

LECTURE: 09

Title: T- LYMPHOCYTES PRODUCTION AND MATURATION

LEARNING OBJECTIVES:

The student should be able to:

- Describe the anatomical feature of the thymus in relation to the mechanism of T-cell maturation.
- Enumerate the type of cells inside the thymus, and identify their locations.
- Identify the type of cell in the thymus which is rich in the MHC II molecules.
- Describe the mechanism of migration during the T-lymphocyte maturation in the thymus starting from:
 - Sub-capsular region (blast, and nurse cells).
 - Outer cortex.
 - Deep cortex.
 - Medulla.
 - Cortico-medullary junction.
- Describe the T-cell's phenotypic variations during maturation in the thymus:
 - Stage I (early stage) thymocytes.
 - Stage II (intermediate or common) thymocytes.
 - Stage III (mature) thymocytes.
- Identify the location where the T-lymphocytes generate their cell surface diversity ($\alpha\beta$, and $\gamma\delta$).
- Describe the mechanism of the positive and negative selection.
- Describe the mechanism of T-cells trafficking "routes of Circulation".

LECTURE REFERENCE:

1. TEXTBOOK: ROITT, BROSTOFF, MALE
IMMUNOLOGY. 6th edition. Chapter 2. pp. 27-29. 30-45.
2. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. Chapter. 2 .pg 16-39.
3. TEXTBOOK: MALE, COOKE. OWEN, TROWSDALE, CHAMPION
ADVANCE IMMUNOLOGY. Chapter 6. pp 6.1-6.14. Chapter 8. pp. 8.2-8.15.
4. TEXTBOOK: auren Sompayrac. How the immune system works. Chapter 6. pp 63-71.
5. TEXTBOOK: JOHN CLANCY, JR. BASIC CONCEPTS IN IMMUNOLOGY. Chapter 5. pp 3947.

T-LYMPHOCYTES PRODUCTION AND MATURATION

INTRODUCTION

Two cell lines arise from pluripotent stem cells, the constituents of these two line of cells are the cells of the immune system. They are found to be of two lineages, these are:

- A. The **lymphoid** lineage produces **lymphocytes**.
- B. The **myeloid** lineage produces **phagocytes** (monocytes, macrophages, and neutrophils) and some other cells, such as; red blood cells, granulocytes (neutrophils, basophils, and eosinophils), mast cells, dendritic cells (although it is still controversial matter).

LYMPHOCYTES

Lymphocytes consist of T cells, B cells, and natural killer cells (NK)

The two main types of lymphocytes are known as T and B cells. These two types of lymphoid cells are developed and differentiated in the primary lymphoid organs. For example, T cells are developed in the thymus, where as the B lymphocytes are differentiated in the adult bone marrow and fetal liver. In birds, B cells are differentiated in the bursa of Fabricius. Further more, in the primary lymphoid organs T and B cells precursors acquire the ability for recognizing antigens through the development of specific surface receptors. NK- cells do not express antigen receptors on their cell membranes. They are capable to lyse certain tumour cell lines in vitro without being sensitized. NK cells are large granular lymphocytes (LGLs)

Lymphocytes are produced in the primary lymphoid organs (thymus and adult bone marrow) at a high rate 10^9 per day. Some of these cells migrate to the blood circulation via the secondary lymphoid tissues (spleen, lymph nodes, tonsils, and mucosa-associated lymphoid tissue). The average human adult has about 10^{12} lymphoid cell, and approximately 2% of the body weight is a lymphoid tissues. Lymphoid cells represent about 20% of the total leukocytes population in the adult circulation. Many mature lymphoid cells are long-lived, and may persist as a memory cells for several years, or even for the live time of the individual.

Lymphocytes are morphologically heterogeneous

Lymphocytes show several variations in the size (6-10 μm) and morphology. These variations are seen in the:

- A. Nuclear to cytoplasmic ratio (N: C ratio).
- B. The nuclear shape.
- C. The presence or absence of azurophilic granules.

Resting blood T cells

Resting lymphocytes in the conventional blood smear stained with Giemsa stain, show two distinct morphological types:

- A. The first are relatively small, typically a granular lymphocytes with higher N: C ratio.
- B. The second type is larger with lower N: C ratio, and contain intracytoplasmic azurophilic granules same as those found in the granulocytes (neutrophils, basophils, and eosinophils) or to that of the monocytes and macrophage, so it should not be confused with them. These lymphocytes are known as the large granular lymphocyte (LGL).

Resting blood T cells can found in the blood smear with either the LGL form **or** the small, granular lymphocytes morphology. More than 90 % of the helper T lymphocytes (TH) and more than 65 % of the T cytotoxic lymphocytes are of the smaller (non-granular with a high N:C ratio). These T cells with LGL morphology include in their cytoplasm “**Gall body**” which is a cluster of primary lysosomes associated with a lipid droplet, other morphological pattern show up to 10 % of Th cells and of 35 % of Tc cells. These cells show the LGL morphology, with primary lysosomes dispersed in the cytoplasm and a well developed Golgi apparatus. Another set of the T cells with LGL morphology is the gamma/delta ($\gamma\delta$) or TCR-1⁺ lymphocytes, which show a dendritic morphology in the lymphoid tissues.

T-Lymphocytes

The ability to reject a foreign skin graft is intact in bursectomized birds. However, removing the thymus gland (thymectomy) in newborn mice subsequently prolongs skin graft survival and reduces an antibody response to specific antigens. From this result, it is clear that T cells develop in the thymus and are responsible for skin graft rejection and other cell-mediated immune responses. Furthermore, a reduction in antibody responses in thymectomized animals indicates that B cells don not function independently but rather require the cooperation of T cells (T cell help).

THYMIC TISSUE ARCHITECTURE

The thymus is responsible for the development of T-lymphocytes involved in cell mediated immune responses (thymus-derived or T-lymphocytes). The gland appears to be master organ important in immunogenesis in the young and in orchestrating the total lymphoid system throughout life. This central lymphoid organ differs in a number of respects from other lymphoid tissues. All the lymphoid tissues described thus far are advantageously and strategically positioned for contact with foreign configurations that may enter or arise within the host. The thymus, on the other hand, is protected from rather than exposed to antigen. In addition, the rate of mitotic activity in the thymus is grater than in any other lymphatic tissue, yet the number of cells leaving it is fewer than the number accounted for by this high rate of mitosis. The assumption made from these findings is that a large number of lymphocytes produced within the thymus die within its substance. Although originally considered to be a mechanism for removal of "forbidden" autoreactive lymphocyte clones, this function of the thymus probably represents homeostatic activity involved in the production of T-lymphocytes.

The thymus consists of two lobes (**Figure-1**) surrounded by a thin capsule of connective tissues. The capsule extends into the substance of the gland, forming septa that partially divide the lobes into lobules. Peripheral portions of the lobule (cortex) are heavily infiltrated with lymphocytes. More central portions (medulla) contain fewer lymphocytes but more epithelial elements. Within the substance of the thymus are cystic structures containing keratin (Hassall's corpuscles) **Figure-2**, and **5**.

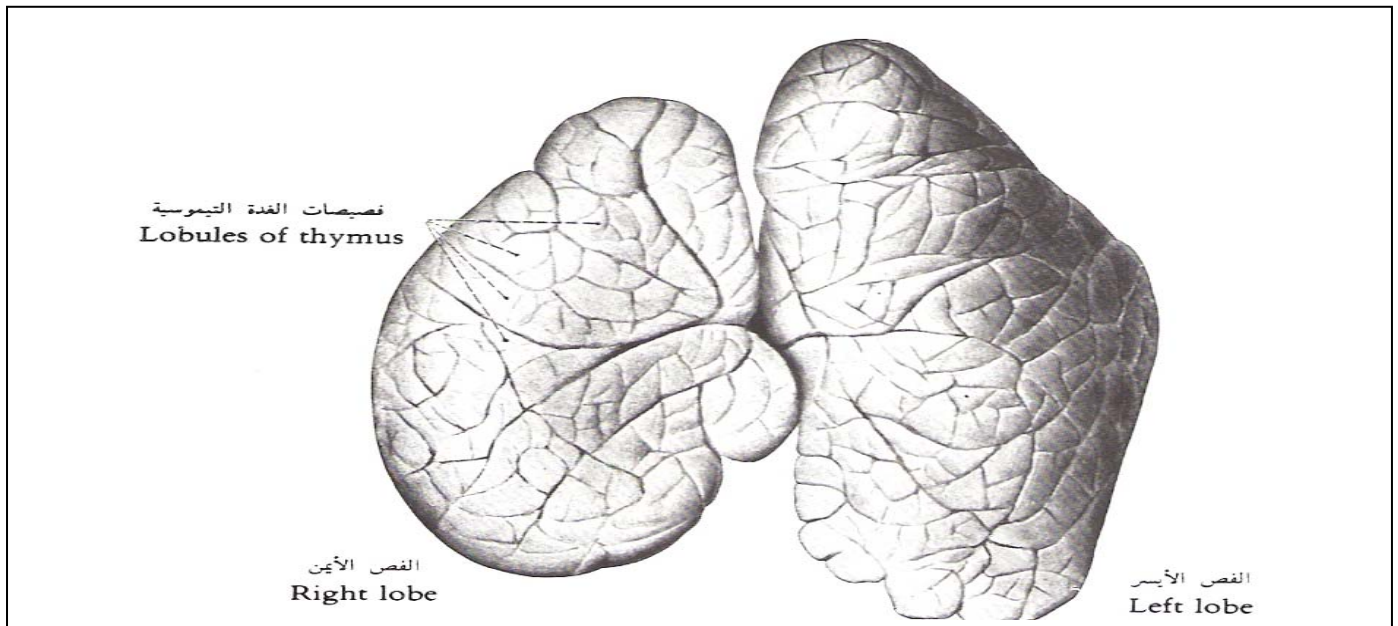


Figure-1 diagrammatic representation of right and left lobes of the thymus gland

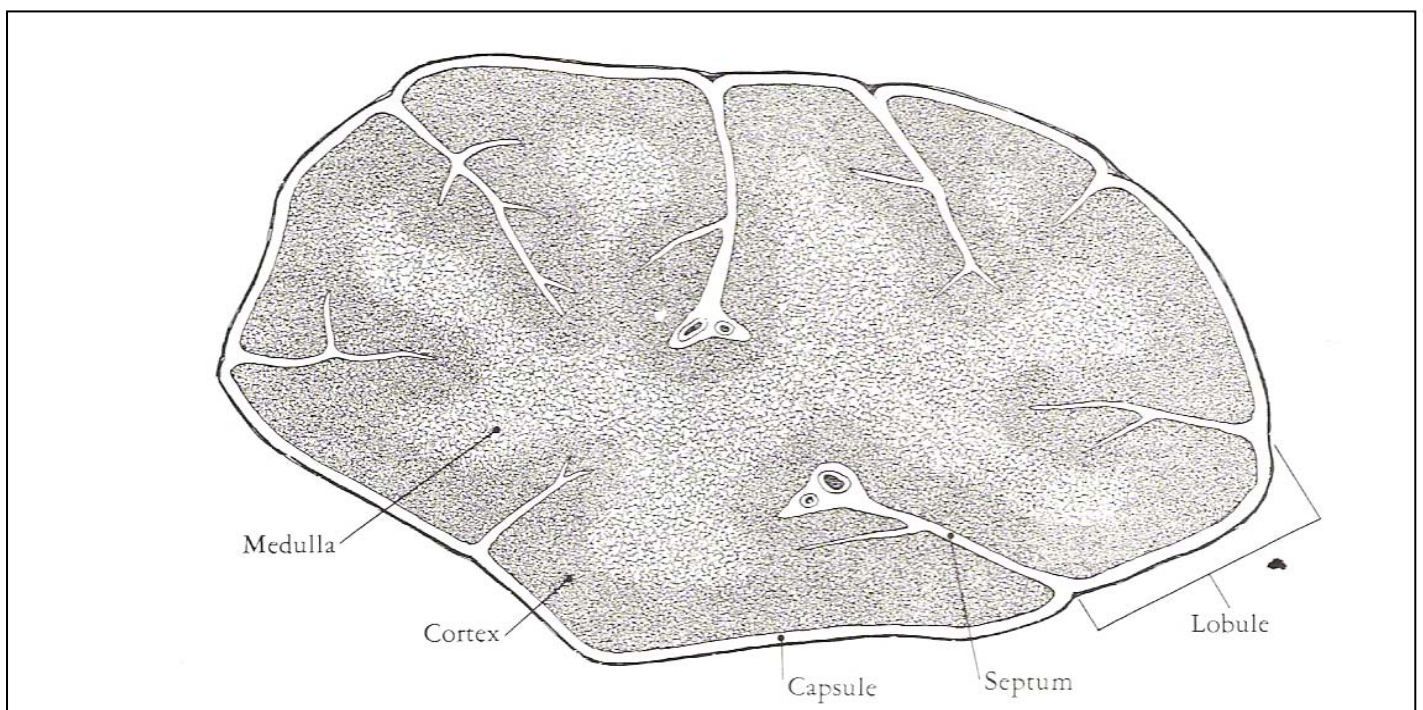


Figure- 2 Schematic representation of thymus gland, showing division into cortex and medulla

The thymus is believed to perform two main functions; the production of lymphocytes within the cortex and the production of a humoral substance (s) by epithelial elements of the gland. These humoral substances (or hormones) may induce differentiation of lymphocytes directly within the thymus or may control their

differentiation in the periphery. Although the thymus gland has a cortex and a medulla, neither contains germinal centers or plasma cells in the normal situation. These may appear when the gland is abnormal, e.g., in thymoma or in certain autoimmune diseases. Unlike other lymphoid organs, the thymus is composed of two tissue types: lymphoid and epithelial. The lymphoid cells are of mesenchymal origin, and the epithelial cells are of endodermal origin. The thymus initially develops as a continuous epithelium of cells from the third and fourth pharyngeal pouches (**Figure-3**). Then the mesenchyme derived lymphoid cells seed this epithelial thymus and convert this structure into a lymphoepithelial organ. The process of differentiation in the human begins as a ventral out pocketing from these pouches about the sixth week of fetal life.

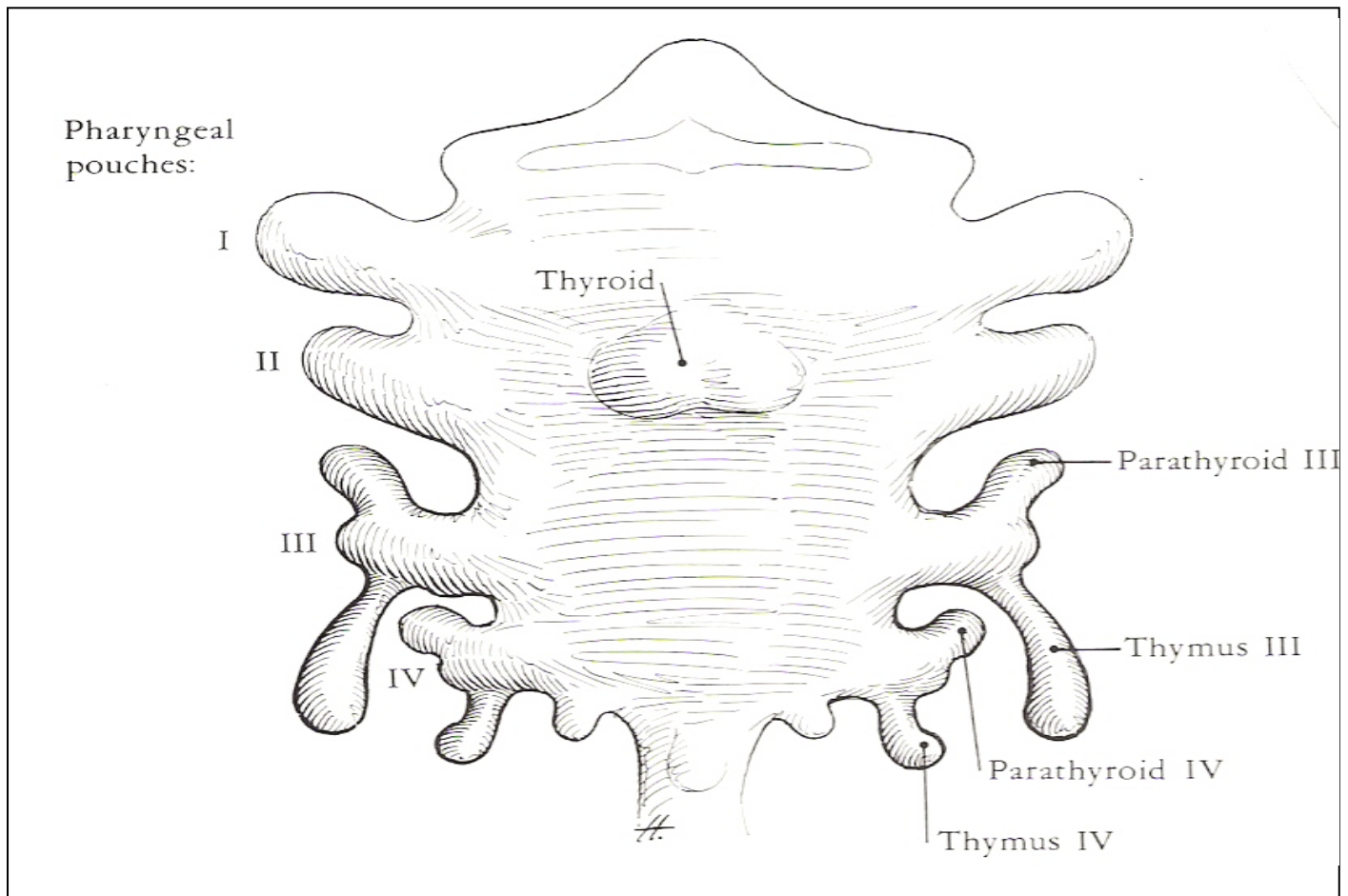


Figure-3 Embryology of the thymus gland from III to IV pharyngeal pouches. Note close proximity of site of differentiation of thyroid gland (II-III) and parathyroid glands (III-IV)

It is note worthy that the parathyroids begin their development about the same time from the same pouches. A caudal migration of epithelium occurs with further differentiation. Failure of this migration is seen in one of the immunologic deficiency disorders- thymic dysplasia. By the tenth week, the thymic epithelium is differentiated into a compact epithelial structure interlaced with a fibrous reticular network. The epithelial cells are secretory cells with a well-developed Golgi apparatus, a rough endoplasmic reticulum, and a large nucleus with multiple nucleoli. With further development, the thymus is infiltrated with precursor cells migrating from the liver and yolk sac during fetal life and bone marrow during adult life. Large lymphoblastoid cells first enter the subcapsular cortex and subsequently undergo further differentiation as they migrate through the different areas of the thymus. The clinical importance of the simultaneous embryogenesis of parathyroid glands and the thymus is seen in another of the immunologic deficiency disorders of man, the DiGeorge syndrome. Infants with this disorder are born not only lacking in thymic function but also without parathyroid glands. Thus they present with hypocalcaemia tetani in the newborn period and with subsequent failure of the development of cell mediated immunity.

After birth the role of the thymus continues to change. The changes in the size of the gland with age are shown in **Figure-4**. Relative to body size it is largest during fetal life and at birth weighs from 10 to 15 gm.

The gland continues to increase in size, reaching a maximum of 30 to 40 gm at puberty. This follows the same pattern of change that occurs in all lymphoid tissue during childhood. It is of interest that this pattern of growth parallels the sequential appearance of T and B cell function during maturation. Following adolescence, the gland begins to involute. The parallel continues in that lymphoid tissues and immunoglobulins also diminish with increasing age. In addition, the development of autoimmune phenomena and malignant disease increase with advancing age with a loss of T cell (e.g., suppressor) function. Thus the thymus and its associated lymphoid tissues and their products play a dynamic role from early embryogenesis throughout the life span of the individual.

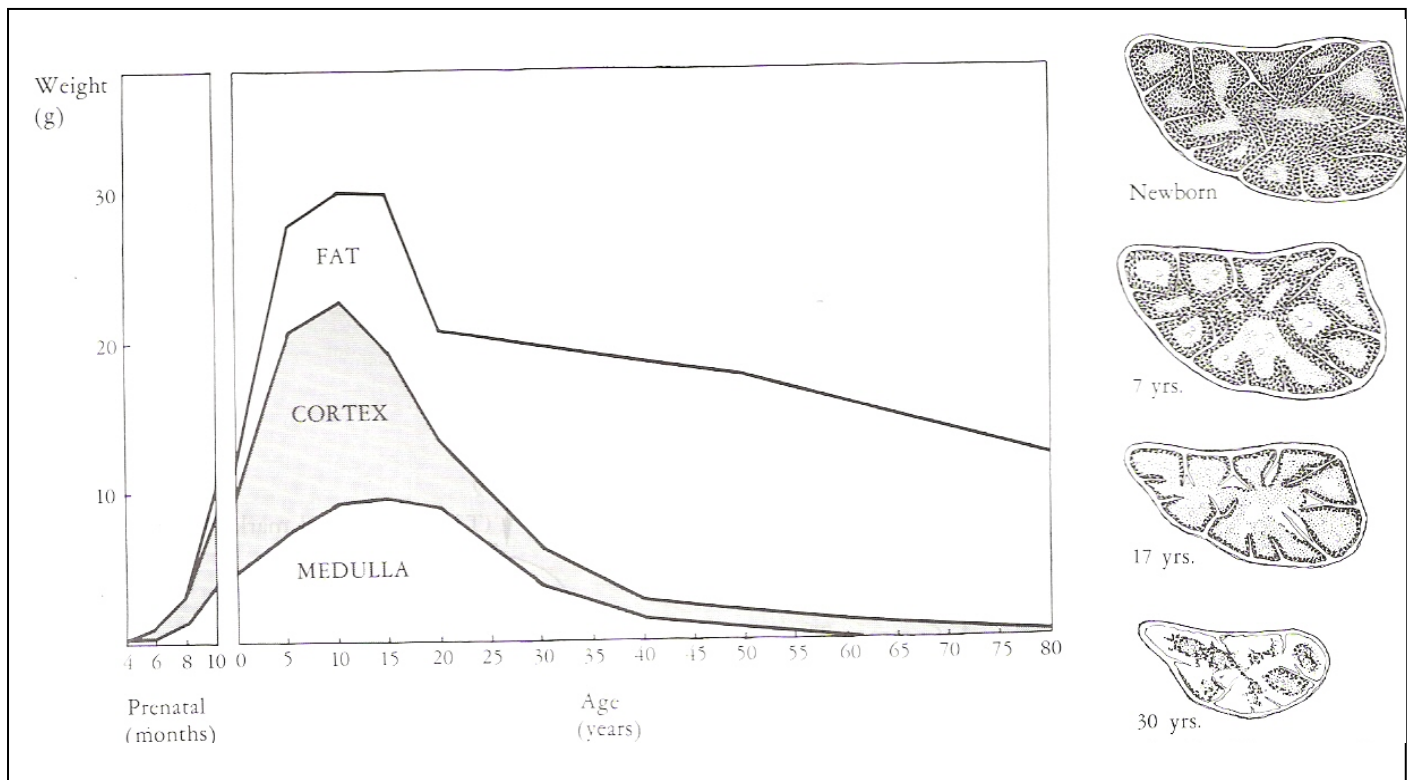


Figure-4 Schematic representation of changes in weight and composition of thymus gland with maturation, showing involution of the gland with age

The thymus thus appears to be equipped to maintain lymphopoiesis while segregated from antigen. This curious finding may be explained in part by the barrier that is made up of a continuous epithelium surrounding blood vessels in the cortex. This epithelial membrane forms a perivascular space between the capillary endothelium and the epithelial sheath. The barrier might prevent macromolecules in the blood stream from entering the substance of the thymus gland. Although macromolecules may be prevented from entering the epithelial barrier, lymphocytes produced within the cortex are capable of passing freely through this epithelium into the blood system, as in other anatomic sites (e.g., postcapillary venule of the lymph nodes) **Figure-5**. Thus the thymus may be viewed as a lymphoid organ, anatomically distinct, upon which all other peripheral lymphoid organs are dependent. It is an organ actively engaged in lymphopoiesis but indecent of antigenic stimulation. It appears important as a central lymphoid tissue essential for the development and maturation of peripheral lymphoid tissues. Two major functions have been attributed to the thymus: **(1)** that it acts by the elaboration of a hormone that expand peripheral lymphocyte populations in much the same way as erythropo9ietin expands erythrocyte populations, and **(2)** that it acts by direct seeding of peripheral lymphoid tissues with lymphocytes.

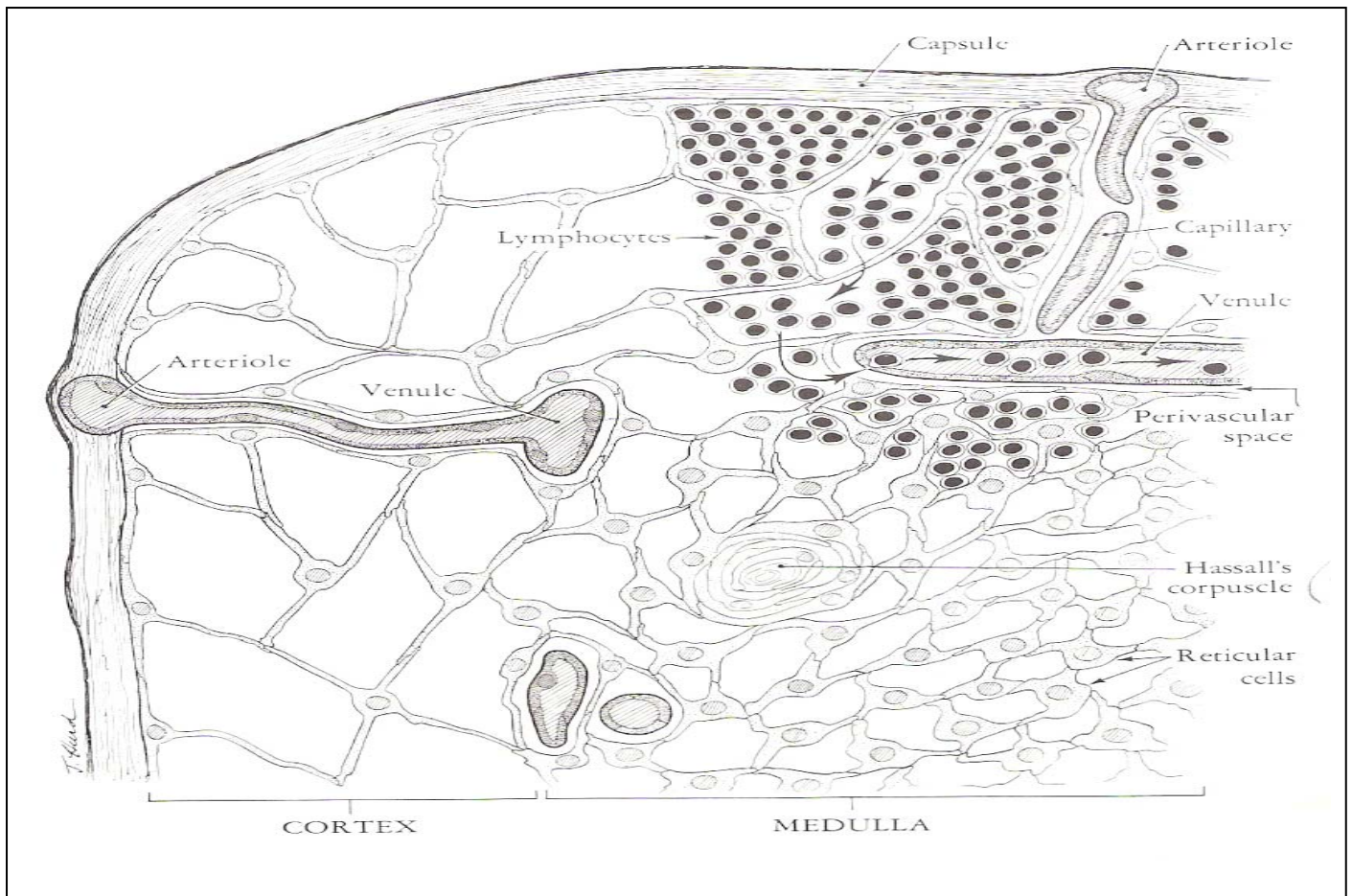


Figure-5 Schematic presentation of the perivascular epithelium surrounding blood vessels in the cortex, note the barrier provides by this sheath and the pathways of lymphocytes formed in the cortex into the blood vessels.

ORIGINS OF THYMUS CELL TYPES

The different thymic cell types are originated from different anatomical organs these are summarized in **Table-1**.

CELL TYPES	CELLULAR ORIGINS
Epithelium	Ectoderm of the third pharyngeal clefts
• Subcapsular cortex	Endoderm of the third pharyngeal pouches
• Cortex	Ectoderm of the third pharyngeal clefts
• Medulla	Epithelium
Thymic nurse cells	Bone marrow
Dendritic cells or interdigitating cells	Bone marrow
Macrophages	Yolk sac, fetal liver, bone marrow
Thymocyte	

Table-1 Illustrates the different cell types of thymus and their origins.

T-cell development occurs as thymocytes move from the cortex to medulla (**Figure-6**). T cells alter their phenotypes during maturation. T cells go through three stages for maturation, these are:

- A. Stage I (early) thymocytes.** These thymocytes express Cd7 together with jCD2 and Cd5. Proliferation markers such as the transferrin receptor CD71 and CD38 (a marker common to all early haemopoietic precursors) are also expressed at this stage. Note that none of the proliferation markers are T lineage-specific. However, the commitment of early thymocytes to become T cells is shown by the TCR β chain gene rearrangements, and by expression of the TCR-associated complex (CD3) in the cytoplasm but not on the membrane.
- B. Stage II (intermediate or common) thymocytes.** These account for around 85% of lymphoid cells in the thymus at any one time. They are characterized by the appearance of additional surface markers such as CD1, and by the coexpression of CD4 and CD8 on the same cell (such as those called "double positives"). Genes encoding the TCR α chain are rearranged in these intermediate thymocytes both chains of the $\alpha\beta$ receptor are expressed at low density on the cell surface in association with polypeptides of the CD3-antigen complex.
- C. Stage III (mature) thymocyte.** These show major phenotypic changes namely loss of CD1, presence on the cell membrane of CD3 associated with the high density $\alpha\beta$ TCR, and the distinction of two subsets of cells expressing either CD4 or CD8. The majority of thymocytes at this stage lack CD38 and the transferrin receptor, are virtually indistinguishable from mature, circulation T cells. All these express the receptor CD44, thought to be involved in migration and homing to peripheral lymphoid tissues> L-selection also develops at this time.

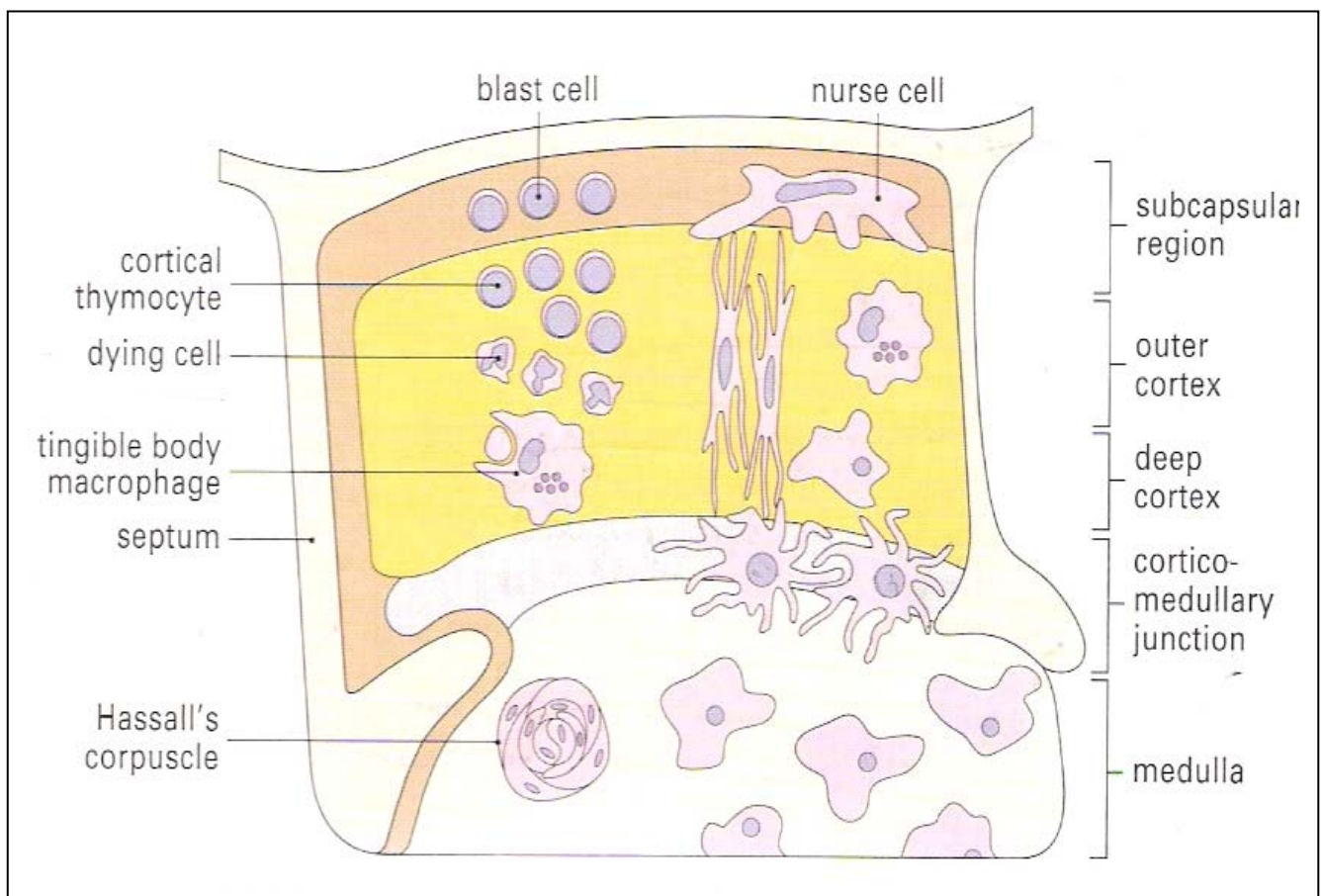


Figure-6 The cortex contains densely packed, dividing cortical thymocytes in a network of epithelial cells which extends into the medulla. The medulla contains fewer lymphocytes, but there are more bone-marrow derived antigen-presenting cells, both interdigitating cells and macrophages. There is a close association of the developing lymphocytes with epithelial cells and interdigitating cells, which are particularly numerous at the corticomedullary junction. The function of the whorled epithelial structures termed "Hassall's corpuscles" are unknown.

Precursor T cells begin to colonize the thymic anlage early during embryonic development. This begins at day 14 of embryonic age in mice and at the 7th to 8th week of gestation in humans. The rate of development of T cells within the thymus is greatest before puberty and declines sharply thereafter, although the number of mature T cells in the periphery does not show a similar reduction. The decline in the production of T cells also correlates with atrophy of the thymic stroma, a normal physiological condition known as thymic involution. Age related thymic involution is known as chronic involution and is distinct from involution caused by acute infection, stress, pregnancy, and lactation. In the aging involuted thymus, one can detect changes in tissue architecture, first with increases in the volume of connective tissue and perivascular spaces and later with the replacement of the above tissues with adipose tissue. However, even in the aged individual, a small thymic rudiment composed of epithelium and thymocytes remains identifiable

The development of the monoclonal antibodies that recognize one specific epitope of a molecule greatly facilitates the characterization and identification of cells at various stages of their differentiation. Monoclonal antibodies that recognize different epitopes of the same differentiation molecule are clustered together and designated as the cluster of differentiation (CD). The earliest precursor cells that arrive in the thymus lack most of the cell surface molecules that are readily detectable on mature T cells. When they arrive in the thymus, the precursor cells physically interact with thymic stromal cells, which then provide stimuli to selectively induce the expression of a group of specific cell surface molecules. In human the first T cell-specific molecule expressed in the thymus is CD1; in mice, CD2 and Thy-1 are expressed by the most immature T cells. These immature T cells do not express either CD4 or CD8 surface molecules and are commonly referred to as the double negative thymocytes. The double negative cells also do not express CD3 and thus are occasionally called the triple negative thymocytes. It was found recently that the earliest precursor T cells express a very low level of cell surface CD4. Thus the most immature thymocyte in the thymus is CD3⁻ CD4^{Lo} CD8⁻ that precedes the double negative stage. The CD3⁻ CD4^{Lo} CD8⁻ and the double negative thymocytes are found in the subcapsular cortex, where they undergo vigorous proliferation. In the next distinct stage of thymocyte maturation, thymocytes express both cell surface molecules CD4 and CD8 and are referred to as the double positive thymocytes; these thymocytes also begin to express the cell surface CD3 and TCR molecules.

The double positive thymocyte population is the largest thymocyte population and is responsible for the dense cellularity of the thymic cortex. In contrast to the double negative cells, the double positive cells do not proliferate and are inactive. In the next stage of T cell development, the double positive cells completely cease to express either CD4⁺ or CD8⁺ (**Table-2**).

THYMIC COMPARTMENTS	THYMOCYTE SUBSETS	STATUS OF TCR GENE REARRANGEMENT	
		α	β
Subcapsular cortex	CD3 ⁻ CD4 ^{Lo} CD8 ⁻	Germline or unarranged	Germline or unarranged
	↓ CD3 ⁻ CD4 ⁻ CD8 ⁻ ↓	Germline or unarranged	Rearranged
Cortex	CD3 ⁺ CD4 ⁺ CD8 ⁺ TCR ⁺	Germline or unarranged	Rearranged
Medulla	↓ CD3 ⁺ CD4 ⁺ TCR ⁺ Or CD3 ⁺ CD8 ⁺ TCR ⁺	Rearranged	Rearranged

Table-2 Compartmentalization of α : β T cell developmental stages in the thymus.

The mature CD4 T cells, the T-helper (Th) cells, provide helper functions and cooperate with B cells in the humoral immune response, while the CD8 cells, the cytotoxic T cells or CTLs, are responsible for recognizing foreign cells, as in foreign grafts, as well as virus-infected cells and are responsible for killing these cells. Thus, as the precursor cells traverse through the subcapsular cortex, the cortex, the corticomedullary junction, and the medulla, they interact with thymic stroma and are induced to develop and mature. The thymic anlage provides an inductive microenvironment that allows precursor T cells to undergo rapid expansion as well as successive and distinct stages of development that can be identified by the expression of cell surface molecules. The three main differentiation cell surface molecules are CD3, CD4, and CD8, and the T cell receptors (TCRs). Developing thymocytes at a specific stage of their maturation are found at a precise location within the thymus. Abnormal development of the thymic anlage results in failure of support for development of T cells and can be found in both mice and humans. In mice, the mutation in the nude locus results in an athymic mouse that also has no hair, the nude mouse. It is now known that mutation in the *when* gene, located on the mouse chromosome 11, is responsible for abnormal development of the thymic anlage. In the DiGeorge syndrome in human, an individual is born with a congenital thymic aplasia. In both condition, only T cell development is affected as B cell develop normally.

T CELL SELECTION IN THE THYMUS

POSITIVE AND NEGATIV SELECTION OF DEVELOPING T CELLS OCCURS IN THE THYMUS

In addition to providing an inductive microenvironment for precursor T cells to develop into mature T cells, the thymus executes two critical screening processes to select for useful, protective T cells (positive selection) and to eliminate irrelevant or potentially harmful autoreactive T cells (negative selection). Both selective processes take place at the double positive stage.

Positive selection

T cells recognize antigenic peptides only when presented by self-MHC molecules on APCs. If effect, T cells show "dual recognition" of both the antigenic peptides and the polymorphic part of the MHC molecules. (CD4, found on some subsets of T cells, also attaches to the class II molecules, but to the non-polymorphic portion). Positive selection (also called thymic education) ensures that only those TCRs with a moderate affinity for self-MHC are allowed to develop further. There is evidence that positive selection is mediated through thymic epithelial cells, acting as APCs. T cells displaying very high or very low receptors affinity for self-MHC undergo apoptosis and die in the cortex. Apoptosis is a pre-programmed "suicide" achieved by activating endogenous nucleases that cause DNA fragmentation.

Negative selection

Some of the positively selected T cells may have receptors that recognize self components other than self-MHC. These cells are deleted by a "negative selection" process, which occurs in the deeper cortex at the corticomedullary junction and in the medulla. The thymocytes interact with antigen, interdigitating cells and macrophages. Only thymocytes that fail to recognize self antigen are allowed to proceed. The rest undergo apoptosis and are destroyed. These, and all the other apoptotic cells generated in the thymus, are phagocytosed by dendritic body macrophages in the deep cortex. The existence of negative selection (also called central tolerance) has recently received strong experimental support from murine studies in which specific V β families are eliminated by certain endogenous superantigens during thymic development.

T cell at this stage of maturation (CD4⁺ or CD8⁺ TCR^{lo}) go on to express TCR at high density and lose either CD4 or CD8, becoming "single positive" mature thymocytes. These separate subsets of CD4⁺ and CD8⁺ cells possess specialized homing receptors, and exit to the T-cell areas of the peripheral lymphoid tissues where they function primarily as mature "helper" and cytotoxic" T cells respectively. Fewer than 5% of thymocytes leave the thymus. The rest die as the result of selection processes and failure to express antigen receptors (**Figure-9**).

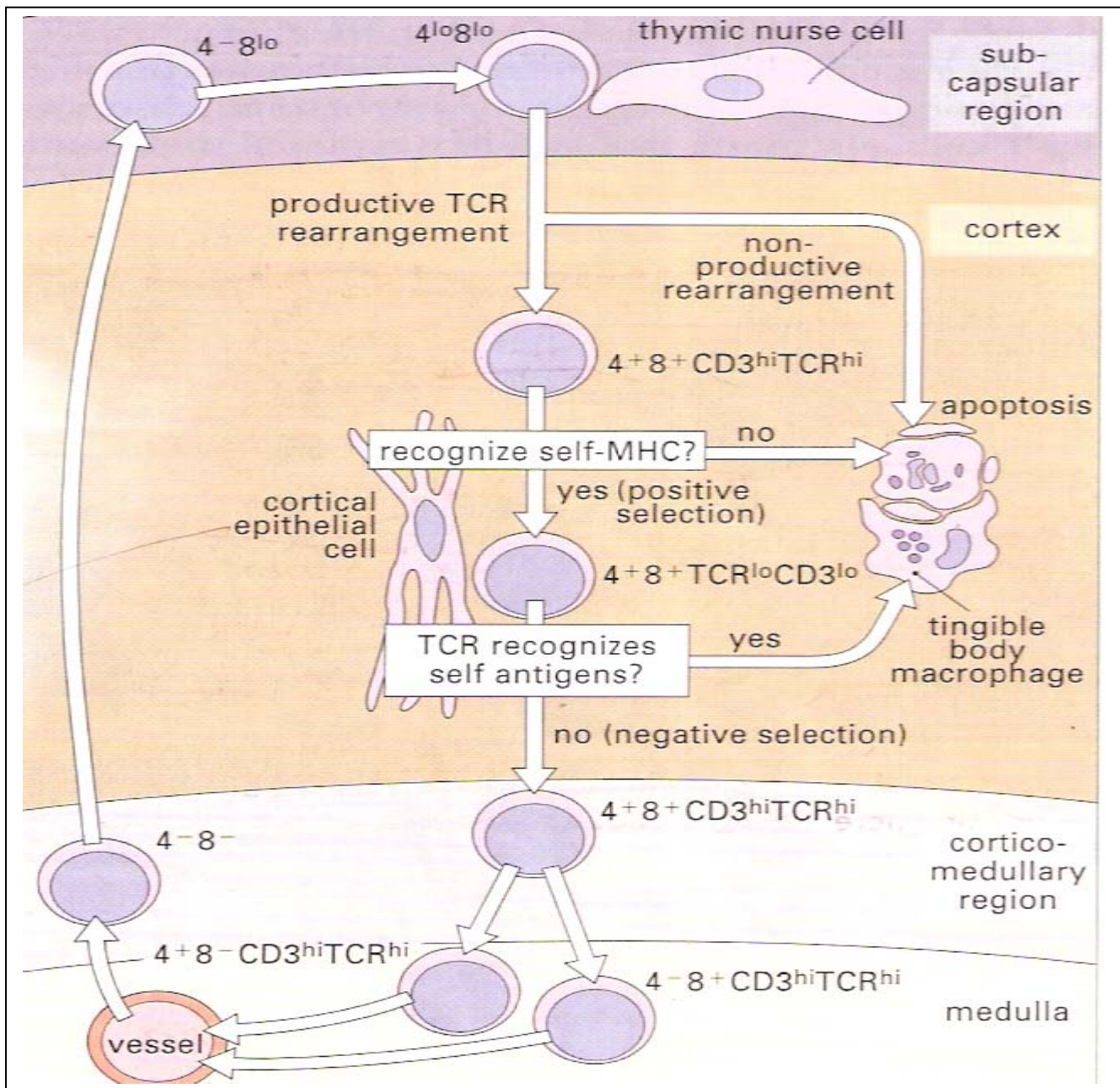


Figure-9 T-cell differentiation and negative and positive selection in the thymus, in this model pre-thymic T cells are attracted to and enter the thymic rudiment. They proliferate below the subcapsular region as large lymphoblast, which replicate and give rise to a pool of cells entering the differentiation pathway. Many of these cells are associated with epithelial thymic nurse cells (TNCs), although the significance of this interaction is still debated. Cells in this region first acquire jCD8 and then CD4 at low density. They also re-arrange their TCR genes and may express the products of these genes at low density on the cell surface > maturing cells move deeper into the cortex and adhere to cortical epithelial cells. These epithelial cells are elongated and branched, and thus provide a large surface area for contact with thymocytes. The TCRs on the thymocytes are exposed to epithelial MHC molecules through these contacts. This leads to positive selection. Those cells which are not selected undergo apoptosis and are phagocytosed by macrophages. There is an increased expression of CD3 TCR, CD4, and CD8 during thymocyte migration from the subcapsular region to the deeper cortex. Those TCRs with self reactivity are now deleted through contact with autoantigens presented by interdigitating cells and macrophages at corticomedullary junction0 a process called negative selection. Medullary epithelial cells might also contribute to this process. Following this stage, cells expressing either jCD4 or CD8 appear and exit to the periphery via specialized

vessels at the corticomedullary junction. (A process of negative selection may also occur in the cortex, leading to the elimination of cells whose TCRs have high affinity for self MHC. The generation of the T cell repertoire by the process of gene rearrangement and recombination is random. Since TCRs can only recognize antigenic peptide associated with MHC and presented by an antigen-presenting cell (APC), the selection for functional TCRs is dependent on the type of MHC expressed on APC. These arguments lay the foundation for the concept of MHC restriction.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) RESTRICTION

It has been proven that when T cells from strain A mice are given a choice to react with foreign antigen presented on APC of strain A or B, they will preferentially react with strain A APC and therefore are restricted by MHC type A. The concept of MHC restriction further separates the antigen recognition specificity of TCR expressed on T cells from the Ig expressed by B cells, whose ability to bind antigen does not require MHC restriction. In general, mature CD4 T cells are selected by MHC class II, while mature CD8 T cells are selected by MHC class I on the cortical thymic epithelium. Thus, MHC expressed by cortical thymic epithelium dictates the specificity of the positively selected TCR.

LYMPHOCYTE TRAFFICKING

T cells begin life in the bone marrow and are educated in the thymus. When they emerge from the thymus, virgin T cells express on their surfaces a mixture of cellular adhesion molecules to travel to any of the secondary lymphoid organs. For example, virgin T cells have a molecule called **L-selectin** on their surfaces that can bind to its adhesion partner, **GlyCAM-1**, which is found on the high endothelial venules of lymph nodes. Virgin T cells also express the integrin **$\alpha 4\beta 7$** , whose adhesion partner, **MadCAM-1**, is found on the high endothelial venules of Peyer's patches and the lymph nodes that drain the tissues around the intestines (the mesenteric lymph nodes). Thus this integrin works as a gate to the gut region. Because of these adhesion molecules, inexperienced T cells are encouraged to circulate through all of the secondary lymphoid organs. In these organs, they pass through fields of antigen presenting cells in the T cell areas. If they are not activated, they re-enter the blood either via the lymph or directly (in the case of the spleen), and continue to recirculate, making a complete circuit every twelve to twenty four hours. If a T cell does not encounter its cognate antigen presented by an MHC molecule, it eventually dies, lonely and unsatisfied, by apoptosis. In contrast, those lucky T cells that do encounter their antigen are activated in the secondary lymphoid organs. These are now "experienced" T cells.

Experienced T cells decrease the expression of certain surface adhesion molecules while increase the expression of other specific adhesion molecules on their surfaces during the activation. This process is not random; the cellular adhesion molecules that activated T cells express depend on where these T cells were activated. For example, T cells activated in a Peyer's patch will express high levels of **$\alpha 4\beta 7$** (the gut specific integrin), and low levels of **L-selectin** (the more general, high endothelial venule adhesion molecule). As a result, these T cells tend to return to Peyer's patches. Thus, when activated T cells recirculate, they usually exit the blood and re-enter the same type of secondary lymphoid organ in which they originally encountered antigen. This restricted traffic pattern makes perfect sense. After all, there is no use having T cells recirculate to the lymph node behind your knee if your lower intestine is inflamed, because you ate some bad food, certainly not. You want those T cells to get right back to the gut to be re-stimulated and to provide help. So by equipping activated T cells with restricted adhesion molecules the immune system insured that the T cells go where they are needed, be it to Peyer's patches, lymph node, or tonsils. T cells also carry some specific adhesion molecules that allow them to exit the blood at sites of inflammation. These T cells use the same "roll, sniff, stop, exit" technique that neutrophils use to squeeze between the endothelial cells that line blood vessels and to exit the blood into inflamed tissues. For example, T cells that gained their experience in the mucosa express the integrin molecule **$\alpha E\beta 7$** , which just happens to have as its adhesion partner an additional molecule that is expressed on inflamed mucosal blood vessels. So adhesion molecules on the surfaces of experienced T cells allow them to leave the blood and enter tissues exactly where the battle is going on.

In summary, naïve T cells have adhesion molecules that allow them to visit all secondary lymphoid organs, but not sites of inflammation. This traffic pattern brings the entire collection virgin T cells into contact (in the secondary lymphoid organs) with invaders that may have entered the body at any point, and greatly increases the probability that the virgin T cells will be activated. The reason that virgin T cells don't carry adhesion molecules to battle sites is that they couldn't do anything there anyway they must be activated first.

In contrast to virgin T cells, experienced T cells have restricted adhesion molecules that encourage them to return to the same type of secondary lymphoid organ as the one in which they gained their experience. By recirculating preferentially to the kind of tissue in which they first encountered antigen, T cells are more likely to be re-stimulated or to find CTLs and B cells that have encountered same invader and need their help. In addition, activated Th cells and CTLs have adhesion molecules that allow them to exit the blood at sites of infection, so that CTLs can kill infected cells and Th cells can provide appropriate cytokines to direct the battle. This marvelous system of cellular adhesion molecules insures delivery to the right weapons to the sites where they are needed.

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