Inflammation and Chemokines

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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.

Acute Inflammation

<table>
<thead>
<tr>
<th>Redness</th>
<th>Pain</th>
<th>Swelling</th>
<th>Heat</th>
</tr>
</thead>
</table>

Triggered by tissue damage or presence of pathogens.

Inflammation

**Activation of TLRs**

Innate Differentiation of Self vs Nonself

- Produces cytokines/chemokines \(\rightarrow\) 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

Schematic picture of HEV

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

Inflamed endothelial tissue = high expression of CAMs

- "Inflamed" 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.
Neutrophil Extravasation

- Integrin
- Chemokine (L8, R)
- CAM
- SRS

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.
- PMN
- Multiwalled nucleus
- Glycogen
- Phagosome
- Secondary granule
- Primary granule
- Lysosome

Mediators of acute inflammation

Role of Neutrophils

Mediators released from Neutrophils

- Oxygen radicals.
- Enzymes: proteases, phospholipases, collagenases.
- Lysosome: 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

<table>
<thead>
<tr>
<th>TABLE 2-7</th>
<th>Some Factors Secreted by Activated Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Function</td>
</tr>
<tr>
<td>Interleukin 1 (IL-1)</td>
<td>Promotes inflammatory response and fever.</td>
</tr>
<tr>
<td>Interleukin 6 (IL-6)</td>
<td>Promotes innate immunity and elimination of pathogens.</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Promotes inflammatory response and elimination of pathogens.</td>
</tr>
<tr>
<td>Complement proteins</td>
<td>Promotes inflammatory response and elimination of pathogens.</td>
</tr>
<tr>
<td>Hyaluronic acid (HA)</td>
<td>Activates cellular genes, resulting in the production of proteins that cause an anaphylactic state in the cell.</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF-α)</td>
<td>Kills tumor cells.</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Promotes inducible hematopoiesis.</td>
</tr>
<tr>
<td>G-CSF</td>
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</tr>
<tr>
<td>M-CSF</td>
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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: Prostaglandins (PGLs)
    - Lipoxygenase pathway: Leukotrienes (LTs)

**Prostaglandins and Leukotrienes**

- Prostaglandins are products of Cyclooxygenase 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.

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

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 all activate production of acute phase proteins.

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

Systemic Acute Inflammation
Acute Phase Response (APR)

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).

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"

- Inflamed endothelium throughout body cells and fluid exit bloodstream
- Stress Hormones (from CNS) act on endothelium to increase CAMs
- Inflammation continued if Pathogen present.
- If not cells should return to bloodstream.

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).