T CELL SELECTION, continued

**Negative Selection**
- Thymocytes die by apoptosis during the double-positive stage if they have affinity for self-MHC (or MHC+self-peptide) that is too high. (Fig. 7.18)
  
  Prevents escape of autoreactive mature T cells into periphery

- The ones that survive positive and negative selection mature to express higher levels of TCR and stop expressing either CD4 or CD8 to become single-positive (SP) cells. CD4+ cells = helper T cells; CD8+ cells = CTL.

**Source of self-peptides**
1. Resident cells in the thymus: epithelial cells, macrophages, thymocytes themselves
2. Bone-marrow-derived macrophages and DC in the medulla and corticomedullary junction. These present ubiquitously expressed self Ag
3. Tissue-specific Ag are produced by a subset of medullary epithelial cells
   -- requires expression of a transcription factor called AIRE
   -- mutations in AIRE cause fatal systemic autoimmune disease called APECED

**Allorecognition**
- during T cell development, thymocytes with TCR that have high affinity for self-MHC/peptides expressed by healthy cells are killed off by clonal deletion (negative selection)
- thymocytes with TCR that has high affinity for another individual’s MHC/peptide on healthy cells are not subject to clonal deletion, and could become mature T cell. The foreign MHC is called allogeneic.
- experimentally it has been shown that 1-10% of an individuals T cells can react with APC’s with foreign MHC, regardless of presence of pathogenic peptide; this is called allorecognition (recognition of allelic difference). The T cell is called alloreactive.
- this is why transplants are rejected unless you find a good MHC match

**Review of thymocyte development and location of events and stages** (Fig. 7.21)

**Cortex**
* Most T cell development happens in the cortex.
* Very outer cortex: DN thymocytes proliferate here.
* Deeper cortex: DP cells.
* Epithelial cells (non-hematopoietic) in the stroma in the inner cortex have long branching processes that express MHC class I and II - the site of positive selection.
* Negative selection involves both cortical epithelial cells, and the dendritic cells and macrophages (of hematopoietic origin) that are abundant at the corticomedullary junction → since they arrive from the blood they can bring self-Ag from distant sites

**Medulla**
* Relatively fewer thymocytes.
* Only mature single-positive thymocytes are found in the medulla. They are SP cells that resemble mature T cells. These may be the mature thymocytes on their way out of the thymus or a specialized subset of T cells that are protecting the thymus.
Central tolerance vs. Peripheral tolerance
-- central tolerance refers to negative selection of autoreactive thymocytes
-- peripheral tolerance refers to other mechanisms that act in the periphery

Regulatory T cells
-- a subset of CD4 T cells that is crucial for peripheral tolerance
-- do not function as helper cells for macrophages or B cells
-- TCRs are autoreactive for self-MHC/peptide
-- they suppress the activation of naïve T cells that are in contact with the same APC (Fig. 7.19)
-- they can develop in the thymus as an alternate fate of thymocytes with strong affinity for self-MHC; mechanisms still being investigated
-- can be induced in the periphery from naïve CD4 T cells under certain conditions
-- can be distinguished by expression of the receptor CD25 and the transcription factor FoxP3
-- FoxP3 is required for regulatory T cell function, and mutations in FoxP3 cause fatal autoimmune disease called IPEX

Preview of T cell activation
-- naïve T cells recognize foreign peptide presented by MHC on mature DCs
-- activated T cells proliferate and differentiate, acquiring new effector functions
-- naïve CD8 cells become cytotoxic T cells
-- naïve CD4 cells become helper T cells of different types, depending partly on cytokines in their environment