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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 adhesive 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 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 $\beta 2$ 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 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/ $\alpha 4/\beta 7$ 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 $\beta 2$ integrin to change to high affinity conformation
 - $\beta 2$ 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 $\alpha 4/\beta 7$ if activated in gut
 - Effector cells
 - Turn-off L-selectin and CCR7
 - Retain $\alpha 4/\beta 7$ 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 α 4-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 β 2 integrin (LFA-1) to change to high affinity conformation
- LFA1-ICAM interaction to cause arrest/migration of PMN
- Deficiency of β 2 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- α 4-integrin monoclonal antibody --> 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