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T Cell Development

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- T cell development in Thymus
  - Common precursor for αβ and γδ T cells
    - Bone marrow derived
    - Migrates to thymus
  - Once mature, T cells leave thymus to reside in secondary lymphoid organs such as spleen, lymph nodes and GALT
  - Thymus
    - Thymocytes = developing T cells
    - Thymic stroma epithelial cells
    - Cortex is densely packed
      - Macrophages
      - Site of beginning of T cell maturation --> move to medulla as they mature
    - Medulla is loosely packed
      - Dendritic cells concentrated at jxn
      - Macrophages
    - DiGeorge's is lack of thymus --> severe immunodeficiency
    - Most active in early life; disappears by 30
    - Thymectomy does not result in immunodeficiency
- Early T Cell Development
  - Early T cells do not express CD4 or CD8 co-receptors (double-negatives)
    - Mature through CD44+CD25- --> CD44+CD25+ --> CD44lowCD25+
    - CD25 is a chain of the IL-2R
    - CD44lowCD25+ rearrangement of β, γ, δ genes initiated
  - αβ vs. γδ first commitment
    - If γδ rearranges first successfully --> committed to γδ lineage
    - More commonly, β rearrangement first and expression of TCRβ at cell surface complex w/ pre-T cell receptor α chain (invariant, non-singaling)
    - Rearrangement at TCRβ locus has second chance due to second locus
  - Signaling from pTα
    - Prevents further rearrangement of TCR genes
    - Proliferative burst initiated --> CD4 and CD8 both expressed (double positive)
    - Following burst, TCR rearrangement at TCRα, γ, δ loci
  - αβ vs. γδ second commitment
    - If γδ rearranges successfully --> committed to γδ lineage
    - More commonly, α rearrangement first and expression of αβ TCR and diverted away from γδ lineage
  - Rearrangement of α
    - Productive rearrangement does not necessarily lead to cessation of additional rearrangement on the same or homologous chromosome
  - γδ T cells
    - TCRγδ also generated in separate pathway very early in embryonic development
    - Early cells populate repro/GI tracts and skin
    - Later in development, αβ predominate and all the T cells produced populate all peripheral lymphoid organs
    - γδ do not recognize MHC/peptide complexes; fxn unknown
    - Successful rearrangement is complete development
- Positive Selection
  - Enough different TCRαβ receptors are produced during T cell development to allow recognition of

each of the different MHC molecules that occur in the population in combination w/ peptide
    - Only those T cells that have TCRs w/ specificity for self MHC plus peptide are allowed to mature further
    - Mediated by epithelial cells in cortex which present class I and II w/ peptide
    - Majority of T cells not selected and undergo apoptosis
    - Double positive thymocytes mature into either CD4 or CD8 depending on TCR MHC specificity
        - Stochastic - random loss then binding to CD4/8, if binds T cell survives
        - Instructional - CD4/8 engages to MHC and directs loss of CD8/4 (more accepted theory)
    - Recombination at TCRα is turned off when T cell expresses a TCR that can be positively selected
        - Mechanism allows the developing T cell multiple attempts at generating TCR that recognize self MHC
- Negative selection
    - Many developing cells express TCR w/ affinity for self MHC+self peptide
        - If allowed to mature and enter circulation, they will cause autoimmune diseases
    - Mediated by dendritic cells/macrophages in medulla of thymus
    - Different signals must be given or signals must be received differently than positive selection - we don't know what the differences are
    - Tregs - TCR-expressing T cells that arise in thymus in response to self peptide +MHC
        - Major role as negative regulators of autoimmune T cell responses in peripheral immune system
- Development of Mature T Cells
    - Single positive T cells that have gone through all of the processes above leave thymus and go to secondary lymphoid organs
    - Mature T cells flow btwn those organs and circulation until they encounter foreign antigens
    - Antigenic challenge of CD4/8 --> T cell differentiation to aid in removal of antigen from host
- BLS and Thymic Selection
    - TAP deficiency --> class I deficiency; CIITA deficiency --> class II deficiency
    - Can treat by irradiating and chemo then transplant bone marrow
    - b/c in thymus, thymocytes are donor derived but selected on recipient HLA allotype
        - Circulating T cells restricted by recipient allotypes
        - APCs present antigens on donor HLA allotypes
        - No response
    - Therefore, successful transplantation requires at least one common class I and class II allele
- T Cell leukemias and thymic selection
    - Intermediate T cells are highly subject to cell death and therefore rarely become leukemias
    - Most T cell leukemias develop from early T cell progenitors or mature T cells