Lymphoid tissues

- ***Lymphoid tissues are classified as generative organs, also called primary or central lymphoid organs, where lymphocytes first express antigen receptors and attain phenotypic and functional maturity,***
- ***and peripheral organs, also called secondary lymphoid organs, where lymphocyte responses to foreign antigens are initiated and develop*** .

in the generative lymphoid organs of adult mammals are the bone marrow and the thymus, the sites of maturation of B cells and T cells, respectively.

- B lymphocytes partially mature in the bone marrow, enter the circulation, then populate secondary lymphoid organs, spleen and lymph nodes, and complete their maturation mainly in the spleen.
- T lymphocytes mature in the thymus, and then enter the circulation and populate peripheral lymphoid organs and tissues.
- Two important functions shared by the generative organs are to provide growth factors and other molecular signals needed for lymphocyte maturation and to present self antigens for recognition and selection of maturing lymphocytes .

FIFTH LECTURE

Primary lymphoid organ

Bone Marrow

- ***The bone marrow is the site of generation of most mature circulating blood cells, including red blood cells, granulocytes, and monocytes, and the site of early events in B cell maturation***.
- The generation of all blood cells, called **hematopoiesis** occurs initially during fetal development in
- 1-blood islands of the yolk sac and
- 2- the para-aortic mesenchyme,
- 3- then shifts to the liver between the third and fourth months of gestation, and
- 4- finally shifts to the bone marrow.
- At birth, hematopoiesis takes place mainly in the bones throughout the skeleton, but it becomes increasingly restricted to the marrow of the flat bones, so that by puberty, hematopoiesis occurs mostly in the sternum, vertebrae, iliac bones, and ribs.

- The peripheral lymphoid tissues include the lymph nodes, spleen, cutaneous immune system, and mucosal immune system. In addition, poorly defined aggregates of lymphocytes are found in connective tissues and in most organs.
- All peripheral lymphoid organs also share common functions, including the delivery of antigens and responding naive lymphocytes to the same location so that adaptive immune responses can be initiated, and an anatomic organization that allows T cells and B cells to interact cooperatively.

In addition to self-renewing stem cells and their differentiating progeny, the marrow contains numerous long-lived antibody-secreting plasma cells. These cells are generated in peripheral lymphoid tissues as a consequence of antigenic stimulation of B cells and then migrate to the bone marrow. The marrow also contains recirculating mature follicular B cells that may respond there to blood borne microbes. In addition, some long lived memory T lymphocytes migrate to and may reside in the bone marrow.

The proliferation and maturation of precursor cells in the bone marrow are stimulated by cytokines.

- Many of these cytokines are called **colony-stimulating factors** because they were originally assayed by their ability to stimulate the growth and development of various leukocytic or erythroid colonies from marrow cells.
- Hematopoietic cytokines are produced by stromal cells and macrophages in the bone marrow, thus providing the local environment for hematopoiesis.
- They are also produced by antigen-stimulated T lymphocytes and cytokine-activated or microbe activated macrophages. The names and properties of the major hematopoietic cytokines are listed in following table.

Thymus

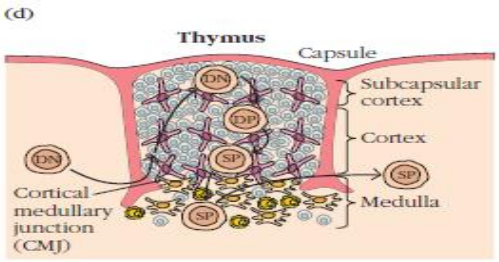
- ***The thymus is the site of T cell maturation.***
- The thymus is a bilobed organ situated in the anterior mediastinum. Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla .
- The cortex contains a dense collection of T lymphocytes,
- and the lighter-staining medulla is more sparsely populated with lymphocytes.
- Bone marrow–derived macrophages and dendritic cells are found almost exclusively in the medulla. Scattered throughout the thymus are non lymphoid epithelial cells, which have abundant cytoplasm.
- Thymic **cortical epithelial cells** produce IL-7, which is required early in T cell development.

TABLE 2-4 Hematopoietic Cytokines

Cytokine	Size	Principal Cellular Sources	Principal Immature Cell Targets	Principal Cell Populations Induced
Stem cell factor (c-Kit ligand)	24 kD	Bone marrow stromal cells	Hematopoietic stem cells	All
Interleukin-7 (IL-7)	25 kD	Fibroblasts, bone marrow stromal cells	Immature lymphoid progenitors	T lymphocytes
Interleukin-3 (IL-3)	20–26 kD	T cells	Immature progenitors	All
Granulocyte-monocyte colony-stimulating factor (GM-CSF)	18–22 kD	T cells, macrophages, endothelial cells, fibroblasts	Immature and committed myeloid progenitors, mature macrophages	Granulocytes and monocytes, macrophage activation
Monocyte colony-stimulating factor (M-CSF)	Dimer of 70–90 kD; 40-kD subunits	Macrophages, endothelial cells, bone marrow cells, fibroblasts	Committed progenitors	Monocytes
Granulocyte colony-stimulating factor (G-CSF)	19 kD	Macrophages, fibroblasts, endothelial cells	Committed granulocyte progenitors	Granulocytes
Flt-3 ligand	30kD	Bone marrow stromal cells	Hematopoietic stem cells, dendritic cell and B cell progenitors	Classical and plasmacytoid dendritic cells, B cells

- Humans with DiGeorge syndrome suffer from T cell deficiency because of a chromosomal deletion that eliminates genes required for thymus development.
- In the nude mouse strain, which has been widely used in immunology research, a mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the thymus and hair follicles. Consequently, these mice lack T cells and hair.
- The lymphocytes in the thymus, also called **thymocytes**, are T lymphocytes at various stages of maturation.
- The most immature cells enter the thymus, and their maturation begins in the cortex. As thymocytes mature, they migrate toward the medulla, so that the medulla contains mostly mature T cells.
- Only mature naïve T cells exit the thymus and enter the blood and peripheral lymphoid tissues.

- A different subset of epithelial cells found only in the medulla, called **medullary thymic epithelial cells** (MTEC), plays a special role in presenting self antigens to developing T cells and causing their deletion.
- This is one mechanism of ensuring that the immune system remains tolerant to self.
- In the medulla there are structures called Hassall's corpuscles, which are composed of tightly packed whorls of epithelial cells that may be remnants of degenerating cells.
- The thymus has a rich vascular supply and efferent lymphatic vessels that drain into ***The*** mediastinal lymph nodes.



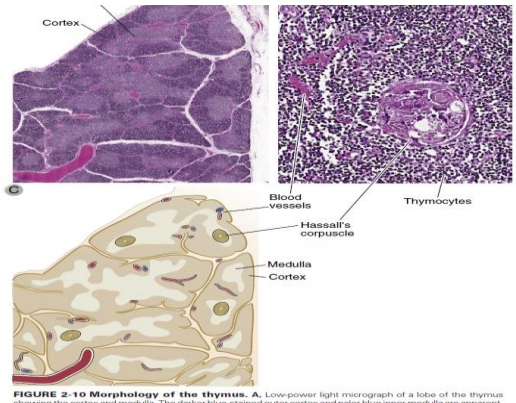


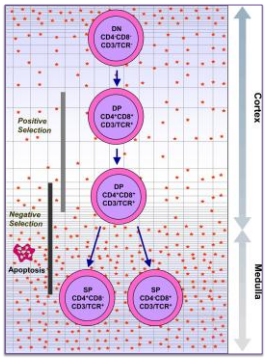
FIGURE 2-10 Morphology of the thymus. A, Low-power light micrograph of a lobe of the thymus showing the cortex and medulla. The darker blue-stained outer cortex and paler blue inner medulla are apparent. **B,** High-power light micrograph of the thymic medulla. The numerous small blue-staining cells are developing T cells called *thymocytes*, and the larger pink structure is Hassall's corpuscle, uniquely characteristic of the thymic medulla but whose function is poorly understood. **C,** Schematic diagram of the thymus illustrating a portion of a lobe divided into multiple lobules by fibrous trabeculae.

- The thymus is a specialized environment where immature T cells generate unique antigen receptors (T cell receptors, or TCRs) and are then selected on the basis of their reactivity to self MHC-peptide complexes expressed on the surface of thymic stromal cells.
- Those thymocytes whose T-cell receptors bind self MHC-peptide complexes with too high affinity are induced to die (**negative selection**),
- and those thymocytes that bind self MHC-peptides with an intermediate affinity undergo **positive selection**, resulting in their survival, maturation, and migration to the thymic medulla.

- T cell development is not complete until the cells undergo selection in the **thymus** .
- The importance of the thymus in T-cell development was not recognized until the early 1960s, when J.F.A.P. Miller, an Australian biologist, worked against the power of popular assumptions to advance his idea that the thymus was something other than a graveyard for cells..
- Miller proved that the thymus was the all important site for the maturation of T lymphocytes.

- DN cells first travel to the region under the thymic capsule, a region referred to as the *subcapsular cortex,* where they proliferate and begin to generate their T-cell receptors.
- Thymocytes that successfully express TCRs begin to express both CD4 and CD8, becoming **double positive (DP) cells**, and populate the cortex, the site where most (85% or more) immature T cells are found.
- The cortex features a distinct set of stromal cells, *cortical thymic epithelial cells* (*cTECs*), whose long processes are perused by thymocytes testing the ability of their T-cell receptors to bind MHC-peptide complexes.
- Thymocytes that survive selection move to the thymic medulla, where positively selected thymocytes encounter specialized stromal cells, *medullary thymic epithelial cells* (*mTECs*).
- Not only do mTECs support the final steps of thymocyte maturation, but they also have a unique ability to express proteins that are otherwise found exclusively in other organs. This allows them to negatively select a group of potentially very damaging, autoreactive T cells that could not be deleted in the cortex.

- Most thymocytes do not navigate the journey through the thymus successfully; in fact, it is estimatedthat 95% of thymocytes die in transit.
- The majority of cells die because they have too low an affinity for the self-antigen-MHC combinations that they encounter on the surface of thymic epithelial cells and fail to undergo positive selection.
- These developmental events take place in several distinct thymic microenvironments
- At this stage thymocytes express neither CD4 nor CD8, markers associated with mature T cells. They are therefore called **double negative (DN) cells**.



- Mature thymocytes, which express only CD4 or CD8 and are referred to as **single positive (SP)**, leave the thymus as they entered: via the blood vessels of the corticomedullary junction.
- Maturation is finalized in the periphery, where these new T cells (*recent thymic emigrants*) explore antigens presented in secondary lymphoid tissue, including spleen and lymph nodes.

The thymus also regulates immune function by the secretion of multiple soluble hormones.

The thymus produces hormone-like proteins that help T lymphocytes mature and differentiate.

Some thymic hormones include

- thympoeitin,
- thymulin,
- thymosin, and
- thymic humoral factor (THF).
- **Thympoeitin** and **thymulin** induce differentiation in T-lymphocytes and enhance T-cell function.
- **Thymosin** increases immune responses. It also stimulates certain pituitary gland hormones (growth hormone, luteinizing hormone, prolactin, gonadotropin releasing hormone, and adrenocorticotropic hormone (ACTH)).
- **Thymic humoral factor** increases immune responses to viruses in particular