Innate Immunity & Inflammation

November 20, 2006
Ch. 22, Ch. 23
Cells & organs of immune system
Innate immune response
Signals (chemokines, cytokines)
Inflammation
Adaptive immune response
Cells of the Immune System

Bone marrow stem cell

Myeloid precursor
- Mast cell
- Monocytes
- Polymorphonuclear Leukocytes (PMN)

Lymphoid precursor
- Maturation in thymus
- Maturation in bone marrow

B cells
- Plasma cells
- Memory cells

T cells
- Dendritic cell
- Macrophages

Figure by MIT OCW.
<table>
<thead>
<tr>
<th>NEUTROPHIL</th>
<th>EOSINOPHIL</th>
<th>BASOPHIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common phagocytic cell</td>
<td>Allergic conditions</td>
<td>Synthesize-store heparin/histamine</td>
</tr>
<tr>
<td></td>
<td>and parasites</td>
<td></td>
</tr>
</tbody>
</table>

Image showing neutrophils, eosinophils, basophils, monocytes, B lymphocytes, and T lymphocytes removed due to copyright restrictions.

<table>
<thead>
<tr>
<th>MONOCYTE</th>
<th>B LYMPHOCYTE</th>
<th>T LYMPHOCYTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A large phagocyte</td>
<td>Antibody production</td>
<td>Destroy targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(viruses and cancer cells)</td>
</tr>
</tbody>
</table>
Diagrams of the human lymphatic system removed due to copyright restrictions.
Cell Characteristics

PMN (neutrophils, basophils, eosinophils)
Monocytes (macrophages, dendritic cells)

• Phagocytic
• Attracted to the site of an active infection or tissue injury by soluble chemoattractants called chemokines
• Recognize pathogen-associated molecular patterns (PAMPs) via a family of membrane-bound pattern-recognition receptors (PRRs)
Activation of Phagocytes

**PRRs**

- Present before infection
- Evolved to recognize microbes
- PRRs interact with PAMPs shared by a variety of pathogens, activating complement and phagocyte effector mechanisms to target and destroy pathogens
- Activation of signaling cascade leads to production of chemokines and cytokines
- First discovered as the Toll receptors in *Drosophila* (the fruit fly), the evolutionarily and functionally related transmembrane proteins are called **Toll-like receptors (TLRs)** in mammals

Figure by MIT OCW.
Phagocytosis

- Phagocytosis stimulates respiratory burst
- NADPH or phagocyte oxidase (Phox)
- PMNs produce myeloperoxidase that converts $\text{H}_2\text{O}_2$ to HOCl
- Efficient killing

Figure by MIT OCW.
Chemokines & Cytokines

Chemokines are potent chemoattractants
- CXC (alpha) act mostly on PMNs (IL-8)
- CC (beta) act on other phagocytes (MCP-1, MIP-1a)
- C (lymphotactin) and CX₃C (fractalkine)

Cytokines are activator molecules
- Acute phase response, septic shock
- Produced by leukocytes (interleukins [IL], IFN-γ, TNF-α)
Inflammation

Redness
Swelling
Heat
Pain

- Reaction of blood vessels leading to the accumulation of fluid and leukocytes (white blood cells) in extravascular tissues
- Inflammation is a process, more than a state, and is closely linked to repair (regeneration and/or fibrosis)
- Although fundamentally protective, some instances of inflammation are harmful to the individual (hypersensitivity, chronic diseases, scarring)
Acute inflammation (vascular events)

1. Increased blood flow
   - After an initial vasoconstriction, there is vasodilation of arterioles, leading to increased blood flow (heat, redness)

2. Increased permeability
   - Structural changes in the microvasculature that permit plasma proteins and leukocytes to leave circulation
   - Loss of protein from plasma results in decreased osmotic pressure relative to the interstitial fluid
   - Combined with increased hydrostatic pressure from vasodilation, this results in outflow of fluid into the interstitial tissue (edema)
   - Slowing of circulation due to increased permeability of the microvasculature, increased viscosity and stasis

3. Emigration of leukocytes from the microcirculation and their accumulation at the site of injury
   - With stasis, margination of leukocytes, followed by rolling, then sticking (pavementing), then diapedesis
Mechanisms of vascular leakage

1. Endothelial gap formation (rapid, reversible, short-lived) occurs in post-capillary venules (20-60 μm in diameter)
2. Cytoskeletal reorganization (delayed, longer lasting)
3. Increased trancytosis (channels)
4. Direct endothelial injury (necrosis of endothelial cells, leading to thrombosis)
5. Delayed prolonged leakage (after a delay of 2-12 hours, lasting hours-days)
6. Leukocyte-mediated endothelial injury
Leukocyte extravasation

1. Margination, rolling, adhesion
   - E-selectin, P-selectin, and L-selectin
   - ICAM-1, VCAM-1, and integrins LFA-1, MAC-1, $\alpha_4\beta_1$, and $\alpha_4\beta_7$

2. Transmigration across the endothelium (diapedesis)

3. Migration in interstitial tissues towards a chemotactic stimulus (chemokines)
<table>
<thead>
<tr>
<th>Rolling</th>
<th>Integrin activation by chemokines</th>
<th>Stable adhesion</th>
<th>Migration through endothelium</th>
</tr>
</thead>
</table>

Leukocyte extravasation

- Sialyl-Lewis X-modified glycoprotein
- Integrin (low affinity state)
- Integrin (high affinity state)
- P-selectin
- E-selectin
- Proteoglycan
- Integrin ligand (ICAM-1)
- Integrin ligand (PECAM-1, CD31)
- Cytokines (TNF, IL-1)
- Macrophage with microbes
- Chemokines
- Fibrin and fibronectin (extracellular matrix)

Figure by MIT OCW.
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Immune Response

1. Innate immunity
   - Antigen destruction
   - Antigen processing

2. Antigen-specific, antibody-mediated immunity
   - Antigen presentation
   - Activate T cells
   - Produce antibody

3. Cell-mediated immunity
   - Antigen-presenting cell
   - MHC
   - TCR
   - Cytokine production
   - Activate B cells

Pathogens with PAMPs and antigens

Inflammation

Adaptive immunity

Complement, opsonization

Antigen binding
Adaptive Immunity

- nonspecific phagocytes present antigen to specific **T cells**
  - triggers the production of effector T cells and antibodies
  - T cells and antibodies react directly or indirectly to neutralize or destroy the antigen

- characterized by
  - **specificity** for the antigen
  - ability to respond more vigorously when reexposed to the same antigen (**memory**)
  - discriminate self antigens from nonself antigens (**tolerance**)

*Specificity*: Immune cells recognize and react with individual molecules (antigens) via direct molecular interactions.
Types of Adaptive Responses

**Antibody-mediated immunity**
particulary effective against pathogens such as viruses and bacteria in the blood or lymph and also against soluble pathogen products such as toxins

**Cell-mediated immunity**
leads to killing of pathogen-infected cells through recognition of pathogen antigens found on infected host cells