

Chapter 19: Natural Defenses against Disease

I Defensive Cells and Proteins

- Components of the defense system are distributed throughout the body.
 - Blood and lymph are central to the function of lymphoid tissues.
 - Blood plasma suspends red and white blood cells and platelets.
 - Red blood cells are found in the closed circulatory system.
 - White blood cells and platelets are found in the closed circulatory and lymphatic system.
 - Lymph is fluid that accumulates outside of the closed circulatory system.
 - The fluids, which are derived from the blood and other tissues, collect in the lymphatic system.
 - The lymphatic system is a branching system of tiny capillaries connecting larger vessels.
 - It finally joins the large lymph duct that connects to a major vein near the heart.
 - At sites along lymph vessels are small, roundish lymph nodes.
 - They contain a type of white blood cells, which inspect the materials that pass.
- *See Figure 19.1.*

A. White blood cells play many defensive roles

- Each milliliter of blood contains about 5 billion red and 7 million white blood cells.
 - White blood cells are clear and have a nucleus and organelles.
 - Red blood cells are smaller, lose their nucleus and are opaque.
 - White blood cells move within and outside the circulatory system.
 - The number of white blood cells sometimes rises in response to invading pathogens.
- There are two main groups of white blood cells.
 - Phagocytes engulf and digest nonself materials.
 - Lymphocytes are most abundant. There are two types: B and T cells.
 - Both come from bone marrow.
 - T cells migrate from the circulation to the thymus where they mature.
 - B cells circulate and also collect in lymph vessels.
- *See Figure 19.2.*

B. Immune system proteins bind pathogens or signal other cells

- Antibodies, produced and secreted by B cells, bind specifically to certain substances.
- T cell receptors are cell surface receptors that bind nonself substances on the surface of other cells.
- Major histocompatibility complex (MHC) proteins are exposed outside cells of mammals.
- Cytokines are soluble signal proteins released by T cells. They bind and alter the behavior of their target cells.

II Innate Defenses

- Innate defenses are general protection mechanisms to stop pathogens.
- These include physical barriers, cellular and chemical defenses.
- See Table 19.1 for a summary.

A. Barriers and local agents defend the body against invaders

- Skin is a primary innate defense against pathogens.
- The bacteria and fungi that normally live on the surface of the body are called normal flora.
- Because they compete for space and nutrients against pathogens, they are part of the innate defense system.
- Mucus-secreting tissues that produce mucus and tears are also part of the innate defense.
 - Lysozyme is present in mucus and tear secretions.
 - This enzyme attacks the cell walls of many bacteria.
- Pathogens that are ingested enter the highly acidic environment of the stomach.
 - In the small intestine, bile salts kill some pathogens.
 - The large intestine harbors many bacteria, which are normal flora.

B. Innate defenses include chemical and cellular processes

- Pathogens that get past the outer and inner surfaces face other innate defenses.
 - Complement proteins are antimicrobial proteins. Vertebrate blood contains about 20 different proteins, which make up the complement system.
 - *See Figure 19.3.*
 - Interferons are produced by cells that are infected by a virus.
 - They increase resistance of neighboring cells to infections by the same or other viruses.
 - All interferons are glycoproteins consisting of about 160 amino acids.
 - Each vertebrate species produces at least three different interferons.
 - Phagocytosis and other cellular assaults:
 - Phagocytes ingest pathogens.
 - There are three types of phagocytes.
 - Neutrophils are abundant, but short-lived.
 - Monocytes mature into macrophages. They live longer and consume larger numbers of pathogens. Some roam, others are stationary in lymph nodes, inspecting the passing fluids.
 - Eosinophils are weakly phagocytic. They kill parasites, such as worms, that have been coated by antibodies.
 - Natural killer cells initiate the lysing of cancer and virus-infected cells.
 - *See Figure 19.4.*
 - Inflammation:
 - Inflammation is redness and swelling.
 - Signals such as histamine trigger inflammation.
 - Mast cells, which adhere to the skin and linings of organs, and white blood cells called basophils, release histamine.

- Inflammation results from histamine induced dilation of blood vessels in the injured or infected region.
- Histamine causes capillaries to become leaky, allowing plasma and phagocytes to escape into the tissue
- Pain is caused by pressure and the action of certain enzymes.
- The whole process is a defense reaction.
- Antibody binding to pathogens, complement proteins and other chemical signals attract phagocytes. Neutrophils arrive first, then monocytes (which become macrophages).
 - The macrophages engulf invaders.
 - They produce several cytokines, one which causes fever.
- Pus may accumulate, which is composed of dead cells and leaked fluid.
- *See Figure 19.5.*

III Specific Defenses: The Immune Response

A. Four features characterize the immune response

- Specificity:
 - Antigens are organisms or molecules that are specifically recognized.
 - Each antigen typically has several different antigenic determinants.
 - It is the antigenic determinants that are recognized by the immune system components from specific T or B cells.
 - *See Figure 19.6.*
- Diversity:
 - It is estimated that human immune system can distinguish 10 million different antigenic determinants.
- Distinguishing self from non self:
 - Each cell has thousands of potential antigens.
 - It is important that the immune system leaves these alone.
 - Failure to do this leads to autoimmune disease, which is an attack on one's own body. Examples are lupus and rheumatoid arthritis.
- Immunological Memory:
 - Once exposed to a pathogen, the immune system remembers it and mounts future responses much more rapidly.
 - Vaccinations exploit this aspect of the system.

B. There are two interactive immune responses.

- The humoral immune response involves antibodies, which recognize antigenic determinants on antigens.
- Each antibody recognizes a certain shape and composition.
- Some antibodies are soluble proteins that travel free in blood and lymph.
- Others are integral membrane proteins on B cells.
- When a pathogen invades the body, it might be detected by and bind to a certain B cell whose membrane antibody just happens to fit one of its potential antigenic determinants.
- This and other system components activate the B cell, which then differentiates into a plasma cell.

- The plasma cell makes multiple copies of the antibody in soluble form with the same specificity as its membrane antibody.
- The cellular immune response is able to detect antigens that reside within cells.
 - It destroys virus-infected or mutated cells.
 - Its main component are T cells.
 - T cells have T cell receptors that can recognize and bind specific antigenic determinants.

C. Clonal selection accounts for the characteristic features of the immune response.

- Several obvious questions arise that are fundamental to understanding the immune system.
 - How does the enormous diversity arise?
 - How do B and T cells specific to antigens proliferate?
 - Why don't they attack and destroy our own bodies?
 - How can the memory of post exposure be explained?
- Clonal selection explains much of this.
 - Many different immune system cells exist, but at low number.
 - The antigen "selects" a particular antibody-producing cell.
 - *See Figure 19.7.*

D. Immunological memory and immunity result from clonal selection

- An activated lymphocyte (B cell or T cell) produces two types of daughter cells, effector and memory cells.
 - Effector cells carry out the attack on the antigen.
 - Memory cells live longer and retain the ability to start dividing quickly to produce more effector and more memory cells.
- When the body encounters a particular antigen for the first time, a primary immune response is activated.
- When the antigen appears again, a secondary response, which is much more rapid, occurs, because of immunological memory.
- *See Figure 19.8.*
- Artificial immunity is acquired by immunization with the purposeful introduction of antigenic proteins from a potential pathogen.
 - Vaccination involves the introduction of whole pathogens, either weak (attenuated) or live or killed (inactivated) pathogens.
 - Smallpox has been eliminated worldwide, using vaccination.

E. Animals distinguish self from nonself and tolerate their own antigens

- The body is tolerant of its own molecules.
- The same molecules that would generate an immune response in a different individual fail to within an individual.
- Clonal deletion eliminates about 90 percent of all B cells made by the bone marrow.
 - Any immature B cell in the marrow that could mount an immune response against self is eliminated.
 - The same is true for T-cells, but the selection occurs in the thymus.
 - Elimination is accomplished by triggering apoptosis.

- Clonal anergy is the suppression of the immune response.
 - Before a mature T cell mounts an immune response it must recognize an antigen on a cell and also another molecule, CD28, which is not present on most body cells
- Immunological tolerance is a poorly understood but clearly observable phenomenon.
 - If the blood from nonidentical twin fetal cows mix before birth, blood, even if a different type, is not rejected between the twins.
 - Exposing a fetus to an antigen before birth provides later tolerance to the antigen.
 - Continued exposure is necessary to maintain the tolerance.
 - Some individuals experience the opposite effect, they lose tolerance to themselves, which results in autoimmune disease.
- See *Figure 19.10*.

IV B Cells: The Humoral Immune Response

- Daily, billions of B cells survive clonal deletion, and are released from the bone marrow to enter the circulation.
- B cells are the basic component of the *humoral* immune system.

A. Some B cells develop into plasma cells

- For a B cell to differentiate into a plasma cell it must bind an antigenic determinant.
- Also, another cell, a T helper cell must also bind the same determinant as it is presented to it by an antigen-presenting cell.
- Cellular division and differentiation of the B cell is stimulated by a signal from the activated T helper cell.
- This series of events are what leads to the formation of plasma cells.
- Activated B cells have a marked increase in ribosome number and endoplasmic reticulum surface area.

B. Antibodies share a common structure, but may be of different classes

- Antibody molecules are proteins called immunoglobulins.
- There are several different kinds. (See Table 19.2)
- All are composed of (a) tetramer(s) of four peptide chains.
- Two identical light chains and two identical heavy chains make up the tetrameric units.
- Disulfide bonds hold the chains together.
- Each individual peptide, both light and heavy chains, have a variable and constant region.
- The constant region is similar between different immunoglobulin of each class.
- The variable regions vary and are responsible for both the diversity and specificity.
- The heavy and light chain variable regions align and are the binding sites.
- Each tetramer has two identical antigen-binding sites.
- The enormous range of antibody specificities is possible by the recombination of numerous versions of coding regions for the variable regions.

- The five immunoglobulin classes are based on differences in the constant regions of the heavy chain.
 - IgG make up 85% of the total immunoglobulin content of the bloodstream.
 - They are the primary product of a secondary immune response.
 - One way they work to help in defense is that after binding to an antigen, macrophages adhere to the heavy chains and ingest the antigen. (See Figure 19.12)

C. Hybridomas produce monoclonal antibodies

- Because most antigens have more than one antigenic determinant, animals injected with a single antigen generally produce several different antibodies, called polyclonal antibodies.
- Polyclonal antibodies might have some cross-reactivity with other molecules that have similar regions within the molecule.
- A monoclonal antibody is a single type of antibody made by a single clonal line of B-cell (plasma cell).
 - To overcome the problem of short lifespan for plasma cells, an immortalized myeloma cell is fused to the plasma cell artificially.
 - These new cells called hybridomas, live long and produce monoclonal antibodies.
 - Monoclonal antibodies are very useful for immunoassays to quantify hormone concentrations and other molecules that are present in minute amounts.
 - Radioactively tagged monoclonal antibodies have been used to target cancer cell destruction. They have even been used to produce passive immunity. When someone is infected with rabies, passive immunity can be applied to fight the pathogen faster than the unaided immune system could.
 - *See Figure 19.13.*

V T Cell: The Cellular Immune Response

A. T cell receptors are found on two types of T cells

- T cells, like B cells, possess specific surface receptors.
- The genes that code for T cell receptors are similar to those for immunoglobulins. (*See Figure 19.14*)
- T cell receptors also have constant and variable regions.
- A major difference between antibodies and T cell receptors is that T cell receptors only bind to a piece of an antigen which is displayed on the surface of an antigen presenting cell.
 - Activated T cells give rise to two types of effector cells.
 - Cytotoxic cells, or T_C , recognize virus-infected cells and kills them by causing them to lyse. (*See Figure 19.15*)
 - Helper T cells, or T_H cells, assist both cellular and humoral immune systems.
 - Activated Helper T cells proliferate and stimulate both B and T_C cells to divide.

B. The major histocompatibility complex encodes proteins that present antigens to the immune system

- Major histocompatibility complex (MHC) gene products are plasma membrane glycoproteins.
- These molecules are called human leukocyte antigens (HLA) in humans, and H-2 proteins in mice.
- There are three classes of MHC proteins:
 - Class I MHC proteins are present on the surface of every nucleated cell in animals.
 - When cellular proteins are degraded in the proteasome, an MHC I protein may bind a fragment and travel to the plasma membrane to expose it outside on the cell's plasma membrane surface.
 - T_C cells have a surface protein called CD8 that recognize MHC I.
 - Class II MHC proteins are found mostly on the surface of B cells, macrophages, and other antigen-presenting cells.
 - When an antigen is ingested by an antigen-presenting cell, it is broken down and fragments are presented at the cell surface by Class II MHC's.
 - T_H cells have CD4 surface proteins that recognize MHC II.
 - Class III MHC proteins include some of the proteins of the complement system that interact with antigen-antibody complexes to cause lysis of foreign cells.
- See Figure 19.17 for further details.
- T cells recognize the MHC I or II and then inspect the attached fragment.
- There are three different loci for each MHC I and for each MHC II.
- The six loci have as many as 100 different alleles.
- This is why different individuals generally have different MHC genotypes.

C. Helper T cells and MHC II proteins contribute to the humoral immune response

- T_H cells bind to an antigen presented to it by an antigen-presenting macrophage. (*See Figure 19.16*)
- The then activated T_H cell produces and secretes cytokine molecules, which act by attaching to its own specific cell membrane receptor proteins.
- The cell can then divide to produce clones capable of interacting with B cells.
- These steps are called the activation phase. They happen in the lymphatic tissues.
- Following the activation phase, B cells are activated to produce antibodies. This is called the effector phase.
- For B cells to become activated by T cells, the T_H cell must bind to an antigen (fragment) presented to it by the B cell.
- There must be a match between the antigen fragment presented to the T_H previously by the macrophage and the one presented by the B cell.
- The fragments of antigen presented by B cells are those that bind to the membrane immunoglobulin (IgM).
- The binding of antigen to the B cell membrane IgM triggers the process of receptor mediated endocytosis. Within the B-cell, partial digestion of the antigen occurs and MHC II transports fragments for presentation to the outer membrane.

- If the activated T cell has a T cell receptor that binds one of the different antigen fragments presented by a particular B cell, it binds it. This T cell then releases cytokines that cause the B cell to produce a clone of plasma cells.
- The plasma cells secrete antibody.
- *See Figure 19.18.*

D. Cytotoxic T cells and MHC I proteins contribute to the cellular immune response

- Class I MHC molecules present fragments of proteins generated by the proteasome of most cell types.
- Fragments of normal proteins are presented but are generally ignored by the immune system.
- Fragments of proteins altered by mutation or fragments of viruses are presented to T_C cells and if a T_C cell binds to this complex, the T_C cell is activated to proliferate and differentiate.
- The effector phase is when T_C cells secrete molecules that lyse the target cells.
 - Also, T_C cells can bind to specific target cell receptors called Fas.
 - This binding initiates apoptosis in the target, e.g. virus infected, cell.
- This system helps rid the body of virus-infected cells. It also helps to destroy some cancer tumors.
- *See Figure 19.18.*

E. MHC molecules underlie the tolerance of self

- To survive clonal selection each new T cell must recognize the body's MHC proteins. If it fails to, it dies within about 3 days.
- If the T cell binds to self MHC proteins *and* to one of the body's own normal antigens, it undergoes apoptosis.
- If the T cell survives these tests, it becomes either a T_C or T_H cell.

F. MHC molecules are responsible for transplant rejection

- MHC molecules must match when organs are transplanted or these same molecules will be seen as antigens.
- The cellular immune system is responsible for rejection.
- Rejection problems can be controlled somewhat by treating patients with immunosuppressing drugs such as cyclosporin.

VI The Genetic Basis of Antibody Diversity

- As B cells develop, their genomes become modified until the cell can produce one specific type of antibody.
- If antibody diversity was due to different genes, our entire genome would be taken up by antibody genes,
- Instead, just a small number of genes that can recombine to generate multitudes of possibilities are responsible for the vast diversity of antibodies.

A. Antibody diversity results from DNA rearrangement and other mutations

- Every cell has hundreds of DNA segments that are capable of participating in the synthesis of variable regions. In all but the cells of the immune system, nothing is changed or expressed.

- During B cell development, these variable regions rearrange and join.
 - Pieces of DNA are deleted and DNA segments formerly distant from one another are joined together.
 - Immunoglobulin genes are assembled from randomly selected pieces of DNA.
 - Each B cell precursor assembles its own unique set of immunoglobulin genes.
- In both humans and mice, the DNA segments coding for immunoglobulin heavy chains are on one chromosome and those for light chains are on another.
- See Figure 19.19.
- There are multiple genes coding for each of the four kinds of segments in the polypeptide chain for the heavy chain in mice: 100V, 30D, 6J, and 8C regions.
 - Each B cell randomly selects one V, D, J and C region.
 - The same occurs for the light chain.
 - The possible combinations of light and heavy are $144,000 \times 144,000 = 21$ billion possibilities.
- Even more diversity is possible because the recombinations do not occur at precise segments.
- Imprecise recombination can create new codons at the junctions.
- After DNA fragments are cut out and before they are joined, an enzyme, terminal transferase, adds some nucleotides to the free end. This adds even more variability by causing frameshifts, and new codons.
- Even more variability is introduced because this region of DNA is more prone to mutation due to methylation of cytosine residues.

B. How does a B cell produce a specific heavy chain?

- Two distinct types of nucleic acid rearrangements contribute to the formation of an antibody. (*See Figure 19.20*)
 - DNA rearrangements before transcription join the *V*, *D*, and *J* segments.
 - RNA splicing after transcription join the variable region (*VDJ*) to the constant.
- First chunks of DNA are deleted from the chromosome during rearrangement of the segments.
- As the result of these deletions a particular *D* is beside a particular *J*.
- Then the *DJ* segments end up, again by splicing out DNA, adjacent to one of the *V* segments.

C. The constant region is involved in class switching

- B cells make only one class of antibody at a time. The constant region determines the class.
- The first made is IgM, which is the membrane associated type. The constant region for IgM is coded for by the μ segment.
- If the cell becomes a plasma cell, another DNA splicing event positions the heavy-chain variable region (*V*, *D* and *J*) next to a constant segment further down the DNA strand, and the μ segment is deleted. This is class switching.
- If any other constant region remains, it is possible that another class switching event will occur. (*See Figure 19.21*)
- Class switching is triggered and controlled by a T_H cell via cytokine signals.

- See Figure 19.22.

VII The Evolution of Animal Defense Systems

- Immunoglobulin diversity by chromosome rearrangement is unique to vertebrates with jaws.
- Multicellular animals, vertebrates and invertebrates, employ mobile phagocytic cells to patrol their bodies.
- Invertebrates have sturdy innate defense systems.
- Vertebrates and invertebrates both reject tissue grafts from other individuals of the same species. Invertebrates reject second grafts, at the same rate as first, which is evidence that they have no immunological memory.
- Invertebrates do not produce immunoglobulins or related components.

VIII Disorders of the Immune System

A. An inappropriately active immune system can cause problems

- Hypersensitivity:
 - The human immune system can overreact to a dose of antigen.
 - Allergies are the most familiar example.
 - Immediate hypersensitivity occurs when too much IgE is made.
 - If the IgE molecules bind antigens, most cells are triggered to release histamine which triggers further histamine release.
 - A severe allergic reaction can lead to death.
 - Delayed hypersensitivity does not begin until hours after exposure to an antigen.
 - Antigen-presenting cells and T cells are involved.
 - The response can activate macrophages and cause tissue damage.
- Autoimmunity:
 - If clonal deletion fails, "forbidden clones", which activate in response to self-antigens, are sometimes made.
 - People with systemic lupus erythematosus have antibodies to many cellular components, including DNA and nuclear proteins.
 - Their antibodies bind cellular components from, get stuck on tissues and trigger inflammation.
 - Rheumatoid arthritis patients have low CTLA4 activity. Joints become inflamed.
 - Multiple sclerosis causes damage to the nervous system. It involves T and B cell mediated attack on myelin, an insulator on some nerves.
 - Insulin-dependent juvenile-onset-diabetes mellitus involves an immune reaction against the cells of the pancreas.

B. AIDS is an immune deficiency disorder

- HIV (human immunodeficiency virus), which leads to AIDS (acquired immune deficiency syndrome), causes a depletion of T_H cells.
- It can be transmitted through blood, or exposure of broken skin or an open wound to the body fluids of an infected person.
- The disease progresses as follows.

- T_H cells and antigen-presenting cells, dendritic cells are infected.
- The dendritic cells transport it to lymphoid tissue where T cells reside.
- The virus infects *activated* T cells.
- Up to 10 billion viruses are made each day.
- The number of T_H cells drop. People show symptoms similar to mononucleosis, such as enlarged lymph nodes and fever.
- These symptoms abate within 3 weeks.
- An immune response is mounted and antibodies appear in the blood. (See Figure 19.23)
- However, antibody-HIV complexes can still infect cells.
- Some people fail to develop the disease for 20 years, most people take 8-10 years and a few succumb within a year.
- It is the depletion of T_H that causes the immune deficiency.
- Kaposi sarcoma, a rare skin tumor, caused by a herpes virus; pneumonia and a lymphoma, caused by Epstein-Barr virus, are opportunistic infections that AIDS patients get because of a weakened immune system.
- See Figure 19.24.

C. HIV infection and replication occur in T_H cells

- HIV uses RNA as its genetic molecule.
- The core of the virus contains two identical molecules of RNA and the enzymes reverse transcriptase, integrase and a protease.
- The envelope is derived from the plasma membrane of the cell in which the virus grew.
- The envelope has glycoproteins gp120 and gp41 protruding. These proteins are necessary for targeting of T_H and other targeted cell types.
- The virus enters the cell via CD4 membrane proteins on T_H cells. The gp120 gets bound to CD4.
- The viral envelope fuses with the membrane of the cell. This requires the virus protein gp41 and a cellular protein called fusin.
- Once in the cell, reverse transcriptase makes a DNA copy of the viral RNA, RNase H degrades the viral RNA, and cellular DNA polymerase makes the complementary strand.
- Reverse transcriptase is error prone, which elevates the mutation rate and adds to the adaptability of the virus.
- The cDNA integrates into the host DNA.
 - The core protein translocates to the nucleus of the host because it contains a nuclear translocation signal peptide.
 - In the nucleus, a viral enzyme called integrase catalyzes the breakage of host DNA and insertion of viral cDNA.
- Viruses are made when the T_H cell is activated.
 - Transcription of the viral DNA requires host transcription factors and a viral protein Tat.
 - The RNA is either spliced and translated or unspliced to become the genetic molecule of a new virus.
 - A viral protease is needed to cleave large viral precursor proteins into smaller functional units.
 - Viral membrane proteins are synthesized on rough ER and glycosylation occurs within the ER and golgi.

- These proteins are transported to the plasma membrane. The cytoplasmic tails of gp120 membrane proteins bind to the core particles, while the core particles package the RNA and associated enzymes.

D. Treatments for HIV infection rely on knowledge of its molecular biology

- Highly active antiretroviral therapy (HAART) was developed in the late 1990's.
 - A protease inhibitor obstructs the active site of the HIV protease.
 - Two reverse transcriptase inhibitors that terminate the cDNA molecules prematurely are used.
- Treatments under development include:
 - Vaccines.
 - Integrase inhibitors.
 - Tat and Rev inhibitors.
 - Antisense RNA and ribozymes directed against HIV RNA.
- *See Figure 19.25.*