The Immune System:

Innate and Adaptive Body Defenses
Lymphatic System

- Lymphatic vessels transport fluid from interstitial spaces to the bloodstream.

**Function:**

- Carries fluid lost from capillaries. This fluid returns to blood in right lymphatic & thoracic ducts.

- Transports products of fat digestion.

- It is a major component of the immune system.
Lymph movement

- Lymphatic capillaries are microscopic, closed-ended tubes that begin in interstitial spaces of most tissues.

- Lymphatic vessels recycle excess tissue fluid that accumulates in interstitium as a result of normal capillary leakage.

- The walls of lymphatic vessels act as one-way valves, only letting fluid enter.

- Along the way, lymph is filtered through several lymph nodes where it is inspected for foreign substances. Upon reaching thoracic duct, lymph re-enters circulation.
Lymph nodes

They are lymph glands that located along lymphatic pathways. They contain large numbers of lymphocytes & macrophages that fight invading microorganisms, as lymph moves through. The germinal centers are sites of lymphocyte production.
Lymph Organs
Tonsils: They are large groups of lymph nodules in the oral cavity & nasopharynx. The three groups of tonsils (a pair of palatine tonsils, a pair of lingual tonsils, & a single pharyngeal tonsil).
Spleen: its Parenchyma of consists of two types of tissue:

Red pulp consists of sinuses & destroys worn-out RBC.

White pulp consists primarily of lymphocytes & macrophage. Foreign substances in blood passing through white pulp & stimulate lymphocytes.
Thymus:

It produces & matures T lymphocytes, which then move to other lymphatic tissues, where they can respond to foreign substances.

Thymus secretes 2 Hs, thymopoietin & thymosins, which stimulate development & activity of T lymphocytes.
Immunity

The ability to resist damage from foreign substances such as microorganisms (m.o).

It divided into:

Innate (non specific immunity),

Adaptive (specific immunity).
Innate immunity:

- Body recognizes & destroys certain foreign substances & the response to them is the same each time.

- Its main components are:

  1- Mechanical (Physical Barrier): e.g: skin, acidity of stomach, & cilia of respiratory tract.

  2- Chemical mediators:

    a- May found on surface of cells (e.g: lysozyme).

    b- Others such as complements, prostaglandins & cytokines.

  3- Cells involved in phagocytosis.
1. Phagocytes

- **Macrophages** are the chief phagocytic cells

- Free macrophages wander throughout a region in search of cellular debris

- **Kupffer cells (liver)** and **microglia (brain)** are fixed macrophages

- **Neutrophils** become phagocytic when encountering infectious material

- **Eosinophils** are weakly phagocytic against parasitic worms
Mechanism of Phagocytosis

1. Microbe adheres to phagocyte
2. Phagocyte forms pseudopods that eventually engulf the particle
3. Phagocytic vesicle is fused with a lysosome (phagolysosome)
4. Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body
5. Indigestible and residual material is removed by exocytosis
2. Natural Killer (NK) Cells

- large granular lymphocytes found in the lymph nodes, spleen, bone marrow, and blood.
- React nonspecifically and eliminate cancerous and virus-infected cells
- Kill their target cells by releasing perforins and other cytolytic chemicals that breaks down the cell membrane, but the way in which they find their targets is not yet completely understood.
- Secrete potent chemicals that enhance the inflammatory response
4 a. Interferon (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a virus.

- Interferon molecules leave the infected cell and enter neighboring cells.

- Interferon stimulates the neighboring cells to activate genes for PKR (an antiviral protein).

- PKR nonspecifically blocks viral reproduction in the neighboring cell.
Interferon (IFN)

**Host Cell 1**
Infected by virus; makes interferon; is killed by virus

**Host Cell 2**
Entered by interferon from cell 1; interferon induces changes that protect it
4 a. Interferon (IFN)

- This substance was first found in cells infected with influenza virus, and it was called interferon because it “interferes” with multiplication and spread of the virus.

- They now are produced by genetic engineering in microorganisms & used to treat certain viral infections, such as hepatitis.

- They have been used with varying success to boost the immune response in the treatment of malignancies, such as leukemia, and cancer associated with AIDS.

- Interestingly, interferon is used to treat autoimmune disorder multiple sclerosis, because it stimulates cells that depress immune response.

- Types: gamma (γ) alpha (α) & beta (β) interferon

- Interferons also activate macrophages and mobilize NKs
4 b. Complement

- 20 or so proteins that circulate in the blood in an inactive form
- Proteins include C1 through C9, factors B, D, and P, and regulatory proteins
- Provides a major mechanism for destroying foreign substances in the body
- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses
- Once activated, complement proteins enhance inflammatory response, form a membrane attack complex (MAC), which destroys microbial membranes, or bind to microbial membrane to enhance phagocytosis, a process called opsonization.
Complement Pathways

- Complement can be activated by two pathways: classical and alternative.

- Classical pathway is linked to the immune system:
  - Depends on the binding of antibodies to invading organisms.
  - Subsequent binding of C1 to the antigen-antibody complexes (complement fixation).

- Alternative pathway is triggered by interaction among factors B, D, and P, and polysaccharide molecules present on microorganisms.
Classical pathway

1. Antibody binds to foreign cell
2. Exposes complement-binding sites on antibody
3. Antibody binds complement proteins C1, C2, and C4
4. C3 splits into fragments C3a and C3b
5. C3a stimulates mast cells and basophils
   - Secrete inflammatory chemicals
6. C3b activates complement proteins C5b to C9 (membrane attack complex)
7. C5b to C9 bind to enemy plasma membrane, creating a hole
8. Binds neutrophils and macrophages
   - Promotes phagocytosis

Alternate pathway

1. Complement factors B, D, and P bind to polysaccharides of microbial cell walls
2. Complement protein C3
3. C3b coats bacterial surfaces
4. Holes allow fluids and salts to enter the bacterium
5. Bacterium expands until it bursts

Summary:
- Inflammation
- Cytolysis
- Opsonization
Cytokines: they are polypeptides produced by virus-infected cells, stimulate many parts of immune system including specific immunity.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
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<tbody>
<tr>
<td>Colony-stimulating factors</td>
<td>Stimulate bone marrow to produce lymphocytes</td>
</tr>
<tr>
<td>Interferons</td>
<td>Block viral replication, stimulate macrophages to engulf viruses, stimulate B cells to produce antibodies, attack cancer cells</td>
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<tr>
<td>Interleukens</td>
<td>Control lymphocyte differentiation and growth</td>
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<tr>
<td>Tumor necrosis factor</td>
<td>Stops tumor growth, releases growth factors, causes fever that accompanies bacterial infection, stimulates lymphocyte differentiation</td>
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</table>
Inflammation
(inflammatory response)

Is a complex sequence of events involving chemical mediators & cells of innate immunity. **Fever** is a nonspecific immune response to infection. Upon recognition of bacterial invasion, lymphocytes release pyrogen that signal to brain to ↑ body temperature which leads to:
 - Creates an unfavorable environment for microbial growth.
 - Enhances the normal immune response.
3. Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are injured
  - Prevents the spread of damaging agents to nearby tissues
  - Disposes of cell debris and pathogens
  - Sets the stage for repair processes
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain
Inflammation Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid

- Inflammatory mediators (chemicals):
  - Include kinins, prostaglandins (PGs), complement, and cytokines
  - Are released by injured tissue, phagocytes, lymphocytes, and mast cells
  - Cause local small blood vessels to dilate, resulting in hyperemia
Inflammatory Response : Vascular Permeability

- Chemicals liberated by the inflammatory response increase the permeability of local capillaries.
- Exudate (fluid containing proteins, clotting factors, and antibodies):
  - Seeps into tissue spaces causing local edema (swelling), which contributes to the sensation of pain.
Inflammatory Response: Edema

- The surge of protein-rich fluids into tissue spaces (edema):
  - Helps to dilute harmful substances
  - Brings in large quantities of oxygen and nutrients needed for repair
  - Allows entry of clotting proteins, which prevents the spread of bacteria
Inflammatory Response: Phagocytic Mobilization

Neutrophils enter blood from bone marrow

1. Neutrophils enter blood from bone marrow
2. Margination
3. Diapedesis
4. Positive chemotaxis

Inflammatory chemicals diffusing from the inflamed site act as chemotactic agents
Complete Antigens

- Important functional properties:
  - **Immunogenicity** – the ability to stimulate proliferation of specific lymphocytes and antibody production
  - **Reactivity** – the ability to react with the products of the activated lymphocytes and the antibodies released in response to them
Haptens (Incomplete Antigens)

- **Small molecules**, such as peptides, nucleotides, and many hormones,
  - not immunogenic (*does not stimulate a response*)
  - reactive when attached to protein carriers
- If they link up with the body’s proteins, the adaptive immune system may recognize them as foreign and mount a harmful attack (**allergy**)
- Haptens are found in **poison ivy, dander, some detergents, and cosmetics**

**Haptens** are small molecules capable of combining with larger molecules like blood proteins to stimulate adaptive immune response.

E.g. of Hapten is **Pencillin**.
Antigenic Determinants

- Only certain parts of an entire antigen are immunogenic

- Antibodies and activated lymphocytes bind to these antigenic determinants

- Most naturally occurring antigens have numerous antigenic determinants that:
  - Mobilize several different lymphocyte populations
  - Form different kinds of antibodies against it

- Large, chemically simple molecules (e.g., plastics) have little or no immunogenicity
Antigenic Determinants

Figure 21.6

Antigen

Antibody A

Antibody B

Antibody C

Antigen-binding sites

Antigenic determinants
Adaptive Immunity

- The ability to recognize, responds to, & remembers a particular substance or antigen.
- Adaptive immunity, response during 2\textsuperscript{nd} exposure is faster & stronger than 1\textsuperscript{st} exposure.
- It is divided into: Humeral & cell mediated immunity.
Cell-Mediated Immunity

This mechanism of immunity does not result in production of Abs, but it is effective against intracellular pathogens (e.g. virus), fungi, malignant cells & grafts of foreign tissue.
Importance of Cellular Response

- T cells recognize and respond only to processed fragments of antigen displayed on the surface of body cells.
- T cells are best suited for cell-to-cell interactions, and target:
  - Cells infected with viruses, bacteria, or intracellular parasites
  - Abnormal or cancerous cells
  - Cells of infused or transplanted foreign tissue

Chapter 21, Immune System
Cell Mediated Immunity

- Recognition of foreign Ag by macrophages & helper T cells (called CD4 T cells), which become activated. These activated T cells, which are antigen specific, divide many times to form **memory T cells** & **cytotoxic (killer) T cells** (called CD8 T cells).

- Memory T cells will remember the specific foreign Ag & become active if it enters the body again, & will quickly initiate response.

- Cytotoxic T cells destroy foreign Ags by:
  1. Disrupting cell membranes so, destroy cells infected with viruses & prevent the viruses from reproducing.
  2. Also produce cytokines, that attract macrophages to the area & activate them to phagocytize foreign Ag & cellular debris.

- CD4 & CD8 T cells also produce feedback chemicals to limit the immune response once the foreign antigen has been destroyed.
Antibody-Mediated Immunity

This mechanism of immunity does involve production of antibodies.
Importance of Humoral Response

- Soluble antibodies
  - The simplest ammunition of the immune response
  - Interact in *extracellular* environments such as body secretions, tissue fluid, blood, and lymph
Recognition of the foreign Ag, this time by B cells as well as by macrophages & helper T cells. The sensitized helper T cell presents the foreign Ag to B cells, which provides a strong stimulus for activation of B cells specific for this Ag. Activated B cells begin to divide many times, & 2 types of cells are formed.

Some of new B cells produced are memory B cells, which will remember the specific Ag & initiate a rapid response upon 2nd exposure.

Other B cells become plasma cells that produce Abs specific for this foreign Ag.
B Antibody-mediated

Macrophage

Self antigens

Receptor sites

Helper T cells

Memory B cell

B cell

Plasma cell

Antibodies

Opsonization

Antigen-antibody complex

Complement fixation

Lysis of cellular antigen
Active Humoral Immunity

- B cells encounter antigens and produce antibodies against them
  - Naturally acquired – response to a bacterial or viral infection
  - Artificially acquired – response to a vaccine of dead or attenuated pathogens
    - Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive

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Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
  - B cells are not challenged by antigens
  - Immunological memory does not occur
  - Protection ends when antigens naturally degrade in the body

- Naturally acquired – from the mother to her fetus via the placenta

- Artificially acquired – from the injection of serum, such as gamma globulin
Types of Acquired Immunity

- **Acquired immunity**
  - **Naturally acquired**
    - **Active**: Infection; contact with pathogen
    - **Passive**: Antibodies pass from mother to fetus via placenta; or to infant in her milk
  - **Artificially acquired**
    - **Active**: Vaccine; dead or attenuated pathogens
    - **Passive**: Injection of immune serum (gamma globulin)
Antibodies

- Also called immunoglobulins
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with that antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE
Basic Antibody Structure

- Consists of four looping polypeptide chains linked together with disulfide bonds
  - Two identical heavy (H) chains and two identical light (L) chains
- The four chains bound together form an antibody monomer
- Each chain has a variable (V) region at one end and a constant (C) region at the other
- Variable regions of the heavy and light chains combine to form the antigen-binding site
Basic Antibody Structure

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Figure 21.12a, b
Antibody Structure

- Antibodies responding to different antigens have different V regions but the C region is the same for all antibodies in a given class.

- C regions form the stem of the Y-shaped antibody and:
  - Determine the class of the antibody
  - Serve common functions in all antibodies
  - Dictate the cells and chemicals that the antibody can bind to
  - Determine how the antibody class will function in elimination of antigens
Antibody Targets

- Antibodies themselves do not destroy antigen; they inactivate and tag it for destruction
- All antibodies form an antigen-antibody (immune) complex
- Defensive mechanisms used by antibodies are neutralization, agglutination, precipitation, and complement fixation
# Antibody Responses

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Prevention of attachment</td>
<td>A pathogen coated with antibody is prevented from attaching to a cell.</td>
</tr>
<tr>
<td>Clumping of antigen</td>
<td>Antibodies can link antigens together, forming a cluster that phagocytes can ingest.</td>
</tr>
<tr>
<td>Neutralization of toxins</td>
<td>Antibodies bind to toxin molecules to prevent them from damaging cells.</td>
</tr>
<tr>
<td>Help with phagocytosis</td>
<td>Phagocytes can attach more easily to antigens that are coated with antibody.</td>
</tr>
<tr>
<td>Activation of complement</td>
<td>When complement attaches to antibody on a cell surface, a series of reactions begins that activates complement to destroy cells.</td>
</tr>
<tr>
<td>Activation of NK cells</td>
<td>NK cells respond to antibody adhering to a cell surface and attack the cell.</td>
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</tbody>
</table>
Antigen-Presenting Cells (APCs)

- Major roles in immunity are:
  - To engulf foreign particles
  - To present fragments of antigens on their own surfaces, to be recognized by T cells
- Major APCs are dendritic cells (DCs), macrophages, and activated B cells.
Lymphocytes

- Immature lymphocytes released from bone marrow are essentially identical

- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
  - B cells mature in the bone marrow
  - T cells mature in the thymus
Two major populations of T cells mediate cellular immunity

- **CD4 cells** (T4 cells) are primarily **helper T cells** (**$T_H$**)
- **CD8 cells** (T8 cells) are **cytotoxic T cells** (**$T_C$**), that destroy cells harboring foreign antigens

Other types of T cells are:

- **Suppressor T cells** (**$T_S$**)
- **Memory T cells**
Major Types of T Cells

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Cells of the Adaptive Immune System

- Two types of lymphocytes
  - B lymphocytes – oversee humoral immunity
  - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity

- Antigen-presenting cells (APCs):
  - Do not respond to specific antigens
  - Play essential auxiliary roles in immunity
Both types of MHC proteins are important for T cell activation.

- Class I MHC proteins:
  - Always recognized by CD8 T cells
  - Display peptides from endogenous antigens
Class I MHC Proteins

1. Endogenous antigen degraded by protease
2. Endogenous antigen peptides enter ER via TAP
3. Endogenous antigen peptide loaded onto class I MHC
4. Loaded MHC protein migrates to the plasma membrane, where it displays the antigenic peptide

Figure 21.15a
Class II MHC Proteins

1. Bacterium (pathogen phagocytosed)
2. After synthesis at the ER, the class II MHC protein, with the invariant chain still attached, migrates to the phagolysosome.
3. In phagolysosome, antigen degraded and invariant chain removed for peptide loading.
4. Loaded MHC protein migrates to the plasma membrane.

Extracellular fluid

Antigenic peptide

Plasma membrane of an APC

Class II MHC

ER cisterna

Invariant chain prevents class II MHC binding to peptides in the ER

Cytoplasm

Lysosome merges with phagosome, forming a phagolysosome
T Cell Activation: Step One – Antigen Binding

- Viral antigen
- Processed viral antigen (peptide) presented in combination with class I MHC protein
- Class I MHC protein
- CD8 protein
- Immunocompetent cytotoxic T cell
- T cell receptor (TCR)
- Infected tissue cell presenting antigenic peptide recognized by cytotoxic T cell

Clone formation

- Cytotoxic T memory cell
- Mature cytotoxic T cells
Immunocompetent T cells are activated when the V regions of their surface receptors bind to a recognized antigen.

T cells must *simultaneously* recognize:

- Nonself (the antigen)
- Self (a MHC protein of a body cell)
Self-Antigens: MHC Proteins

- **Our cells** are dotted with protein molecules (self-antigens) that are **not antigenic to us** but are strongly antigenic to others *(reason for transplant rejection)*

- One type of these, MHC proteins, mark a cell as self

- The two classes of MHC proteins are:
  - **Class I MHC proteins** – found on virtually all body cells
  - **Class II MHC proteins** – found on certain cells in the immune response
MHC Proteins

- Are **coded for by genes** of the major histocompatibility complex (MHC) and are unique to an individual.

- Each MHC molecule has a deep groove that displays a peptide, which is a normal cellular product of protein recycling.

- In infected cells, MHC proteins bind to fragments of foreign antigens, which play a crucial role in mobilizing the immune system.
Helper T Cells ($T_H$)

- Regulatory cells that play a central role in the adaptive immune response

- Once primed by APC presentation of antigen, they:
  - Chemically or directly stimulate proliferation of other T cells
  - Stimulate B cells that have already become bound to antigen

- Without $T_H$, there is no immune response
Helper T Cells ($T_H$)

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Helper T Cell

- $T_H$ cells interact directly with B cells that have antigen fragments on their surfaces bound to MHC II receptors

- $T_H$ cells **stimulate B cells to divide** more rapidly and begin antibody formation

- B cells may be activated without $T_H$ cells by binding to T cell–independent antigens

- Most antigens, however, require $T_H$ co-stimulation to activate B cells

- Cytokines released by $T_H$ amplify nonspecific defenses
Helper T Cells

Activated B cell

Helper T cell CD4 protein

Interleukins 13 and 4 released by helper T cell

Activated helper T cell

MHC II receptor of B cell displaying processed antigen

TCR

Figure 21.17b

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Cytotoxic T Cell (T_c)

- T_c cells, or killer T cells, are the only T cells that can directly attack and kill other cells.
- They circulate throughout the body in search of body cells that display the antigen to which they have been sensitized.
- Their targets include:
  - Virus-infected cells
  - Cells with intracellular bacteria or parasites
  - Cancer cells
  - Foreign cells from blood transfusions or transplants.
Cytotoxic T Cells

- Bind to self-antiself complexes on all body cells
- Infected or abnormal cells can be destroyed as long as appropriate antigen and co-stimulatory stimuli (e.g., IL-2) are present
- Natural killer cells activate their killing machinery when they bind to MICA receptor
- MICA receptor – MHC-related cell surface protein in cancer cells, virus-infected cells, and cells of transplanted organs
Mechanisms of T_c Action

- In some cases, T_C cells:
  - Bind to the target cell and release perforin into its membrane
    - In the presence of Ca^{2+} perforin causes cell lysis by creating transmembrane pores
  - Other T_C cells induce cell death by:
    - Secreting lymphotoxin, which fragments the target cell’s DNA
    - Secreting gamma interferon, which stimulates phagocytosis by macrophages
Mechanisms of T<sub>c</sub> Action

![Diagram of T<sub>c</sub> cell action](image)
Other T Cells

- Suppressor T cells (T<sub>S</sub>) – regulatory cells that release cytokines, which suppress the activity of both T cells and B cells

- Gamma delta T cells (T<sub>gd</sub>) – 10% of all T cells found in the intestines that are triggered by binding to MICA receptors