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# Cytokines and Chemokines

Friday, February 15, 2008  
9:00 AM

- Cytokines/chemokines are chemical messengers that allow cells to communicate with each other w/o cell-to-cell contact.
  - Can act in endocrine, paracrine or autocrine manner
  - Have multiple functions and multiple targets, ex. IL-1
    - Induces fever
    - Mobilizes lymphocytes from bone marrow
    - Mobilizes insulin and glucagon
    - Activates endothelial cells for increased adhesion to circulating leukocytes
    - Activates lymphocytes to produce more IL-2
  - Shared activities
    - IL-1, IL-6, TNF
    - Liver --> acute phase proteins --> complement opsonization
    - Bone marrow endothelium --> neutrophil mobilization --> phagocytosis
    - HT --> increased body temperature
    - Fat, muscle --> protein and energy mobilization
    - Activation of B and T lymphocytes
  - When secreted in normal amounts cytokines are important in normal homeostasis like maintenance of circadian rhythm
    - When secreted in larger amounts, important in cell recruitment, differentiation, inflammation
    - In excess, can lead to pathology --> cytokine storm
- Cytokine storm (septic shock)
  - Bacterial toxins or LPS from gram-negative bacteria bind to TLRs on monocytes systematically
  - Results in production of TNF, IL-1, other pro-inflammatory cytokines --> fever
  - n'phils are recruited to blood stream; lymphocytes/monocytes decrease
  - Endothelial cells respond lowering BP and allowing n'phils to leave blood stream
  - n'phils activate oxidative response and more vascular leakage --> lowers BP even more
  - Kinin proteolytic cascade is induced, results in production of bradykinin and increased vascular permeability
  - Coagulation cascade is initiated --> microclotting, DIC --> liver, heart, kidney tissue don't get perfused
  - Pro-inflammatory cytokines --> other tissues --> more inflammatory molecules
  - Myocardial fxn reduced by TNF and IL-1 --> more vascular leakage problems
- Cytokine signaling via Jak-Stat
  - Binds to receptor
  - Jak is phosphorylated
  - Stat is phosphorylated and released
  - Stat dimerizes
  - Stat travels to nucleus and causes transcription
- Therapeutics
  - TNF is pro-inflammatory cytokine prod by mono/lymphocytes
  - Therapy w/ anti-TNF antibodies remarkably successful for improving symptoms of rheumatoid arthritis, Crohn's and psoriasis
  - Made via hybridoma technology
    - In order to prevent immune response to mouse constant region --> humanize anti-TNF
    - Recombinant technology to replace mouse constant region w/ human constant region
    - Result is chimeric Ig genes
    - Can even hybridize to the point that just the HV regions are from mouse

- Chemokines
  - 40 small polypeptides secreted by many cells including lymphoid cells
  - Act on n'phils to cause chemotaxis/activation
  - Classified according to number and spacing of cysteines
    - CC - adjacent, disulfide linked cysteines
    - CXC - one separating the two
    - "XC" or C w/ only one cysteine
    - CX3C w/ three intervening
  - Receptors usually named by chemokine they bind
- Type I interferons ( $\alpha$  and  $\beta$ ) produced by most cells
  - Important in innate immunity against viruses
  - Induce resistance to viral replication
  - Increase MHC-I expression and antigen presentation in all cells
  - Activates NK cells to kill virus-infected cells
- Viruses
  - IL-10 anti-inflammatory by suppressing expression of other cytokines by T lymphocytes
    - Also stimulates cell division and differentiation of B cells
    - Epstein-barr encodes own version of IL-10 that increases B cell lifespan but blunts inflammatory responses against EBV
  - Can also express soluble cytokine receptors that neutralize activity of pro-inflammatory cytokines
  - Can use receptors as co-receptors to enter cell