Module 10

Innate Immunity
The Concept of Immunity

- **Immunity**: ability to protect against disease from microbes and their products
  - Aka, resistance
- **Susceptibility**: vulnerability or lack of immunity
- Two general mechanisms of immunity
  - **Innate immunity**: defenses against any pathogen
  - **Adaptive immunity**: immunity or resistance to a specific pathogen
# Host Defenses

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Adaptive Immunity (Chapter 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line of defense</td>
<td>Second line of defense</td>
</tr>
<tr>
<td>- Intact skin</td>
<td>- Phagocytes, such as neutrophils, eosinophils, dendritic cells, and macrophages</td>
</tr>
<tr>
<td>- Mucous membranes and their secretions</td>
<td>- Inflammation</td>
</tr>
<tr>
<td>- Normal microbiota</td>
<td>- Fever</td>
</tr>
<tr>
<td>- Antimicrobial substances</td>
<td></td>
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</tbody>
</table>

- Always present and available
- Does not involve specific recognition
- Acts against all microbes in the same way
- Early warning system to prevent spread
- Involve recognition of *specific* microbes
- Slower to respond
- Has memory component
- Involves “lymphocytes”
First Line of Defense: Physical Factors

Skin

- Top layer is dead, shed continually
- No space in between cells, microbes can’t penetrate
- Dryness of skin inhibits most growth
  - In moist conditions, skin infections common
- **Keratin**: protective protein in skin
- Most infections are **subcutaneous** – below the skin
Mucous membranes

- Inhibit entrance of many microbes
- **Mucus**: slightly viscous fluid composed of glycoprotein
  - Traps invading microbes
  - Some pathogens can grow in mucus
First Line of Defense: Physical Factors

Lacrimial apparatus, saliva, urine, secretions

- Continual washing helps wash away microbes
First Line of Defense: Physical Factors

Ciliary escalator
- Cilia in respiratory tract move trapped microbes up
- Coughing and sneezing speeds up process

Defecation, vomiting
- Expels microbes
First Line of Defense: Chemical Factors

Sebum

- Oily substance produced by glands in skin
- Forms protective film over skin
- Contains fatty acids that inhibit growth of some pathogens
- Lower pH (3 to 5)
- Some bacteria can metabolize sebum → acne
First Line of Defense: Chemical Factors

Lysozyme

- Enzyme that breaks down cell wall
- Found in perspiration, tears, saliva, and tissue fluids

Low pH

- Skin (3-5)
- Gastric juice (1.2-3)
- Vaginal secretions (3-5)
Normal Microbiota

- Normal microbiota protect via **microbial antagonism** or **competitive exclusion**
- Normal microbiota compete with pathogens for space
Second Line of Defense

- If microbes penetrate first layer, infection begins
- Second line of defense to invasion include defensive cells, inflammation, fever, antimicrobial substances
Second Line of Defense

- **Formed elements**: cells and cell fragments in blood
  - **Leukocytes**: white blood cells, WBC
- Different WBC, different functions
## Types of WBC

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (White Blood Cells)</td>
<td></td>
</tr>
</tbody>
</table>
| A. Granulocytes (stained)  | 1. Neutrophils (PMNs)  
                        60–70% of leukocytes |
| 2. Basophils (0.5–1%)    |                                                                             |
| 3. Eosinophils (2–4%)   |                                                                             |
| 4. Dendritic cells      |                                                                             |

**Neutrophils**
- Highly phagocytic against bacteria
- Active in initial stages of infection
- Can leave blood, move into tissue

**Basophils**
- Release histamine, important in inflammation

**Eosinophils**
- Produce toxins against large parasites
- Can leave bloodstream, move into tissue

**Dendritic cells**
- Destroy microbes by phagocytosis
- Activate adaptive immune response
**TABLE 16.1**  
**Formed Elements in Blood (continued)**

<table>
<thead>
<tr>
<th>Type of Cell</th>
<th>Numbers per Microliter (Cubic mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agranulocytes (stained)</td>
<td></td>
</tr>
<tr>
<td>1. Monocytes (3–8%)</td>
<td></td>
</tr>
<tr>
<td>2. Lymphocytes (20–25%)</td>
<td></td>
</tr>
<tr>
<td>• Natural killer (NK) cells</td>
<td></td>
</tr>
<tr>
<td>• T cells</td>
<td></td>
</tr>
<tr>
<td>• B cells</td>
<td></td>
</tr>
</tbody>
</table>

**Monocytes**
- Not phagocytic in bloodstream
- Can move into tissue → “macrophages”
  - Highly phagocytic

**Lymphocytes**
- **Natural killer (NK) cells**
- Kill infected body cells, tumor cells
- Any cell that displays “abnormal” membrane proteins

**T cells**

**B cells**
- Play central role in adaptive immunity

Discussed in Chapter 17.
Differential White Cell Count

- Percentage of each type of WBC in a patient sample

<table>
<thead>
<tr>
<th>White Blood Cell Type</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Neutrophils</td>
<td>60–70%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.5–1%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2–4%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>3–8%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20–25%</td>
</tr>
</tbody>
</table>
Differential WBC Count

- **Leukocytosis**: increase in WBC count
  - Can double, triple, quadruple, etc ….

- **Leukopenia**: decrease in WBC count
  - Due to impairment of WBC production, activity

- Differential white blood cell count can help diagnose type of infection or disease
Differential WBC Count

- Why are these numbers important?
- What change would you expect to the WBC ratio during a *Staphylococcus* (a bacterium) infection?
- What change would you expect to the WBC ratio during a viral infection?

Turn over after your responses
Differential White Blood Cell Count

- Why are these numbers important?
- Since WBC have specific functions, the results of WBC counts can be used to diagnose diseases.
- What change would you expect to the WBC ratio during a *Staphylococcus* (a bacterium) infection?  
  Number of neutrophils will increase.
- What change would you expect to the WBC ratio during a viral infection?  
  Number of lymphocytes will increase.
Phagocytosis

- Phago: from Greek, meaning eat
- Cyte: from Greek, meaning cell
- Ingestion of microbes or particles by a cell
- Phagocytes: cells that perform phagocytosis
  - Neutrophils, macrophages, dendritic cells
Phagocytes

- During infection, neutrophils and monocytes migrate to infected area
- Neutrophils dominate in initial stages of bacterial infection
  - Phagocytize bacteria
- As infection progresses, macrophages dominate
  - Clear up cell debris
- In viral, fungal infections, macrophages always dominate
Mechanism of chemotaxis

1. **Chemotaxis**: chemical attraction of phagocytes to microbes
   - Attracted to microbial products, damaged cells, chemicals

2. **Adherence**: attachment of phagocyte to microbe

3. **Ingestion**: internalization of microbe
   - Projections called **pseudopods**
   - Microbe internalized in **phagosome**

4. **Digestion**: degradation of microbe
   - Phagosome fuses with lysosome → **phagolysosome**, destroys microbe
   - Indigestible material expelled from cell
## Microbial Evasion of Phagocytosis

<table>
<thead>
<tr>
<th>Activity</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit adherence: M protein, capsules</td>
<td><em>Streptococcus pyogenes, S. pneumoniae</em></td>
</tr>
<tr>
<td>Kill phagocytes: Leukocidins</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Lyse phagocytes: Membrane attack complex</td>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td>Escape phagosome</td>
<td><em>Shigella, Rickettsia</em></td>
</tr>
<tr>
<td>Prevent phagosome–lysosome fusion</td>
<td><em>HIV, Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Survive in phagolysosome</td>
<td><em>Coxiella burnettii</em></td>
</tr>
</tbody>
</table>
Inflammation

- Local response to infection
- Characterized by redness, pain, swelling, heat
- **Acute inflammation**: short, intense
  - Cause of inflammation removed quickly
- **Chronic inflammation**: longer lasting, less intense
  - Cause of inflammation difficult to remove
- Functions
  - To destroy injurious agent
  - To limit the effects on body by confining injurious agent
  - Repair or replace damaged tissue
Stages of Inflammation

- Vasodilation and increased permeability of blood vessels
- Phagocyte migration and phagocytosis
- Tissue Repair
Vasodilation and increased permeability of blood vessels

- **Vasodilation**: dilation of blood vessels
  - Increases blood flow to area
  - Responsible for *erythema* (redness), heat

- Vasodilation also results in increased permeability
  - Allows WBC, chemicals to pass from blood to injured area
  - Responsible for *edema* (swelling)
Figure 16.8a-b The process of inflammation.

(a) Tissue damage

1. Chemicals such as histamine, kinins, prostaglandins, leukotrienes, and cytokines (represented as blue dots) are released by damaged cells.

2. Blood clot forms.

3. Abscess starts to form (orange area).

(b) Vasodilation and increased permeability of blood vessels
Phagocyte migration and phagocytosis

- Blood flow eventually brings phagocytes to site of infection
  - Destroy invading microbes

In response to bacteria, neutrophils first, then macrophages

1. Blood vessel endothelium
2. Monocyte
3. Neutrophil
4. Bacterium
5. Erythrocyte

(c) Phagocyte migration and phagocytosis

Phagocytes often die after killing many cells; contribute to pus
Stages of Inflammation

- Histamine release from mast cells, basophils result in vasodilation, permeability.
- Blood clots around injury prevents spread.
- Localized collection of pus called an abscess.
Tissue repair

- Replacement of dead or damaged cells
- Speed of repair depends on tissue
  - Skin heals fast, cardiac muscle heals slow
Fever

- Abnormally high body temperature
- Systemic response to infection
- Most commonly caused by bacterial, viral infections
- Certain chemicals trigger a “re-setting” of body “thermostat” to a higher body temperature
  - LPS endotoxin
- **Chill**: response to increase body temperature
- **Crisis**: response to decrease body temperature
Fever

- Fever is helpful to a certain degree
  - Helps increase WBC production, tissue repair, etc ...
- Complications include
  - **Tachycardia**: rapid heart rate, may compromise weak hearted
  - Increased metabolism
  - Seizures in young children
  - Delirium
  - Coma
  - 44-46°C (112-114°F) = death
Antimicrobial Substances

- **Complement system**: defensive system consisting of 30+ proteins in blood
- Destroy microbes by:
  - Cytolysis (bursting) of bacteria
  - Triggering inflammation
  - Helping with phagocytosis
The Complement System

Opsonization
Enhancement of phagocytosis by coating with C3b (see also Figure 16.6)

Enhance phagocytosis

Cytolysis
Formation of membrane complex

Bursting of microbe due to inflow of extracellular fluid through transmembrane channel formed by membrane attack complex (see also Figure 16.10)

Cytolysis

Histamine

Mast cell

Inflammation
Increase of blood vessel permeability and chemotactic attraction of phagocytes (see also Figure 16.11)

Trigger inflammation

Enhance phagocytosis

Cytolysis

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Evading complement system

- Some capsules prevent complement activation
- Some gram-negative bacteria can lengthen surface glycolipids to prevent cytolysis
  - “Serum-resistant”
- Some gram-positive cocci release enzymes that break down complement proteins
Interferons, IFN

- Proteins produced by viral infected cells that interfere with viral multiplication
- Effective against many different types of viruses
- Protect uninfected cells by causing them to produce “antiviral proteins” (AVP)
  - Enzymes that inhibit synthesis of viral particles
- Effective for short time only
- High levels toxic to heart, liver, kidneys, bone marrow
Interferons, IFN

1. Viral RNA from an infecting virus enters the cell.
2. The infecting virus replicates into new viruses.
3. The infecting virus also induces the host cell to produce interferon mRNA (IFN-mRNA), which is translated into alpha and beta interferons.
4. Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.
5. New viruses released by the virus-infected host cell infect neighboring host cells.
6. AVPs degrade viral mRNA and inhibit protein synthesis—and thus interfere with viral replication.
Antimicrobial peptides

- Newly discovered, may be most important component of innate immunity
- Small peptides $\rightarrow$ 10-20 amino acids
- Bind to plasma membranes causing cell lysis
- Produced by mucous membranes, phagocytes
Antimicrobial Peptides

- Peptide neutralises a patch of outer membrane and enters through resulting crack.
- Peptide binds the divalent cation binding site of LPS and disrupts the membrane.
- Peptide binds to membrane.
- Peptide flip-flops across the membrane.
- Peptides aggregate into membrane-spanning micelle-like structure.
- Translocation into cell.
1. C3b, a complement protein, is an opsonin. LAD is a genetic disease in which neutrophils can’t recognize C3b. What is the consequence of LAD?

2. The signs and symptoms of hay fever occur when pollen leads to basophil activation. What are the effects of this activation?

3. Interferon deficiency syndrome describes a series of diseases that affect the ability of cells to produce and/or release interferons. What is the consequence of this?

See next slide for answers
1. C3b, a complement protein, is an opsonin. LAD is a genetic disease in which neutrophils can’t recognize C3b. What is the consequence of LAD?
   - Since opsonins aid in phagocytosis by coating microbes → defective phagocytosis
2. The signs and symptoms of hay fever occur when pollen leads to basophil activation. What are the effects of this activation?
   - Release of histamine → inflammation
3. Interferon deficiency syndrome describes a series of diseases that affect the ability of cells to produce and/or release interferons. What is the consequence of this?
   - Since interferons protect against viruses → more susceptible to viral infection