open.michigan

Author(s): Aken Desai, Michael Mathis, 2008

T Cell Activation

Monday, February 18, 2008
9:00 AM

- Antigen Encouter
  - Occurs in secondary lymphoid organs
  - Antigen carried from site of infection by APCs
- T Cell Recirculation
  - T cells constantly recirculating btwn secondary lymphoid organs
  - Enter secondary lymphoid organs from blood
  - W/in secondary lymphoid organs T cells interact w/ APC
    - If antigen encountered on APC, T cell becomes activated
    - After several days, effector T cell enters back into blood to site of infection
  - To enter lymph nodes, T cell diapedese through high endothelial venules
  - Adhesion and Recirculation
    - T cell adhesion to HEV involves interaction btwn integrins, immunoglobulin-superfamily molecules, selectins and vascular addressins
    - T cell L-selectin interacts w/ carb groups on HEV endothelial cell addressins (GLYCAM-1 and CD34) to allow rolling o T-cells on vessel wall
    - Chemokines bound to endothelial cell surface increase avidity of integrin (LFA-1) on T cell surface for immunoglobulin-superfamily member, ICAM-1 on endothelial cell surface
    - Binding of LFA-1 to ICAM-1 promotes strong interaction btwn T cell and HEV cell --> diapedesis
- Adhesion and T Cell Activation
  - w/in lymphoid organs T cells make transitory contacts w/ APCs
  - Adhesion mediated by LFA-1, ICAMs
  - CD2 and LFA-3 also involved
  - Steps of activation
    - If T cell encounters the right antigen on an APC, avidity of LFA-1 for ICAM increased
    - T cell-APC interaction stabilized and activation/proliferation proceeds
    - Progeny of activated T cell remain in close contact w/ APC to be stimulated to undergo further rounds of activation/proliferation
- T Cell Costimulation
  - In addition to TCR signal, T cells must also receive a costimulatory signal to become activated
  - CD28
    - Among most important receptors on T cell
    - Binds B7, expressed by professional APCs
- Professional APCs
  - Dendritic cells solely for antigen processing and presentation
    - MHC class I pathway leading to activation of CD8 T cells
    - Mature DC have poor phagocytic capacity, but usually immature cells do the phagocytosis
    - Immature DC encounters antigen at site of infection
    - Langerhans cell
      - In skin
      - Ingest extracellular material but express low levels of MHC and B7
      - In response to infection, migrate to lymph nodes to mature and upregulate expression of MHC and B7
    - Antigen processing and presentation at different developmental stages
  - Macrophages
    - Initiate immune responses to particulate extracellular antigens
    - Take up antigens by phagocytosis
    - Peptides are presented on MHC class II and stimulate CD4 T cell actvation

        - Some bacteria avoid degradation in macrophage by escaping to cytosol
            - Bacterial derived peptides presented by class I
        - MHC class II and B7 not expressed constitutively
            - Induced by bacteria
            - Cytokines
    - B Cells
        - Cell surface Ig molecule take up soluble protein via receptor-mediated endocytosis
        - MHC class II pathway --> CD4 T cells
        - Do not normally express B7 molecules although can be induced to express B7 by infection
- T Cell Signal Transduction
    - At outset of activation, TCR, CD4/8, CD28 and adhesion molecules cluster to appose MHC/peptide complexes on APC
    - ITAMs in CD3γ, δ, ε chains and in TCRζ phosphorylated by Src-family TyrK such as FYN
    - ZAP-70 binds to phosphorylated ITAMs
    - CD4/8 associated w/ LCK Src-family TyrK upon recognition of MHC juxtapose LCK to ZAP-70
    - LCK phosphorylates (activates) ZAP-70
    - ZAP-70 triggers eventual activation of transcription factors to turn on expression of new genes involved in T cell activation
        - NFAT
        - NFκB
        - AP
    - CD28 binding to B7 results in amplification of some but not all signaling pathways
    - IL-2
        - Secreted T cell growth factor
        - Drives clonal expansion of antigen activated T cells
        - Induces T cell proliferation through binding to high affinity receptors
        - Receptor not expressed by resting T cells
- T Cell Anergy
    - Recognition of MHC/peptide w/o costimulation drives T cell into prolonged hypo-responsiveness (anergy)
    - Fail to become activated by MHC/peptide even when costimulatory signals provided
    - Mechanism for self-tolerance
    - Basis for anergy is inability to produce IL-2
- T Cell Differentiation
    - CD4
        - Th1 cells activate macrophages and help B cells for certain types of antibody response
        - Th2 cells only help B cells in antibody production
        - Th17 cells recruit n'phils to site of infection
        - Most of the time mixture produced although one type may dominate
        - Factors controlling differentiation include
            - Nature of cytokines present at time of activation
            - Antigen concentration
            - Affinity of TCR for MHC/peptide complex
        - Which predominates can have profound circumstances on course of infection
            - Mycobaterium Leprae
            - Th1 --> tuberculoid leprosy
            - Th2 --> lepromatous leprosy
        - Host mounts response appropriate for elimination of infectious agent
    - CD8
        - Higher levels of B7 costimulation to activate
        - Only dendritic cells express enough to activate directly
        - CD4 cells can assist in activation
        - Effector CD4 T cells can stimulate APC to express enough B7 to activate CD8 T cells
        - Naïve CD4 T cells can produce IL-2 that binds to receptors on CD8 cell