8. T Cell Development

LEARNING OBJECTIVES:

1. Become familiar with the architecture of the thymus and the role of different cellular compartments in the generation of T cells.
2. Understand the coordinated process of TCR rearrangement and T cell development.
3. Understand the mechanisms that mediate the generation of alpha-beta and gamma-delta T cells.
4. Understand the mechanisms and importance of positive and negative selection of developing thymocytes for the generation of functional T-cells.

SUMMARY

1. The thymus is the organ responsible for T cell development. Hematopoietic precursors interact with the thymic stroma and develop in a coordinated process that involves: (i) rearrangement of T cell receptors (TCRs), (ii) cell proliferation, (iii) selection of immune competent cells and (iv) ablation of auto-reactive clones.

2. Rearrangement of gamma-delta TCRs drives gamma-delta T-cell fate. Rearrangement at the gamma, delta, and beta TCR gene loci occurs simultaneously during double negative (DN) stages of T cell development.

3. Successful TCR beta rearrangement generates a preTCR complex, which signals proliferation and differentiation of DN cells into double positive (DP) cells.

4. PreTCR expansion is followed by rearrangement of the TCR alpha and positive selection.

5. Positive selection occurs in the cortex of the thymus and involves the interaction of the TCR with MHC complexes expressing self antigens. If the interaction is successful the cell receives a survival signal (positive selection) and matures to become a CD8 (if a TCR-MHC-class I interaction) or CD4 (if a TCR-MHC class II interaction) single positive cell. Most cells fail to express successful TCRs and die by apoptosis.

6. Negative selection occurs primarily in the thymic medulla via interaction of TCRs with MHC complexes expressing self antigens in the surface of dendritic cells and macrophages. A broad repertoire of self antigens is expressed in the thymus. Cells with TCRs showing strong interaction with self antigen-containing MHCs are eliminated (negative selection) by apoptosis.