The lymphatic system and the immune system

The **lymphatic system** has three main functions

1. Fluid balance
2. Fat absorption
3. Defense via the immune system

Lymph vessels - begin as small closed end tubes found in the intercellular spaces within tissue. Once the interstitial fluid enters the lymph capillaries it is referred to as lymph. Lymph capillaries will drain into lymph vessels. Lymph vessels have some smooth muscle and lots of valves. The lymph moves through these vessels via three mechanisms

1. Skeletal muscle pumps
2. Smooth muscle contraction
3. Thoracic pressure changes

Afferent lymph vessels lead into lymph nodes. Efferent lymph vessels drain lymph nodes into lymph trunks that are draining their respective areas of the body. These lymph trunks drain into lymphatic ducts. The lymph ducts merge to form two principal lymph vessels

1. thoracic duct - drains the left side of the head, neck, and body as well as both upper and lower extremities on the left and the right lower extremity. It drains into the left subclavian vein
2. Right lymphatic duct -drains the right side of the head and neck, the right upper extremity, and the right side of the thorax. It drains into the right subclavian vein

In a small number of people the lymphatic trunks from the abdomen and lower extremities unite to form a small sac at the beginning of the thoracic duct. This sac is called the cysterna chyli. Here we should discuss lacteals – these are special lymphatic vessels in the wall of the small intestine. The lymph absorbed here has a high fat concentration which gives it a milky appearance. This lymph is referred to as chyle.

LYMPH TISSUE

Lymph organs - the spleen and thymus

Spleen - filters blood, produces lymphocytes as well as produces and destroys old erythrocytes (RBCs)

Thymus - activates immune cells, is located in the anterior thorax (anterior mediastinum)

Lymph tissue contains mainly lymphocytes (some macrophages, dendritic cells, reticular cells, etc.). Microorganisms (foreign substances) cause lymphocytes to divide (therefore increase in numbers). In lymph nodes there are reticular fibers. Lymphocytes attach to the reticular fibers and form a meshwork that traps microorganisms, etc.

Lymphatic tissue may be encapsulated or non-encapsulated:

Encapsulated lymph tissue includes:

1. Lymph nodes
2. Spleen
3. Thymus

The non-encapsulated lymph tissue is often referred to as MALT (mucous associated lymphoid tissue). This is lymphoid tissue associated with the mucous lined tissues of the body (GI tract, Lungs, urinary system, reproductive system). This includes diffuse lymphatic tissue, lymphatic nodules, and tonsils.

Diffuse lymphatic tissue has no clear boarders and blends in with the surrounding tissue.

Lymphatic nodules are denser arrangements of lymphoid tissue. They also line the mucous lined tissues. A good example is the Peyer's patches found in the small intestine. Lymphatic nodules can be, and often are, found in lymph nodes and the spleen. When this happens, they are often referred to as lymphatic follicles.

Lymph nodes: there are two varieties of lymph nodes

1. Superficial – These are found in the skin associated with the dermis and hypodermis
2. Deep – These are found everywhere else

Briefly, lymph nodes are encapsulated structures with in folded trabeculae to form a fibrous network throughout the entire node. Lymphocytes and macrophages live along the fibers of this network. Sometimes the fibers form open spaces called lymphatic sinuses. The layout generally gives the lymph node two layers. A cortex and a medulla

1. Cortex – here we find many lymphatic nodules with many lymphocytes (in area called germinal centers). Microorganisms in the lymph can stimulate the lymphocytes to divide. These increasing numbers of lymphocytes result in swelling of the lymph node.
2. Medulla – contains large blood vessels, sinuses, and medullary cords. The medullary cords hold lymphatic tissue such as plasma cells, macrophages, and B cells

This is a good time to review a picture of a lymph node.

Spleen: encapsulated with trabeculae

The spleen is divided into two types of tissue:

1. White pulp – comprises about ¼ of the spleen. Here we find lymphatic tissue surrounding the arteries of the spleen.
2. Red pulp – comprises about ¾ of the spleen. This portion of the spleen surrounds the veins of the spleen and contains many macrophages and RBCs

The spleen is described as having an open circulation. This means that there is no direct connection between the arterial and venous vessels.

The spleen plays two major roles:

1. As we have already seen, the spleen plays a role in the destruction of old RBCs. Old RBCs don't fold as well and cannot pass through capillaries as readily as younger RBCs. This causes the RBCs to rupture in the splenic sinuses and macrophages quickly eat up the cellular debris (including hemoglobin).
2. The spleen also acts as a giant lymph node. There are many T cells (in the periarterial lymphatic sheath) and many B cells (in the lymphatic nodules).

This is a good time to review a picture of the splenic sinuses.

Thymus

The thymus is located in the superior mediastinum/anterior mediastinum. It functions to activate T cells that were produced in the bone marrow. Only about 5% of T cells will ever get activated by the thymus. The thymus grows until about the age of 1, then holds steady for many years, but then will begin to shrink (atrophy). In old age the thymus may be completely replaced by fatty tissue.

Keep in mind that both B cells and T cells are produced in the bone marrow, but T cells must be activated by the thymus.

Immunity

Immunity is generally divided into two types of immunity

1. Innate immunity – also known as non-specific immunity. In this type of immunity the response is the same each time
2. Adaptive immunity – also known as specific immunity. In this type of immunity the body learns so that it can respond faster and more efficiently the next time the organism (antigen) is encountered.

Innate immunity uses two main techniques to fight infection

1. Mechanical barriers to block out microbes
2. Chemical mediators – such as the complement cascade (complement fixation pathway)

This is a good time to review a chart of the complement cascade

Revisit the various leukocytes

Neutrophils (PMNs) – recall their function from the blood lecture. Pus is an accumulation of dead neutrophils.

Mast cells – from the red bone marrow. Once thought to be derived from basophils but recent evidence indicates a different cell lineage. They are granulated cells that contain histamine (inflammatory) and heparin (anticoagulant).

Basophils – refer to information from the blood cell lecture.

Both mast cells and basophils can be activated through innate immunity (complement) or through adaptive immunity via the antibody system to be discussed later. Basophils and mast cells, when activated, release histamine and leukotrienes, both of which result in inflammation, etc.

Eosinophils -clear the chemical released by the basophils and mast cells. Eosinophil numbers greatly increase when there is inflammation or perhaps a parasitic infection. Eosinophils often secrete enzymes that kill some parasites.

Natural killer cells – These cells are lymphocytes from the red bone marrow. These cells recognize cells such as tumor cells or virus infected cells in general rather than a specific tumor cell or a specific viral infection. They do not exhibit a memory response.

THE INFLAMMATORY RESPONSE

The inflammatory response is a sequence of events and is considered to be part of innate immunity. Any tissue damage/injury can cause inflammation.

Tissue damage results in the release of chemical mediators, usually prostaglandins and leukotrienes. Histamine and complement are two of the more well know of these mediators. These chemical mediators bring about a 3 step sequence of events.

1. Vasodilation for increased blood flow. This brings more WBCs into the area
2. Chemotactic attraction of phagocytes from the blood into the tissue (diapedesis)
3. Increased vascular permeability. Fibrinogen and complement move into the tissue. Fibrinogen converts to fibrin which in turn walls off the area preventing the spread of infection.

INFECTION

There are generally considered to be two types of infections, localized infection and systemic infection.

Localized infection -The infection is confined to a certain area. The symptoms of a localized infection are redness, heat, swelling, pain, and loss of function. The redness, heat, and swelling are caused by increased blood flow and increased vascular permeability. The loss of function is generally due to tissue damage and pain.

Systemic infection – Occurs in many parts of the body. In addition to local symptoms 3 other factors are present

1. Increased numbers of neutrophils are produced. This promotes phagocytosis.
2. Pyrogens (from the pathogen or from macrophages and neutrophils) stimulate fever. Here the hypothalamus tells the body to retain heat. Higher heat activates many types of immune cells, induced phagocytosis, and inhibits some microbial growth.
3. In some cases increased vascular permeability can lead to extreme fluid loss from the blood to the tissue. This can lead to shock and death.

ADAPTIVE IMMUNITY

In adaptive immunity the immune system can recognize, respond to, and remember an invading antigen.

Antigens are substances that stimulate adaptive immunity. Antigens are generally divided into two categories, foreign antigens and self antigens

1. Foreign antigens – As their name implies, are introduced from outside of the body. These are substances such as bacteria, viruses, pollen, animal dander, mite feces, food, drugs. etc.
2. Self antigens – As their name implies are produced by the body. These are molecules produced by the body that trigger and adaptive immune response

Antigens can also be classified by their source. Antigens that are found in body fluids, such as serum, are called humoral antigens. Injection of serum from an immune animal will cause immunity in the injected animal. Antigens may also be bound to cells. For example blood cells from an immune animal will activate the cell mediate portion of the immune system and confer immunity to the injected animal.

In some cases molecules produce by the body can be used in that same body. If such molecules result in destruction of a tumor, that is a good thing. But sometime these molecules can result in an autoimmune disease in which the body starts reacting to/killing its own tissues.

Immunity essentially results from the activation of B cells and T cells. Recall that T cells and B cells are lymphocytes (cells associated with lymph).

B cells make cells that produce plasma proteins called antibodies. Since these antibodies are in the plasma they are part of the humoral immunity often called antibody-mediated immunity.

T Cells are responsible for cell mediated immunity. Note that there are many subpopulations of T cells (effector T cells, cytotoxic T cells, etc.).

ACTIVATION OF A LYMPHOCYTE

Activation of a lymphocyte is a multistep process, but we will simplify it.

1. The lymphocyte must recognize the antigen (antigen recognition).
2. Following recognition the lymphocyte must multiply in numbers to destroy the antigen.

It should be noted that lymphocytes do not recognize the entire antigen, but rather recognize specific pieces of an antigen called epitopes.

Lymphocytes have antigen receptor on their cell surface that can bind with the epitopes. This recognition generally uses MHC class 1 and MHC class 2 systems.

MAJOR HISTOCOMPATABILTY COMPLEX

The immune system cannot respond to an antigen if it is inside a cell. For viruses this presents a problem since viruses replicate inside cells. To work around this problem cells have adapted the MHC class 1 system. In this system viral proteins are broken down in the cytoplasm where the Endoplasmic Reticulum can combine them with MCH class 1 molecules that will then be incorporated into the cell surface. Once these viral proteins are on the cell

surface T cell receptor on T cells can recognize them and activate the T cells. So basically we have put a flag on the cell surface that says "KILL ME".

Another similar system is the MHC class 2 system. MCH class 2 molecules are found on antigen presenting cells (B Cells, Monocytes, Macrophages). IN this system the cells take in foreign antigens via endocytosis. The antigen is then broken down to form processed antigen vesicles. The golgi apparatus which contain MCH class 2 molecules will combine the MHC class 2 molecule and the endocytotic vesicle and transport this new structure to the cell surface. Once on the cell surface they are displayed to other immune cells. This differs from the MCH class 1 system in that here the antigen presenting cell is not killed but instead presents a "rallying flag" that causes other immune cells to respond to the antigen. One book likened this to Paul Revere yelling "the British are coming" which rallied the militia to meet the British.

ANTIBODY MEDIATED IMMUNITY

This system requires the activation of B cells which will in turn produce antibodies. Antibodies are found in extracellular fluids so they are effective against extracellular antigens (bacteria, viruses, protozoa, funguses, parasites, etc.)

Antibodies are produced in response to antigens. Antibodies are usually globular plasma proteins. Recall the three main plasma proteins from the blood lecture. The globular proteins are further subdivided into alpha, beta, and gamma globulins. Antibodies are made from the gamma group of globulins so are often referred to as gamma globulins. Because of their role in the immune system they are more commonly referred to as immunoglobulins.

There are 5 general classes of immunoglobulins (IgG, IgM, IgA, IgE, and IgD). All of these immunoglobulins have a variable region and a constant region.

Antibodies effect antigens in two ways:

1. Antibodies can bind to antigens and interfere with the antigens ability to function
2. Antibodies can cause antigenic determinants to bind to each other thus rendering them ineffective. This is what happens during a blood typing test. In incompatible blood types, enough antigens are bound together that they become visible as a clump or a precipitate.

When IgG of IgM combine with an antigen via their variable region the constant region can initiate the complement (Classical) Pathway. The complement pathway is beyond the scope of this course. Basically there is a cascade of chemicals that ends in the destruction of the cell.

Opsonins – are substances that make an antigen more likely to by phagocytized. IgG acts as an opsonin by connecting to an antigen through the variable region of the antibody and to a macrophage through the constant region. The macrophage the phagocytizes the antigen and the antibody.

ANTIBODY PRODUCTION

In this system we need to consider the primary response versus the secondary response.

In the primary response, the first exposure of a B cell to an antigen for which it is specific leads to a series of cell divisions and cell differentiation and antibody production. The B cells surface receptors are usually IgM and IgD. The receptors will have the same variable regions as the antibodies that are eventually produced by the B cell. Before stimulation the B cells are small lymphocytes, but after activation the B cells become large lymphocytes, with some of these becoming plasma cells which produce antibodies. Others of these lymphocytes revert back to small lymphocytes called memory B cells. Usually IgM is the first antibody produced in a response to an antigen. Normally is take 3 – 14 days to produce enough antibodies to be effective against an antigen.

The secondary response (also known as the memory response) happens when the immune system is exposed to an antigen for which it has already had a primary response. Here the memory B cells rapidly divide to produce plasma cells and antibody. This secondary response takes less time to start producing the antibodies and much more

antibody is produced, thus the antigen is quickly destroyed. This happens fast enough that no disease symptoms occur and the individual is said to be immune.

Interferons are chemicals that can protect the body against viral infection (and maybe even cancer). Some cells produce interferons. These then stimulate other cells in the general area to produce antiviral proteins.

Think about the Acquired immunity pathway (4 ways)

It is possible to acquire adaptive immunity if 4 ways

1. Natural – antigens are introduced through natural exposure
2. Artificial – antigens are deliberately introduced in a vaccine
    a. 1 and 2 will lead to active immunity where the individuals own immune system is the cause of the immunity
3. Natural – antibodies from the mother are transferred to the child across the placenta of in milk
4. Artificial – antibodies produced by another person or animal are injected
    a. 3 and 4 lead to passive immunity where the immunity is transferred from another person or animal

All 4 of the above will lead to an acquired adaptive immunity.