The Immune System

Ch 43

1.5 µm
Overview: Reconnaissance, Recognition, and Response

- Barriers help an animal to defend itself from the many dangerous **pathogens** it may encounter.

- The **immune system** recognizes foreign bodies and responds with the production of immune cells and proteins.

- Two major kinds of defense have evolved: innate immunity and acquired immunity.
• *Innate immunity* is present before any exposure to pathogens and is effective from the time of birth

• It involves nonspecific responses to pathogens

• Innate immunity consists of external barriers plus internal cellular and chemical defenses
• **Acquired immunity**, or adaptive immunity, develops after exposure to agents such as microbes, toxins, or other foreign substances.

• It involves a very specific response to pathogens.
<table>
<thead>
<tr>
<th>Pathogens (microorganisms and viruses)</th>
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<tbody>
<tr>
<td><strong>INNATE IMMUNITY</strong></td>
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<tr>
<td>• Recognition of traits shared by broad ranges of pathogens, using a small set of receptors</td>
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<tr>
<td>• Rapid response</td>
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<tr>
<td><strong>ACQUIRED IMMUNITY</strong></td>
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<tr>
<td>• Recognition of traits specific to particular pathogens, using a vast array of receptors</td>
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<tr>
<td>• Slower response</td>
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**Barrier defenses:**
- Skin
- Mucous membranes
- Secretions

**Internal defenses:**
- Phagocytic cells
- Antimicrobial proteins
- Inflammatory response
- Natural killer cells

**Humoral response:** Antibodies defend against infection in body fluids.

**Cell-mediated response:** Cytotoxic lymphocytes defend against infection in body cells.
Concept 43.1: In innate immunity, recognition and response rely on shared traits of pathogens

- Both invertebrates and vertebrates depend on innate immunity to fight infection.
- Vertebrates also develop acquired immune defenses.
In innate immunity of invertebrates:

- In insects, an exoskeleton made of chitin forms the first barrier to pathogens.
- The digestive system is protected by low pH and lysozyme, an enzyme that digests microbial cell walls.
- Hemocytes circulate within hemolymph and carry out phagocytosis, the ingestion and digestion of foreign substances including bacteria.
The immune system recognizes bacteria and fungi by structures on their cell walls.

An immune response varies with the class of pathogen encountered.
Innate Immunity of Vertebrates

The immune system of mammals is the best understood of the vertebrates

Innate defenses include barrier defenses, phagocytosis, antimicrobial peptides

Additional defenses are unique to vertebrates: the inflammatory response and natural killer (NK) cells
MAMMAL BARRIER DEFENSES

• Barrier defenses include the skin and mucous membranes of the respiratory, urinary, and reproductive tracts

• *Mucus* traps and allows for the removal of microbes

• Many body fluids including saliva, mucus, and tears are hostile to microbes

• The low pH of skin and the digestive system prevents growth of microbes
Cellular Innate Defenses

White blood cells (leukocytes) engulf pathogens in the body.

Groups of pathogens are recognized by TLR, Toll-like receptors.

EXTRACELLULAR FLUID

Lipopolysaccharide

Helper protein

Flagellin

TLR4

WHITE BLOOD CELL

VESICLE

CpG DNA

TLR9

ds RNA

TLR3

Inflammatory responses
White Blood Cells

• A white blood cell engulfs a microbe, then fuses with a lysosome to destroy the microbe.

• There are different types of phagocytic cells:
  – **Neutrophils** engulf and destroy microbes.
  – **Macrophages** are part of the lymphatic system and are found throughout the body.
  – **Eosinophils** discharge destructive enzymes.
  – **Dendritic cells** stimulate development of acquired immunity.
Inflammatory Responses

- Changes in the **inflammatory response** increase local blood supply and allow more phagocytes and antimicrobial proteins to enter tissues

- *Pus*, a fluid rich in white blood cells, dead microbes, and cell debris, accumulates at the site of inflammation
Following an injury, **mast cells** release **histamine**, which promotes changes in blood vessels.
• Inflammation can be either local or systemic (throughout the body)

• Fever is a systemic inflammatory response triggered by pyrogens released by macrophages, and toxins from pathogens

• *Septic shock* (sepsis) is a life-threatening condition caused by an overwhelming inflammatory response
Natural Killer Cells

- All cells in the body (except red blood cells) have a class 1 MHC protein on their surface.
- Cancerous or infected cells no longer express this protein; natural killer (NK) cells attack these damaged cells.
Innate Immune System Evasion by Pathogens

- Some pathogens avoid destruction by modifying their surface to prevent recognition or by resisting breakdown following phagocytosis
- Tuberculosis (TB) is one such disease and kills more than a million people a year
Concept 43.2: In acquired immunity, lymphocyte receptors provide pathogen-specific recognition

- White blood cells called **lymphocytes** recognize and respond to antigens, foreign molecules

- Lymphocytes that mature in the **thymus** above the heart are called **T cells**, and those that mature in bone marrow are called **B cells**
• Lymphocytes contribute to immunological memory, an enhanced response to a foreign molecule encountered previously

• **Cytokines** are secreted by macrophages and dendritic cells to recruit and activate lymphocytes
Acquired Immunity: An Overview

- B cells and T cells have receptor proteins that can bind to foreign molecules
- Each individual lymphocyte is specialized to recognize a specific type of molecule
Antigen Recognition by Lymphocytes

- An **antigen** is any foreign molecule to which a lymphocyte responds.
- A single B cell or T cell has about 100,000 identical **antigen receptors**.
Fig. 43-9

(a) B cell receptor

(b) T cell receptor

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• All antigen receptors on a single lymphocyte recognize the same **epitope**, or **antigenic determinant**, on an antigen

• B cells give rise to **plasma cells**, which secrete proteins called **antibodies** or **immunoglobulins**
Antigen-binding sites

Antigen

Antibody A

Antibody B

Antibody C

Epitopes (antigenic determinants)
The Antigen Receptors of B Cells and T Cells

- **B cell receptors** bind to specific, intact antigens.
- The B cell receptor consists of two identical **heavy chains** and two identical **light chains**.
- The tips of the chains form a **constant (C) region**, and each chain contains a **variable (V) region**, so named because its amino acid sequence varies extensively from one B cell to another.
Secreted antibodies, or immunoglobulins, are structurally similar to B cell receptors but lack transmembrane regions that anchor receptors in the plasma membrane.
• Each **T cell receptor** consists of two different polypeptide chains

• The tips of the chain form a variable (V) region; the rest is a constant (C) region

• T cells can bind to an antigen that is free or on the surface of a pathogen
- T cells bind to antigen fragments presented on a host cell
- These antigen fragments are bound to cell-surface proteins called MHC molecules
- **MHC** molecules are so named because they are encoded by a family of genes called the **major histocompatibility complex**
The Role of the MHC

• In infected cells, MHC molecules bind and transport antigen fragments to the cell surface, a process called **antigen presentation**

• A nearby T cell can then detect the antigen fragment displayed on the cell’s surface

• Depending on their source, peptide antigens are handled by different classes of MHC molecules
Top view: binding surface exposed to antigen receptors

Antigen

Class I MHC molecule

Plasma membrane of infected cell
• **Class I MHC molecules** are found on almost all nucleated cells of the body

• They display peptide antigens to **cytotoxic T cells**
Infected cell

Antigen

Antigen fragment

Class I MHC molecule

T cell receptor

(a) Cytotoxic T cell

1. Antigen associates with MHC molecule

2. T cell recognizes combination

Microbe

Antigen-presenting cell

Antigen fragment

Class II MHC molecule

T cell receptor

(b) Helper T cell

1. Antigen-presenting cell
• **Class II MHC molecules** are located mainly on dendritic cells, macrophages, and B cells

• Dendritic cells, macrophages, and B cells are **antigen-presenting cells** that display antigens to cytotoxic T cells and **helper T cells**
Lymphocyte Development

• The acquired immune system has three important properties:
  – Receptor diversity
  – A lack of reactivity against host cells
  – Immunological memory
Generation of Lymphocyte Diversity by Gene Rearrangement

- Differences in the variable region account for specificity of antigen receptors

- The *immunoglobulin (Ig)* gene encodes one chain of the B cell receptor

- Many different chains can be produced from the same Ig chain gene by rearrangement of the DNA

- Rearranged DNA is transcribed and translated and the antigen receptor formed
DNA of undifferentiated B cell

1. DNA deleted between randomly selected V and J segments

DNA of differentiated B cell

2. Transcription

pre-mRNA

3. RNA processing

mRNA

4. Translation

Light-chain polypeptide

Variable region

Constant region

B cell receptor

B cell

V C

V C

V C

V C
Origin of Self-Tolerance

- Antigen receptors are generated by random rearrangement of DNA
- As lymphocytes mature in bone marrow or the thymus, they are tested for self-reactivity
- Lymphocytes with receptors specific for the body’s own molecules are destroyed by apoptosis, or rendered nonfunctional
Amplifying Lymphocytes by Clonal Selection

• In the body there are few lymphocytes with antigen receptors for any particular epitope.

• The binding of a mature lymphocyte to an antigen induces the lymphocyte to divide rapidly.

• This proliferation of lymphocytes is called clonal selection.

• Two types of clones are produced: short-lived activated effector cells and long-lived memory cells.
B cells that differ in antigen specificity

Antigen molecules

Antigen receptor

Antibody molecules

Clone of memory cells

Clone of plasma cells
The first exposure to a specific antigen represents the **primary immune response**.

During this time, effector B cells called **plasma cells** are generated, and T cells are activated to their effector forms.

In the **secondary immune response**, memory cells facilitate a faster, more efficient response.
Primary immune response to antigen A produces antibodies to A.

Secondary immune response to antigen A produces antibodies to A; primary immune response to antigen B produces antibodies to B.

Antibody concentration (arbitrary units)

Exposure to antigen A

Exposure to antigens A and B

Time (days)

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Concept 43.3: Acquired immunity defends against infection of body cells and fluids

• Acquired immunity has two branches: the humoral immune response and the cell-mediated immune response

• **Humoral immune response** involves activation and clonal selection of B cells, resulting in production of secreted antibodies

• **Cell-mediated immune response** involves activation and clonal selection of cytotoxic T cells

• Helper T cells aid both responses
Humoral (antibody-mediated) immune response

Antigen (1st exposure)

Engulfed by

Antigen-presenting cell

B cell

Helper T cell

Memory Helper T cells

Plasma cells

Memory B cells

Secreted antibodies

Defend against extracellular pathogens by binding to antigens, thereby neutralizing pathogens or making them better targets for phagocytes and complement proteins.

Cell-mediated immune response

Key

Stimulates

Gives rise to

Cytotoxic T cell

Active Cytotoxic T cells

Memory Cytotoxic T cells

Antigen (2nd exposure)

Defend against intracellular pathogens and cancer by binding to and lysing the infected cells or cancer cells.

Antigen-presenting cell

Helper T cell

Memory B cells

Cytotoxic T cell

Plasma cells

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Helper T Cells: A Response to Nearly All Antigens

• A surface protein called **CD4** binds the class II MHC molecule

• This binding keeps the helper T cell joined to the antigen-presenting cell while activation occurs

• Activated helper T cells secrete cytokines that stimulate other lymphocytes
Antigen-presenting cell

Peptide antigen

Class II MHC molecule
CD4
TCR (T cell receptor)

Helper T cell

Humoral immunity (secretion of antibodies by plasma cells)

B cell

Cytokines

Cytotoxic T cell

Cell-mediated immunity (attack on infected cells)
Cytotoxic T Cells: A Response to Infected Cells

- Cytotoxic T cells are the effector cells in cell-mediated immune response
- Cytotoxic T cells make CD8, a surface protein that greatly enhances interaction between a target cell and a cytotoxic T cell
- Binding to a class I MHC complex on an infected cell activates a cytotoxic T cell and makes it an active killer
- The activated cytotoxic T cell secretes proteins that destroy the infected target cell
Fig. 43-18-3

Cytotoxic T cell

- Perforin
- Granzymes
- CD8
- TCR

Class I MHC molecule

Target cell

- Peptide antigen

Dying target cell

- Pore

Released cytotoxic T cell
B Cells: A Response to Extracellular Pathogens

- The humoral response is characterized by secretion of antibodies by B cells
- Activation of B cells is aided by cytokines and antigen binding to helper T cells
- Clonal selection of B cells generates antibody-secreting plasma cells, the effector cells of humoral immunity
Antigen-presenting cell

Bacterium

Peptide antigen

B cell

Class II MHC molecule

TCR

CD4

Helper T cell

Activated helper T cell

Cloned helper T cell

Cytokines

Clone of plasma cells

Clone of memory B cells

Secreted antibody molecules

Endoplasmic reticulum of plasma cell

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Antibody Classes

- The five major classes of antibodies, or immunoglobulins, differ in distribution and function.
- Polyclonal antibodies are the products of many different clones of B cells following exposure to a microbial antigen.
- **Monoclonal antibodies** are prepared from a single clone of B cells grown in culture.
<table>
<thead>
<tr>
<th>Class of Immunoglobulin (Antibody)</th>
<th>Distribution</th>
<th>Function</th>
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<tbody>
<tr>
<td>IgM (pentamer)</td>
<td>First Ig class produced after initial exposure to antigen; then its concentration in the blood declines</td>
<td>Promotes neutralization and cross-linking of antigens; very effective in complement system activation</td>
</tr>
<tr>
<td>IgG (monomer)</td>
<td>Most abundant Ig class in blood; also present in tissue fluids</td>
<td>Promotes opsonization, neutralization, and cross-linking of antigens; less effective in activation of complement system than IgM</td>
</tr>
<tr>
<td>IgA (dimer)</td>
<td>Present in secretions such as tears, saliva, mucus, and breast milk</td>
<td>Provides localized defense of mucous membranes by cross-linking and neutralization of antigens</td>
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<tr>
<td></td>
<td>Secretory component</td>
<td>Presence in breast milk confers passive immunity on nursing infant</td>
</tr>
<tr>
<td>IgE (monomer)</td>
<td>Present in blood at low concentrations</td>
<td>Triggers release from mast cells and basophils of histamine and other chemicals that cause allergic reactions</td>
</tr>
<tr>
<td>IgD (monomer)</td>
<td>Present primarily on surface of B cells that have not been exposed to antigens</td>
<td>Acts as antigen receptor in the antigen-stimulated proliferation and differentiation of B cells (clonal selection)</td>
</tr>
</tbody>
</table>
The Role of Antibodies in Immunity

• **Neutralization** occurs when a pathogen can no longer infect a host because it is bound to an antibody.

• **Opsonization** occurs when antibodies bound to antigens increase phagocytosis.

• Antibodies together with proteins of the complement system generate a *membrane attack complex* and cell lysis.
Viral neutralization

Opsonization

Bacterium

Macrophage

Activation of complement system and pore formation

Complement proteins

Formation of membrane attack complex

Flow of water and ions

Pore

Foreign cell
Active and Passive Immunization

- **Active immunity** develops naturally in response to an infection.
- It can also develop following **immunization**, also called **vaccination**.
- In immunization, a nonpathogenic form of a microbe or part of a microbe elicits an immune response to an immunological memory.
Passive immunity provides immediate, short-term protection.

It is conferred naturally when IgG crosses the placenta from mother to fetus or when IgA passes from mother to infant in breast milk.

It can be conferred artificially by injecting antibodies into a nonimmune person.
Immune Rejection

- Cells transferred from one person to another can be attacked by immune defenses

- This complicates blood transfusions or the transplant of tissues or organs
Allergies

- Allergies are exaggerated (hypersensitive) responses to antigens called **allergens**

- In localized allergies such as hay fever, IgE antibodies produced after first exposure to an allergen attach to receptors on mast cells
Allergic reactions

• The next time the allergen enters the body, it binds to mast cell–associated IgE molecules

• Mast cells release histamine and other mediators that cause vascular changes leading to typical allergy symptoms

• An acute allergic response can lead to anaphylactic shock, a life-threatening reaction that can occur within seconds of allergen exposure
Autoimmune Diseases

In individuals with autoimmune diseases, the immune system loses tolerance for self and turns against certain molecules of the body.

Autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, and multiple sclerosis.
Immunodeficiency Diseases

- Inborn immunodeficiency results from hereditary or developmental defects that prevent proper functioning of innate, humoral, and/or cell-mediated defenses.

- Acquired immunodeficiency results from exposure to chemical and biological agents.

- **Acquired immunodeficiency syndrome (AIDS)** is caused by a virus.
Latency

- Some viruses may remain in a host in an inactive state called latency.
- Herpes simplex viruses can be present in a human host without causing symptoms.
- Chicken pox lies dormant for years before it returns as shingles.
You should now be able to:

1. Distinguish between innate and acquired immunity
2. Name and describe four types of phagocytic cells
3. Describe the inflammation response
4. Distinguish between the following pairs of terms: antigens and antibodies; antigen and epitope; B lymphocytes and T lymphocytes; antibodies and B cell receptors; primary and secondary immune responses; humoral and cell-mediated response; active and passive immunity.

5. Explain how B lymphocytes and T lymphocytes recognize specific antigens.

6. Explain why the antigen receptors of lymphocytes are tested for self-reactivity.
7. Describe the cellular basis for immunological memory

8. Explain how a single antigen can provoke a robust humoral response

9. Describe an allergic reaction, including the roles of IgE, mast cells, and histamine

10. Describe some of the mechanisms that pathogens have evolved to thwart the immune response of their hosts