Two major kinds of defense that counter the threats.

- **Innate immunity:**
  - present before any exposure to pathogens and is effective from the time of birth
  - quickly recognizing
  - nonspecific

- **Acquired immunity** (adaptive immunity):
  - develops only after exposure to inducing agents
  - specific
  - slow (~10-14 D)
  - achieved by lymphocytes
Overview of vertebrate defenses against bacteria, viruses, and other pathogens

**External defenses (first line)**

1. The skin:
   - Largest organ of the body
   - Makes up about 16% of body weight, Avg. surface area ~1.8 m²
   - Epidermis, dermis and subcutis (fat)
2. Mucous membranes
- mucus, a viscous fluid that traps microbes and other particles.
- microvilli (cilia), sweep mucus and any entrapped microbes

(Goblet cells the trachea)

3. Secretions
eg. mucus, saliva, and tears

- Functions:
  - constantly bathe the surfaces to avoid microbial colonization
  - create acidic environments
    eg. skin, stomach
    Some pathogens would survive (hepatitis A virus)
  - contains antimicrobial proteins.
    eg. lysozyme: digests the cell walls of many bacteria
**Internal defenses (second-line)**

1. **Phagocytosis**
   - Pseudopodia surround microbes (recognized by receptors)
   - Microbes are engulfed into cell.
   - Vacuole containing microbes forms.
   - Vacuole and lysosome fuse.
   - Toxic compounds and lysosomal enzymes destroy microbes.
   - Microbial debris is released by exocytosis.

**Lysosome**
- Found in both plant and animal cells,
- Produced from the **Golgi apparatus** by budding.
- Stabilizes the low pH4.8 by pumping in protons (H+) from the cytosol (pH7).

**Destroyed mechanisms in the lysosomes**
1. **Nitric oxide and other toxic forms of oxygen**
   - Poison the engulfed microbes.
2. **Enzymes (only work in low pH)**
   - Lysozyme, which digests the cell walls of many bacteria
   - Lipase, which digests lipids,
   - Carbohydrases, which digest carbohydrates (e.g., sugars),
   - Proteases, which digest proteins,
   - Nucleases, which digest nucleic acids.
Internal defenses (second-line)

Introduction of Phagocytic Cells: (leukocytes)
- neutrophils
  most abundant, about 60–70% of all WBC
  life span: ~ few days.
  self-destruct in the process of phagocytosis
- macrophages
  develop from monocytes, ~5% of circulating WBC.
  migrated
  reside permanently, eg. in the spleen, lymph nodes

lumphatic system

- Intestinal fluid bathing the tissues, along with the white blood cells in it, continually enters lymphatic capillaries.
- Fluid inside the lymphatic capillaries, called lymph, flows through lymphatic vessels throughout the body.
**Internal defenses (second-line)**

**Eosinophils** 嗜“伊紅”血球 (readily stained with eosin)
- low phagocytic activity
- defense against multicellular parasitic invaders eg. blood fluke 血蛭
- discharge destructive enzymes rather than engulfing

**Dendritic cells**
- ingest microbes like macrophages do
- primary role is to stimulate the development of acquired immunity. (learn later)

---

**Internal defenses (second-line)**

**Antimicrobial Proteins**

- **Complement system**
  - contains ~30 serum proteins
  - triggered by some surface markers of microbes and lyse them
  - trigger inflammation or play a role in acquired defense

- **Interferon: defense against viral infections**
  - interferon (α and β)
  - secreted by virus-infected body cells and induce neighboring uninfected cells to produce substances that inhibit viral reproduction.

  - interferon (γ)
  - secreted by some lymphocytes
  - activate macrophages, enhancing their phagocytic ability.

- **Defensins**
  - secreted by activated macrophages (and neutrophils)
  - Mechanism: Cationic, Chemotactic, Stabilize clotting ……
Internal defenses (second-line)

Inflammatory Response  
(Figure 43.6)

Step 1: dilation and swelling triggered by chemical signals

- **Histamine**: secreted by mast cells found in connective tissues.
  - triggering dilation and increased permeability of nearby capillaries

- **Prostaglandins**: secreted by activated macrophages and other cells
  - promote blood flow to the injured site.

Step 2: deliver clotting elements and antimicrobial proteins

- **Blood clotting**: block the entering and the spread of microbes

- **Antimicrobial proteins** (complements, defensins...)
  - lyse microbes, promote the release of histamine, stabilize the clotting...
Internal defenses (second-line)

Inflammatory Response (Figure 43.6)

Step 3: chemotaxis

Chemokines: secreted from blood vessel endothelial and other cells near a site of injury or infection.

→ direct the migration of the phagocytes (neutrophils and macrophages)

Step 4: phagocytosis

• Neutrophils and macrophages phagocytose pathogens and cell debris
• Bring signals for acquired immunity
**Inflammatory Response**

- Injured cells put out a call for reinforcements and signal amplification
  - Swelling and fever
- Local inflammation
  - Fasten the cleaning process of infection
- Systemic inflammation: caused by a severe infection
  - eg. meningitis (腦膜炎) or appendicitis
  - the number of WBC increase severalfold within hours
  - high fever
  - eg. Septic shock:
  - very high fever and low blood pressure
  - a common cause of death after surgery or bacteria infection

**Internal defenses (second-line)**

- Natural killer (NK) cells
  - Target to virus–infected body cells and cancer cells by their surface receptors.
  - NK cells release chemicals that lead to the death of the stricken cell by apoptosis
- Cell surface markers recognized by NK cells
  - Oligosaccaride
  - MHC (major histocompatibility complex)
**major histocompatibility complex (MHC)**

- Discovery: from the phenomena of skin graft rejection
- Function: carry small peptide to provide a biochemical fingerprint

### Class I MHC molecules
- on almost all nucleated cells

### Class II MHC molecules
- phagocytes, e.g. dendritic cells, macrophages

---

**Express yourself or die: peptides, MHC molecules, and NK cells.**


- normal cell $\rightarrow$ not killed
- mutant (cancer) cell $\rightarrow$ killed
- foreign cell $\rightarrow$ killed
- virus-infected cell $\rightarrow$ killed
**Acquired immunity (third-line)**

- Lymphocytes provide specific defenses induced by
  
  (1) Direct contact with microbes
  
  (2) Signals from active innate defenses cause lymphocytes to join the fight.

**INNATE IMMUNITY**
- Rapid responses to a broad range of microbes - nonspecific

**ACQUIRED IMMUNITY**
- Slower responses to specific microbes

<table>
<thead>
<tr>
<th>External defenses</th>
<th>Internal defenses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Phagocytic cells</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Antimicrobial proteins</td>
</tr>
<tr>
<td>Secretions</td>
<td>Inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Natural killer cells</td>
</tr>
</tbody>
</table>

**Invading microbes (pathogens)**

**Antigens:**
- Molecules that was recognized by lymphocytes and elicits a response

**Epitope (antigenic determinant):**
- A small portion where a lymphocyte actually recognizes and binds

**Figure 43.7 Epitopes**
Lymphocytes (B cells and T cells)

The vertebrate body is populated by two types of lymphocytes: -- B lymphocytes (B cells) and T lymphocytes (T cells)

- A single B or T cell bears about 100,000 antigen receptors
- All the receptors on a single cell are identical

**Lymphocytes (B cells and T cells)**

**Difference 1: receptor conformation**

(a) A B cell receptor consists of two identical heavy chains and two identical light chains linked by several disulfide bridges.

(b) A T cell receptor consists of one α chain and one β chain linked by a disulfide bridge.

Figure 43.8
**Difference 2: antigen recognition**

- B cell receptors recognize an intact antigen in its native state
- T cell receptors recognize small Ag fragments that are bound to MHC presented by Ag presenting cells.

**Why antigen presentation??**

- Easier to kill virus-infected cells before virus amplification than to kill individual virus particles

**Why MHC needed??**
- Duel-specificity model
Two types of MHC molecules

(all nucleated cells)

1. A fragment of foreign protein (antigen) inside the cell associates with an MHC molecule and is transported to the cell surface.

2. The combination of MHC molecule and antigen is recognized by a T cell, alerting it to the infection.

(antigen–presenting cells)

mainly dendritic cells, macrophages, and B cells

Cluster of differentiation (CD) markers, CD8 and CD4, help the selection of MHC molecules

- Cytotoxic T cell (CD4⁻/CD8⁺) → MHC class I
- Helper T cell (CD4⁺/CD8⁻) → MHC class II

Figure 43.9
Overview of lymphocyte development

- Lymphocytes originate from pluripotent stem cells in the bone marrow.

Lymphocyte development

- It is estimated that each person has ~ 1 million different B cells and 10 million different T cells.

Three key events in the life of a lymphocyte

1. Generation of Diversity by Gene Rearrangement
2. Testing and Removal of Self–Reactive Lymphocytes
3. Clonal Selection of Lymphocytes
   - Induced by encountered antigens.
1. Generation of Lymphocyte Diversity by Gene Rearrangement

- DNA of undifferentiated B cell
  - \( V_1 \) \( V_2 \) \( V_3 \) \( V_{10} \) \( J_1 \) \( J_2 \) \( J_3 \) \( J_4 \) \( J_5 \) Introns \( C \)
- DNA of differentiated B cell
  - \( V_1 \) \( V_2 \) \( V_3 \) \( V_{10} \) \( J_1 \) \( J_2 \) \( J_3 \) \( J_4 \) \( J_5 \) Introns \( C \)

- 1. Deletion of DNA between a V segment and J segment and joining of the segments
- 2. Transcription of resulting permanently rearranged, functional gene
- 3. RNA processing (removal of intron; addition of cap and poly (A) tail)
- 4. Translation

eg. immunoglobulin (Ig) genes

2. Testing and Removal of Self–Reactive Lymphocytes

- The rearrangements of antigen receptor genes are random, which may generate receptors against self antigens.
  - Failure of selection can lead to autoimmune diseases

- B cells and T cells are maturing and are tested for potential self–reactivity in the bone marrow, thymus, and even lymphoid organs
  - Lymphocytes with self-targeting receptors will be destroyed
**Clonal selection of B cells**
(antigen–driven cloning of lymphocytes)

Some proliferating cells develop into long-lived memory cells that can respond rapidly upon subsequent exposure to the same antigen. Some proliferating cells develop into short-lived plasma cells that secrete antibodies specific for the antigen.

**secondary immune response (2-7D)**

**The specificity of immunological memory**

- Antibodies produced in the secondary response tend to have greater affinity than those secreted in the primary response.
An overview of the acquired immune response

Humoral immune response

First exposure to antigen

Intact antigens

Antigens engulfed and displayed by dendritic cells

Antigens displayed by infected cells

Activate

Gives rise to

B cell

Helper T cell

Plasma cells

Memory B cells

Active and memory helper T cells

Secrete antibodies that defend against pathogens and toxins in extracellular fluid

Defend against infected cells, cancer cells, and transplanted tissues

Cell-mediated immune response

Secreted cytokines activate

Activate

Gives rise to

Cytotoxic T cell

Memory cytotoxic T cells

Active cytotoxic T cells

Helper T cell

• recognize peptide antigens displayed on phagocytes
  • in turn stimulates the activation of nearby B cells and cytotoxic T cells

The central role of helper T cells
The central role of helper T cells immune responses

**Dendritic cells**
effective in presenting antigens to naive helper T cells in **primary immune response**

**Macrophages**
effective in presenting antigens to memory helper T cells in **secondary immune response**

---

**Cytotoxic T Cells: A Response to Infected Cells and Cancer Cells**

- Cytokines secreted from nearby helper T cells promote cytotoxic T cells to release **perforins** and **proteolytic enzymes** (granzymes).

- Certain cancers and viruses actively reduce the number of **class I MHC molecules** on affected cells, helping them escape detection by cytotoxic T cells.
Express yourself or die: peptides, MHC molecules, and NK cells.


- **Normal cell** → not killed
  - Oligosaccharide conjugate
  - Self MHC class I
  - Self peptide
  - Triggering receptor
  - Inhibitory receptor
  - NK

- **Mutant (cancer) cell** → killed
  - Oligosaccharide conjugate
  - Self MHC class I
  - Self peptide
  - Triggering receptor
  - Inhibitory receptor
  - NK

- **Foreign cell** → killed
  - Foreign MHC class I
  - Foreign peptide
  - Viral peptide
  - NK

- **Virus-infected cell** → killed
  - Foreign MHC class I
  - Foreign peptide
  - Viral peptide
  - NK

---

**B Cells: A Response to Extracellular Pathogens**

- Each plasma cell secretes an estimated 2,000 antibody molecules per second over the cell’s 4– to 5–day life span.
The five classes of immunoglobulins (antibodies)

<table>
<thead>
<tr>
<th>Antibody Class</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM (penta-mer)</td>
<td>First Ig class produced after initial exposure to antigen; then its concentration in the blood declines. Promotes neutralization and agglutination of antigens; very effective in complement activation (see Figure 43.19).</td>
</tr>
<tr>
<td>IgG (monomer)</td>
<td>Most abundant Ig class in blood; also present in tissue fluids. Only Ig class that crosses placenta, thus conferring passive immunity on fetus. Promotes opsonization, neutralization, and agglutination of antigens; less effective in complement activation than IgM (see Figure 43.19).</td>
</tr>
<tr>
<td>IgA (dimer)</td>
<td>Present in secretions such as tears, saliva, mucus, and breast milk. Provides localized defense of mucous membranes by agglutination and neutralization of antigens (see Figure 43.19). Presence in breast milk confers passive immunity on nursing infant.</td>
</tr>
<tr>
<td>IgE (monomer)</td>
<td>Triggers release from mast cells and basophils of histamine and other chemicals that cause allergic reactions (see Figure 43.20).</td>
</tr>
<tr>
<td>IgD (monomer)</td>
<td>Present primarily on surface of naive B cells that have not been exposed to antigens. Acts as antigen receptor in antigen-stimulated proliferation and differentiation of B cells (clonal selection).</td>
</tr>
</tbody>
</table>

Four antibody-mediated mechanisms of antigen disposal

- **Neutralization**: Present in secretions such as tears, saliva, mucus, and breast milk.
- **Agglutination**: Triggers release from mast cells and basophils of histamine and other chemicals that cause allergic reactions.
- **Precipitation**: Present primarily on surface of naive B cells that have not been exposed to antigens.
- **Activation of complement**: Acts as antigen receptor in antigen-stimulated proliferation and differentiation of B cells (clonal selection).
**Antibody-mediated mechanisms of antigen disposal**

- **Binding of antibodies to antigens inactivates antigens by:**
  - Viral neutralization (blocks binding to host)
  - Opsonization (increases phagocytosis)

- **Agglutination of antigen-bearing particles, such as microbes**

- **Precipitation of soluble antigens**

- **Activation of complement system and pore formation**

**Positive immune feedback**
antibodies promote phagocytosis, enables APC to present antigens and stimulate helper T cells, which in turn stimulate the very B cells.

**Activate complement proteins**
To generate a membrane attack complex (MAC) that forms a pore in the membrane.

---

**Applications of immunology**

- **Blood Groups and Transfusions**
  - **Blood types:** A, B, AB, O
  - A-antigen individuals naturally have antibodies against the B antigen, even if they have never been exposed to type B blood!
  - Q: where are the antibodies from??

  - **Explanation**
    The antibodies arise in response to bacterial inhabitants of the body that have epitopes very similar to blood group antigens.

  Polysaccharides on bacteria
  - A-type person
  - Bone marrow
  - Anti-A
  - Anti-B
  - Anti-B Ab
Blood Groups That Can and Cannot Be Safely Combined in Transfusion

<table>
<thead>
<tr>
<th>Recipient’s Blood Group</th>
<th>Antibodies in Recipient’s Blood</th>
<th>Presence (+) or Absence (-) of Transfusion Reaction: Donated Blood Group (Packed Cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-B</td>
<td>A: +, B: --, AB: --, O: --</td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
<td>A: --, B: +, AB: --, O: --</td>
</tr>
<tr>
<td>AB</td>
<td>No anti-A or anti-B</td>
<td>A: --, B: --, AB: --, O: --</td>
</tr>
<tr>
<td>O</td>
<td>Anti-A and anti-B</td>
<td>A: --, B: --, AB: --, O: +</td>
</tr>
</tbody>
</table>

*Individuals with type AB blood are universal recipients (blue row); those with type O blood are universal donors (green column).*

Type AB: “universal recipient”
Type O: “universal donor”

Epitopes: polysaccharides.
- No memory cells are generated.
- Antibodies are always IgM. IgM does not cross the placenta

Difference between T–dependent and T–independent antigens

T–dependent antigens:
Antigens that induce antibody production by B cells with assistance from helper T cells

T–independent antigens
Antigens evoke a B cell response without involvement of helper T cells.
- eg. polysaccharides of many bacterial capsules
  - proteins that make up bacterial flagella
- generates no memory B cells
**Blood Group that can induce IgG and memory response**

- **Rh factor**
  - a protein antigen
  - allows immune responses to induce IgG and memory cells

- Rh(+) contain Rh factor
- Rh(−): lacks the Rh factor, will induce anti-Rh antibody

**A potentially dangerous situation**

Rh(−) mother carries a Rh(+) child
- Rh IgG antibodies can cross the placenta and destroy fetus red blood cells

**Strategy:**
- mother is injected with anti-Rh antibodies around the seventh month of pregnancy and again just after delivering

---

**Problems during Tissue and Organ Transplants**

- **Major histocompatibility complex (MHC)**
  - No two people have identical MHC, except identical twins and “clones”

  **Strategy:**
  - The recipient takes medicines that suppress immune responses

- **Bone marrow transplant**

  **Strategy:**
  - The recipients are treated with irradiation to eliminate their own bone marrow cells, including any abnormal cells.

  **Side effect**
  - New donated lymphocytes will react against the recipient

- **New hope ➔ stem cells and clone**
Autoimmune Diseases

Immune system turns against certain molecules of the body

Systemic lupus erythematosus (lupus)

- Self-antibodies against a wide range of self molecules, including histones and DNA released by the normal breakdown of body cells.
  - skin rashes, fever, arthritis, and kidney dysfunction.

- 1 million sufferers in the U.S.
  - Strikes women nine times more often than men

Butterfly rash of lupus  Damaged kidney (left) caused by immunoglobulin deposits (right)

Autoimmune Diseases

- rheumatoid arthritis 類風濕性關節炎
  - Self-antibodies target to the cartilage and bone of joints

rheumatoid arthritis
- **Inborn (Primary) Immunodeficiencies**
  - An immunodeficiency disease caused by a genetic or developmental defect in the immune system
  - Treatment: bone marrow transplant

- **Acquired (Secondary) Immunodeficiencies**
  - Immune dysfunction develops later in life following exposure to various chemical and biological agents
    - **AIDS (acquired immunodeficiency syndrome)**: caused by a virus
    - Certain cancers that damage the lymphatic system.
    - Drugs used to fight autoimmune diseases or to prevent the rejection of a transplant

- **Human Immunodeficiency Virus (HIV)**
  - A retrovirus (reverse–transcribed, integrated, production of new virus)

- **HIV infected mechanism**
  - Use three proteins that participate in normal immune responses.
  - 1. CD4 molecule on the helper T cells
  - 2. co-receptor 1: chemokine receptor fusin (CXCR4)
    - on all the cell types infected by HIV
  - 3. co-receptor 2: chemokine receptor CCR5
    - only on macrophages and helper T cells

  *Partially defective CCR5 confers increased HIV Resistance*
Death of the helper T cells:

- damaging effects of virus reproduction,
- both infected and uninfected cells may undergo inappropriately timed apoptosis triggered by the virus.

Figure 43.22 A T cell infected with HIV