Biology

IMMUNE AND LYMPHATIC SYSTEMS

Chapter

The immune and lymphatic systems are two closely related organ systems that share several organs and physiological functions. The immune system is our body's defense system against infectious pathogenic viruses, bacteria, and fungi as well as parasitic animals and protists. The immune system works to keep these harmful agents out of the body and attacks those that manage to enter.

The lymphatic system is a system of capillaries, vessels, nodes and other organs that transport a fluid called lymph from the tissues as it returns to the bloodstream. The lymphatic tissue of these organs filters and cleans the lymph of any debris, abnormal cells, or pathogens. The lymphatic system also transports fatty acids from the intestines to the circulatory system.

ANATOMY

Red Bone Marrow and Leukocytes

It is a highly vascular tissue found in the spaces between trabeculae of spongy bone. It is mostly found in the ends of long bones and in the flat bones of the body. Red bone marrow is a hematopoietic tissue containing many stem cells that produce blood cells. All of the leukocytes, or white blood cells, of the immune system are produced by red bone marrow. Leukocytes can be further broken down into 2 groups based upon the type of stem cells that produces them: myeloid stem cells and lymphoid stem cells. Myeloid stem cells produce monocytes and the granular leukocytes—eosinophils, basophils, and neutrophils. Lymphoid stem cells produce T lymphocytes and B lymphocytes.

- T lymphocytes, also commonly known as T cells, are cells involved in fighting specific pathogens in the body. T cells may act as helpers of other immune cells or attack pathogens directly. After an infection, memory T cells persist in the body to provide a faster reaction to subsequent infection by pathogens expressing the same antigen.
- B lymphocytes, also commonly known as B cells, are also cells involved in fighting specific pathogens in the body. Once B cells have been activated by contact with a pathogen, they form plasma cells that produce antibodies. Antibodies then neutralize the pathogens until other immune cells can destroy them. After an infection, memory B cells persist in the body to quickly produce antibodies to subsequent infection by pathogens expressing the same antigen.

Natural killer cells

They are also known as NK cells, are lymphocytes that are able to respond to a wide range of pathogens and cancerous cells. NK cells travel within the blood and are found in the lymph nodes, spleen, and red bone marrow where they fight most types of infection.

Lymph Capillaries

As blood passes through the tissues of the body, it enters thin-walled capillaries to facilitate diffusion of nutrients, gases, and wastes. Blood plasma also diffuses through the thin capillary walls and penetrates into the spaces between the cells of the tissues. Some of this plasma diffuses back into the blood

of the capillaries, but a considerable portion becomes embedded in the tissues as interstitial fluid. To prevent the accumulation of excess fluids, small dead-end vessels called lymphatic capillaries extend into the tissues to absorb fluids and return them to circulation.

Lymph

The interstitial fluid picked up by lymphatic capillaries is known as lymph. Lymph very closely resembles the plasma found in the veins: it is a mixture of about 90% water and 10% solutes such as proteins, cellular waste products, dissolved gases, and hormones. Lymph may also contain bacterial cells that are picked up from diseased tissues and the white blood cells that fight these pathogens. A special type of lymph, known as chyle, is produced in the digestive system as lymph absorbs triglycerides from the intestinal villi.

Lymph Nodes

Lymph nodes are small, kidney-shaped organs of the lymphatic system. There are several hundred lymph nodes found mostly throughout the thorax and abdomen of the body with the highest concentrations in the axillary (armpit) and inguinal (groin) regions. The outside of each lymph node is made of a dense fibrous connective tissue capsule. Inside the capsule, the lymph node is filled with reticular tissue containing many lymphocytes and macrophages. The lymph nodes function as filters of lymph. The various lymphatic tissues in the body are:

- **Tonsils**

  There are 5 tonsils in the body—2 lingual, 2 palatine, and 1 pharyngeal. The tonsils contain many T and B cells to protect the body from inhaled or ingested substances. The tonsils often become inflamed in response to an infection.

- Peyer's patches

  They are small masses of lymphatic tissue found in the ileum of the small intestine. Peyer's patches contain T and B cells that monitor the contents of the intestinal lumen for pathogens. Once the antigens of a pathogen are detected, the T and B cells spread and prepare the body to fight a possible infection.

- Spleen

  It is a flattened, oval-shaped organ located in the upper left quadrant of the abdomen lateral to the stomach. The spleen is made up of a dense fibrous connective tissue capsule filled with regions known as red and white pulp.

- Thymus

  It is a small, triangular organ found just posterior to the sternum and anterior to the heart. The thymus produces T cells during foetal development and childhood. T cells formed in the thymus and red bone marrow mature, develop, and reproduce in the thymus throughout childhood. The surviving T cells spread throughout the body to the other lymphatic tissues to fight infections. By the time a person reaches puberty, the immune system is mature and the role of the thymus is diminished. After puberty, the inactive thymus is slowly replaced by adipose tissue.

PHYSIOLOGY

Types of Immunity

The body employs many different types of immunity to protect itself from infection from a seemingly endless supply of pathogens.

These defenses may be external and prevent pathogens from entering the body. Conversely, internal defenses fight pathogens that have already entered the body. Among the internal defenses, some are specific to only one pathogen or may be innate and defend against many pathogens. Some of these specific defenses can be acquired to preemptively prevent an infection before a pathogen enters the body.

Innate Immunity

The body has many innate ways to defend itself against a broad spectrum of pathogens. These defenses may be subdivided into.

- **External Defenses**

  The coverings and linings of the body constantly prevent infections before they begin by barring pathogens from entering the body. Epidermal cells are constantly growing, dying, and shedding to provide a renewed physical barrier to pathogens. Secretions like sebum, cerumen, mucus, tears, and saliva are used to trap, move, and sometimes even kill bacteria that settle on or in the body.

  Stomach acid acts as a chemical barrier to kill microbes found on food entering the body. Urine and acidic vaginal secretions also help to kill and remove pathogens that attempt to enter the body. Finally, the flora of naturally occurring beneficial bacteria that live on and in our bodies provide a layer of protection from harmful microbes that would seek to colonize our bodies for themselves.

- **Internal Defenses**

  - **Fever**

    In response to an infection, the body may start a fever by raising its internal temperature out of its normal homeostatic range. Fevers help to speed up the body's response system to an infection while at the same time slowing the reproduction of the pathogen.

  - **Inflammation**

    The body may also start an inflammation in a region of the body to stop the spread of the infection. Inflammations are the result of a localized vasodilation that allows extra blood to flow into the infected region. The extra blood flow speeds the arrival of leukocytes to fight the infection. The enlarged blood vessel allows fluid and cells to leak out of the blood vessel to cause swelling and the movement of leukocytes into the tissue to fight the infection.

  - **Natural Killer Cells (NK)**

    These cells are special lymphocytes that are able to recognize and kill virus-infected cells and tumour cells. NK cells check the surface markers on the surface of the body's cells, looking for cells that are lacking the correct number of markers due to disease. The NK cells then kill these cells before they can spread infection or cancer.

  - **Phagocytes**

    The term phagocyte means "eating cell" and refers to a group of cell types including neutrophils and macrophages. A phagocyte engulfs pathogens with its cell membrane before using digestive enzymes to kill and dissolve the cell into its chemical parts. Phagocytes are able to recognize and consume many different types of cells, including dead or damaged body cells.

Cell-mediated Specific Immunity

When a pathogen infects the body, it often encounters macrophages and dendritic cells of the innate immune system. These cells can become antigen-presenting cells (APCs) by consuming and processing pathogenic antigens. The APCs travel into the lymphatic system carrying these antigens to be presented to the T cells and B cells of the specific immune system.

Inactive T cells are found in lymphatic tissue awaiting infection by a pathogen. Certain T cells have antigen receptors that recognize the pathogen but do not reproduce until they are triggered by an APC. The activated T cell begins reproducing very quickly to form an army of active T cells that spread through the body and fight the pathogen. Cytotoxic T cells directly attach to and kill pathogens and virus-infected cells using powerful toxins. Helper T cells assist in the immune response by stimulating the response of B cells and macrophages.

After an infection has been fought off, memory T cells remain in the lymphatic tissue waiting for a new infection by cells presenting the same antigen. The response by memory T cells to the antigen is much faster than that of the inactive T cells that fought the first infection. The increase in T cell reaction speed leads to immunity—the reintroduction of the same pathogen is fought off so quickly that there are few or no symptoms. This immunity may last for years or even an entire lifetime.

Antibody-mediated Specific Immunity

During an infection, the APCs that travel to the lymphatic system to stimulate T cells also stimulate B cells. B cells are lymphocytes that are found in lymphatic tissues of the body that produce antibodies to fight pathogens. Once a B cell has been contacted by an APC, it processes the antigen to produce an MHC-antigen complex. Helper T cells present in the lymphatic system bind to the MHC-antigen complex to stimulate the B cell to become active. The active B cell begins to reproduce and produce 2 types of cells: plasma cells and memory B cells.

1. Plasma cells become antibody factories producing thousands of antibodies.
2. Memory B cells reside in the lymphatic system where they help to provide immunity by preparing for later infection by the same antigen-presenting pathogen.

Antibodies are proteins that are specific to and bind to a particular antigen on a cell or virus. Once antibodies have latched on to a cell or virus, they make it harder for their target to move, reproduce, and infect cells. Antibodies also make it easier and more appealing for phagocytes to consume the pathogen.

Acquired Immunity

Under most circumstances, immunity is developed throughout a lifetime by the accumulation of memory T and B cells after an infection. There are a few ways that immunity can be acquired without exposure to a pathogen. Immunization is the process of introducing antigens from a virus or bacterium to the body so that memory T and B cells are produced to prevent an actual infection. Most immunizations involve the injection of bacteria or viruses that have been inactivated or weakened. Newborn infants can also acquire some temporary immunity from infection thanks to antibodies that are passed on from their mother. Some antibodies are able to cross the placenta from the mother's blood and enter the infant's bloodstream. Other antibodies are passed through breast milk to protect the infant.

DISEASES

Immunodeficiency disorders prevent your body

from being able to fight infections and diseases the way it should. An immunodeficiency disorder makes you considerably more susceptible to catching viruses and bacterial infections.

Immune disorders are oftentimes categorized as either congenital or acquired. When you're born with a disorder, it's sometimes called a congenital or primary disorder. Acquired disorders are sometimes called secondary disorders. Secondary disorders are more common than primary.

Primary disorders include:

- Severe Combined Immunodeficiency (SCID disorders)

  Secondary disorders happen when your body is attacked by an outside source, such as a toxic chemical or an infection. Severe burns and radiation also can cause secondary disorders. Secondary disorders include:

- AIDS
- Cancers of the immune system, such as leukemia

Autoimmune Diseases and Disorders

Sometimes the immune system's recognition apparatus breaks down, and the body begins to manufacture T cells and antibodies directed against its own cells and organs. The mechanism by which the enormous diversity of B and T cells is generated is a random process that inevitably gives rise to some receptors that recognize the body's own constituents as foreign. Lymphocytes bearing such self-reactive receptors, however, are eliminated or rendered impotent by several different mechanisms, so that the immune system does not normally generate significant amounts of antibodies or T cells that are reactive with the body's components (selfantigens). Nevertheless, an immune response to self, called autoimmunity, can occur, and some of the ways that self-directed immune responses cause damage have been mentioned in the section Allergies. Understanding and identifying autoimmune disorders is difficult given that all humans have many self-reactive antibodies in the blood but most show no sign of disease. Consequently the identification of auto-antibodies is not a sufficient diagnostic tool for determining the presence of an autoimmune disorder. There is a difference between an autoimmune response and disease: in the former case the autoantibodies do not cause dysfunction, but in the latter case they do.

Examples of autoimmune disorders

The spectrum of autoimmune disorders is wide, ranging from those that involve a single organ to others that affect several different organs as a secondary consequence of the presence of immune complexes in the circulation. It is not possible in this article to discuss them all. The following disorders have been chosen to illustrate some of the very different complications that can arise from autoimmunity.

AUTOIMMUNE DISEASES OF THE THYROID GLAND

Hashimoto disease involves swelling of the gland (a condition called goiter) and a loss of thyroid hormone production (hypothyroidism).

Graves disease is a type of overactive thyroid disease (hyperthyroidism) involving excess production and secretion of thyroid hormones.

In both Hashimoto disease and Graves disease, the thyroid gland becomes infiltrated with lymphocytes and is partially destroyed. If the gland is completely destroyed, a condition called myxedema may ensue, involving a swelling of tissues, especially those around the face.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory disease that affects connective tissues throughout the body, particularly the synovial membranes that line the peripheral joints.

MULTIPLE SCLEROSIS

It is an autoimmune disease that results in the gradual destruction of the myelin sheath that surrounds nerve fibres. It is characterized by progressive degeneration of nerve function, interjected with periods of apparent remission. The cerebrospinal fluid of persons with multiple sclerosis contains large numbers of antibodies directed against myelin basic protein and perhaps other brain proteins. Infiltrating lymphocytes and macrophages may exacerbate the destructive response. The reason the immune system launches an attack against myelin is unknown, but several viruses have been suggested as initiators of the response.

TYPE 1 DIABETES MELLITUS

It is the autoimmune form of diabetes and often arises in childhood. It is caused by the destruction of cells of the pancreatic tissue called the islets of Langerhans. Those cells normally produce insulin, the hormone that helps regulate glucose levels in the blood. Individuals with type I diabetes have high blood glucose levels that result from a lack of insulin.

Immunodeficiency Disorders

When the immune system is missing one or more of its components, the result is an immunodeficiency disorder. Immunodeficiency disorders can be inherited, acquired through infection, or produced unintentionally by drugs such as those used to treat people with cancer or those who have received transplants.

Some children are born with poorly functioning immune systems. Some have flaws in the B cell system and cannot produce antibodies. Others, whose thymus is either missing or small and abnormal, lack T cells. Very rarely, infants are born lacking all of the major immune defenses. This condition is known as severe combined immunodeficiency disease or SCID. AIDS is an immunodeficiency disorder caused by a virus (HIV) that infects immune cells. HIV can destroy or disable vital T cells, paving the way for a variety of immunologic shortcomings. HIV also can hide out for long periods in immunecells. As the immune defenses falter, a person with AIDS falls prey to unusual, often life-threatening infections and rare cancers. A contagious disease, AIDS is spread by intimate sexual contact, transfer of the virus from mother to infant during pregnancy, or direct blood contamination.

Allergies

The terms allergy and *hypersensitivity* are commonly used to describe inappropriate immune responses that occur when an individual becomes sensitized to harmless substances. Allergic reactions do not as a rule cause symptoms to arise on the first exposure to an antigen. At the initial exposure reactive lymphocytes are generated that go into action only when the individual is re-exposed to the antigen.

Immunologists use the Gell-Coombs classification system to recognize four types of hypersensitivity reactions. Types I, II, and III involve antibody-mediated mechanisms and are of rapid onset.

❐ Type I hypersensitivity

Type I, also known as atopic or anaphylactic hypersensitivity, involves IgE antibody, mast cells, and basophils.

The overall result of the type I reaction is an acute inflammation marked by local seepage

of fluid from and dilation of the blood vessels, followed by ingress of granulocytes into the tissues. This inflammatory reaction can be a useful local protective mechanism. If, however, it is triggered by an otherwise innocuous antigen entering the eyes and nose, it results in swelling and redness of the linings of the eyelids and nasal passages, secretion of tears and mucus, and sneezing—the typical symptoms of hay fever. If the antigen penetrates the lungs, not only do the linings of the bronchial tubes become swollen and secrete mucus, but the muscle in their walls contracts and the tubes are narrowed, making breathing particularly difficult. These are the symptoms of acute asthma. If the antigen is injected beneath the skin—for example, by the sting of an insect or in the course of some medical procedure—the local reaction may be extensive. Called a wheal-and-flare reaction, it includes swelling, produced by the release of serum into the tissues (wheal), and redness of the skin, resulting from the dilation of blood vessels (flare). If the injected antigen enters the bloodstream and interacts with basophils in the blood as well as with mast cells deep within the tissues, the release of active agents can cause hives, characterized by severe itching. If the antigen enters through the gut, the consequences can include painful intestinal spasms and vomiting. Local reaction with mast cells increases the permeability of the mucosa of the gut, and in many cases the antigen enters the bloodstream and also produces hives. Regardless of whether the allergen is injected or ingested, if it ends up in the bloodstream, it can induce anaphylaxis, a syndrome that in its most severe form is characterized by a profound and prolonged drop in blood pressure accompanied by difficulty in breathing. Death can occur within minutes unless an injection of epinephrine is administered immediately. This type of severe allergic reaction can occur in response to foods, drugs such as penicillin, and insect venom.

Another feature of type I hypersensitivity reactions is that, once the immediate local reaction to the allergen has taken its course, there may occur an influx of more granulocytes, lymphocytes, and macrophages at the site. If the allergen is still present, a more prolonged form of the same reaction—the so-called late-phase reaction, which lasts a day or two rather than minutes—may supervene. This is a feature of asthmatic attacks in some subjects, in whom repeated episodes also lead to increased sensitivity of the air passages to the constrictive action of histamine. If such persons can escape exposure to the allergen for several weeks, subsequent exposure causes much less severe attacks. A prolonged IgE-induced reaction also causes atopic dermatitis, a skin condition characterized by persistent itching and scaly red patches. These often develop at sites where the skin is bent, such as the elbows and knees. The persistence is due to the influx of mast cells stimulated by the continued presence of the allergen, which is often a harmless substance such as animal hair or dander.

❐ Type II hypersensitivity

Allergic reactions of this type, also known as cytotoxic reactions, occur when cells within the body are destroyed by antibodies, with or without activation of the entire complement system. When antibody binds to an antigen on the surface of a target cell, it can cause damage through a number of mechanisms. When IgM or IgG molecules are involved, they activate the complete complement system, which leads to the formation of a membrane attack complex that destroys the cells. Unlike type I reactions, in which antigens interact with cell-bound IgE immunoglobulins, type II reactions involve the interaction of circulating

immunoglobulins with cell-bound antigens.

Type II reactions only rarely result from the introduction of innocuous antigens. More commonly, they develop because antibodies have formed against body cells that have been infected by microbes (and thus present microbial antigenic determinants) or because antibodies have been produced that attack the body's own cells. This latter process underlies a number of autoimmune diseases, including autoimmune hemolytic anemia, myasthenia gravis, and Goodpasture syndrome.

Type II reactions also occur after an incompatible blood transfusion, when red blood cells are transfused into a person who has antibodies against proteins on the surface of these foreign cells (either naturally or as a result of previous transfusions).

❐ Type III hypersensitivity

Type III, or immune-complex, reactions are characterized by tissue damage caused by the activation of complement in response to antigen-antibody (immune) complexes that are deposited in tissues. The classes of antibody involved are the same ones that participate in type II reactions—IgG and IgM—but the mechanism by which tissue damage is brought about is different.

❐ Type IV hypersensitivity

Type IV hypersensitivity is a cell-mediated immune reaction. In other words, it does not involve the participation of antibodies but is due primarily to the interaction of T cells with antigens. Reactions of this kind depend on the presence in the circulation of a sufficient number of T cells able to recognize the antigen. The specific T cells must migrate to the site where the antigen is present. Since this process takes more time than reactions involving antibodies, type IV reactions first were distinguished by their delayed onset and are still frequently referred to as delayed hypersensitivity reactions. Type IV reactions not only develop slowly—reactions appear about 18 to 24 hours after introduction of antigen to the system—but, depending on whether the antigen persists or is removed, they can be prolonged or relatively transient.

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