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T Cell Antigen Receptor

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- TCR Structure
  - Membrane anchored heterodimeric glycoprotein (α/β chains)
  - Both chains have V and C domains
    - Structurally related to V/C domains of Ig (β-pleated)
    - V domain involved in antigen binding
      - Three HV regions/chain = CDR 1-3
      - Located in loops
      - Directly involved w/ antigen binding
  - Short cytoplasmic tails
  - Overall similarity of TCR to Fab fragment of antibodies
  - Many different α/β chains expressed w/in a single individual
  - Each T cell expresses just one α/β chain --> clonally distributed
- TCR Genes
  - Assembled by somatic DNA recombination during T cell development in thymus
    - No somatic hypermutation or isotype switching
    - Never secreted
  - SCID
    - Loss of T/B cell function
    - Deficient expression of RAGs involved in VDJ joining
  - Omenn's syndrome
    - Loss of T and B cell fxn; B cells more severly affected
    - Caused by missense RAG mutations resulting in reduced activity
  - α gene
    - Encoded by rearranged V and J gene segments
    - Random recombination
    - RNA splicing fuses VJ to C
  - β gene
    - V, D, J gene segments
    - Single cluster of V genes, two clusters of D, J, C genes
    - D to J joining occurs first followed by recombination to any of a large number of V genes
    - RNA splicing fuses VDJ to C
  - Generation of TCR Diversity
    - Multiple Vα/β - CDR1,2,3
    - Multiple Jα/β - CDR3
    - Combinatorial V-J joining/V-D-J - CDR3
    - N-nucleotide addition at VJ/VDJ jxns - CDR3
- TCR Complex
  - Found w/ CD3 and TCRζ transmembrane proteins - do not differ btwn receptors
  - Three CD3 proteins: γ, δ, ε form heterodimers that associate w/ TCR
    - ε-δ
    - ε-γ
  - CD3δ and ε required for transport of TCR to cell surface
  - ζchain associates w/ TCR as homodimer
  - CD3 and ζchain relay signals from TCR to cytoplasm
    - Contain ITAMs (tyrosine) that get phosphorylated to trigger intracellular signaling cascades
- T Cell Antigen Recognition
  - Peptide fragments of antigens on surface of other cells in complex w/ MHC molecules

    - MHC restriction
        - TCR recognizes only the right MHC and right antigen
        - Learned w/ development
    - MHC I
        - Has α1,2,3 and β2 microglobulin
        - CD8 (killer) T cells recognize + peptide
        - Cell cytosol
    - MHC II
        - Has α1,2, β1,2 domains
        - w/ peptide, recognized by CD4 (helper)
    - CD4/CD8 interaction sites distinct from TCR interaction sites
        - TCR and CD4 or CD8 are capable of recognizing the same MHC/peptide complex simultaneously
        - CD4 and CD8 facilitate signal transduction
- TCR γ-δ receptor
    - Minority of T cells
    - Genes similarly organized to α/β genes
    - Assembled by somatic DNA recombination
    - δ locus embedded within α gene (deleted when α rearrangements occur)
    - γ locus on separate chromosome