The Immune System

Innate immunity
Acquired immunity
Antibody Classes
Examples of immune system disorders
Overview

• An animal must defend itself from the many dangerous pathogens it may encounter in the environment.

• Two major kinds of defense have evolved that counter these threats:
  • Innate immunity
  • Acquired immunity, also called adaptive immunity
What are the differences?

**Innate immunity**
- Present before any exposure to pathogens
- Effective from the time of birth
- Involves nonspecific responses to pathogens
- Provides broad defenses against infection

**Acquired immunity**
- Develops only after exposure to inducing agents such as microbes, toxins, or other foreign substances
- Involves a very specific response to pathogens
INNATE IMMUNITY
- Recognition of traits shared by broad ranges of pathogens, using a small set of receptors
- Rapid (ready) response

ACQUIRED IMMUNITY
- Recognition of traits specific to particular pathogens, using a vast array of receptors
- Slower (unready) response

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.
Innate immunity

**Barrier Defenses**

- Barrier defenses include **skin and mucous membranes** of the respiratory, urinary, and reproductive tracts
  - Mucus traps and allows 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
Innate immunity

Internal defenses

Cells of the Immune System: White Blood Cells

- **Lymphocytes**
  - Produce antibodies

- **Phagocytes**
  - Internal cellular defenses depend mainly on phagocytosis
  - *Neutrophils* & *Macrophages* are two types of WBC that do phagocytosis
  - They are produced throughout life by the bone marrow.
  - They work as Scavengers – remove dead cells and microorganisms.
Macrophages

- Larger than neutrophils.
- Found in the organs, not the blood.
- Made in bone marrow as monocytes, called macrophages once they reach organs.
- Long lived
- **Initiate** immune responses as they display antigens from the pathogens to the lymphocytes.

Neutrophils

- 60% of WBCs
- ‘Patrol tissues’ as they squeeze out of the capillaries.
- Large numbers are released during infections
- Short lived – die after digesting bacteria
- Dead neutrophils make up a large proportion of...
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
Phagocytic cells - White blood cells

- A white blood cell engulfs a microbe, then fuses with a lysosome to destroy the microbe
  - attach to their prey via **surface receptors** and engulf them, forming a vacuole that fuses with a lysosome
  - Initiate the **inflammatory response**

Groups of pathogens are recognized by **TLR** [Toll-like receptors]
Phagocytosis

- If cells are under attack they release histamine.
- Histamine plus chemicals from pathogens mean neutrophils are attracted to the site of attack.
- Pathogens are attached to antibodies and neutrophils have antibody receptors.
- Endocytosis of neutrophil membrane $\rightarrow$ phagocytic vacuole $\rightarrow$ Lysosomes attach to phagocytic vacuole $\rightarrow$ pathogen digested by proteases
Antimicrobial Peptides and Proteins

- Numerous proteins function in innate defense by attacking microbes directly by **impeding their reproduction**
- About 30 proteins make up the complement system which can cause **lysis of invading cells** and help trigger inflammation
- **Interferons (IFN)** provide innate defense against **viruses** and help activate macrophages
  - Among the molecules with important biological functions induced by IFN is the double-stranded RNA (dsRNA)-dependent protein kinase (**PKR**), an enzyme with multiple effects in cells, which plays a critical role
Internal defenses

Inflammatory Responses

- Following an injury, mast cells release histamine, which promotes changes in blood vessels; this is part of inflammatory response
- Inflammatory responses are these changes which 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
- 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 is a life-threatening condition caused by an overwhelming
Major events in the local inflammatory response

1. Chemical signals released by activated macrophages and mast cells at the injury site cause nearby capillaries to widen and become more permeable.

2. Fluid, antimicrobial proteins, and clotting elements move from the blood to the site. Clotting begins.

3. Chemokines released by various kinds of cells attract more phagocytic cells from the blood to the injury site.

4. Neutrophils and macrophages phagocytose pathogens and cell debris at the site, and the tissue heals.
Internal defenses

Natural Killer Cells

- Natural killer (NK) cells
  - Patrol the body and attack virus-infected body cells and cancer cells
  - Trigger apoptosis in the cells they attack

- How do Natural killer (NK) cells work?
  - All cells in the body (except red blood cells) have a class-I of MHC (Major Histocompatibility Complex) protein on their surface
  - Cancerous or infected cells no longer express this protein; causing 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

• Mycobacterium Tuberculosis (TB) 
السل is one such disease that kills more than a million of people a year
INNATE IMMUNITY

- Recognition of traits shared by broad ranges of pathogens, using a small set of receptors
- Rapid response

Barrier defenses:
- Skin
- Mucous membranes
- Secretions

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

ACQUIRED IMMUNITY

- Recognition of traits specific to particular pathogens, using a vast array of receptors
- Slower response

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

Cell-mediated response:
- Cytotoxic lymphocytes defend against infection in body cells.

Pathogens (microorganisms and viruses)
Acquired immunity

- **Lymphocytes** the white blood cells recognize and respond to antigens, foreign molecules

- Lymphocytes contribute to *immunological memory*, an enhanced response to a foreign molecule encountered previously

- **Two types of lymphocytic cells:**
  - **T cells**, mature in *Thymus*
  - **B cells**, mature in *Bone marrow* then concentrate in lymph nodes and spleen

Mature (B) and (T) cells then circulate in the blood
Acquired immunity

- Acquired immunity has two responses where Helper T cells aid both:
  1. **Humoral immune response** involves activation and clonal selection of B cells, resulting in production of secreted antibodies
  2. **Cell-mediated immune response** involves activation
The lymphatic system plays an active role in defending the body from pathogens

1. Interstitial fluid bathing the tissues, along with the white blood cells in it, continually enters lymphatic capillaries.

2. Fluid inside the lymphatic capillaries, called lymph, flows through lymphatic vessels throughout the body.

3. Within lymph nodes, microbes and foreign particles present in the circulating lymph encounter macrophages, dendritic cells, and lymphocytes, which carry out various defensive actions.

4. Lymphatic vessels return lymph to the blood via two large ducts that drain into veins near the shoulders.
Antigen Recognition by Lymphocytes

- Lymphocytes are activated by **Cytokines** which are secreted by **macrophages** and **dendritic cells**
- Lymphocyte receptors provide **pathogen-specific recognition**
- 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
- 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
• All antigen receptors on a single lymphocyte recognize the same **Epitope** (or *antigenic determinant*) on an antigen.

• B cells give rise to **effector cells** (or Plasma Cells), which secrete proteins called **Antibodies**.
The Antigen Receptors of B 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.
The Antigen Receptors of T Cells

- 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
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
Immunoglobulin (antibody) gene rearrangement

- The capacity to generate diversity is built into the structure of the Ig light-chain gene.

- A receptor light chain is encoded by three gene segments:
  - a variable (V) segment,
  - a joining (J) segment
  - a constant (C) segment.

- The V and J segments together encode the variable region of the receptor chain, while the C segment encodes the entire constant region.
Immunoglobulin (antibody) gene rearrangement

- DNA sequencing reveals that the light-chain gene contains
  - 40 different \( V \) segments
  - 5 different \( J \) segments
  - a single \( C \) segment

- These alternative copies of the \( V \) and \( J \) segments are arranged within the gene in a series.

- Because a functional gene is built from one copy of each type of segment, the pieces can be combined in 200 (40 \( V \) x 5\( J \) x 1 \( C \)) different ways.
  - The number of different heavy-chain genes is even
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
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
Stem cell

Cell division and gene rearrangement

Elimination of self-reactive B cells

Clonal selection

Formation of activated cell populations

Memory cells

Effector B cells

Receptors bind to antigens

Antigen

Antibody

Microbe
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
  - long-lived Memory cells
In infected cells, MHC molecules bind and transport antigen fragments to the cell surface, a process called "antigen presentation." These antigen fragments are bound to cell-surface proteins called MHC molecules (Major Histocompatibility Complex; they are so named because they
Antigen Presentation

- Different classes of MHC molecules:
  - **Class I MHC molecules**: are found on almost all nucleated cells of the body and display antigens to **cytotoxic T cells**
  - **Class II MHC molecules** are located mainly on dendritic cells, macrophages, and B cells that display to **cytotoxic T cells** and **helper T cells**

![Diagram of Antigen Presentation](image)
Cytotoxic T Cells related to class I MHC

- **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*:
  1. they attach to the cells to be killed and release proteins called **perforins** that create holes in the cell membrane of the target cell, with consequent cell lysis.
  2. they attach to a cell and kill it by triggering
The killing action of cytotoxic T cells

Cytotoxic T cell
- Perforin
- Granymes
- Class I MHC molecule
- CD8
- TCR
- Target cell
- Peptide antigen

Target cell
- Peptide antigen
- MHC molecule

Released cytotoxic T cell
- Pore

Dying target cell
Antigen Presentation

- Different classes of MHC molecules:
  - **Class I MHC molecules**: are found on almost all nucleated cells of the body and display antigens to cytotoxic T cells
  - **Class II MHC molecules**: are located mainly on dendritic cells, macrophages, and B cells that display to cytotoxic T cells and helper T cells

![Diagram of Antigen Presentation](image)

1. Antigen associates with MHC molecule
2. T cell recognizes combination

(a) Cytotoxic T cell
(b) Helper T cell
**Helper T Cells related to class II MHC**

- The two main subpopulations of T cells are:
  - Helper T Cells
  - Cytotoxic T lymphocytes (CTLs).

- **Helper T cells** have a marker called \( \text{CD}4 \) on their surfaces and are, hence, called \( \text{CD}4^+ \) T cells binds to 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.
Acquired immunity

- Acquired immunity has two responses where Helper T cells aid both:
  
  1. **Humoral immune response** involves activation and clonal selection of B cells, resulting in production of secreted antibodies.
  
  2. **Cell-mediated immune response** involves activation...
• **Helper T cells** play very important roles in the immune **response** by being responsible for:
  1. cytokine production (*Many of the following actions are mediated by cytokines*)
  2. interaction with B cells to promote their differentiation into effector cells
  3. activation of macrophages to phagocytose
  4. activation of cytotoxic lymphocytes
  5. induction of an inflammatory reaction
  6. respond to nearly all antigens
The first encounter of a CD4$^+$ or CD8$^+$ T cell with its specific epitope is followed by amplification of that clone.

- some of the cells of this increased population become **effector cells** and some remain **memory helper or memory cytotoxic T cells**, reacting rapidly to the next presentation of the same epitope.
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 effector cells (**plasma cells**), the effector cells of humoral immunity
B cell activation in the humoral immune response
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.
- **Activation of complement system and pore formation**: Antibodies together with proteins of the complement system generate a membrane attack complex and cell lysis.

**Viral neutralization**
- Virus

**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
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>
</tr>
</thead>
<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>
</tbody>
</table>

**J chain**
<table>
<thead>
<tr>
<th>Class of Immunoglobulin (Antibody)</th>
<th>Distribution</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Only Ig class that crosses placenta, thus conferring passive immunity on fetus.
<table>
<thead>
<tr>
<th>Class of Immunoglobulin (Antibody)</th>
<th>Distribution</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>J chain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory component</td>
<td></td>
<td>Presence in <em>breast milk</em> confers passive immunity on nursing infant</td>
</tr>
<tr>
<td>Class of Immuno-globulin (Antibody)</td>
<td>Distribution</td>
<td>Function</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------</td>
<td>----------</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>Class of Immunoglobulin (Antibody)</td>
<td>Distribution</td>
<td>Function</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------</td>
<td>----------</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>

Transmembrane region
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
The exposure to a specific antigen

- The first exposure to a specific antigen represents the “primary immune response”
  - During this time, effector B cells (or 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
Antibodies to A

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.

The specificity of immunological memory
Examples of immune system disorders
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
Blood Groups

- Antigens on red blood cells determine whether a person has blood type A (A antigen), B (B antigen), AB (both A and B antigens), or O (neither antigen)
- Antibodies to nonself blood types exist in the body
- *Transfusion* with incompatible blood leads to destruction of the transfused cells
- *Recipient-donor combinations* can be fatal or safe
Tissue and Organ Transplants

- MHC molecules are different among genetically nonidentical individuals.
- Differences in MHC molecules stimulate rejection of tissue grafts and organ transplants.
- Chances of successful transplantation increase if donor and recipient MHC tissue types are well matched.
- **Immunosuppressive drugs** facilitate transplantation.
- Lymphocytes in bone marrow transplants may cause the donor tissue to reject the recipient.
Exaggerated, self-directed, or diminished immune responses can cause disease

- Disruption in immune system function can elicit or exacerbate disease
  - Some pathogens have evolved to diminish the effectiveness of host immune responses

- If the delicate balance of the immune system is disrupted the effects on the individual can range from minor to often fatal consequences
  - Allergies
  - Autoimmune Diseases
  - Immunodeficiency Diseases
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**
Allergies

- 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, الذئبة الحمامية الجهازية
  - rheumatoid arthritis, التهاب المفاصل الروماتويدي
  - insulin-dependent diabetes
Exertion, Stress, and the Immune System

- **Moderate exercise** improves immune system function

- **Psychological stress** has been shown to disrupt hormonal, nervous, and immune systems
Antigenic Variation

- Through antigenic variation, some pathogens are able to change epitope expression and prevent recognition.

- *The human influenza virus* mutates rapidly, and new flu vaccines must be made each year.

- Human viruses occasionally exchange genes with the viruses of domesticated animals.

- This poses a danger as human immune systems are unable to recognize the new viral strain.
Weeks after infection

Millions of parasites per mL of blood

Antibodies to variant 1 appear

Antibodies to variant 2 appear

Antibodies to variant 3 appear

Variant 1

Variant 2

Variant 3

25
26
27
28

Weeks after infection
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
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.

- **Acquired immune system evasion** by Pathogens
Attack on the Immune System: HIV

- Human immunodeficiency virus (HIV) *infests* helper T cells
- The loss of helper T cells impairs both the humoral and cell-mediated immune responses and leads to AIDS
- HIV eludes the immune system because of antigenic variation and an ability to remain latent while integrated into host DNA
- People with AIDS are highly susceptible to opportunistic infections and cancers that take advantage of an immune system in collapse
- The spread of HIV is a worldwide problem
- The best approach for slowing this spread is
The progress of an untreated HIV infection

- **Latency**
- **AIDS**

**Relative antibody concentration**

**Relative HIV concentration**

**Helper T cell concentration**

Years after untreated infection:
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
Cancer and Immunity

- The frequency of certain cancers increases when the immune response is impaired

- Two suggested explanations are
  - Immune system normally suppresses cancerous cells
  - Increased inflammation increases the risk of cancer