

Lymphatic System & Immunity

I. Lymphatic Vessels- About 3 L of fluid is lost at the capillaries daily. Excess is collected by lymph vessels and carried back to the blood.

A. Distribution and Structure-

1. Lymphatic vessels are one-way: to the right and left subclavian veins in the shoulder. They are always associated with capillaries, to absorb lost fluid. They are blind ended, so fluid can enter them but not leave.
2. Lymph capillaries are 1 cell thick, like blood capillaries. Lymph capillaries are intertwined with blood capillaries in a tissue, and this is where fluid absorption occurs. The blind opening is caused because cells lining the lymph capillary overlap in such a way that they open inward when pushed by interstitial fluid, but close when pushed by lymph fluid.
3. Lymph vessel walls are thinner than corresponding blood vessel walls. Larger lymph vessels have all 3 tunics, just like larger blood vessels.
4. Lymph vessels have lots of valves that function like venous valves. The pressure of lymph fluid is extremely low, so the valves function to prevent backflow. Larger lymph vessels bulge where the valves are located, so the vessels look beaded.
5. Lymph vessels are typically associated with blood vessels in their distribution. Like blood vessels, they converge into larger and larger vessels. Vessels eventually dump lymph fluid into one of two large collecting ducts:
 - a. thoracic duct- collects lymph from left side of body superior to diaphragm, and all of the body inferior to the diaphragm. The cisternae chyli is an expanded pouch where lymph fluid inferior to the diaphragm collects before making its way up the thoracic duct.

b. right lymphatic duct- collects lymph from the right side of the body superior to the diaphragm.

These ducts will connect with the left and right subclavian veins respectively, and return fluid to the blood.

B. Lymph transport (Movement of lymph)- Like veins, relies primarily on movement of muscles, and valves to prevent backflow. The collecting ducts contract rhythmically.

II. Lymphoid Cells, Tissues and Organs- Lymph nodules, like tonsils, are considered lymph tissue located along lymph vessels or in other organs; lymph nodes are considered organs located along lymph vessels. Both house immune cells and check out lymph fluid for pathogens and debris. Other lymph organs include: thymus, where T-cells grow up; spleen, where blood is checked out by immune cells.

A. Lymphoid Cells: Lymphocytes (Quick introduction; we'll get into them more in specific immunity)

1. Produced in red marrow

2. Types:

a. Natural Killer cells- phagocytic, kill abnormal and infected "self" cells

b. T-cells- Different types of T-cells have different "jobs." The 2 best understood T-cells are Killer Ts and Helper Ts. Killer Ts kill abnormal self cells and pathogens. Helper Ts activate B cells.

c. B-cells- make antibodies. T and B cells work together to figure out how to make the right antibodies for specific pathogens.

3. Birth, school, work, death (production, circulation and life span)- review Chapter 19 for the production of lymphocytes. All three types are derived from lymphoid stem cells. Those lymphocytes destined to become NK and B cells stay in red marrow for maturation, while those destined to become T-cells are transported to the thymus for maturation.

Lymphocytes cruise around, looking for invaders/abnormal cells. They use blood and lymph for fast transport, then migrate out to interstitium of tissues. Lots of lymphocytes take up temporary residence in lymph tissues/organs, and check out lymph fluid as it passes by. The same is true of the spleen, except that blood (not lymph) is examined in the spleen.

They are long-lived cells, many years.

B. Lymphoid tissue- lymph nodules are considered lymphoid tissue. Larger lymph structures (organs) are composed of lymph tissue in addition to other tissue.

1. Functions: house lymphocytes, and run lymph through a series of passageways to look for invaders (like a security check-point)

2. Lymph tissue is composed of lots of reticular fibers, areolar tissue, and lymphocytes. Nodules occur in clusters in lymph nodes. They also occur as free-standing in areas of the digestive tract; these nodules together are called the MALT (Mucosa Associated Lymphoid Tissue). The MALT nodules occur in the pharynx (tonsils), small intestine (Peyer's Patches), and appendix.

Nodules are highly folded, and the folds allow bacteria and particles to be trapped. They contain numerous germinal centers, areas where B-cells are dividing.

C. Lymph Organs

1. Nodes- located along lymph vessels

Structure- typically bean shaped, $\sim < 1$ inch; afferent lymph vessels deliver fluid to the convex side of the node, and efferent lymph vessels carry fluid out of the concave side.

Surrounded by a dense fibrous capsule (dense connective tissue), which extends into the node creating partitions, or compartments, in the node. There are two distinct regions: the cortex and the medulla. The cortex is further divided into an outer and an inner cortex.

Lymph fluid moves through the cortex and medulla, encountering a series of lymphocytes, macrophages and dendritic cells, which remove most pathogens and debris by the time the fluid leaves. In addition, if pathogens are detected, specific immune responses are initiated.

Medullary cords are lines of B-cells in the medulla

2. Thymus- where T-cells mature and differentiate

Produces thymosins, hormones that aid the development of T-cells; developing T-cells are isolated from many substances in blood by the blood-thymus barrier.

3. Spleen- similar in function as nodes, except that the spleen checks out blood for pathogens. In the spleen, arterioles open into sinusoidal capillaries, which let lots of blood components leak out and into the meshwork of the spleen, where lymphocytes and macrophages look for pathogens.

Also: old RBC are phagocytized here, and iron is stored temporarily

Blood enters the spleen via the splenic artery and leaves via the splenic vein

The Immune System

III. Non-Specific Defenses

A. Overview

B. Details-

1. Physical barriers- hair, skin, mucus, stomach acid, secretions (how does each of these elements help to prevent invasion?)
2. Phagocytes- use a variety of weapons, including NO and H₂O₂ (hydrogen peroxide)
 - a. Neutrophils & Eosinophils- microphages; neutrophils are the most abundant.
 - b. Macrophages- some move around, some set up residence in particular organs: ex, Microglia, Kupfer cells
 - c. Movement of phagocytes- amoeboid; they get out of (and into) capillaries by squeezing between cells- "diapedesis." They can follow the chemical trail of cells in distress, or other WBC calling for help- "chemotaxis."
3. Immunological surveillance- by NK cells, which cruise around checking out self cells for abnormalities (indicated by abnormal antigens on the membrane). NK cells can also kill foreign cells. NK cells have a really cool system for killing their target cells; see your text and listen to lecture!
4. Interferons- when cells are infected with a virus, they release interferons, proteins that can act as local hormones. The interferons bind to receptors of neighboring cells. Binding of interferons causes neighboring cells to build protective proteins (via 2nd messenger) that will prevent the virus from dividing in

the neighboring cell. This is kind of like an "early warning" system.

5. Complement- A suite of plasma proteins. Like coagulation proteins, complement proteins are inactive. Certain complement proteins can be activated by either: a) binding to a foreign antigen, or b) binding to an antibody attached to a pathogen. Once the initial complement proteins are activated, they will activate the next, and so on, in a cascade. The suite of activated proteins interact in such a way that they pierce the membrane of the pathogen and create a pore (much like perforins of NK cells): the Membrane Attack Complex.

Complement proteins can also coat pathogens ("opsonization"), slowing them down, preventing them from adhering, and making them easier for WBC to catch.

6. Inflammation- symptoms: redness, swelling, heat, pain. This is a process, whose function is to prevent or combat infection, and get elements to the area that will repair damage.

a. Damaged cells release chemical "SOS" messages, for example, prostaglandins (a type of eicosanoid) and K^+ . In response, Mast cells release histamine and heparin.

b. Histamine causes local dilation and causes local capillaries to become more permeable, so blood flow to the affected area increases, and large solutes can leave the blood. This serves to: flush the area, bring in elements such as clotting proteins (for the periphery), WBC, complement proteins, O_2 and nutrients.

Heparin prevents clots from forming in the area.

Increased flow to capillaries and damage to vessels allows fluid to leak into tissues (damaged vessels leak all blood elements, including proteins). The combination of blood flow and edema causes the symptoms of Red, Heat

(blood), Swelling (leakage), Pain (pressure on nociceptors and binding of released chemicals to nociceptors).

c. Phagocytes move in, attracted by chemical signals. Neutrophils arrive first, followed by macrophages. Macrophages also stick around and perform clean-up. Eosinophils may be used. Phagocytes arriving at an injury or infection release cytokines*, which will enhance the clean-up/immune response.

d. If a pathogen was introduced, macrophages and dendritic cells will rush to the nearest lymph node to alert T and B cells.

*Side note: Cytokines are paracrine factors of the immune system. They serve a variety of functions. One thing many of the cytokines does is attract WBC. So, by releasing cytokines, phagocytes call more WBC to the area. Cytokines can have local effects, but can also effect cells in other parts of the body, so this is an example of a local hormone that can have endocrine function.

A couple other examples of things certain cytokines do: enhance division of activated T- and B-cells, and reset the thermostat in the hypothalamus (there's an example of an endocrine effect; the hypothalamus is typically far from the release of this cytokine). End side note*

e. Clot forms around the area, isolating it.

7. Fever (>99 F, 37 C)- speeds enzymatic reactions, enhances WBC activity, may inhibit certain pathogens. Fever is initiated by a type of cytokine: interleukin-1. Interleukin-1 is a type of pyrogen, which cause the hypothalamic thermostat to be reset. It is released by macrophages responding to infection by a pathogen.

IV. Specific Defenses- know your enemy

Please read your text for an overview of forms and properties of immunity.

A. Brief overview- A pathogen is detected and ingested by a macrophage, OR, infects a cell. The macrophage, or the infected cell, move pieces of the pathogen to their membranes, and display these pieces on their outer membranes (like a "Wanted: DOA" sign). These pieces are typically peptides, proteins or glycoproteins, and they are antigens.

Tcells &/or Bcells check out the antigens on display by macrophages or infected cells. Some Tcells kill the infected cell. Others will activate the B-cells, so they can make antibodies. Activated B-cells divide like crazy, making and releasing thousands of antibodies. Antibodies are proteins that bind to pathogenic antigens; that is, antibodies end up coating the pathogens, which incapacitates them and makes them easier for phagocytes to catch.

B. Some background: Major HistoCompatibility proteins (MHC)- these are our "self" antigens, our cellular ID badges. (That's I-D as in identification, not the cellular psyche). Two major classes of MHC proteins exist:

1. Class 1: found on most cells
2. Class 2: found only on certain cells of the immune system (macrophages, dendritic cells and Bcells)

Cells constantly produce these proteins, which migrate up through the cell on their way to the membrane. When a phagocyte ingests a pathogen, or a body cell is infected, pathogenic antigens bind to the MHC proteins on their way to the membrane. So, when the MHC protein gets to the membrane, it's holding an antigen, like a "Wanted: Dead or Alive" sign.

C. T-cells: activity of T-cells is referred to as Cell-Mediated Immunity

1. Three types of T-cells-

- a. Cytotoxic (T_c)- kill cells (bacterial and/or infected self)
- b. Helper (T_H)- Activate B-cells
- c. Suppressor (T_S)- Stop the immune response

2. T-cell activation-

- a. T-cells roam around the body, and are found in large numbers in lymph organs. When a macrophage or infected cell is holding up an antigen, T-cells check out that antigen. **Each T-cell recognizes a specific antigen.**

T-cells have receptors on their membranes that bind antigen. Each T-cell has a specific receptor that binds a specific antigen, so a dendritic cell may have to display its antigen to many T-cells before it finds a T-cell that can recognize it.

- b. Costimulation- in order for a T-cell to be activated fully, it must be sure it is the right type of T-cell for the job. For example, a macrophage who has ingested a bacterium would not want to activate a T_c cell; the macrophage is perfectly healthy and doesn't want to be killed, instead it would like to continue devouring pathogens. So, T-cells contain a second type of receptor that binds to the MHC protein of the presenting cell.

T_H cells have receptors called CD-4, and they bind MHC-2. When they are activated, they will activate B-cells.

Tc cells have receptors called CD-8, and they bind MHC-I. When they are activated, they will seek out and kill infected self cells.

- c. After costimulation occurs, the T-cell is fully activated. The first thing it will do is undergo rapid division. This process is called **clonal selection**. Why? Because a specific T-cell has been selected, and now it's dividing to produce thousands of clones.

Many of those divisions produce T-cells that will immediately start performing active duty to halt the present infection. It will take at least 2 days to produce enough active T-cells to launch an effective response to a major infection.

However, some of them (thousands) will go into storage as memory T-cells, so that a second (later in life) infection by the same pathogen will produce a rapid and effective deployment of these "reserve troops." Incidentally, the same thing happens with B-cells, and this capacity of the immune system, to "remember" specific pathogens and react extremely quickly and effectively to later infections is referred to as "secondary response."

3. Cytotoxic T-cells- These respond to antigens held by MHC-I proteins, those displayed by all cells. Tc cells kill cells displaying foreign antigens, which explains why they don't respond to MHC-2 proteins; if they did, they would kill uninfected macrophages, which could have gone on to attack more pathogens. Instead, Tc cells focus on body cells that are actually infected with a pathogen. Tc cells use a variety of methods to kill their targets, including lysing via perforins, causing apoptosis (cell suicide) via Tumor Necrosis Factor, and poisoning.

Tc cells can also attack cancerous cells and bacterial cells. FYI, cancerous self cells contain abnormal genes; these genes will code for abnormal proteins. The abnormal proteins can be displayed by the MHC-I, and the cancerous cell can be identified.

4. Helper T-cells- These respond to antigens held by MHC-2 proteins, those displayed by macrophages, B-cells, and dendritic cells. When activated, Th cells secrete a variety of cytokines that will direct the immune response, for example, by attracting more WBC and inducing B-cell division. The major event of helper T activation, though, is that it will interact with a B-cell that can recognize the same antigen. When it does so, it activates the B-cell.

5. Suppressor T-cells- not as well understood, they put the brakes on an immune response by releasing inhibitory cytokines.

D. B-cells and antibodies: activity of B-cells is referred to as Antibody Mediated Immunity, or Humoral Immunity.

Like T-cells, B-cells wander around, but are found en masse in the lymph nodes. To be activated, a B-cell must interact with a helper T. Activation occurs in a couple of steps. Like T-cells, each B-cell is designed to recognize one antigen.

1. Sensitization- First, a B-cell encounters the antigen it can recognize (usually presented by a dendritic cell or macrophage, but can be from a pathogen). The B-cell engulfs the antigen, and presents it on its own MHC-2 proteins. Now, it needs to find a T-cell for approval to activate.

2. Activation- The sensitized B-cell presents its antigen to a T-cell that's been activated by the same type of antigen. The T-cell will bind to the antigen, and then secrete cytokines that will activate the B-cell. Once activated, the B-cell will undergo rapid division. Some of the daughter cells produced will go into

storage as memory B-cells, as did T-cells. The others become **plasma cells**, which pump out tons of antibodies. It will take at least 3 days for plasma cell populations to launch an effective attack against a first major infection by a specific pathogen. As with T-cells, a second infection will be dealt with much faster, because of the memory B-cells in storage.

3. Antibody functions- Antibodies bind to the antigens of the pathogen. They coat the pathogen, making it easier for phagocytes to grab onto them (opsonization), and making it harder for the pathogens to adhere to body surfaces. Some antibodies bind lots of pathogens at the same time, causing them to clump (agglutination, the same we saw in blood typing). They also attract WBC, make pathogens easier for WBC to recognize and capture, and activate complement proteins.

4. Antibody structure- antibodies are composed of 2 types of protein chains: 2 heavy chains (long, with a bend), and 2 short chains (short, straight). Each of the 4 total chains contains a constant segment (same amino acid sequence, regardless of the antibody) and a variable segment (each antibody type contains a different sequence of amino acids here)

It is the variable segment that determines what antigen an antibody will bind to. The variable segment binds to the antigen via weak attractions such as Hydrogen bonding.

5. Antibody classes- antibodies are also called immunoglobulins, and the antibody classes are called "Ig..." for that name.

IgG- the primary (most abundant) antibody of the antibody-mediated immune response. (these ones have "Gusto" and Gluttons like them)

IgM- the first antibody released in antibody-mediated immune response. IgM antibodies are responsible for agglutination, because they contain several antigen-

binding sites (so each one can bind several pathogens).
(These ones have Many, Mucho binding sites)

IgD- these antibodies don't attack pathogens. Instead, they coat B-cells, with their variable ends sticking out. They allow B-cells to recognize specific antigens; they are the antigen receptors of B-cells. (B-cells Don these ones)

IgE- like IgD, these don't attack pathogens. Instead, they coat mast cells and basophils (basophils are similar to mast cells in function, but are more mobile and are WBC in origin). When antigens bind to IgE antibodies, the mast cell or basophil releases histamine. People with severe allergies would probably prefer to get rid of some of their IgE antibodies. (Any ideas for a mnemonic here?)

IgA- these antibodies are constantly produced and distributed in body fluids as a first line of specific defense. IgA antibodies are found in, for example, mucus, saliva, skin secretions, and blood. (These ones are the first line of defense, just like A is the first letter. I know, it's pretty weak)

E. T and B cell Development

1. As you know, T-cells migrate from the red marrow to the thymus to complete development. B-cells develop in red marrow.
2. Receptor variety- As you also know, each T-cell and each B-cell are "born" able to recognize a specific antigen. While this may sound like it's purposeful and directed, it's actually random. We produce such a huge variety of T and B cells that it's very unlikely we will ever meet a pathogen that can't be recognized; but this is by chance. In fact, when you die you'll take thousands of T and B cells who never got to work because they never met the antigen they could recognize. "How is this possible?!" you ask, riveted. Well, let me tell you.

The genes that code for antigen receptors of T and B cells (specifically, for B cells these are antibodies) are scattered throughout the chromosomes. Remember, receptors are proteins, genes code for proteins.

There are three specific segments of DNA that hold the instructions for making a receptor or antibody.

During a T or B cell's development, each of these segments experiences a random cutting and splicing of the nucleotides. Then the segments are brought together. Once activated together they will have the instructions for making a receptor. Remember that the instructions are read as the specific sequence of amino acids.

Now, in every cell the instructions are randomly rearranged. So, every cell ends up having different instructions. So, every cell makes a different protein for its receptor. For example, Tcell #1 might have a receptor that starts with: tyrosine-phenylalanine-glutamate-lysine-lysine- etc. On the other hand, since Tcell #2 had instructions that were arranged differently, ITS receptor might start with: alanine-phenylalanine-glutamate-cysteine-lysine- etc.

Different amino acid sequence means different protein shape. Different protein shape means different ability to bind different antigens.

There are almost infinite combinations that can occur.

Okay, now THIS part is really cool: as each cell is developing, it is tested with self antigens. If it binds to self antigens, it will either be killed, OR the DNA of the receptor segments will be rearranged again, and the cell retested!

3. Affinity Maturation- this applies only to B cells:

We are now jumping ahead in the life of a B cell. Let's take a look at a mature B-cell. It's already gone through all the cutting, splicing and testing.

We are going to look at a B cell who has just been activated; there is a pathogen in the body whose antigen is recognized by our B-cell. We know that this B cell will now undergo clonal selection, producing thousands of memory and plasma cells.

Let's consider the memory B-cells. With all this rapid division going on, there's bound to be some mutation. In fact, there is, and specifically some occurs at the gene segments that code for the antibodies.

Because of this, some of the memory B-cells will have a different ability to bind the antigen than the parent Bcell. Some will not bind as well, but some will bind better!

So, if you are exposed to the same pathogen again, you will have some memory B's that produce super-duper antibodies, and those B cells will be most likely to be activated, because they bind so well. This phenomenon also strengthens the efficiency of the secondary response.

Phew! I bet you're ready to move onto respiration!

Finally, see fig. 22-25, pg. 812 (Martini 6th ed), for a really nice overview of the immune response. This figure separates response to a bacteria from response to a virus.