Lymphatic System

- Organs, vessels and a fluid called lymph
  - similar to interstitial fluid
- Organs and structures involved
  - red bone marrow
  - thymus
  - spleen
  - lymph nodes
  - diffuse lymphatic tissue
    - tonsils, adenoids & peyers patches
Functions of the Lymphatic System

• Draining excess interstitial fluid from tissue spaces
• Transporting dietary lipids & vitamins from GI tract to the blood
• Facilitating immune responses
Lymphatic Vessels & Circulation

- Capillaries that begin as closed-ended tubes found in spaces between cells
- Combine to form lymphatic vessels
  - resemble veins with thin walls & more valves
- Fluid flows through lymph nodes towards large veins (subclavian veins) above the heart
  - lymph emptied into bloodstream
Lymphatic Capillaries

- Found throughout the body except in Avascular tissue (cartilage, epidermis & cornea)
- Structure is designed to let tissue fluid in but not out
Formation & Flow of Lymph

- Fluid & proteins escaping from vascular capillaries is collected by lymphatic capillaries & returned to the blood
- Lymphatic vessels empty into subclavian veins
Lymphatic Organs & Tissues

• Widely distributed throughout the body
• Primary lymphatic organs
  – provide environment for stem cells to divide & mature into B and T lymphocytes
    • red bone marrow gives rise to mature B cells
    • thymus is site where T cells mature
• Secondary lymphatic organs & tissues
  – site where most immune responses occur
    • lymph nodes, spleen & lymphatic nodules
Thymus Gland
(Primary lymphatic organ)

- Large organ in infants (70 g) but atrophied as adult (3 g)
- 2 lobed organ located in mediastinum
- Each lobule has cortex & medulla
- Cortex
  - tightly packed lymphocytes, macrophages, and epithelial cells
  - Epithelial cells help “educate” T cells
- Medulla
  - Same cells but less dense
  - Hassall’s corpuscles- clusters of dying cells, function unknown
Lymph Nodes
(secondary lymphatic organ)
Lymph Nodes

- Bean-shaped organs, up to 1 inch long, located along lymphatic vessels
  - scattered throughout body but concentrated near mammary glands, axillae & groin

- cortex
  - lymphatic nodules containing dendritic cells
    - antigen-presenting cells and macrophages
  - B cells proliferate into antibody-secreting plasma cells

- medulla
  - contains B cells & plasma cells in a network of reticular fibers and reticular epithelial cells
Lymph Nodes

- Flow is in one direction
  - afferent vessels lead in
  - sinuses lead to efferent vessels that exit at hilus
- Only nodes filter lymph
Metastasis Through Lymphatic System

- Characteristic of malignant tumors
- Spread of disease from one organ to another
  - cancer cells travel via blood or lymphatic system
  - cells establish new tumors where they lodge
- Secondary tumor sites can be predicted by direction of lymphatic flow from primary site
- Cancerous lymph nodes are firm, enlarged and nontender -- infected lymph nodes are not firm and are very tender
Spleen—secondary lymphatic organ

- 5 inch organ between stomach & diaphragm
- Hilus contains blood & lymphatic vessels
- White pulp and red pulp
  - white is lymphatic tissue (lymphocytes & macrophages) around branches of splenic artery
  - red pulp is venous sinuses filled with blood & splenic tissue (splenic cords)
Functions of Spleen

White pulp:

Lymphocytes and macrophages destroy foreign substances

Red pulp:

1. Removal of damaged blood cells
2. Storage of platelets
3. Production of blood cells during fetal life
Lymphatic Nodules

- Concentrations of lymphatic tissue not surrounded by a capsule scattered throughout connective tissue of mucous membranes
  - mucosa-associated lymphoid tissue (MALT)
- Peyer’s patches in the ileum of the small intestine
- Appendix
- Tonsils form ring at top of throat
  - adenoids (pharyngeal tonsil)
  - palatine tonsils (on each side wall)
  - lingual tonsil in the back of the tongue
Resistance
Ability to ward off damage or disease

• Nonspecific resistance
  – general defensive mechanisms effective on a wide range of pathogens

• Specific resistance (immunity)
  – Ability to fight a specific pathogen
  – cell-mediated immunity (T cells)
  – antibody-mediated immunity (B cells)
Nonspecific Resistance to Disease

• Immediate protection against wide variety of pathogens & foreign substances
  – lacks specific responses to specific invaders

• Mechanisms function regardless of type of invader
  – external mechanical & chemical barriers
  – internal nonspecific defenses
    • antimicrobial proteins
    • natural killer cells & phagocytes
    • inflammation & fever
Skin & Mucous Membranes

• Mechanical protection
  – skin (epidermis) closely packed, keratinized cells
    • shedding helps remove microbes
  – mucous membrane secretes viscous mucous
    • cilia & mucus trap & move microbes toward throat
  – washing action of tears, urine and saliva

• Chemical protection
  – sebum inhibits growth bacteria & fungus
  – perspiration lysozymes breakdown bacterial cells
  – acidic pH of gastric juice and vaginal secretions destroys bacteria
Internal Defenses

- Antimicrobial proteins discourage microbial growth
  - interferons
    - produced by virally infected lymphocytes & macrophages
    - diffuse to neighboring cells to induce synthesis of antiviral proteins
  - complement proteins
    - inactive proteins in blood plasma
    - when activated enhance immune, allergic & inflammatory reactions
  - transferrins
    - iron-binding proteins inhibit bacterial growth by reducing available iron
Natural Killer Cells & Phagocytes

• NK cells kill a variety of microbes & tumor cells
  – found in blood, spleen, lymph nodes & red marrow
  – attack cells displaying abnormal MHC antigens

• Phagocytes (neutrophils & macrophages)
  – ingest microbes or particulate matter
  – macrophages developed from monocytes
    • fixed macrophages stand guard in specific tissues
      – kupffer cells in the liver
    • wandering macrophages in most tissue
Phagocytosis

- **Chemotaxis**
  - attraction to chemicals from damaged tissues, complement proteins, or microbial products

- **Adherence**
  - attachment to plasma membrane of phagocyte

- **Ingestion**
  - engulf by pseudopods to form phagosome

- **Digestion & killing**
  - merge with lysosome containing digestive enzymes
  - exocytosis residual body
Inflammation

• Damaged cell initiates

• Signs of inflammation
  – redness
  – heat
  – swelling
  – pain

• Function is to trap microbes, toxins or foreign material & begin tissue repair
Fever

• Abnormally high body temperature that occurs because the hypothalamic thermostat is reset
• Occurs during infection & inflammation
  – bacterial toxins trigger release of fever-causing cytokines such as interleukin-1
• Benefits
  – intensifies effects of interferons, inhibits bacterial growth, speeds up tissue repair
Specific Resistance: Immunity

- Immunity is the body's ability to defend itself against specific foreign material or organisms – bacteria, toxins, viruses, cat dander, etc.
- Differs from nonspecific defense mechanisms – specificity----recognize self & non-self – memory----2nd encounter produces even more vigorous response
- Immune system is cells and tissues that produce the immune response
- Immunology is the study of those responses
Maturation of T and B Cells

- **T cell mature in thymus**
  - Cell-mediated response
  - Cell directly attacks the invading antigen
  - Effective against fungi, viruses, parasites, cancer, and tissue transplants

- **B cells in bone marrow**
  - Antibody-mediated response
  - Plasma cells secrete antibodies which affect antigens
  - Effective against bacteria
Antigens

• Molecules or bits of foreign material
  – entire microbes, parts of microbes, bacterial toxins, pollen, transplanted organs, incompatible blood cells

• Required characteristics to be considered an antigen
  – immunogenicity = ability to provoke immune response
  – reactivity = ability to react to cells or antibodies

• Get past the bodies nonspecific defenses
  – enter the bloodstream to be deposited in spleen
  – penetrate the skin & end up in lymph nodes
  – penetrate mucous membrane & lodge in associated lymphoid tissue
Chemical Nature of Antigens/Epitopes

- Large, complex molecules, usually proteins
  - if have simple repeating subunits are not usually antigenic (plastics in joint replacements)
  - small part of antigen that triggers the immune response is epitope
Diversity of Antigen Receptors

• Immune system can recognize and respond to a billion different epitopes -- even artificially made molecules.

• Explanation for great diversity of receptors is genetic recombination of few hundred small gene segments.

• Each B or T cell has its own unique set of gene segments that codes its unique antigen receptor in the cell membrane.
Major Histocompatibility Complex Antigens

- All our cells have unique surface markers (1000s molecules)
- MHC-I molecules are found in cell membrane of all cells except red blood cells
- MHC-II markers seen only on membrane of antigen presenting cells (macrophages, B cells, thymus cells)
- Function
  - if cell is infected with virus MHC-I contain bits of virus marking cell so T cells recognize there is a problem
  - if antigen presenting cells (macrophages or B cells) ingest foreign proteins, they will display as part of their MHC-II
Pathways of Antigen Processing

- B and T cells must recognize a foreign antigen before beginning their immune response
  - B cells can bind to antigen in extracellular fluid
  - T cells can only recognize fragments of antigens that have been processed and presented to them as part of a MHC molecule
    - Helper T cells “see” antigens if they are part of MHC-II molecules on surface of antigen presenting cell
    - Cytotoxic T cells “see” antigens if they are part of MHC-I molecules on surface of body cells
Processing of Exogenous Antigens

- Foreign antigen in body fluid is phagocytized by APC – macrophage, B cell, dendritic cell (Langerhans cell in skin)
- Antigen is digested and fragments are bound to MHC-II molecules stuck into antigen presenting cell membrane
- APC migrates to lymphatic tissue to find T cells
Processing of Endogenous Antigens

• Endogenous antigens are foreign proteins produced within a body cell --- viral or cancerous

• Fragments of proteins become part of MHC-I molecules displayed at surface of cell

• T cells recognize the antigen presented by the MHC-I molecule as foreign and initiates immune response.
Cell-Mediated Immunity

• Begins with activation of T cell by a specific antigen
• Result is T cell capable of an immune attack
  – elimination of the intruder by a direct attack
Activation, Proliferation & Differentiation of Cytotoxic T Cells

- Receptor on T cell binds to foreign antigen fragment part of MHC-I
- Costimulation from helper T cell
  - prevents accidental immune response
- Proliferates & differentiates into population (clone) of Tc cells and memory Tc cells
- Occurs in secondary lymphatic organs such as lymph node
Activation, Proliferation & Differentiation of Helper T Cells

- Receptor on CD4 cell binds to foreign antigen fragment associated with MHC-II
- Costimulation
- Proliferates & differentiates into population (clone) of T<sub>H</sub> cells and long-lived memory T<sub>H</sub> cells
Types of Mature T Cells

- Helper T cells (CD4)
- Cytotoxic (killer) T cells (CD 8)
- Memory T cells
Helper T Cells

- Display CD4 on surface so also known as T4 cells or $T_\text{H}$ cells
- Recognize antigen fragments associated with MHC-II molecules & activated by APCs
- Function is to costimulate all other lymphocytes
  - secrete cytokines (small protein hormones)
    - autocrine function in that it costimulates itself to proliferate and secrete more interleukin (positive feedback effect causes formation of many more helper T cells)
**Cytotoxic T Cells**

- Display CD8 on surface
- Known as T8 or Tc or killer T cells
- Recognize antigen fragments associated with MHC-I molecules
  - cells infected with virus
  - tumor cells
  - tissue transplants
- Requires costimulation by cytokine from helper T cell
Memory T Cells

• T cells from a clone that did not turn into cytotoxic T cells during a cell-mediated response

• Available for swift response if a 2nd exposure should occur
Antigen-presenting cell (APC) 

Costimulation 

Antigen recognition 

Inactive CD4+ T cell 

CD4+ T cell 

Activated helper T cell 

Proliferation and differentiation 

Clone of T_H cells secrete IL-2 and other cytokines 

Memory T_H cells (long-lived) 

(a) Helper T (T_H) cells or CD4+ cells 

(b) Cytotoxic T (T_C) cells or CD8+ cells
Elimination of Invaders

- Cytotoxic T cells migrate to site of infection or tumor formation
- Recognize, attach & attack
  - secrete granules containing perforin that punch holes in target cell
  - secrete lymphotoxin that activates enzymes in the target cell causing its DNA to fragment
  - secrete gamma-interferon to activate phagocytic cells
Immunological Surveillance

- Cancerous cell displays weird surface antigens (tumor antigens)
- Surveillance = immune system finds, recognizes & destroys cells with tumor antigens
  - done by cytotoxic T cells, macrophages & natural killer cells
  - most effective in finding tumors caused by viruses
- Transplant patients taking immunosuppressive drugs suffer most from viral-induced cancers
Antibody-Mediated Immunity

• Millions of different B cells that can recognize different antigens and respond
• B cells sit still and let antigens be brought to them – stay put in lymph nodes, spleen or peyer’s patches
• Once activated, differentiate into plasma cells that secrete antibodies
• Antibodies circulate in lymph and blood – combines with epitope on antigen similarly to key fits a specific lock
Activation, Proliferation, & Differentiation of B Cells

• B cell receptors bind to antigen
• Helper T cell costimulates
• Rapid cell division & differentiation occurs
  – long-lived memory cells
  – clone of plasma cells
    • produce antibody at 2000 molecules/sec for 4-5 days
    • secrete only one kind antibody
• Antibody enters the circulation to attack antigen
Antibody Structure

- Glycoproteins called immunoglobulins
  - 4 polypeptide chains -- 2 heavy & 2 light chains
  - hinged midregion lets assume T or Y shape
  - tips are variable regions -- rest is constant region
  - 5 different classes based on constant region
    - IgG, IgA, IgM, IgD and IgE
  - tips form antigen binding sites
Antibody Actions

• Neutralization of antigen by blocking effects of toxins or preventing its attachment to body cells
• Immobilize bacteria by attacking cilia/flagella
• Agglutinate & precipitate antigens by cross-linking them causing clumping & precipitation
• Complement activation
• Enhances phagocytosis
Role of the Complement System

• Defensive system of plasma proteins that attack and destroy microbes
• System activated by 2 different pathways
• Produce same result
  – inflammation: dilation of arterioles, release of histamine & increased permeability of capillaries
  – opsonization: protein binds to microbe making it easier to phagocytize
  – cytolysis: a complex of several proteins can form holes in microbe membranes causing leakiness and cell rupture
Immunological Memory

• Primary immune response
  – first exposure to antigen response is steady, slow
  – memory cells may remain for decades

• Secondary immune response with 2nd exposure
  – 1000’s of memory cells proliferate & differentiate into plasma cells & cytotoxic T cells
  – recognition & removal occurs quickly

![Graph showing primary and secondary immune responses](image-url)
Self-Recognition & Immunological Tolerance

- T cells must learn to recognize self & lack reactivity to self proteins
- T cells mature in thymus
  - those that can’t recognize self or react to it
    - destroyed by programmed cell death (apoptosis or deletion)
    - inactivated (anergy) -- alive but unresponsive
  - only 1 in 100 emerges immunocompetent T cell
- B cells develop in bone marrow same way
Development of Self-Recognition & Immunological Tolerance

(a) Positive and negative selection of T cells in the thymus gland

- Does immature CD4+ cell recognize MHC-II and does CD8+ cell recognize MHC-I?
  - Yes: Positive selection
  - No: Death of cells that cannot recognize self-MHC

- Is TCR capable of binding to and recognizing self-peptides?
  - Yes: Anergy (inactivation) of T cell
  - No: Survival of T cells that can recognize self-MHC molecules but not self-peptides

- Deletion (death) of T cell

(b) Selection of T cells after they emerge from the thymus gland

- Mature T cell in lymphatic tissue
  - Antigen recognition with costimulation: Activation of T cell, which proliferates and differentiates
  - Antigen recognition without costimulation: Anergy (inactivation) of T cell
  - Deletion signal (?): Death of T cell

(c) Selection of B cells

- Does immature B cell in bone marrow recognize self-MHC molecule or other self-antigens?
  - Yes: Negative selection
  - No: Mature B cell recognizes antigen (first signal)

- Costimulation (second signal)
  - Yes: Activation of B cell, which proliferates and differentiates into clone of plasma cells
  - No: Anergy (inactivation) of B cell in secondary lymphatic tissues and blood

Key:
- Green: Cell survival or activation
- Red: Cell death or anergy (inactivation)