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Processing and Presentation of Antigens for TCR Recognition and Myeloma Small Group

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- MHC Class I Pathway
  - Characteristics
    - Peptides presented to CD8 T cells in complex w/ MHC I
    - Peptide fragments usually from intracellular source like viral proteins
    - Function is to alert CD8 T cells to an ongoing viral infection
    - All nucleated cells can become infected w/ virus and therefore class I expressed on all nucleated cells
  - Structure of MHC I
    - Transmembrane heavy (α chain) non-covalently complexed by β2
    - α chain has variable sequence; β2 is invariant
    - α chain has 3 separate domains (1-3)
    - α1 and 2 domains are involved in peptide binding
    - α3 and β2 domains are immunoglobulin like supports for α1/2
  - Peptide binding
    - Binding site are deep grooves on molecule surface
    - Non-covalent binding
    - Single peptide can bind many different peptides
    - Ends of peptide grasped by pockets at ends of groove
    - Constraint upon peptide length (8-10 residues)
    - Additional general sequence requirements may be filled, but peptide may still not bind
  - Processing and Presentation
    - Peptides generated from proteins in cytosol by proteasome
    - Peptides transported into ER lumen by TAP (selective for peptides able to bind to class I)
      - Bare lymphocyte syndrome results from TAP deficiency
      - Patients don't express fxn'l TAP and little class I at surface
      - Highly susceptible to viral infections
    - Newly synthesized class I heavy chain and β2 microglobulin are translocated to ER
      - Calnexin assists in folding and prevents exit from ER
      - β2 interaction causes calnexin to dissociate and calreticulin associates
      - Tapasin positions class I to TAP
    - Peptide binding results in completion of folding, release from calreticulin, tapasin
    - Transport of vesicle containing peptide-class I complex to cell surface via golgi
    - Binding of peptide required for transport to cell surface
    - Viruses (HIV) have evolved mechanisms to interfere w/ processing/presentation
    - Processing and presentation occurs continuously in absence of infection
  - TCR Interaction
    - CD8 = cytotoxic T cells recognize class I-peptide complex
      - CD8 binds α3 domain of class I heavy chain
    - TCR binds to both peptide and parts of MHC molecule
    - Sits diagonally and symmetrically across the complex
    - CDRs 1 and 2 of Vα and Vβ contact helical regions of α1/2 of heavy chain
    - CRD3s of Vα/β contact peptide
- MHC Class II Pathway
  - Characteristics
    - Antigens derived from extracellular sources
    - Peptide-class Ii complexes recognized by CD4 T cells
    - Fxn of class II is to alert CD4 T cells to presence of extracellular infections

        - Only expressed on professional antigen presenting cells (m'phages, B and dendritic cells)
    - Structure
        - Comprises of two non-covalently bound transmembrane chain (α and β)
        - Both chains have variable sequences
        - Two domains/chain
            - 1 domains similar and involved in peptide binding
            - 2 domains Ig-like support 1 domains
    - Peptide binding
        - Ends of peptide not grasped by pockets at end of groove
        - Peptides bound are longer and more variable (13-25 residues)
    - Processing and Presentation
        - Antigen uptake via endo/phagocytosis
        - Vesicle becomes fused w/ lysosome
        - Phagolysosome breaks down protein into framgents
        - Vesicles containing class II bud-off golgi and fuse w/ phagolysosome
            - Newly synthesized class II α and β chains assemble in ER and bind to invariant chain
            - Invariant chain blocks peptide binding to class II in ER and aids in transport to vesicles
            - In early vesicle, proteases (cathepsin L) break invariant chain --> CLIP
            - HLA-DM removes CLIP
        - Peptides associate w/ class II vesicles
        - Translocation to cell surface
    - TCR Interaction
        - TCR binds to both peptide and parts of class II
        - Does not interact symetrically
        - CDRs 1 and 2 of Vα make stronger contact than those of Vβ
- Bacterial Superantigen
    - Toxins that bind to MHC and TCR fundamentally different way
    - Does not require processing
    - Involves distinct binding sites on MHC and TCR molecules
    - Mimic signal delivered by MHC peptide
    - Large number of T cells activated by superantigens --> massive T cell cytokine secretion --> shock
- Induction of MHC
    - Expression increased by inflammatory cytokines, esp interferons
    - Increased expression results in increased immune system activation directed toward elimination of infectious agent
- Myeloma Small Group
    - Use ELISA testing w/ IgG1-4 antibodies to verify monoclonality; can sequence to get exact clone
    - Sequencing
        - Bence-Jones (light chains in urine) will be all one light chain
        - Serum will show a dominance of one light chain but not clear sequence
        - Normal individual will not show any particular sequence
    - Bone deformities
        - Plasma cells accumulate in bone marrow --> physical mass
        - Plasma cells also release enzymes that break down bone
        - Bone marrow biopsy shows lots of plasma cells
        - Anemia due to competition from plasma cells --> don't produce enough RBCs