T-CELL LYMPHOPOIESIS

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OVERVIEW

Pluripotent stem cells (in bone marrow) → Lymphoid progenitor cells → Lymphoid stem cells →

Lymphoid stem cells (in blood) → Lymphoid stem cells (in thymus cortex) → Double negative lymphoid cells → Double positive lymphoid cells → T-cells (CD8+ or CD4+)

PROCESS

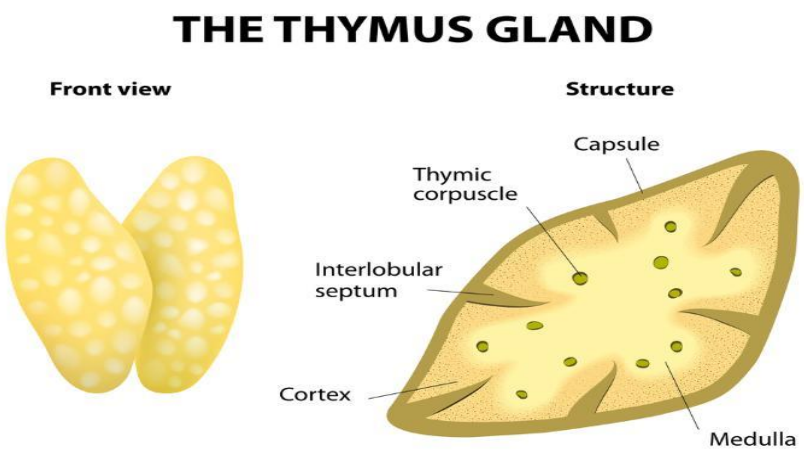
Origin of T-cells is from pluri-potent stem cells of bone marrow. The lymphoid stem cells then move to blood. These lymphoid stem cells are then attracted to the thymus by a chemical substance produced by thymus called thymotaxin.

THYMUS

Thymus is situated behind the sternum and infront of trachea.

Embryologically, thymus has double origin. Part of thymus develops from endoderm and a part of it from mesoderm. The endodermal portion of thymus develops from 3rd and 4th pharyngeal pouches of endoderm. (From same pouches, parathyroid glands also develop). Mesodermal origin of thymus is from bone marrow.

Thymus is capsulated structure. The **capsule** is made of connective tissue. **Septa** arises from capsule, which are directed inwards. The outer region of thymus is called **cortex** while the inner region is called **medulla**.



The lymphoid stem cells enter the cortex region and is matured inside the cortex. Once they are fully developed, they move to medulla.

The epithelial cells in the cortex produce **thymotaxin**, which is chemotactic for the lymphoid stem cells. The cortical epithelial cells also produce thymopoietin, serum thymic factor, thymosin and thymolin.

Lymphocytes are very tightly packed in cortex while in medulla they are far apart. In the medulla, special type of epithelial cells aggregate in concentric circles and are called **Hassals corpuscles**. With age, these Hassals corpuscles are keratinized.

In the cortex, there is **blood thymus barrier** consisting of tight junctions of endothelial cells, basal lamina from capillary and epithelial cell processes from cortex. The blood thymus barrier is a barrier separating T-cells from blood and cortical capillaries present in the cortex of the thymus. The blood–thymus barrier regulates exchange of substances between the circulatory system and thymus, providing a sequestered environment for immature T cells to develop. The barrier also prevents the immature T cells from contacting foreign antigens.

DEVELOPMENT OF LYMPHOID STEM CELLS IN THYMUS CORTEX

Lymphoid stem cells, initially in the thymus do not have any surface molecules (e.g. CD4, CD8) and hence, called double negative cells (lacking CD4 and CD8).

Epithelial cells in thymus called **thymic nurse cells** (TNCs) produce thymosin, thymopoietin and serum thymic factor. These soluble molecules help in

maturation of lymphoid stem cells. They activate certain genes called **RAG-1** and **RAG-2** and produce special type of enzymes called **recombinases** in lymphoiod stem cells, which acts on variable region of TCR genes, and produce **T-cell-receptors (TCRs**). The different TCRs produced on different cells may have different variable regions but on a single cell, only one type of TCRs are found. In this way, different T-cells recognize different antigens. The lymphoid stem cells, which develops surface TCRs, are called **pre T-cells**.

Soluble products from thymic nurse cells then reach pre T-cell and activate genes for production of CD4 and CD8 proteins and both are expressed on surface. These cells are called Double positive cells (CD4+ and CD8+).

The thymus cells then produce MHC-molecules (MHC-1 and MHC-2). CD4 molecules recognize MHC-2 molecules while CD8 molecules recognize MHC-1 molecules. The cells which are not recognized by MHC molecules are killed by **Fas receptors/ligands** expressed by thymic nurse cells. The other cells which are recognized by MHC molecules are said to be **positively selected cells**.

The nurse cells then produce other self-antigens. Some positively selected cells will recognize these self antigens while some will not. Any cell which recognize these antigens will react with our own antigens in future and will attack our own tissue thus become a source of auto-immune reaction. Such type of cells are killed by Fas ligands expressed by nurse cells. Those lymphocytes which do not recognize self-antigens are allowed to proceed further.

The nurse cells in the cortical-medullary junction express MHC-1 and MHC-2 molecules. If MHC-1 touches the cell first, it will activate CD8 producing gene and turn off the gene for CD4. If MHC-2 touches the cell, CD4 gene will be activated forever and CD8 gene will be turned off. So the double positive cells are converted into single positive cells, now called T-cells, in the cortical-medullary junction.

These T-cells will move to blood and finally to the paracortical areas of lymph nodes and PALS (Periarteriolar lymphoid sheaths) of spleen.

TYPES OF T-CELLS

1. Helper T-cells (CD4+)
2. Cytotoxic T-cells (CD8+)

3. Regulatory/ suppressor T-cells (CD4+ or CD8+)

T-cells to B-cells ration (T:B) = 3:1

AN OVERVIEW OF LYMPHOCYTES

1. B-lymphocytes
2. T-lymphocytes
3. NK cells

B-CELLS

For most mature B cells the key markers include IgM and CD19, a protein receptor for antigens. On activation, B cells produce plasma cells.

HELPER T-CELLS

All helper T-cells have TCR+, CD3+ and CD4+.

If interleukin-4 acts on helper T-cells, TH2 is produced. If interleukin-12 acts on helper T-cells, TH1 is produced.

Both TH1 and TH2 produce interleukin-2. These interleukin-2 acts on TH1 and TH2 while some may help stimulate cytotoxic T-cells.

TH2 produce interleukin-4 and interleukin-5. Interleukin-4 is a B-cell growth factor while interleukin-5 is B-cell differentiation factor.

TH1 produce tumor necrotic factors and gamma interferon. Both acts on macrophages and convert them into super active macrophages or modified epithelioid cell macrophages.

TH2 with B cells and plasma cells are components of humoral immunity.

TH1, macrophages and cytotoxic T-cells are components of cell mediated immunity.

NK CELLS

- Non-specific in their killing action
- Part of innate immune system
- Functions:

1. NK cells destroy cells not expressing MHC-1 antigens (include cells infected by virus, tumor cells, transplanted tissue cells)

2. NK cells have receptors for mica. Mica is a protein which may be expressed on some tumor cells. So whenever NK cells recognize mica, they induce cell apoptosis and kill the cell.
3. NK cells have receptors for IgG and kills IgG-coated target cells.