serve useful functions in the body. Double-positive cells ($CD4^+/CD8^+$) that interact well with **MHC *class II* molecules will eventually become $CD4^+$ "helper" cells,** whereas thymocytes that interact **well with MHC *class I* molecules mature into $CD8^+$ "killer" .**



Antigen presentation stimulates T cells to become either "cytotoxic" CD8+ cells or "helper" CD4+ cells

Negative selection

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). Some mTECs are phagocytosed by thymic dendritic cells; this makes them antigen presenting cells (APCs), allowing for presentation of self-antigens on MHC *class II* molecules (positively selected $CD4^+$ cells must interact with these MHC class II molecules, Thymocytes that interact too strongly with the self-antigen receive an apoptotic signal that leads to cell death. The remaining cells exit the thymus as mature naive 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.

II-Bone marrow

Some lymphoid cells develop and mature within the bone marrow and are referred to as ***B cells***. 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. **Immature B cells proliferate and differentiate within the bone marrow.** Stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for the development of B cells. Like thymic selection during T-cell maturation, a selection process within the bone marrow eliminates B cells with self-reactive antibody receptors. B lymphocytes develop their B-cell receptors (BCRs) by DNA rearrangement. **The B lymphocytes are transformed into plasma cells and secrete antibodies.** B lymphocytes are primarily responsible for **antibody-mediated immunity.**

- **B-Peripheral (Secondary) Lymphoid Organs**

Peripheral or secondary lymphoid organs consist of **(*a*) lymph nodes**, **(*b*) spleen**, and (***c*) nonencapsulated structures, such as mucosa associated lymphoid tissues (MALT).** These organs serve as the sites for **interaction of mature lymphocytes with antigens .**

I- 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. Lymph nodes measure 1–25 mm in diameter and are

surrounded by a connective tissue capsule. The lymph node has two main parts: cortex and medulla.

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

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

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

II-Spleen

The spleen is the largest lymphoid organ. It is a large, ovoid secondary lymphoid organ situated high in the left abdominal cavity. It is surrounded by a capsule made up of connective tissue.

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

■ 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**.

■ 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.** In addition, the spleen traps blood-borne antigens and microbes. The main filtering function is performed by the macrophages lining up the splenic cords.

III-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 contain both T and B lymphocytes. 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 .

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.**

***Functions of the 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. MALTs facilitate interaction among circulating leukocytes.

