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

Thursday, February 14, 2008  
11:00 AM

- 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 ( $\alpha$  chain) non-covalently complexed by  $\beta 2$
    - $\alpha$  chain has variable sequence;  $\beta 2$  is invariant
    - $\alpha$  chain has 3 separate domains (1-3)
    - $\alpha 1$  and 2 domains are involved in peptide binding
    - $\alpha 3$  and  $\beta 2$  domains are immunoglobulin like supports for  $\alpha 1/2$
  - 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  $\beta 2$  microglobulin are translocated to ER
      - Calnexin assists in folding and prevents exit from ER
      - $\beta 2$  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  $\alpha 3$  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  $V\alpha$  and  $V\beta$  contact helical regions of  $\alpha 1/2$  of heavy chain
    - CRD3s of  $V\alpha/\beta$  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 ( $\alpha$  and  $\beta$ )
  - 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 fragments
  - Vesicles containing class II bud-off golgi and fuse w/ phagolysosome
    - Newly synthesized class II  $\alpha$  and  $\beta$  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  $V\alpha$  make stronger contact than those of  $V\beta$
- 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