Chapter 10: The Immune System

Objectives

1. Define immunity, antigen, phagocytosis, degranulation, memory-T/memory-B cells, active-T/active-B cells, T-cell receptors, antibody, B-cell receptor, allergy, allergen, antihistamine, autoimmunity, immunodeficiency, immunization, vaccine
2. Name the first, second, and third lines of defense
3. Name and briefly describe the types and all subtypes of white blood cells
4. Describe the body's physical, mechanical, and chemical barriers to infection
5. Describe the processes involved in the body's second line of defense
6. Explain the steps of inflammation and describe its symptoms
7. Explain the benefits of a fever
8. Describe treatment options for a fever (keeping in mind the age of a patient)
9. Compare and contrast cell-mediated and antibody-mediated immunity1
10. Describe how antibodies help an immune response
11. Describe the structure of antibodies and how antibodies from same/different types are similar/different
12. Name the 5 classes of antibodies
13. Briefly explain how the variable region of antibodies and T/B-cell receptors is produced
14. Describe immunological memory
15. Identify a scenario as describing either active or passive immunity
16. Explain why a person could still get the flu after getting a flu shot
17. Describe the causes and symptoms of anaphylactic shock
18. Define lymph
19. Name and describe the major structures of the lymphatic system

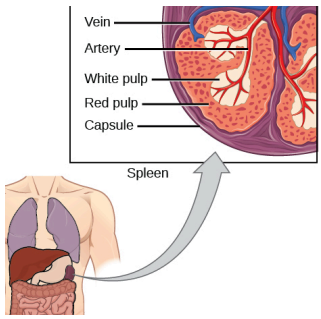
Structures, Barriers, and Innate Immune Response

➢ 10.1a: Structures of the Immune System

- Although the immune system is characterized by circulating cells throughout the body, the regulation, maturation, and intercommunication of immune factors occur at specific sites
  - Immune cells, proteins, and other factors ⇒ circulated by the blood
  - Lymph ⇒ transported via lymphatic vessels
    - Lymph - watery fluid that bathes tissues and organs with protective white blood cells (WBCs) and does not contain erythrocytes
- Cells of the immune system travel between the distinct lymphatic and blood circulatory systems, separated by interstitial space
- Cells of the immune system come from blood stem cells in bone marrow
- Cytokines stimulate the stem cells to differentiate into specialized immune cells: B and T

B and T Immune Cells	
B Immune Cells	T Immune Cells
mature in the bone marrow	transit from the bone marrow to the thymus for maturation - in the thymus, immature T cells that target self cells are destroyed
post-maturation, B lymphocytes circulate to various locations	post-maturation, T lymphocytes circulate to various locations
housed in the spleen with other white blood cells	

- Lymph gathers antigens as it drains from tissues
- These antigens are filtered through lymph nodes before the lymph is returned to circulation
- APCs in the lymph nodes capture and process antigens and inform nearby lymphocytes about potential pathogens
  - Antigen-Presenting Cell (APC)/Accessory Cell - displays antigen complexed with major histocompatibility complexes (MHCs) on their surfaces
- Spleen - site where some of these immune cells that have trapped foreign particles in the blood can communicate with lymphocytes
  - Where antibodies are synthesized and activated
  - Filters foreign substances and antibody-complexes pathogens from the blood
  - Functionally, the spleen is to the blood as lymph nodes are to the lymph



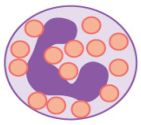
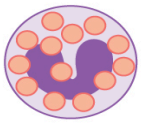
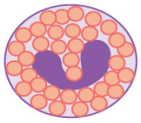
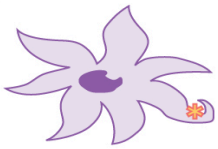
➢ 10.1b: Physical and Chemical Barriers

- Skin - functions as a continuous, impassable barrier to potentially infectious pathogens
  - Pathogens are killed here by desiccation and its acidity
  - Beneficial microorganisms that coexist on the skin compete with invading pathogens, preventing infection
- Areas not protected by skin have different ways to protecting themselves
  - Eyes ⇒ tears and mucus secretions (rap and rinse away pathogens)
  - Nasal Passages and Respiratory Tract ⇒ cilia (push mucus with pathogens out of the body)
  - Stomach ⇒ low pH/acidity (inhibits growth of pathogens)
  - Urinary Tract ⇒ urination (flushes out the pathogens)
  - Blood ⇒ blood proteins (bind and disrupt bacterial cell membranes)
- Pathogens may still be able to enter the body by abrasion/puncture of the skin or by collecting on mucosal surfaces (so much so that it overwhelms the cilia)

- When pathogens do enter the body, the *innate immune system* responds with inflammation, pathogen engulfment, and secretion of immune factors and proteins

➢ 10.1c: Pathogen Recognition

- Innate Immune System (IIS) - refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body
- Infection may be intracellular or extracellular, depending on the pathogen
- Virus - an infectious agent of small size and simple composition that can multiply only in living cells of animals, plants, or bacteria
  - All viruses infect cells and replicate within those cells (intracellularly)
- Bacteria - any of a group of microscopic single-celled organisms that live in enormous numbers in almost every environment on Earth, from deep-sea vents to deep below Earth's surface to the digestive tracts of humans
  - Bacteria and other parasites may replicate intracellularly or extracellularly, depending on the species
- IIS must respond
  - Identify extracellular pathogen and/or identifying host cells already infected
- When a pathogen enters the body, cells in the blood and lymph detect the specific *pathogen-associated molecular patterns* (PAMPs) on the pathogen's surface
  - Pathogen-Associated Molecular Patterns (PAMPs) - carbohydrate, polypeptide, and nucleic acid "signatures" that are expressed by viruses, bacteria, and parasites but which differ from molecules on host cells
  - Immune cells recognize these as "bad guys"
- Many types of *white blood cells* (WBSs) are involved in recognition and response
  - Categorized into 2 groups: granular and agranular
    - Granular Cells - neutrophils, basophils, eosinophils, and mast cells; called that because they appear grainy under a light microscope
    - Agranular Cells - all other WBCs; don't look grainy under a light microscope

Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	
			
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	

➢ 10.1c.1: Cytokine Release - signal that a pathogen is present and needs to be destroyed along with any infected cells

- Cytokine - a chemical messenger that regulates cell differentiation (form and function), proliferation (production), and gene expression to affect immune responses
- WBC and PAMP binding triggers cytokines release

➢ 10.1c.2: Phagocytosis and Inflammation

- First cytokines released cause inflammation because they're pro-inflammatory
- Inflammation - the localized redness, swelling, heat, and pain that result from the movement of leukocytes and fluid through increasingly permeable capillaries to a site of infection
  - Amount of leukocytes that arrive depends on the nature of the infecting pathogen
- Macrophages and dendritic cells engulf pathogens and cellular debris through phagocytosis

        - Neutrophil - a phagocytic leukocyte that engulfs and digests pathogens; most abundant leukocytes of the immune system
            - Have a nucleus w/ 2-5 lobes
            - Contain organelles (lysosomes) that digest pathogens
        - Eosinophil - a leukocyte that works with other eosinophils to surround a parasite; involved in allergic response and protection against helminths (parasitic worms)
        - Mast Cell - a leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens
        - Basophil - a leukocyte that, like a neutrophil, releases chemicals to stimulate the inflammatory response; involved in allergy and hypersensitivity responses and induce specific types of inflammatory responses
    - Neutrophils and eosinophils are important leukocytes especially when the pathogen is large
    - Eosinophils and basophils produce additional inflammatory mediators to recruit more leukocytes
    - Cytokines also send feedback to cells of the nervous system to bring about the overall symptoms of feeling sick, which include lethargy, muscle pain, and nausea
    - Cytokines increase core body temperature (fever) which causes the liver to withhold iron from the blood
        - Without iron, certain pathogens, such as some bacteria, are unable to replicate; this is called nutritional immunity

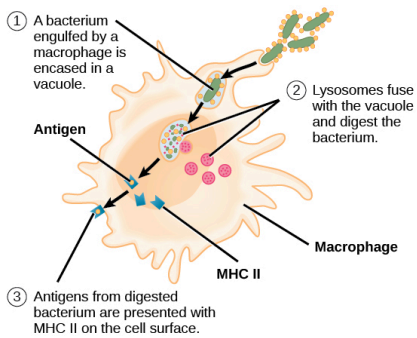
➢ 10.1d: Natural Killer (NK) Cells - identify and destroy infected cells; lymphocytes that can kill cells infected with viruses or tumor cells (abnormal cells that uncontrollably divide and invade other tissue)
    - Lymphocytes - leukocytes that are histologically identifiable by their large, darkly staining nuclei; small cells with very little cytoplasm; include B and T cells

➢ 10.1e: Complement
    - Complement System - an array of approximately 20 types of soluble proteins that function to destroy extracellular pathogens; named because it is complementary to the antibody response of the adaptive immune system
    - Cells of the liver and macrophages synthesize complement proteins continuously
        - Proteins are abundant in the blood serum
        - Capable of responding immediately to infecting microorganisms
    - Complement proteins bind to the surfaces of microorganisms and are particularly attracted to pathogens that are already bound by antibodies
    - Binding of complement proteins occurs in a specific and highly regulated sequence
        - Each successive protein being activated by cleavage and/or structural changes induced upon binding of the preceding protein(s)
    - After the first few complement proteins bind, a sequential binding event follows; the pathogen rapidly becomes coated in complement proteins
        - The proteins serve as a marker to indicate the presence of a pathogen to phagocytic cells, such as macrophages and B cells, and enhance engulfment

Adaptive Immune Response

➢ 10.2 Introduction
    - Adaptive Immunity - occurs after exposure to an antigen either from a pathogen or a vaccination; activated when the innate immune response is insufficient to control an infection—without information from the innate immune system, the adaptive response could not be mobilized
        - Involves a memory to provide the host with long-term protection from reinfection with the same type of pathogen; on re-exposure, this memory will facilitate an efficient and quick response
        - 2 types of responses: cell-mediated and antibody-mediated
            - Cell-Mediated Immune Response - carried out by T cells
            - Antibody-Mediated Immune Response - carried out by B-cells and antibodies
                - Antibody - a blood protein produced in response to and counteracting a specific antigen
        - Activated T cells and B cells that are specific to molecular structures on the pathogen proliferate and attack the invading pathogen
        - They kill pathogens directly or secrete antibodies that enhance the phagocytosis of pathogens and disrupt the infection

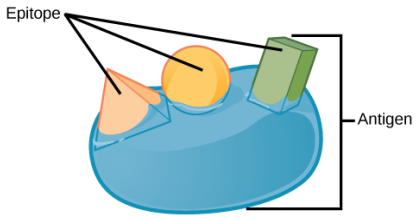
➢ 10.2aa: Antigen-Presenting Cell (APC) - an immune cell that detects, engulfs, and informs the adaptive immune response about an infection
    - Unlike NK cells of the innate immune system, B cells (B lymphocytes) are a type of WBC that gives rise to antibodies
    - T cells (T lymphocytes) are a type of WBC that plays an important role in the immune response
        - Key component in the cell-mediated response
    - Antigen - foreign or "non-self" macromolecule that reacts with cells of the immune system
        - Some antigens won't provoke a response



- Individuals produce innumerable "self" antigens and are constantly exposed to harmless foreign antigens, such as food proteins, pollen, or dust
- Tolerance - immune response is highly regulated and suppressed so that it doesn't attack harmless macromolecules and harm the host
- The innate immune system contains cells that detect potentially harmful antigens and inform the adaptive immune response about the presence of these antigens, like APCs
  - APCs phagocytose the pathogen and digest it to form fragments
  - Fragments are transported to the APC's surface to indicate to other immune cells

➢ 10.2b: T and B Lymphocytes

- In human blood, lymphocytes are 80-90% T cells and 10-20% B cells
  - Recall that the T cells are involved in the cell-mediated immune response, whereas B cells are part of the antibody-mediated immune response
- T Cells
  - Encompass a heterogeneous population of cells with extremely diverse functions
  - Some respond to APCs of the innate system and indirectly induce immune response by releasing cytokines
  - Some stimulate B cells to respond
  - Some are involved in protection (suppressing inappropriate immune reactions to harmless or "self" antigens)
- T and B cells exhibit a common pattern
  - recognize/bind to specific antigens cia a complementary receptor
  - Activate and self-amplify/mature
  - Specially bind to the antigen of the infecting pathogen
- They only express a single type of antigen receptors per cell
  - The collective population can express a near limitless variety of antigen receptors
- They are activated when they detect epitopes
  - Epitopes/Antigenic Determinants - small components of antigens
  - Occurs at specific epitope rather than on the entire antigen
- In the absence of information from APCs, T and B cells remain inactive, or naïve, and are unable to prepare an immune response
- The requirement for information from the APCs of innate immunity to trigger B cell or T cell activation illustrates the essential nature of the innate immune response to the functioning of the entire immune system



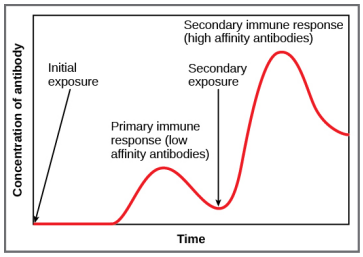
- T-Cell Receptors (TCRs) - receptors that give mammalian T cells their enormous diversity; consists of two polypeptide chains that span the T cell membrane
  - Each polypeptide chain is comprised of a constant domain and a variable domain
    - Domain - specific region of a protein that may be regulatory or structural
  - A single T cell will express thousands of identical copies of one specific TCR variant on its cell surface
  - The specificity of the adaptive immune system occurs because it makes millions of different T cell populations, each expressing a TCR that differs in its variable domain
  - TCR diversity is achieved by the mutation and recombination of genes that encode these receptors in stem cell precursors of T cells
- B Lymphocytes
  - Plasma Cells - differentiated naïve B cells; secrete antibodies
  - Naïve B cells initially are coated in thousands of B Cell Receptors (BCRs), which are membrane-bound forms of Ig (immunoglobulin, or an antibody)
  - Has nearly 2 heavy chains and 2 light chains connected by disulfide linkages
    - Each chain has a constant and variable region (involved in antigen binding)

➢ 10.2b.1: Immunity Regulation

- Immune system must be regulated to prevent wasteful, unnecessary responses to harmless substances or the self
- Immune Tolerance - acquired ability to prevent an unnecessary or harmful immune response to a detected foreign substance known not to cause disease
  - Crucial for maintaining mucosal homeostasis
  - Brought about by specialized APCs in liver, lymph nodes, small intestine, and lung
  - Regulatory T Cells (T_{reg} Cells) - specialized lymphocytes that suppress local inflammation and inhibit the secretion of stimulatory immune factors
    - Prevent immunologic activation and inflammation in undesired tissue compartments
    - Allow the immune system to focus on pathogens instead
    - Prevent the *autoimmune response*
      - Autoimmune Response - an inappropriate immune response to host cells or self-antigens
    - Suppresses immune response to harmful pathogens after the infection is cleared

- Minimizes host cell damage from inflammation and cell lysis

➢ 10.2c: Immunological Memory - a memory component that allows for an efficient and dramatic response upon reinvasion of the same pathogen
- Memory is handled by the adaptive immune system
  - Doesn't rely much on cues from the innate response
- Primary Response - the adaptive immune response to a pathogen that has not been encountered before
  - Plasma cells secreting antibodies and differentiated T cells increase
  - B and T cells mature into *effector cells*
    - Effector Cells - a subset of the naïve populations differentiates into B and T memory cells with the same antigen specificities
- Memory Cell - an antigen-specific B or T lymphocyte that does not differentiate into effector cells during the primary immune response, but that can immediately become effector cells upon re-exposure to the same pathogen
  - Do not respond during primary response
  - After the infection is cleared, effectors undergo apoptosis, memory cells persist in circulation
- B and T memory cells for the pathogen will circulate for a long time, even if the body never encounters the same infection again
- Re-exposure prompts the memory cells to differentiate into plasma cells and cytotoxic T cells without input from APCs or Helper T cells
  - The adaptive immune response is delayed is because it takes time for naïve B and T cells with the appropriate antigen specificities to be identified and activated
    - With re-exposure, this step is unnecessary
  - The antibody response may be to rapid that the individual is unaware of exposure

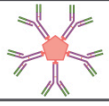


➢ 10.2c.1: Vaccination - a biological preparation that provides active acquired immunity to a particular disease; based on the knowledge that exposure to noninfectious antigens, derived from known pathogens, generates a mild primary immune response
- May not be perceived as illness but still registers in the immune memory
- When exposed to the corresponding pathogen to which an individual was vaccinated, the reaction is similar to a secondary exposure
- Each reinfection generates more memory cells and increases resistance
  - Certain vaccine courses involve one or more booster vaccinations to mimic repeat exposures

Antibodies

➢ 10.3 Introduction
- Antibody/Immunoglobulin (Ig) - a protein that is produced by plasma cells after stimulation by an antigen; the functional basis of humoral immunity
  - Occur in blood, gastric and mucus secretions, and breast milk
  - Bind to pathogens and mark them for destruction by phagocytes before they can infect cells

➢ 10.3a: Antibody Structure

Name	Properties	Structure
IgA	Found in mucous, saliva, tears, and breast milk. Protects against pathogens.	
IgD	Part of the B cell receptor. Activates basophils and mast cells.	
IgE	Protects against parasitic worms. Responsible for allergic reactions.	
IgG	Secreted by plasma cells in the blood. Able to cross the placenta into the fetus.	
IgM	May be attached to the surface of a B cell or secreted into the blood. Responsible for early stages of immunity.	

- Similar to TCRs and BCRs, antibody diversity is produced by the mutation and recombination of approximately 300 different gene segments

        - Variable domains from the heavy and light chains interact to form the binding site through which an antibody can bind a specific epitope on an antigen
    - The numbers of repeated constant domains in Ig classes are the same for all antibodies corresponding to a specific class
    - Antibodies are structurally similar to the extracellular component of BCRs
    - Antibodies can be divided into five classes: IgM, IgG, IgA, IgD, IgE—organized based on physicochemical, structural, and immunological properties
- 10.3b: Antibody Functions
    - Antibodies circulate freely and act independently of plasma cells
        - Can be transferred from one individual to another to temporarily protect them
    - Passive Immunity - the phenomenon in which a person who has recently produced a successful immune response against a particular disease agent can donate blood to a nonimmune recipient and confer temporary immunity through antibodies in the donor's blood serum
    - Active Immunity - the phenomenon in which a person has generated their own antibodies—either through natural means (illness) or artificial means (vaccination)

Disruptions in the Immune System

- 10.4 Introduction
    - A functioning immune system is essential for survival, but even the sophisticated cellular and molecular defenses of the mammalian immune response can be defeated by pathogens at virtually every step
    - In the competition between immune protection and pathogen evasion, pathogens have the advantage of more rapid evolution because of their shorter generation time and other characteristics
- 10.4a: Immunodeficiency - failure, insufficiency, or delay in the response of the immune system, which may be acquired or inherited
    - Can be acquired from certain pathogens, chemical exposure, malnutrition, and/or extreme stress
    - Genetic Disorders
        - Severe Combined Immunodeficiency (SCID)
        - Bare lymphocyte syndrome
        - MHC II deficiencies
        - Neutropenia - the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes; bacterial infections may go unrestricted in the blood, causing serious complications
- 10.4b: Hypersensitivities - maladaptive immune responses toward harmless foreign substances or self antigens that occur after tissue sensitization
    - Allergy - immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen
        - Upon initial exposure, IgE is synthesized via the typical process of APCs presenting processed antigen to the T_H cells that stimulate B cells to produce IgE
        - The constant domain of the IgE molecules interact with mast cells embedded in connective tissues, priming/sensitizing, the tissue
        - Upon subsequent exposure to the same allergen, IgE molecules on mast cells bind the antigen via their variable domains and stimulate the mast cell to release the modified amino acids histamine and serotonin
            - Histamine and serotonin recruit eosinophils which mediate allergic responses
    - Autoimmunity - the state in which the immune system reacts against the body's own normal components, producing disease or functional changes
        - Autoantibody - antibody that inappropriately marks self components as foriegn
        - Can develop with time
        - May have caused rooted in molecular mimicry
            - Antibodies and TCRs may bind self antigens that are structurally similar to pathogen antigens, which the immune receptors first raised