Chapter 15: Innate Immunity

1. Overview of Innate Immunity
2. Inflammation & Phagocytosis
3. Antimicrobial Substances
1. Overview of Innate Immunity

Chapter Reading – pp. 449-456
The Body’s Defenses

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<th>Innate (Nonspecific) Immunity</th>
<th>Adaptive (Acquired) Immunity (Chapter 17)</th>
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<td>Antibodies</td>
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The body has 2 types of defense against infection:

**Innate Immunity**
- physical barriers (the skin & mucous membranes)
- immediate, non-specific responses to pathogens, injuries

**Adaptive Immunity** (covered in ch. 16)
- delayed, highly specific responses to foreign material
Innate Immunity

The innate immune defenses are the body’s 1st line of defense and includes:

1) physical barriers between inside & outside
   • the skin and the mucous membranes of the digestive, respiratory and genito-urinary tracts
   • all substances secreted at these barriers and all of the normal microbiota that live on these surfaces

2) non-specific cellular & physiological responses
   • i.e., inborn (innate) general responses to the presence of pathogens that breach the body’s physical barriers
   • independent of prior exposure, response is immediate
   • eliminates the vast majority of pathogens that gain entry
Physical Defenses

Key defensive features of the Skin:

- dry, acidic surface (resists microbial growth)
- multiple layers of tough yet dead keratinized cells
- continual loss of outer dead skin layers removes microbes on skin surface
- sebum from hair follicles (lowers pH), lysozyme, antimicrobial peptides & sweating help resist microbial colonization
Defense of the **Eyes:**

- tears continually released by lacrimal ducts
- contain antimicrobial substances (e.g. lysozyme), wash away any microbes, debris on the eye surface

The **Mucous Membranes:**

- includes the linings of the respiratory, digestive & genito-urinary tracts which are vulnerable due to very thin epithelial layer, moist surface
- produce **mucus**, a viscous glycoprotein that traps microbes and debris, lysozyme, antibodies, antimicrobial peptides
- continual shedding and replacement of epithelial cells
Roles of the Normal Microbiota

The “normal microbiota” are the microorganisms that live on the body surfaces of a healthy individual and inhibit the growth of pathogens as follows:

• acidifying body surfaces
  • e.g., inhibits pathogens in the female reproductive tract

• the production of bacteriocins and other toxins
  • i.e., toxins that are specific for other microorganisms

• out-competing pathogens for nutrients
  • on the skin and basically all mucous membranes

• stimulating innate and acquired immune defenses
  • activation of immune cells, antimicrobial substances
Organs of the Immune System

Thymus gland

Lymph node

Red bone marrow

Spleen
The Lymphoid Organs

Bone Marrow

• blood cell formation
  • “where all blood cells (red & white) are born”

Thymus

• where T cells are “educated”
  • weeds out T cells that would react to “self” molecules

Spleen

• immune response to pathogens, foreign material in blood
...the Lymphatic System

Lymph Nodes

- immune response to pathogens, foreign material in lymph

Lymph (& Blood)

- fluids through which immune cells patrol the body
Cells of the Immune System...

These include all of the white blood cells (aka leukocytes), some of which appear “granular”...

**TABLE 16.1** Formed Elements in Blood (continued)

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

**Granulocytes**
- phagocytes w/strangely shaped nuclei, poorly stained granular vesicles

**Neutrophils**
- phagocytes w/strangely shaped nuclei, poorly stained granular vesicles

**Basophils**
- release histamine, other mediators of inflammation, vesicles bind basic dyes

**Eosinophils**
- phagocytic, attack parasites w/toxic proteins, vesicle bind acidic eosin dye

**Dendritic Cells**
- phagocytes with very important roles in initiating adaptive immune response
...more Cells of the Immune System

...& others which have an “agranular” appearance

Monocytes/Macrophages
- monocytes become actively phagocytic macrophages when stimulated via infection, injury

Natural Killer (NK) cells
- recognize and destroy cells with features of tumor cells, cells with intracellular pathogens

T & B cells (lymphocytes)
- have central roles in adaptive immunity (covered in ch. 16)
Innate immunity, second line of defense

Phagocytosis

Inflammation, clotting

Gas transportation

Erythrocyte
Platelets
Basophil
Neutrophil
Eosinophil
Monocyte
Lymphocyte

Hematopoietic (blood) stem cell in bone marrow

Erythroid stem cell
Myeloid stem cell
Lymphoid stem cell
2. Phagocytosis & Inflammation

Chapter Reading – pp. 456-458, 463-65
What is Phagocytosis?

It’s the process by which a cell ingests a solid extracellular particle (such as a bacterium) by engulfing it within a membrane enclosed vesicle (sometimes called a vacuole).

- cells that normally carry out this function are referred to as *phagocytic*, or simply as *phagocytes*
Types of Phagocytes

All of the phagocytes in the human body are types of white blood cells (leukocytes):

**Neutrophils**
- highly phagocytic cells that rapidly exit the blood into damaged or infected tissue, “gobble up” bacteria, etc…

**Macrophages**
- monocytes migrate to damaged, infected tissue from blood & differentiate into highly phagocytic macrophages
- some are fixed (non-mobile) in various tissues & organs

**Dendritic Cells**
- found in skin, mucous membranes, thymus, lymph nodes

**Eosinophils** (occasionally)
The Process of Phagocytosis
Opsonization

2 kinds of proteins involved in the immune response bind to pathogens and greatly enhance phagocytosis:

- antibodies
- complement proteins C3b & C4b

This process is called opsonization and such proteins are called opsonins.
What is Inflammation?

Inflammation is a localized response initiated by damaged or infected tissues to aid tissue repair and the elimination of pathogens.

The basic stages of inflammation are as follows:

**Vasodilation & increased capillary permeability**
- increases blood flow to area, blood fluid in tissue

**Migration of phagocytes, phagocytosis**
- phagocytes exit the blood, enter affected tissue via chemotaxis & consume pathogens

**Tissue repair**
- removal of dead cells, regeneration of the tissue
Inflammation Triggers

Any type of physical damage to and/or microbial penetration of a tissue will trigger a local inflammatory response:

- can be short-lived (acute) or extended (chronic)
- initiated by the release of inflammatory mediators from cells in the tissue that is damaged
e.g. histamine prostaglandins leukotrienes
Vasodilation & Increased Permeability

Increased blood flow due to **vasodilation** and the increased permeability of capillaries results in fluid from blood seeping into affected tissue:

- facilitates clotting, entry of antimicrobial proteins & phagocytic cells

**Normal permeability of venule**
- Venule wall
- Small amount of fluid
- Monocyte

**Increased permeability of venule during inflammation**
- Interstitial spaces
- More fluid and antimicrobial chemicals
- Monocyte squeezing through interstitial space (diapedesis)
- More fluid
Phagocyte Migration (Chemotaxis)

- Endothelium of capillaries in the area expresses proteins that "stick to" phagocytes
- Phagocytes then "squeeze" their way out into the tissue and follow a "trail" of chemical signals toward the source (chemotaxis) and gobble up microbes
Tissue Repair

Once the area has been secured (all pathogens are destroyed, all breaches are sealed), dead & damaged cells can be broken down and the tissue can regenerate.

(d) Tissue repair
A cut penetrates the epidermis barrier, and bacteria invade.

1. Damaged cells release prostaglandins, leukotrienes, and histamine (shown in green here).

2. Prostaglandins and leukotrienes make vessels more permeable. Histamine causes vasodilation, increasing blood flow to the site.

3. Macrophages and neutrophils squeeze through walls of blood vessels (diapedesis).

4. Increased permeability allows antimicrobial chemicals and clotting proteins to seep into damaged tissue but also results in swelling, pressure on nerve endings, and pain.

5. Blood clot forms.

6. More phagocytes migrate to the site and devour bacteria.

7. Accumulation of damaged tissue and leukocytes forms pus.

8. Undifferentiated stem cells repair the damaged tissue. Blood clot is absorbed or falls off as a scab.

9. Summary of Inflammation
3. Antimicrobial Substances

Chapter Reading – pp. 458-463
Some Antimicrobial Substances

There are many different kinds of antimicrobial substances, however we will focus our attention on 2 of the more interesting ones*:

*Complement system
  • a set of proteins present in the blood important for the destruction of pathogenic cells

*Interferons
  • a class of cytokines that are especially important in controlling viral infections

Transferrins (bind & keep iron away from pathogens)

Antimicrobial peptides (cause lysis of microbes)
The Complement System

The complement system (aka “complement”) is a set of >30 proteins produced by the liver that circulate in the blood in an inactive state.

The presence of microbial pathogens activates the “complement cascade” in 1 of 3 ways to eliminate the pathogens by:

- cytolysis (cell lysis)
  - eukaryotic pathogens, Gram⁻ bacteria (not Gram⁺)
- triggering inflammation
- enhancing phagocytosis (opsonization)
The Complement Cascade

- the activation of complement proteins C3 & C5-C9 as shown is central to complement carrying out its roles

- the key event setting off the process is the splitting of C3 protein into C3a & C3b fragments

- C3b triggers the cascade resulting in a cytolytic structure…
Cytolysis by Complement

- C3b binds to outer membrane of Gram- bacteria and splits C5 into C5a & C5b
- C5b on the outer membrane then recruits C6, C7, & C8
- the C5b-C8 complex triggers multiple C9 proteins to complete the circular membrane attack complex (MAC)
- MAC formation produces a hole in membrane & cytolysis

**C3b also functions as an opsonin to aid phagocytosis**

Cytolysis: Bursting of microbe due to inflow of extracellular fluid through transmembrane channel formed by membrane attack complex C5–C9 (see also Figure 16.10)
The Classical Complement Pathway

The “classical” pathway was characterized first and activates C3 as follows:

1. specific antibody binds to the surface of a target cell
2. this activates C1 which then splits C2 into C2a & C2b, and C4 into C4a and C4b
3. C2a & C4b form a complex which then cleaves C3 setting off the formation of the MAC

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The “alternative” pathway activates C3 in a different way:

- spontaneously formed yet unstable complexes of C3 & Factors B, D & P become stabilized on the surface of a pathogen

- stabilized C3-BDP acts to cleave other C3 molecules and trigger cascade

**This is antibody-independent!**
Lectin Complement Pathway

Lectins are protein produced by the liver that bind specific carbohydrate structures

- mannose-binding lectin (MBL) is produced during infections and binds carbohydrates with the sugar mannose on pathogens
- MBL on the cell surface triggers the complement cascade as does C1 in the classical pathway

*Antibody-independent!
Classical pathway

Antigen

Antibody

Complement proteins 1, 2, 4

Alternative pathway

C3b

Endotoxin and glycoproteins

C3b

Factors B, D, and P

Lectin pathway

Mannose

Lectins

Complement cascade

Activation

(C3 → C3a + C3b)

Opsonization

Inflammation

C5 convertases

C5 → C5a + C5b

Inflammation

Membrane attack complex and cell lysis

Summary

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Inflammation via Complement

C3a & C5a are powerful inducers of inflammation
- bind to receptors on mast cells triggering the release of histamine, etc, causing vasodilation, incr. in permeability

C3a & C5a are also chemoattractants for phagocytes
- phagocytes follow gradient of C5a, C3a to site of infection
Interferons

The interferons (IFN-α, IFN-β & IFN-γ) are a class of cytokines (soluble protein signals) released by virally infected cells and certain white blood cells to stimulate other cells to protect themselves from viral infection:

- the presence of viral proteins, RNA in a cell triggers IFN production & release
- neighboring cells bind IFNs via specific receptors
- this triggers the expression of various anti-viral genes in the cell receiving the IFN signal
- the resulting anti-viral proteins (AVPs) inhibit viral replication
Effects of Interferons

1. Virus infects cell.

2. Viral replication in cell triggers expression of α or β interferon (IFN).

3. Interferon is released, diffuses to neighboring uninfected cells, and binds to receptors.

4. Binding triggers expression of inactive antiviral proteins (AVPs).

5. Meanwhile, the infected cell dies and releases the virus.

6. Double-stranded RNA of the virus activates AVP.

7. AVPs degrade mRNA, inhibit protein synthesis and viral replication.

Infected cell

Uninfected neighboring cell
Key Terms for Chapter 15

• innate vs adaptive immunity

• granulocytes: neutrophils, basophils, eosinophils, dendritic cells

• agranulocytes: monocytes, macrophages, NK cells, T & B cells

• opsonization, opsonin, diapedesis

• complement: classical, alternative, MBL paths

• lectins, interferons, cytokines, transferrins

Relevant Chapter Questions
MC: 2-5, 7-10    TF: 1-10    M: 1-15