

## Lecture 32: Inflammation – General Mechanisms

\* The notes for this lecture were primarily generated from Goldsby et al. Ch. 15

### Inflammation

- Hallmarks of localized acute inflammatory response are:
  - swelling- caused by increased vascular permeability (fluid leaks into tissue) and migration of leukocytes to infection site
  - redness- caused by increased blood volume, vasodilation
  - heat- caused by increased blood volume and endogenous pyogens (TNF- $\alpha$ , IL-1 $\beta$ , IL-6)
  - pain- caused by stimulation of neuronal pathways
  - loss of function
- Local inflammation provides early protection (innate immunity) by restricting tissue damage to site of infection
  - Microbes activate macrophages (macs), dendritic cells (DCs), and mast cells through interaction w/ their pattern recognition receptors (PRRs)
  - Activated macs produce proinflammatory cytokines, chemokines, and lipid 2<sup>nd</sup> messengers (e.g. prostaglandins and leukotrienes)

### Proinflammatory Cytokines

- have pleiotropic effects – multiple activities can be caused by a single cytokine
- the classical proinflammatory cytokines are **TNF- $\alpha$** , **IL-1 $\beta$** , and **IL-6**
- What they do and how they work:
  - TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 act on the hypothalamus to induce fever
  - TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 act on the liver to induce production of acute-phase proteins (e.g. C-reactive protein (CRP), serum amyloid A, fibrinogen, mannose-binding protein, complement components)
  - TNF- $\alpha$  and IL-6 act on vascular endothelial cells and macs to induce secretion of colony stimulating factors (CSFs) that subsequently act on bone marrow to increase white blood cells
  - TNF- $\alpha$  and IL-1 $\beta$  act on vascular endothelial cells to increase both vascular permeability (for leukocyte migration) and expression of cell adhesion molecules (for rolling and firm adhesion of leukocytes)

### NF- $\kappa$ B (nuclear factor-kappa B)

- NF- $\kappa$ B is a transcription factor
- What stimuli activate NF- $\kappa$ B?
  - cytokines
  - oxidants
  - viruses
  - TLRs and other pattern recognition receptors (PRRs)
- What genes does NF- $\kappa$ B activate?
  - proinflammatory cytokines
  - chemokines (esp. IL-8)

- cell adhesion molecules needed for leukocyte extravasation (CAMs, selectins)
- enzymes
  - 1) COX-2 – required for prostaglandin synthesis (discussed later)
  - 2) inducible nitric oxide synthase – used to aid in killing ingested microbes
- What are the steps in NF-κB activation?
  - The inactivated form of NF-κB is bound to its inhibitor, IκB, in the cytoplasm
  - A stimulated cell will activate IκB kinase (IKK), which results in phosphorylation and degradation of IκB
  - NF-κB is now free to translocate into nucleus and activate gene transcription
- Case Study #8: X-linked Hypohydrotic Ectodermal Dysplasia and Immunodeficiency
  - A mutation in NEMO gene (component of IKK) prevents the activation of NF-κB
  - Patients have ectodermal dysplasia b/c a receptor required for ectodermal development depends on NF-κB activation
  - Characteristics features of disease: abnormal hair growth, pointed teeth, lack of eccrine sweat glands (hypohydrosis)
  - Patients have recurrent cytomegalovirus infections, bacterial infections (esp. mycobacteria), and hypogammaglobulinemia b/c of inability to activate NK cells, macs, and B cells, respectively.

### Corticosteroids

- anti-inflammatory drugs
- Effects:
  - lysis of lymphocytes (lympholysis)
  - inhibit NF-κB activation – block gene expression of cytokines
- How do corticosteroids inhibit NF-κB?
  - They are hydrophobic so they easily pass through cell membrane
  - Direct - Once inside cell it binds to glucocorticoid receptor, this complex translocates into nucleus and binds to free NF-κB – inactivates NF-κB
  - Indirect – corticosteroid binds to glucocorticoid response element on DNA, induces the expression of IκB gene (inhibitor of NF-κB)
- Corticosteroids have several adverse side effects so long-term use is not encouraged

### Prostaglandins

- How are they made?
  - During inflammation, phospholipases convert phospholipids into arachidonic acid
  - Cyclooxygenases convert arachidonic acid to prostaglandins (and other lipid 2<sup>nd</sup> messengers)
- What is their function?
  - Increase vascular permeability, increase vascular dilation, induce neutrophil chemotaxis
  - Act on nerve endings causing hypersensitivity to pain
  - Prostaglandins produced in hypothalamus elevate the thermal set-point, induces fever

## NSAIDS (Nonsteroidal anti-inflammatory drugs)

- Class of drugs that inhibit cyclooxygenases (COXs)
- What are the different COXs?
  - COX-1: GI tract homeostasis, expressed in platelets
  - COX-2, induced during inflammation by cytokines (IL-1, TNF- $\alpha$ )
  - COX-3, found in brain
- What are the different NSAIDS?
  - acetyl-salicylic acid (Aspirin): irreversibly acetylates COX-1 and COX-2, but only inhibits activity of COX-1
  - acetaminophen (Tylenol): targets COX-3 in the brain
  - ibuprofen (Advil, Motrin, Nuprin): inhibits COX-1 and COX-2
  - Coxibs (Celebrex, Vioxx, etc): specifically inhibit COX-2
    - 1) COX-1 still able to maintain homeostatic prostaglandin levels in GI tract
    - 2) Some patients still have GI complications b/c of genetic predisposition
    - 3) adverse side-effect: cardiovascular toxicity leading to increased risk of myocardial infarction in people w/ genetic predisposition

## Chronic Inflammatory Diseases

- Chronic inflammatory diseases are characterized by persistent reciprocal activation between macs and T cells!!!

- Hallmark of chronic inflammation is the accumulation and activation of macrophages, also elevated cytokines
- How does **rheumatoid arthritis** develop?
  - Antigen-activated CD4+ T cells play a key role. They:
    - 1) stimulate monocytes, macrophages, and synovial fibroblasts (SFs) to produce IL-1, IL-6, and TNF- $\alpha$  - leads to tissue damage
    - 2) stimulate B cells to produce rheumatoid factor (IgM antibody against IgG)
    - 3) express osteoprotegerin ligands – stimulates osteoclastogenesis
  - Current treatments for rheumatoid arthritis: anti- TNF- $\alpha$  antibodies
    - 1) Etanercept
    - 2) Infliximab

## Atherosclerosis development

- endothelial damage (smoking, ox-LDL, etc.)
  - Increased endothelial permeability and adhesion
  - Leukocyte extravasation
- fatty streak formation
  - earliest atherosclerotic lesion
  - contains lipid-filled macrophages (aka foam cells) and activated T cells
- fibrous cap
  - advanced atherosclerotic lesion
  - its purpose is to wall off the lesion from the lumen

- formation of necrotic core
- plaque rupture
  - material inside the plaque is released and thrombosis occurs
- Treatment: statins
  - Inhibit cholesterol synthesis – stabilizes plaque
  - Improve endothelial function
  - Decrease synthesis of nitric oxide – reduce tissue damage
  - Inhibit leukocyte adhesion to endothelium
- glucocorticoids and anti-TNF being investigated as a treatment

#### - **Inflammatory Bowel Disease (IBD)**

- Results from persistent activation of mucosal immune system to normal luminal flora
- Mucosa of IBD patients dominated by CD4+ T cells – activates macrophages to secrete proinflammatory cytokines, prostaglandins, leukotrienes, and nitric oxide
- Ulcerative colitis and Crohn's disease (the 2 types of IBD) are both characterized by fever, diarrhea, rectal bleeding, and weight loss
- NOD2 identified as Crohn's susceptibility gene – encodes a PRR for peptidoglycan
- Treatments:
  - 1) corticosteroids: decrease synthesis of cytokines
  - 2) 5-aminosalicylate: blocks production of prostaglandins and leukotrienes; esp. used for Crohn's
  - 3) broad spectrum antibiotics and probiotics useful for some patients w/ Crohn's disease
  - 4) infliximab: anti-TNF antibody; esp. used for Crohn's disease
  - 5) cyclosporine: inhibits production of cytokines by T cells; esp. used for ulcerative colitis