Leukocyte Development and Trafficking During Inflammation and Immunity + Myasthenia Gravis Small Group

Wednesday, February 20, 2008
9:00 AM

- Memory B and T cells circulate
- Innate and adaptive response must deliver proper combination of cells to site of injury
  - Bacterial infections/ischemic necrosis require neutrophils mostly
  - Viral infections, cancers, autoimmune conditions involve macrophages, NK cells, effector T-cells
  - Either way, adhesion molecules are required
    - ICAM-LFA binding
    - Cytokines, chemokines --> specificity of recruitment
- Innate Inflammatory Response
  - Cytokines (IL-1, TNF) from injured cells/APC cause expression of tether/roll receptors on endothelial cells
    - Cytokines bind to cytokine receptors on endothelial cells
    - Cytokine receptors are always on venule endothelial cells
    - ICAMs also expressed on venule
  - Tether
    - Weak interaction betw PMN/other cell tether/roll receptor and endothelium
    - Interaction causes chemokine secretion from injured cell/APC
  - Chemokines bind to receptors on PMN to cause β2 integrin (LFA-1) to change to high affinity conformation
  - LFA1-ICAM interaction to cause arrest/migration of PMN
  - N'philis are attracted to bacterial chemical products such as fMLP
- Adaptive Immune Response
  - Specialized lymphoid organs drain all tissues (nodes, spleen)
    - Naïve and memory lymphocytes "recirculate" through lymphoid tissues
    - Once a dendritic cell takes up an antigen, it is made motile and travels to a draining node to interact w/ T/B cells
    - Naïve/memory lymphocytes recognize adhesion receptors and chemokines synthesized by HEV in lymphoid organs (except spleen)
  - Cytokines interact to cause tethering
    - L-selectin ligands in lymph node HEV interact w/ L-selectin on naïve/memory lymphocytes
    - MadCAM1 on GALT HEV interacts w/ α4/β7 on naïve/memory lymphocytes
    - This interaction causes the HEV to secrete a chemokine, secondary lymphoid organ chemokine
  - SLC interacts w/ CCR-7 on lymphocytes to cause β2 integrin to change to high affinity conformation
  - β2 integrin interacts w/ ICAMs to cause arrest/migration of lymphocytes
  - Memory cells retain homing receptors for lymphoid tissues while effector T-cells acquire receptors for tissues
    - Memory cells
      - retain L-selectin and CCR7
      - increase α4/β7 if activated in gut
    - Effector cells
      - Turn-off L-selectin and CCR7
      - Retain α4/β7 if made in gut
      - Turn-on shared and unique tethering, arrest, migration and chemokine receptors that allow cells to enter inflamed tissues
- Effector T-Cells
  - Share several adhesion receptors w/ innate response and also use some of their own
- Cytokines (IL-1, TNF) from injured cells/APC cause expression of tether/roll receptors on endothelial cells
  - Cytokines bind to cytokine receptors on endothelial cells
  - Cytokine receptors are always on venule endothelial cells
  - ICAMs also expressed on venule
- Tether/roll receptors
  - Weak interaction btwn PMN/other cell tether/roll receptor and endothelium
  - Interaction causes chemokine secretion from injured cell/APC
  - E and P-selectins on venules bind to ligands on T cells (also used by PMN, eos., mono., NKs)
  - VCAM on venules binds to α4-integrins on T-cells (also used by eos., mono., NKs)
  - Stiffness of cells can be enough in certain tissues, primarily lung, where T cells get stuck and move across capillary
- Chemokines bind to receptors on PMN to cause β2 integrin (LFA-1) to change to high affinity conformation
- LFA1-ICAM interaction to cause arrest/migration of PMN
- Deficiency of β2 integrins can cause LAD-1 --> severe dysfunction of multiple leukocytes
- Deficiencies in one or more of the selectin ligands can cause LAD2 --> less severe than LAD1
- Novel anti-inflammatory drugs have tried targeting recruitment
  - MS: progressive autoimmune disease causing demyelination
  - 2 year Phase 3 trial w/ humanized anti-α4-integrin monoclonal antity --> Tysabri
    - 42% reduction in disability progression
    - 67% reduction in clinical relapse
    - These results lead to early approval
- Trial w/ β-interferon
  - Two patients die of progressive multifocal leukoencephalopathy (immunosuppression --> brain infection)
  - One dies in original trial
  - Drug pulled --> back on market now but only w/ close monitoring and not in combination w/ β-interferon
- Demonstrates delicate balance of immune system and mechanism of recruitment
- Myasthenia Gravis Small Group
  - Genesis of MG involves B cells, plasma cells, T-cells, professional APC (usually dendritic cells)
    - As long as T-cells are self-tolerant autoreactive B cells don't become activated
  - Effector: B-cells
  - Tissue: muscle Ach-R
    - Ab binds to Ach-R to trigger endocytosis of receptors
  - Cholinesterase increases concentration of Ach to counteract low amount of receptors
  - Even if negative selection in thymus didn't work, T-cell will not be costimulated --> anergic
  - So how did T-cells become self activated?
    - Molecular mimicry - infectious agent has peptides similar to Ach-R thus activating Ach-R specific T-cells
    - Leads to Th2 response
  - Azathioprine --> metabolic inhibitor of T/B cell division --> immunosuppression