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T Cell Effector Function

Monday, February 18, 2008
10:00 AM

- T cell-mediated immunity
  - Following activation, most T cells leave secondary lymphoid organ
    - Th2 cells remain
    - Effector fxn mediated by various effector molecules
    - Effector fxn triggered by MHC/peptide binding
  - T Cell Effectors
    - Change in types of cell surface adhesion molecule expressed
    - L-Selectin turned-off and cells cease to recirculate btwn secondary lymphoid organs
    - Expression of VLA-4 integrin turned-on to allow T cell binding to vascular endothelium and access to extracellular space where infection might be focused
    - Expression of LFA-1 and CD2 increased
    - Upon recognition of specific MHC/peptide complexes, integrin avidity increased to allow stable association w/ tgts
    - Effector T cells do not require costimulation to act
  - Effector Molecules
    - Cytokines
      - Hematopoietins - IL-2,3,4,5 and GMCSF
      - Interferons - IFN-γ
      - TNF-family: TNF, FasL, CD40L
      - Others: IL-10, TGF, IL-17
      - Secreted or membrane bound
      - Synergistic actions
      - Act locally over short distance
      - Act via JAK-STAT pathway
    - Cytotoxins
      - Perforin
      - Granzymes
- T Cell Effector Fxn
  - General
    - CD8 utilize cytokines and cytotoxins
    - CD4 only uses cytokines
    - Different combinations used by Th1 and Th2
      - Th1 uses Il-2, IFN-γ, TNF-β
      - Th2 uses IL-4,5,10
  - CD8
    - Main fxn is to kill tgt cells that have become overwhelmed by virus
    - Importance of CTL demonstrated by lack of CTL --> persistent viral infections
    - Killing fxn triggered by TCR recognition of MHC/viral peptide displayed upon surface of infected tgt cells
    - Mechanism
      - As soon as CD8 activated by APCs, perforin and granzymes synthesized by the developing CTL and loaded into specialized granules
      - Upon tgt cell recognition, granules fuse w/ CTL membrane and contents released twd tgt cell
      - Perforin forms pores in tgt cell membrane
      - Granzymes (serine proteases) enter cell
      - Granzymes cleave and activate tgt cell proteases (Caspases)
      - Caspases degrade many proteins --> cell death

        - Viral proteins also degraded as part of apoptotic death process
        - Death is irreversible after 5 mins of interaction
    - Death is selective for infected cells and single CTL can kill multiple tgts
    - Death is by apoptosis (cell shrinkage, nuclear condensation, DNA fragmentation)
    - CTLs also express FasL on cell surface to bind to Fas death receptor on tgt cells
        - Engagement also results in Caspase activation
        - Induction of apoptosis
        - Defective Fas or FasL --> autoimmune lymphoproliferative syndrome
    - MHC/peptide + B7 from APC --> expansion of T cells --> apoptotic death (receptor mediated and mitochondrial dysfunction)
    - Tissue cell --> limited expansion --> apoptosis and elimination
    - CTLs also produce IFN-γ upon ligand recognition
        - Inhibits viral replication
        - Augments MHC class I antigen processing
        - Activates macrophages
- Th1
    - Activate macrophages
    - Triggered by TCR recognition of class II/peptide complexes
    - Macrophage activation important for destruction of ingested microbes that are able to survive w/in macrophage vesicular system and are resistant to standard macrophage killing mechanisms
    - Macrophage Activation
        - Mycobacteria are able to resist m'phage killing by preventing acidification of phagolysosome (req to activate lysosomal hydrolases)
        - Activated m'phages have increased rate of phago-lyso fusion and increased synthesis of microbicidal substances
        - Activated m'phages also express more class II and B7
        - Two signals delivered by Th1 to m'phage
            - Sensitizing signal from CD40L interaxn w/ m'phage CD40
            - Activating signal from IFN-γ
                - TNFα acts synergistically
    - Synthesis of CD40L and IFN-γ induced by TCR recognition of MHC/peptide
    - Activated m'phages have higher expression of receptors for CD40 and TNFα
    - Th1 cells coordinate multi-faceted attack
        - IFN-γ and CD40L --> mphage actvation
        - FasL
        - IL-2
        - IL-3+GM-CSF --> m'phage differentiation in bone marrow
        - LT + TNFα --> diapedesis of WBCs
        - MCP --> m'phages accumulate at site of infection
    - Granulomas
        - Microbes resist killing --> granuloma
        - Central core of fused activated m'phages surrounded by single activated m'phages and T cells
        - Prevent widespread dissemination of pathogen w/in host
- Th2
    - Provide help to B cells in production of antibodies
    - Involves cognate interaxn btwn Th2 and B cells
    - TCR recognition of MHC/peptide displayed on B cell surface triggers Th2
    - Antigen-specific
        - Cognate interaction required for effective help b/c cytokines act only over short distances and CD40L is membrane bound
        - B cells w/ cell surface antibodies of antigenic specificities different from that of Th2

cell will process Th2 antigen very poorly
    - Linked recognition has important implications for vaccine design and regulation of self-tolerance
- Th2 cells that recognize B cells w/ class II-peptide complex in 2ndary lymphoid organs increases integrin avidity to form stable Th2-B cell conjugates
- Th2 expresses CD40L and IL-4 which together with signals from B cell antigen receptor stimulates B cell clonal expansion
- Th2 cell derived IL-5 and 6 promote B cell differentiation into plasma cells