

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

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T Cell Activation

Monday, February 18, 2008
9:00 AM

- Antigen Encounter
 - 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 activation

- 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 CD3 γ , δ , ϵ chains and in TCR ζ 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
 - NF κ B
 - 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