Topic 10 Lymphatic System and Immunity

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Introduction

Lymphatic or *lymphoid* system consists of a fluid called lymph, vessels called lymphatic vessels that transport the lymph, a number of structures and organs containing lymphatic tissue and red bone marrow.

Primary Functions of Lymphatic System
The lymphatic system has three primary functions:

1) *Drains excess interstitial fluid*. Lymphatic vessels drain excess interstitial fluid from tissue spaces and return it to the blood. It reabsorbs excess interstitial fluids and returns it to the venous circulation, Thus, maintaining blood volume levels and preventing interstitial fluid levels from rising out of control.

2) *Transports dietary lipids.* Lymphatic vessels transport lipids and lipid-soluble vitamins (A, D, E, and K) absorbed by the gastrointestinal tract.

3) *Carries out immune responses.* Lymphatic tissue initiates highly specific responses directed against particular microbes. It serves as major staging areas for the development of critical immune responses through the lymph node.

Organization of Immune Function
The immune function is organized into three phases based on the onset of their effects which are:

a. Barrier defenses such as the skin and mucous membranes, which act instantaneously to prevent pathogenic invasion into the body tissues.
b. The rapid but nonspecific innate immune response, which consists of a variety of specialized cells and soluble factors.
c. The slower but more specific and effective adaptive immune response, which involves many cell types and soluble factors, but is primarily controlled by white blood cells (leukocytes) known as lymphocytes, which help control immune responses.

2. Lymphatic Structures and Function
a. Lymphatic Vessel and Lymph Circulation

Lymph Circulation
Below is the sequence of fluid flow in Lymph Circulation

Bloodstream -----→ Interstitial spaces (interstitial fluid) --→ lymphatic capillaries (Lymph) -→ Lymphatic vessel (lymph) -→ Lymphatic trunks or duct--→ junction of the internal jugular and subclavian veins (blood)

How does lymph kept flowing? What mechanisms are responsible for keeping the flow of lymph?

a) Respiratory pump
Lymph flow is maintained by pressure caused by inhalation. Lymph flows from abdominal region going to thoracic region, that is, from region with higher pressure going to region with lower pressure. In exhalation, where pressure reverses, the valves prevent backflow of blood from the thoracic veins to the abdominal veins.

Also, when a lymphatic vessel distends, the smooth muscle in its wall contracts, which helps move lymph from one segment of the vessel to the next.

b) Skeletal muscle pump
Skeletal muscle pump, on the other hand, works through the "milking action" of skeletal muscle contractions. In lymphatic circulation, milking compresses lymphatic vessels which drives lymph toward the junction of the internal jugular and subclavian veins.

Lymphatic capillaries

These are thin-walled tubes made up of endothelial cells located in the spaces between cells and are closed at one end. They have greater permeability and larger in diameter than blood capillaries. It where the interstitial fluid enters the lymphatic system to become the lymph fluid. They are found throughout the body except in avascular tissues, central nervous system, portion of the spleen and bone marrow. Lymphatic capillaries consist of overlapping endothelial cells, valves and anchoring filaments/ fibers.

During filtration, the fluid inside the arteries goes out into the interstitial space due to hydrostatic pressure. These interstitial fluids will eventually be reabsorbed back in the venous system. However, not all fluids are reabsorbed in venous system. Only 85% is reabsorbed in the venous system and the remaining 15% of the fluid is reabsorbed in the lymphatic system preventing the accumulation of fluid in the interstitial space causing edema.

When pressure is greater in the interstitial fluid than in lymph, the lymph capillary walls separate slightly, and interstitial fluid enters the lymphatic capillary. And when pressure is greater inside the lymphatic capillary, the walls adhere more closely which prevents the lymph from going out the lymph capillary.

The pressure is relieved as lymph moves further down the lymphatic capillary.
How about the anchoring filaments? When excess interstitial fluid accumulates and causes tissue swelling, the anchoring filaments are pulled, making the openings between cells even larger so that more fluid can flow into the lymphatic capillary

Lymphatic vessels

These are the vessels where the lymphatic capillaries drain their fluid and their walls resembles resembles small veins but have thinner walls and more valves. All lymphatics vessels are directed to thoracic cavity and they drain tissue spaces throughout the body except in nervous system
From lymphatic vessel, the lymph passes through the lymph nodes. → the lymph will pass through the lymph trunks

Lymph Trunks

There are four pairs of lymph trunks: jugular lymph trunks (which drains from head and neck), subclavian lymph trunks (Subclavian trunks which drains from upper limbs), bronchomediastinal lymph trunks, (drains lymph from the thoracic wall, lung, and heart) and lumbar lymph trunks (drain lymph from the lower limbs, the wall and viscera of the pelvis, the kidneys, the adrenal glands, and the abdominal wall). In addition, the intestinal lymph trunk is unpaired. Intestinal trunk drains lymph from stomach, intestines, pancreas, spleen, and part of the liver.

Lymph ducts

The right lymphatic duct receives lymph only from the upper right side of the body. The lymph from the rest of the body enters the bloodstream through the thoracic duct via all the remaining lymphatic trunks.

b. Lymphatic Organs and Tissues

Primary Lymphatic Organ

Primary lymphatic organs are the sites where stem cells divide and become immunocompetent. The primary lymphatic organs are the red bone marrow and the thymus.

Thymus

Thymus is bilobed organ located between the sternum and the aorta. It is in the thymus where the pre-t cells become immunocompetent T cells after they migrated from the bone marrow. Each thymic lobule consists of a deeply staining outer cortex and a lighter-staining central medulla.
Outer cortex is composed of large numbers of t cells (immature), and scattered dendritic cells, epithelial cells, and macrophages while medulla consists of widely scattered, more mature T cells, epithelial cells, dendritic cells, and macrophages. It is largest at puberty and then the functional portion atrophies with age.

Bone Marrow

The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a thymocyte, leaves the bone marrow and matures largely in the thymus gland.

Secondary Lymphatic Organs are the sites where most immune responses occur. They include lymph nodes, the spleen, and lymphatic nodules (follicles). The thymus, lymph nodes, and spleen are considered organs

Lymph nodes

The capsule, trabeculae, reticular fibers, and fibroblasts constitute the *stroma* (supporting framework of connective tissue) of a lymph node. The *parenchyma* (functioning part) of a lymph node is divided into a superficial cortex and a deep medulla. The cortex consists of an
outer cortex and an inner cortex. Within the outer cortex are mostly T cells and dendritic while the medulla contains B cells. As lymph enters one end of a lymph node, foreign substances are trapped by the reticular fibers within the sinuses of the node. Then macrophages destroy some foreign substances by phagocytosis, while lymphocytes destroy others

Spleen

It is located in the left hypochondriac region between the stomach and diaphragm. The spleen is sometimes called the "filter of the blood" because of its extensive vascularization and the presence of macrophages and dendritic cells that remove microbes and other materials from the blood, including dying red blood cells. The spleen also functions as the location of immune responses to blood-borne pathogens.

Lymphatic nodules (MALT)

are egg-shaped masses of lymphatic tissue that are not surrounded by a capsule. Because they are scattered throughout the lamina propria (connective tissue) of mucous membranes lining the gastrointestinal, urinary, and reproductive tracts and the respiratory airways, lymphatic nodules in these areas are also referred to as **mucosa-associated lymphatic tissue (MALT).**

3. Concept of Immunity

Immunity or resistance is the ability to ward off damage or disease through our defenses while susceptibility means vulnerability or lack of resistance.

There are two general types of immunity and they are (1) innate immunity and (2) adaptive immunity.

Innate or nonspecific immunity are defenses which are present since birth. This includes the external physical and chemical barriers. It does not involve specific recognition of a microbe and can start acting immediately on encounter with infectious agents. This type of immunity does not generate long-term protective immunological memory. This serves as immunity's warning system and prevents microbes from entering body and eliminates those that gain access.

First line of defense are structures that provide both physical and chemical barriers that discourage pathogens and foreign substances from penetrating the body and causing diseases which include the following:

Physical

- the skin
- mucous membranes (hairs/cilia)
- Tears from lacrimal apparatus
- Saliva

Chemical

- Sebum
- Gastric juices

Second line of defense includes the following: internal antimicrobial substances, phagocytes, natural killer cells, inflammation, and fever.

- Antimicrobial substances discourage microbial growth and have four main types namely: interferons, complement, iron-binding proteins, and antimicrobial proteins.
    - Antimicrobial proteins. Theses are short peptide that can attract dendritic cells and mast cells which participate in immune responses. Examples of AMPs are dermicidin (produced by sweat glands),Defensins and cathelicidins (produced by neutrophils, macrophages, and epithelia), and thrombocidin (produced by platelets).
    - Interferons. These are proteins produced when lymphocytes, macrophages and fibroblasts got infected. IFNs induces synthesis of antiviral proteins that interfere with viral replication.
    - Iron-binding. They inhibit the growth of certain bacteria by reducing the amount of available iron. Examples of Iron- binding proteins are *transferrin, ferritin, lactoferrin & hemoglobin*
    - Complement system. They are the group of normally inactive proteins which, when activated, complement or enhance certain immune reactions. With the help of complement system, cytolysis of microbes, phagocytosis and inflammation can occur.
- Natural killer cells have the ability to kill a wide variety of infected body cells and certain tumor cells. These cells attack any body cells that display abnormal or unusual plasma. The binding of NK cells to a target cell may either cause cytolysis (cell bursting) or apoptosis (self destruction) because of granules containing protein called perforin and granzymes, respectively
membrane proteins.
- Phagocytosis the ingestion of microbes or other particles such as cellular debris. It occurs in five phases: chemotaxis, adherence, ingestion, digestion, and killing.

- Inflammation is a nonspecific, defensive response of the body to tissue damage. It has three stages (This will be further discussed under Lymphatic Homeostasis)

- Fever, which commonly occurs during inflammation and infection. is an abnormally high body temperature that occurs because the hypothalamic thermostat is reset. It intensifies the effects of interferons, inhibits the growth of some microbes, and speeds up body reactions that aid
repair.

2**. Humoral immunity (adaptive immunity)**

Adaptive or specific immunity

Refers to defenses that involve specific recognition of a microbe once it has breached the innate immunity defenses. This is the ability of the body to defend itself against specific invaders such as bacteria, toxins, viruses, and foreign tissues.

Two properties of adaptive immunity: (1) *specificity* for particular foreign molecules (antigens), which also involves distinguishing self from non-self molecules and (2) *memory* for most previously encountered antigens so that a second encounter prompts an even more rapid and vigorous response.

T cells must have two traits: (1) self-recognition or being able to *recognize* your own major histocompatibility complex (MHC) proteins, and (2) self- tolerance or *lack reactivity* to peptide fragments from your own proteins.

The lymphocytes called T lymphocytes (T cells) and B lymphocytes (B cells) are involved in this type of immunity. For a review, lymphocyte is one of the components of WBC. These are your agranulocytes.

Maturation of T cells and B cells

We have discussed that B cells and pre- T cells arise from bone marrow and thymus. B- cells develop and mature (immunocompetent) in bone marrow while pre- t cells(thymocyte) migrate to thymus in order to mature and become immunocompetent.

B- cells and T- cells are said to be immunocompetent when they have proteins that functions as **antigen-receptors** in their plasma membrane. Antigen receptors are **molecules capable of recognizing specific antigens**

There are two major types of mature T cells that exit the thymus: helper T cells and cytotoxic T cells. Helper T cells are aka as CD4 T cells while cytotoxic T cells are also referred to as CD8 T cells because their plasma membranes contain not only antigen receptors but also a protein known as CD4 & CD8 respectively.

Clonal Selection Principle

Clonal selection is the process by which a lymphocyte *proliferates* (divides) and *differentiates* (forms more highly specialized cells) in response to a specific antigen. Clone is what you call the cells that resulted from the process of clonal selection. The clones have the ability to recognize the same specific antigen as the original Lymphocyte that undergo clonal selection give rise to **effector cells and memory cells.** Clonal selection occurs in secondary lymphatic organs and tissues. Most effector cells eventually die after the immune response has been completed while memory cells have long life

Antigens and Antigen Receptors

Antigens (Ags) or *antibody generators* are substances that are recognized as foreign and provoke immune responses.

Antigens have two important characteristics: immunogenicity and reactivity. Immunogenicity is the ability to provoke an immune response by stimulating the production of specific antibodies, the proliferation of specific T cells, or both. Reactivity is the ability of the antigen to react specifically with the antibodies or cells it provoked.

Epitopes are small parts of a large antigen molecule that act as the triggers for immune response. They are known as antigenic determinants. Most antigens have many epitopes, each of which induces production of a specific antibody or activates a specific T cell.

Hapten is a smaller substance that has reactivity but lacks immunogenicity. In order to stimulate immune response, it has to be attached to a larger carrier molecule.

Major Histocompatibility Complex Antigens

Major histocompatibility complex antigens or your self-antigens are located in the plasma membrane of body cells. They mark the surface of your body cells except for RBC. These antigens are unique to each person's body cells. Their main function is to help T cells recognize the that an antigen is foreign, not self. Such recognition is an important first step in any adaptive immune response.

MCH Antigens have two types, name Class 1 MHC (MHC-1) molecules are built into the plasma membranes of all body cells except red blood while Class II MHC (MHC-II) molecules appear on the surface of antigen-presenting cells.

Antigen Processing and Presenting

For an immune response to occur, B cells and T cells must recognize if a foreign antigen is present. B cells directly recognize antigen present in lymph, interstitial fluid or blood plasma. However, t cells only recognize antigen when they are processed and presented.

Antigen processing involves breaking down of antigen protein into peptide framework while antigen presentation is the insertion of the antigen-MCH complex into the plasma membrane after antigen processing.

There are two ways of processing and presenting depending on the location, whether inside or outside the body cells. These are processing and presenting exogenous and endogenous antigens.

(1)Processing and presenting Exogenous antigen happens in body cells that are not yet infected. In this type, antigen-presenting cells (APCs)--- dendritic cells, macrophages and B cells--- process and present antigens. Exogenous antigens (formed outside body cells) are presented with MHC-II molecules.

(2) Processing and presenting Endogenous antigen happen in infected cells. Fragments of endogenous antigens are processed and then presented with MHC-I proteins on the surface of an infected body cell.

Types of Adaptive Immunity

Cell mediated immunity works against intracellular pathogens which includes viruses, bacteria or fungi that are inside the cells. This immune response begins with activation of a small number of T cells by a specific antigen. T cells receptors recognize antigen fragments associated with MHC molecules on the surface of a body cell. Only activated t-cells undergo clonal selection.

Three cells involved: Helper t-cells, Cytotoxic cells and Memory cells
Cytotoxic t cells are the ones that eliminates foreign invader in cell mediated responses. They leave the secondary lymphatic organs and migrate to destroy infected targets cells, cancer cells. Cytotoxic T delivers "lethal hit " which kills the infected target cells in two ways:

(1) The cytotoxic T cell then releases granzymes, protein-digesting enzymes that trigger apoptosis Once the infected cell is destroyed, the released microbes are killed by phagocytes
(2) Release two proteins from their granules: perforin and granulysin. Cytotoxic T cells release granzymes that trigger apoptosis and perforin that triggers cytolysis of infected target cells.

In antibody-mediated immunity, B cells transform into plasma cells, which synthesize and secrete specific proteins called antibodies (Abs) or *immunoglobulins* (*Igs*) . A given antibody can bind to and inactivate a specific antigen.

Activation and clonal Selection of B cells

Although B cells can respond to an unprocessed antigen present in lymph or interstitial fluid, they too, undergo the process of activation. When B cells are activated, the response of B cell is greater. Unlike cytotoxic t cells which seek foreign antibody, **B cells stays and become activated in secondary lymphatic organs—spleen, lymph nodes and MALT.**

Activation occurs when antigen is taken into by the B-cell, then being processed and presented—antigen is broken down into fragments and combined with MHC-II and moved to B cell membrane. The helper T cell produces interleukin-2 and other cytokines that function as costimulators to activate B cells. Once activated, a B cell undergoes clonal selection. The result is the formation of a clone of B cells that consists of plasma cells and memory B cells

For animated explanation, please click on the link

Antigen processing, presentation and activation
https://youtu.be/Bgd1qxQ0Dh4

Helper T cells aid the immune responses of both cell-mediated and antibody-mediated immunity
An antibody (Ab) can combine specifically with the epitope on the antigen that triggered its production.

Antibodies
Antibodies belong to a group of glycoproteins called globulins, and for this reason they are also known as immunoglobulins (Igs).

Because they appear first and are relatively short-lived, IgM antibodies indicate a recent invasion. In a sick patient, the responsible pathogen may be suggested by the presence of high levels of IgM specific to a particular organism

Antibody actions

- Neutralizing antigen antibody blocks or neutralizes some bacterial toxins and prevents attachment of some viruses to body cells.
- *Immobilizing bacteria.* If antibodies form against antigens on the cilia or flagella of motile bacteria, the antigen–antibody reaction may cause the bacteria to lose their motility, which limits their spread into nearby tissues
- *Agglutinating and precipitating antigen*. the antigen–antibody reaction may cross-link pathogens to one another, causing agglutination (clumping together). Phagocytic cells ingest agglutinated microbes more readily. Likewise, soluble antigens may come out of solution and form a more easily phagocytized precipitate when cross-linked by antibodies.
- *Activating complement.* Antigen–antibody complexes initiate the classical pathway of the complement system , the complement proteins destroy microbes by causing phagocytosis, cytolysis, and inflammation; they also prevent excessive damage to body tissues.
- *Enhancing phagocytosis.* The stem region of an antibody acts as a flag that attracts phagocytes once antigens have bound to the antibody's variable region

Note: Please see ppt slides for classes of immunoglobulins

Immunological memory s due to the presence of long-lasting antibodies and very long-lived lymphocytes that arise during clonal selection of antigen-stimulated B cells and T cells. Basis for immunization by vaccination

Titer- measure of immunological memory

Ways to Acquire Adaptive Immunity

Naturally acquired active immunity. After exposure to a microbe, processing and presenting, recognition by B cells and T cells and costimulation lead to formation of antibody secreting plasma cells, cytotoxic T cells, and B and T memory cells.

Naturally acquired passive immunity. IgG antibodies are transferred from mother to fetus across placenta during pregnancy or IgA antibodies are transferred from mother to baby in milk during breast-feeding.

Artificially acquired active immunity. Antigens introduced during vaccination stimulate cell-mediated and antibody-mediated immune responses, leading to production of memory cells.

Artificially acquired passive immunity Intravenous injection of immunoglobulins (antibodies)

Lymphatic Homeostasis

Stress and Immunity

Inflammatory Response

- namely:
  (1) Vasodilation and increased permeability of blood vessels. Vasodilation allows more blood to flow through the damaged area, and increased permeability permits defensive proteins such as antibodies and clotting factors to enter the injured area from the blood. Due to this, fibrinogen is converted to fibrin threads that localizes and traps microbes and blocks the spread.

  Dilation of arterioles and increased permeability of capillaries produce three of the signs and symptoms of inflammation: heat, redness (erythema), and swelling (edema)

  The following substances contribute to vasodilation, increased permeability, and other aspects of the inflammatory response:
  a. Histamine -released by mast cells, basophils and platelets in response to injury. Neutrophils and macrophages which are attracted to the site of injury stimulate the histamine release that causes vasodilation and permeability.
  b. Kinins -serves as chemotactic agent for phagocytes aside from aiding in vasodilation and permeability. An example of this is bradykinin.
  c. Prostaglandin- released by damaged cells to intensify the effects of histamine and kinins and stimulate the emigration of phagocytes through capillary walls
  d. Leukotrienes –produced by mast cells and basophils that causes increased permeability. They function in adherence of phagocytes to pathogens and chemotactic agent.
  e. Complement- stimulate histamine release, attract neutrophils by chemotaxis, promote phagocytosis.

  (2) emigration (movement) of phagocytes from the blood into interstitial fluid. Due to blood accumulation, neutrophils squeeze through the of blood vessel to reach the damaged area. This process is called emigration. Neutrophils kills pathogen via phagocytosis. Pre-demonate in early stages if infection but die rapidly, After neutrophils, monocytes follow and transform into wandering macrophages that help in phagocytic activity of fixed macrophages.
  phagocytes appear. Eventually they die. After few days, pus formation occurs. This the pocket of dead phagocytes and damaged tissue forms. Usually formed during inflammatory process and continues until the infection subsides.

  (3) and tissue repair.

  Inflammation may either be acute and chronic inflammation

Inflammation can be classified as acute or chronic:

Acute inflammation- signs and symptoms develop rapidly and usually last a few weeks. It is usually mild and self-limiting and the principal defensive cells are neutrophils. Examples of acute inflammation are a sore throat, appendicitis, cold or flu, bacterial pneumonia, and a scratch on the skin.

Chronic inflammation- the signs and symptoms develop more slowly and can last for up to several months or years. It is often severe and progressive and the principal defensive cells are monocytes and macrophages. Examples of chronic inflammation are mononucleosis, peptic ulcers, tuberculosis, rheumatoid arthritis

Imbalances of Immune Function

Hypersensitivity- a state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign agent.

Autoimmunity- Immune system fails to display self- tolerance and attack’s the person own tissues