The Immune System

- All animals have innate immunity, a defense active immediately upon infection
- Vertebrates also have adaptive immunity

Innate Immunity of Vertebrates

- The immune system of mammals is the best understood of the vertebrates
- Innate defenses include barrier defenses, phagocytosis, antimicrobial peptides
- Additional defenses are unique to vertebrates: natural killer cells, interferons, and the inflammatory response
**Barrier Defenses**

- Barrier defenses include the skin and mucous membranes of the respiratory, urinary, and reproductive tracts
- Mucus traps and allows for the removal of microbes
- Many body fluids including saliva, mucus, and tears are hostile to many microbes
- The low pH of skin and the digestive system prevents growth of many bacteria

**Cellular Innate Defenses**

- Pathogens entering the mammalian body are subject to phagocytosis
- Phagocytic cells recognize groups of pathogens by TLRs, Toll-like receptors

**Antimicrobial Peptides and Proteins**

- Function in innate defense by attacking pathogens or impeding their reproduction
- Interferon proteins provide innate defense, interfering with viruses and helping activate macrophages
- About 30 proteins make up the complement system, which causes lysis of invading cells and helps trigger inflammation

**Inflammatory Responses**

- The inflammatory response, such as pain and swelling, is brought about by molecules released upon injury of infection
- Mast cells, a type of connective tissue, release histamine, which triggers blood vessels to dilate and become more permeable
- Activated macrophages and neutrophils release cytokines, signaling molecules that enhance the immune response
- Pus, a fluid rich in white blood cells, dead pathogens, and cell debris from damaged tissues
Evasion of Innate Immunity by Pathogens

- Some pathogens avoid destruction by modifying their surface to prevent recognition or by resisting breakdown following phagocytosis
- Tuberculosis (TB) is one such disease and kills more than a million people a year

In adaptive immunity, receptors provide pathogen-specific recognition

- Lymphocytes that mature in the thymus are called T cells, and those that mature in bone marrow are called B cells
- Antigens can elicit a response from a B or T cell
- Exposure to the pathogen activates B and T cells with antigen receptors specific for parts of that pathogen
- The small accessible part of an antigen that binds to an antigen receptor is called an epitope
Antigen Recognition by B Cells and Antibodies

- Each B cell antigen receptor is a Y-shaped molecule
- The constant regions vary little among B cells, whereas the variable regions differ greatly
- The variable regions provide antigen specificity

- Binding of a B cell antigen receptor to an antigen is an early step in B cell activation
- This gives rise to cells that secrete a soluble form of the protein called an antibody or immunoglobulin (Ig)
- Secreted antibodies are similar to B cell receptors but lack transmembrane regions that anchor receptors in the plasma membrane

Antigen Recognition by T Cells

- Each T cell receptor consists of two different polypeptide chains (called α and β)
- The tips of the chain form a variable (V) region; the rest is a constant (C) region
- T cell and B cell antigen receptors are functionally different

- T cells bind to antigen fragments displayed or presented on a host cell
- These antigen fragments are bound to cell-surface proteins called MHC molecules
- MHC (major histocompatibility complex) molecules are host proteins that display the antigen fragments on the cell surface
- In infected cells, MHC molecules bind and transport antigen fragments to the cell surface, a process called antigen presentation
- A T cell can then bind both the antigen fragment and the MHC molecule
- This interaction is necessary for the T cell to participate in the adaptive immune response
B Cell and T Cell Development

• The adaptive immune system has four major characteristics
  – Diversity of lymphocytes and receptors
  – Self-tolerance; lack of reactivity against an animal’s own molecules
  – B and T cells proliferate after activation
  – Immunological memory

Generation of B and T Cell Diversity

• By combining variable elements, the immune system assembles a diverse variety of antigen receptors
• The immunoglobulin (Ig) gene encodes one chain of the B cell receptor
• Many different chains can be produced from the same gene by rearrangement of the DNA
• Rearranged DNA is transcribed and translated and the antigen receptor formed

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
• Some B and T cells with receptors specific for the body’s own molecules are destroyed by apoptosis, or programmed cell death
• The remainder are rendered nonfunctional

Proliferation of B Cells and T Cells

• In the body there are few lymphocytes with antigen receptors for any particular epitope
• In the lymph nodes, an antigen is exposed to a steady stream of lymphocytes until a match is made
• This binding of a mature lymphocyte to an antigen initiates events that activate the lymphocyte
• Once activated, a B or T cell undergoes multiple cell divisions
• This proliferation of lymphocytes is called clonal selection
• Two types of clones are produced: short-lived activated effector cells that act immediately against the antigen and long-lived memory cells that can give rise to effector cells if the same antigen is encountered again

Immunological Memory

• Immunological memory is responsible for long-term protections against diseases, due to either a prior infection or vaccination
• The first exposure to a specific antigen represents the primary immune response
• During this time, selected B and T cells give rise to their effector forms
• In the secondary immune response, memory cells facilitate a faster, more efficient response
Adaptive immunity defends against infection of body fluids and body cells

- Acquired immunity has two branches: the humoral immune response and the cell-mediated immune response
- In the **humoral immune response** antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph
- In the **cell-mediated immune response** specialized T cells destroy affected host cells

**Helper T Cells: A Response to Nearly All Antigens**

- A type of T cell called a **helper T cell** triggers both the humoral and cell-mediated immune responses
- Signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells
- **Antigen-presenting cells** have class I and class II MHC molecules on their surfaces

- Class II MHC molecules are the basis upon which antigen-presenting cells are recognized
- Antigen receptors on the surface of helper T cells bind to the antigen and the class II MHC molecule; then signals are exchanged between the two cells
- The helper T cell is activated, proliferates, and forms a clone of helper T cells, which then activate the appropriate B cells

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

- **Cytotoxic T cells** are the effector cells in the cell-mediated immune response
- Cytotoxic T cells recognize fragments of foreign proteins produced by infected cells and possess an accessory protein that binds to class I MHC molecules
- The activated cytotoxic T cell secretes proteins that disrupt the membranes of target cells and trigger apoptosis
B Cells and Antibodies: A Response to Extracellular Pathogens

- The humoral response is characterized by secretion of antibodies by B cells
- Activation of the humoral immune response involves B cells and helper T cells as well as proteins on the surface of pathogens
- In response to cytokines from helper T cells and an antigen, a B cell proliferates and differentiates into memory B cells and antibody-secreting effector cells called plasma cells

Antibody Function

- Antibodies do not kill pathogens; instead they mark pathogens for destruction
- In neutralization, antibodies bind to viral surface proteins preventing infection of a host cell
- Antibodies may also bind to toxins in body fluids and prevent them from entering body cells

- In opsonization, antibodies bind to antigens on bacteria creating a target for macrophages or neutrophils, triggering phagocytosis
- Antigen-antibody complexes may bind to a complement protein—which triggers a cascade of complement protein activation
- Ultimately a membrane attack complex forms a pore in the membrane of the foreign cell, leading to its lysis
• B cells can express five different forms (or classes) of immunoglobulin (Ig) with similar antigen-binding specificity but different heavy chain C regions
  — IgD: Membrane bound
  — IgM: First soluble class produced
  — IgG: Second soluble class; most abundant
  — IgA and IgE: Remaining soluble classes

Summary of the Humoral and Cell-Mediated Immune Responses

• Both the humoral and cell-mediated responses can include primary and secondary immune response
• Memory cells enable the secondary response

Active and Passive Immunization

• Active immunity develops naturally when memory cells form clones 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
• It can be conferred artificially by injecting antibodies into a nonimmune person

Antibodies as Tools

— Antibody specificity and antigen-antibody binding have been harnessed in research, diagnosis, and therapy

Immune Rejection

— Cells, tissues, and organs
— MHC molecules are different among genetically nonidentical individuals

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)

Disruptions 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, effects range from minor to sometimes fatal
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
- 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, 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, rheumatoid arthritis, insulin-dependent diabetes mellitus, and multiple sclerosis

Exertion, Stress, and the Immune System

- Moderate exercise improves immune system function
- Psychological stress has been shown to disrupt immune system regulation by altering the interactions of the hormonal, nervous, and immune systems
- Sufficient rest is also important for immunity

Immunodeficiency Diseases

- Inborn **immunodeficiency** results from hereditary or developmental defects that prevent proper functioning of innate, humoral, and/or cell-mediated defenses
- Acquired immunodeficiency develops later in life and results from exposure to chemical and biological agents
- **Acquired immunodeficiency syndrome (AIDS)** is caused by a virus
- Pathogens have evolved mechanisms to thwart immune responses: **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
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

Attack on the Immune System:
HIV
• Human immunodeficiency virus (HIV) infects 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

Cancer and Immunity
• The frequency of certain cancers increases when adaptive immunity is impaired
• 20% of all human cancers involve viruses
• The immune system can act as a defense against viruses that cause cancer and cancer cells that harbor viruses
• In 2006, a vaccine was released that acts against human papillomavirus (HPV), a virus associated with cervical cancer