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

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- Memory B and T cells circulate
- Innate and adhevise response must deliver proper combination of cells to site of injury
    - Bacterial infections/ischemic necrosis require neutrophils mostly
    - Viral infections, cancers, autoimmune conditions involve machrophages, 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 cels
        - ICAMs also expressed on venule
    - Tether
        - Weak interaction btwn 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'phils 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 adhension 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 secret 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

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        - Cytokines bind to cytokine receptors on endothelial cells
        - Cytokine receptors are always on venule endothelial cels
        - 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 recruiment
    - MS: progressive autoimmune disease causing demyelination
    - 2 year Phase 3 trial w/ humanized anti-α4-integrin monoclonal antiby --> 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 mutlifocal 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