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T Cell Antigen Receptor

Wednesday, February 13, 2008

11:00 AM

- 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 severely 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 $V\alpha/\beta$ - CDR1,2,3
 - Multiple $J\alpha/\beta$ - CDR3
 - Combinatorial V-J joining/V-D-J - CDR3
 - N-nucleotide addition at VJ/VDJ jxns - CDR3
- TCR Complex
 - Found w/ CD3 and TCR ζ transmembrane proteins - do not differ btwn receptors
 - Three CD3 proteins: γ , δ , ϵ form heterodimers that associate w/ TCR
 - ϵ - δ
 - ϵ - γ
 - CD3 δ and ϵ required for transport of TCR to cell surface
 - ζ chain associates w/ TCR as homodimer
 - CD3 and ζ chain 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 $\alpha 1,2,3$ and $\beta 2$ microglobulin
 - CD8 (killer) T cells recognize + peptide
 - Cell cytosol
- MHC II
 - Has $\alpha 1,2$, $\beta 1,2$ 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