Inflammation and Chemokines

Robert Beatty
MCB150

Initiation of Acute Inflammation

◆ **Vasodilation**
  – Increase in the diameter of blood vessels.
◆ **Increased capillary permeability**
  – Allows influx of fluid and cells into tissue.
◆ **Influx of inflammatory cells**
  – Increased permeability and more CAMs are induced by CKs to allow for neutrophil/monocyte/lymphocyte extravasation.
How do Pathogens directly initiate inflammation?

◆ Activation through recognition of invariant parts of pathogens (LPS, peptidoglycan, mannans, flagellin).
◆ Pathogen Associated Molecular Patterns (PAMPs) are invariant parts of pathogens.
◆ PAMPs (especially on bacteria) bind to pattern recognition receptors (PRRs) on macrophages and dendritic cells.

Activation of TLRs
Innate Differentiation of Self vs Nonself
◆ Produces cytokines/chemokines --> inflammation.
◆ Activation of APCs produces cytokines, increased MHC, and costimulatory molecules.
◆ Part of the "DANGER SIGNAL"

How do we get the immune cells to the lymph nodes or a site of infection?
High endothelial venules (HEVs) in LNs and spleen

Lymphocyte circulation is controlled by chemokines and cell adhesion molecules (CAMs).

Schematic picture of HEV

Inflammed endothelial = high expression of CAMs
◆ "Inflammed" endothelial tissue is found in the blood vessels near the site of inflammation in tissue.
◆ CAM expression is different at site of inflammation than in HEV of lymph node.
Trafficking of Different T cell Populations

- **Naive cells** some CAMs primarily travel through to LNs.
- **Activated Effector T cells** have more CAMs and leave bloodstream for LNs and tissues.
- **Memory** T cells express specific adhesion molecules.

## Selectins
Bind to Mucin-like CAMs

- Have lectin domain which binds to CHO.
- Only 3 in family.
  - P-selectin found on endothelium.
  - E-selectin found on endothelium.
  - L-selectin expressed on neutrophils and lymphocytes.

## Mucin-Like CAMs
Bind to Selectins

- CHO structures to bind lectins.
- Expressed on endothelium as signal for cells to exit bloodstream.
  - EXAMPLES
    - GlyCAM-1 found on HEV.
    - MadCAM-1 mucosal endothelium.
Chemokines

Chemokines and their receptors are very pleiotropic and redundant.

Four sub-types distinguished by positions of N-terminal cysteines: C, CC, CXC and CXXXC.

Net positive charge leads to association with proteoglycans in tissues.

Receptors are seven transmembrane domain G-protein coupled molecules.

Selective expression of chemokines establish the architecture of the lymph node.
Extravasation
Cells leaving the bloodstream

◆ Inflammatory mediators act on the endothelium to increase the expression of CAMs.
  – The cells must adhere strongly enough not to be swept away.
◆ HEV or inflamed endothelium express the right combination of vascular addressins
  – e.g. E, P, selectin. GlyCAM-1, ICAM 1,2,3. MadCAM1.

Neutrophil Extravasation

1. Rolling and Tethering. E-P selectin on endothelium bind to mucin-like on Neutrophils.
2. Activation of Neutrophils by chemokine (IL-8).
3. Arrest/adhesion from ICAMs on endothelium bind to integrins on neutrophils.
4. Trans-endothelial migration of Neutrophil from bloodstream to tissue.

T Cell Extravasation
Mediators of acute inflammation

Inflammatory cells

Neutrophils and macrophages
◆ These phagocytic cells scavenge and clean up area.
◆ Release mediators which kill pathogens.
◆ Activate immune system.

Role of Neutrophils

Short lived cells.
Chemoattractants: IL-8, C3a, C5a, lipid mediators.

Phagocytosis mostly opsonization with Fc Receptors.

Mediators released from Neutrophils
◆ Oxygen radicals.
◆ Enzymes: proteases, phospholipases, collagenases.
◆ Lysozyme splits the proteoglycan cell wall of bacteria.
◆ These anti-microbial enzymes and reactive molecules are used inside in phagolysosomes but can be released from granules to kill extracellular microorganisms and cause tissue damage.

Activated Macrophages
activated by antigen or cytokines
phagocytosis OR opsonization (binding through CRs and FcRs).

• Produce oxygen radicals and enzymes for killing.
• Have increased antigen presentation and costimulation for T cell activation.
Activated macrophages

Mediators of acute inflammation
Cytokines

Pro-inflammatory cytokines
- IL-1, TNF-α, IL-6. Primarily produced by activated macrophages.

Chemokines
- Responsible for chemotaxis and leukocyte localization.

Mediators of acute inflammation
Complement

By-products of complement activation.

C3a, C4a, and C5a activate inflammation.

C3a, C4a, and C5a are called anaphylatoxins for their ability to induce "anaphylaxis".

Mediators of acute inflammation
Plasma Enzyme Activators

Produced in response to blood vessel injury.

Kinin System
- Bradykinin causes vasodilation, C5--> C5a, C5b.

Clotting Factors
- Thrombin and Fibrin are part of clotting cascade but also activate inflammation.
Mediators of acute inflammation

**Lipid Inflammatory Mediators**
Produced by inflammatory cells -- macrophages and polymorphonuclear cells (PMNs).

Membrane phospholipids are cleaved into Platelet-Activating Factor (PAF) and Arachidonic Acid Metabolites

**Prostaglandins and Leukotrienes**

**Arachidonic Acid Metabolites**

- **Arachidonic Acid**
  - Cyclooxygenase pathway
  - Lipoxigenase pathway

**EXAMPLE**

- Prostaglandin E2 (PGE2) activate neutrophils and cause increased vascular permeability.
- Leukotrienes are products of Lipoxygenase pathway
  - LTA4 and LTB4 --- Neutrophil chemotaxis.
  - LTC4, D4, E4 --> bronchial smooth muscle contraction.

---

**Anti-Inflammatory Agents**

**Steroids**
- Corticosteroids (e.g. Prednisone) mimic hormones with immunosuppressive effects.
- Prednisone increases production of IκB and inhibits NF-κB signaling.

**Non-steroidal**
- Non-steroidal anti-inflammatory drugs (NSAIDS) block cyclooxygenase pathway and therefore production of prostaglandins.

---

**Anti-inflammatories NSAIDS**

**Cyclooxygenase inhibitors**

- Arachidonic acid
- Aspirin (salicylates) covalently modify COX-2.
- Ibuprofen competitive inhibitor of COX1 and COX2.
Many Different Mechanisms to Initiate Acute Inflammation

Class Details

- New article posted on website for section
- Problem set coming on Complement/Inflammation
- Beatty OH Thursdays 1-2

Outcome of Acute Inflammation

- Short term and local acute inflammation is beneficial to attract immune response, activate clotting mechanisms, and trigger tissue repair.
- Clearance of antigen by neutrophils and macrophages will limit inflammation.
- However, prolonged local activation or systemic inflammation will result in disease.

Systemic Acute Inflammation

IL-1 IL-6, TNF-α

Large amounts of IL-1 IL-6, TNF-α can cause many disseminated effects.

Some good such as fever, increased metabolism.

Some bad such as in massive fluid loss and shock.
Systemic Acute Inflammation
IL-1 IL-6, TNF-α

Acute Phase Response (APR) is activated by IL-1 IL-6, TNF-α if:
- localized inflammatory responses do not contain the injury or infection.
- systemic activation of inflammation (through systemic infection or toxins).

Acute Phase Response (APR)
Activation of Innate Immune Responses

Liver produces
Acute Phase Proteins
C-reactive protein, AP Complement proteins, fibrinogen, and others.
◆ These proteins trigger increased complement activation, increased production of ACTH, steroids, fever etc.
◆ Part of "stress response".
Stress and the Immune Response

Immune ➞ Central Nervous System

- CNS can activate APR in the liver.
  - IL-1, IL-6, TNF-α, Oncostatin-M, Leukemia inhibitory factor, produced by CNS can activate production of acute phase proteins.

- Acute phase proteins and cytokines can activate hormonal pathways and CNS.

Effects of "Stress" on Immune Response

- Stress hormones (e.g. glucocorticoids) can be made by the CNS and have immunosuppressive effects (inhibit Th1).

- Stress hormones and cytokines made by CNS can act on endothelium to initiate inflammatory cascade.

Effects of "Stress" on Immune Response "Systemic Inflammation"

- Stress Hormones (from CNS) act on endothelium to increase CAMs.

Chronic Stress vs Chronic Inflammation

- Acute stress can activate acute inflammation.
  "Chronic stress" = chronic acute inflammation (can lead to activation of innate and suppression of adaptive).

- "Chronic inflammation" usually a result of adaptive immune response.
  - characterized by Th1 cells and macrophages making IFN-γ and TNF-α.
Adaptive Immune Responses Leading to Chronic Inflammation

◆ Infectious agent persisting.
◆ Autoimmunity.
◆ Cancer. Tissue damage or an adaptive immune response to tumor can result in chronic inflammation in area surrounding tumor.
◆ Delayed type hypersensitivity (DTH).