Overview of the Immune System

The Organs of the Immune System:

Bone Marrow -- All the cells of the immune system are initially derived from the bone marrow. They form through a process called hematopoiesis. During hematopoiesis, bone marrow-derived stem cells differentiate into either mature cells of the immune system or into precursors of cells that migrate out of the bone marrow to continue their maturation elsewhere. The bone marrow produces B cells, natural killer cells, granulocytes and immature thymocytes, in addition to red blood cells and platelets.

Thymus -- The function of the thymus is to produce mature T cells. Immature thymocytes, also known as prothymocytes, leave the bone marrow and migrate into the thymus. Through a remarkable maturation process sometimes referred to as thymic education, T cells that are beneficial to the immune system are spared, while those T cells that might evoke a detrimental autoimmune response are eliminated. The mature T cells are then released into the bloodstream.

Spleen -- The spleen is an immunologic filter of the blood. It is made up of B cells, T cells, macrophages, dendritic cells, natural killer cells and red blood cells. In addition to capturing foreign materials (antigens) from the blood that passes through the spleen, migratory macrophages and dendritic cells bring antigens to the spleen via the bloodstream. An immune response is initiated when the macrophage or dendritic cells present the antigen to the appropriate B or T cells. This organ can be thought of as an immunological conference center. In the spleen, B cells become activated and produce large amounts of antibody. Also, old red blood cells are destroyed in the spleen.

Lymph Nodes -- The lymph nodes function as an immunologic filter for the bodily fluid known as lymph. Lymph nodes are found throughout the body. Composed mostly of T cells, B cells, dendritic cells and macrophages, the nodes drain fluid from most of our tissues. Antigens are filtered out of the lymph in the lymph node before returning the lymph to the circulation. In a similar fashion as the spleen, the macrophages and dendritic cells that capture antigens present these foreign materials to T and B cells, consequently initiating an immune response.

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The Cells of the Immune System:

Leukocytes

Learning all of these different names and the function of each cell type takes a bit of effort, but you can understand scientific articles a lot better once you get it all figured out! Here's a quick summary to help you get all of the different cell types organized in your brain.

All white blood cells are known officially as **leukocytes**. White blood cells are not like normal cells in the body -- they actually act like independent, living single-cell organisms able to move and capture things on their own. White blood cells behave very much like amoeba in their movements and are able to engulf other cells and bacteria. Many white blood cells cannot divide and reproduce on their own, but instead have a factory somewhere in the body that produces them. That factory is the bone marrow.

Leukocytes are divided into three classes:

- Granulocytes - Granulocytes make up 50% to 60% of all leukocytes. Granulocytes or polymorphonuclear leukocytes (PMNs). Granulocytes are composed of three cell types identified as neutrophils, eosinophils and basophils, based on their staining characteristics with certain dyes. These cells are predominantly important in the removal of bacteria and parasites from the body. They engulf these foreign bodies and degrade them using their powerful enzymes. Granulocytes get their name because they contain granules, and these granules contain different chemicals depending on the type of cell.
- Lymphocyte - Lymphocytes make up 30% to 40% of all leukocytes. Lymphocytes come in two classes: B cells (those that mature in bone marrow) and T cells (those that mature in the thymus).
- Monocyte - Monocytes make up 7% or so of all leukocytes. Monocytes evolve into macrophages.

Different Roles

Each of the different types of white blood cells have a special role in the immune system, and many are able to transform themselves in different ways. The following descriptions help to understand the roles of the different cells.

1. **Granulocytes**
    - **Neutrophils** are by far the most common form of white blood cells that you have in your body. Your bone marrow produces trillions of them every day and releases them into the bloodstream, but their life span is short -- generally less than a day. Once in the bloodstream neutrophils can move through capillary walls into tissue. Neutrophils are attracted to foreign material, inflammation and bacteria. If you get a splinter or a cut, neutrophils will be attracted by a process called chemotaxis. Many single-celled organisms use this same process -- chemotaxis lets motile cells move toward higher concentrations of a chemical. Once a neutrophil finds a foreign particle or a bacteria it will engulf it, releasing enzymes, hydrogen peroxide and other chemicals from its granules to kill the bacteria. In a site of serious infection (where lots of bacteria have reproduced in the area), pus will form. Pus is simply dead neutrophils and other cellular debris.
    - **Eosinophils and basophils** are far less common than neutrophils. Eosinophils seem focused on parasites in the skin and the lungs, while Basophils carry histamine and therefore important (along with mast cells) to causing inflammation. From the immune system's standpoint inflammation is a good thing. It brings in more blood and it dilates capillary walls so that more immune system cells can get to the site of infection.
2. **Monocytes**: Of all blood cells, **macrophages** are the biggest (hence the name "macro"). Monocytes are released by the bone marrow, float in the bloodstream, enter tissue and turn into macrophages. Macrophages are important in the regulation of immune responses. Phagocytes, are the soliders in the immune army. They hunt for invaders, and then ingest and kill them. They are often referred to as scavengers or antigen-presenting cells (APC) because they pick up and ingest foreign materials and present these antigens to other cells of the immune system such as T cells and B cells. This is one of the important first steps in the initiation of an immune response. Unlike Neutrophils who travel to the battlefield, macrophages can be stationary or mobile. Complement is a battalion of proteins that fight infection and promote inflammation.

3. The **lymphocytes** handle most of the bacterial and viral infections that we get. Lymphocytes start in the bone marrow. Those destined to become B cells develop in the marrow before entering the bloodstream. T cells start in the marrow but migrate through the bloodstream to the thymus and mature there. T cells and B cells are often found in the bloodstream but tend to concentrate in lymph tissue such as the lymph nodes, the thymus and the spleen. There is also quite a bit of lymph tissue in the digestive system. B cells and T cells have different functions. Using a battlefield analogy, think of T-cells as the generals, B cells as the sergeants, and their antibodies—or immunoglobulins—as the soldiers.
    - **B cells**, are considered sergeants in our immune army because they prepare the troops. They produce antibodies, or immunoglobulins (Igs), which shield us from attack by binding to invaders, and then signal macrophages and other scavenger cells to move in for the kill. The blood contains five classes of immunoglobulins, listed here from most to least abundant: IgG, which neutralizes toxins, deactivates viruses and bacteria, stimulates complement, and enhances phagocytosis; IgM, the biggest antibody, which functions as a first responder; IgA, which has potent antiviral activity and is more abundant in the saliva, tears, and colostrums, and on the surfaces of the respiratory, gastrointestinal, and genital tracts than in the blood; IgD, found mainly on the surface of B-cells, which may play a role in B-cell activation and suppression; and IgE, which plays a significant role in anaphylactic reactions by promoting inflammation and vasodilation.

    - We refer to the **T-cells** as "generals" because they call most of the shots. They play a role in both cell-mediated immunity and delayed hypersensitivity. The major generals are the T-helpers and T-suppressors. They control the activity of B-cells and some of the other T-cells, instructing them when to start and stop fighting. **T cells** actually bump up against cells and kill them. All types of T cells can be found throughout the body. They often depend on the secondary lymphoid organs (the lymph nodes and spleen) as sites where activation occurs, but they are also found in other tissues of the body, most conspicuously the liver, lung, blood, and intestinal and reproductive tracts.

      T cells known as **T killer/suppressor subset or CD8+ T cell** are important for directly killing certain tumor cells, viral-infected cells and sometimes parasites. The CD8+ T cells are also important in down-regulation of immune responses..

      Two other types of T cells, known as T-Helpers and Suppressor T cells, help sensitize Killer T cells and control the immune response.

        - The **T helper subset, also called the CD4+ T cell**, is a pertinent coordinator of immune regulation. The main function of the T helper cell is to augment or potentiate immune responses by the secretion of specialized factors that activate other white blood cells to fight off infection. **T-helpers** identify invaders, like bacteria and viruses, and collaborate with macrophages to get B-cells to produce antibodies. They also secrete cytokines, such as interleukins and interferons, which call the neutrophils, NK-cells, and killer T-cells to battle.

- **Suppressor T cells** - slow and then shut down the immune response after a successful defense. They ensure that the immune response does not get out of control and destroy normal cells once the immune response is no longer needed.

Because white blood cells are so important to the immune system, they are used as a measure of immune system health. When you hear that someone has a "strong immune system" or a "suppressed immune system", one way it was determined was by counting different types of white blood cells in a blood sample. A normal white blood cell count is in the range of 4,000 to 11,000 cells per microliter of blood. 1.8 to 2.0 helper T-cells per suppressor T-cell is normal. A normal absolute neutrophil count (ANC) is in the range of 1,500 to 8,000 cells per microliter.

One important question to ask about white blood cells (and several other parts of the immune system) is, "How does a white blood cell know what to attack and what to leave alone? Why doesn't a white blood cell attack every cell in the body?" There is a system built into all of the cells in your body called the Major Histocompatibility Complex (MHC) (also known as the Human Leukocyte Antigen (HLA)) that marks the cells in your body as "you". Anything that the immune system finds that does not have these markings (or that has the wrong markings) is definitely "not you" and is therefore fair game.
MHC molecules are important components of the immune response. They allow cells that have been invaded by an infectious organism to be detected by cells of the immune system called T lymphocytes, or T cells. The MHC molecules do this by presenting fragments of proteins (peptides) belonging to the invader on the surface of the cell. The T cell recognizes the foreign peptide attached to the MHC molecule and binds to it, an action that stimulates the T cell to either destroy or cure the infected cell. In uninfected healthy cells the MHC molecule presents peptides from its own cell (self peptides), to which T cells do not normally react. However, if the immune mechanism malfunctions and T cells react against self peptides, an autoimmune disease arises.

4. **Natural Killer Cells --** are called "natural killers" because it initially looked as if they needed no activating to do their job. We now know that cytokines activate these lymphocytes, and that NK-cells kill by causing apoptosis in the target cell. Natural killer cells, often referred to as NK cells, are similar to the killer T cell subset (CD8+ T cells). They function as effector cells that directly kill certain tumors such as melanomas, lymphomas and viral-infected cells, most notably herpes and cytomegalovirus-infected cells. NK cells, unlike the CD8+ (killer) T cells, kill their targets without a prior "conference" in the lymphoid organs. However, NK cells that have been activated by secretions from CD4+ T cells will kill their tumor or viral-infected targets more effectively.

Dendritic Cells -- Another cell type, addressed only recently, is the dendritic cell. Dendritic cells, which also originate in the bone marrow, function as antigen presenting cells (APC). In fact, the dendritic cells are more efficient apcs than macrophages. These cells are usually found in the structural compartment of the lymphoid organs such as the thymus, lymph nodes and spleen. However, they are also found in the bloodstream and other tissues of the body. It is believed that they capture antigen or bring it to the lymphoid organs where an immune response

is initiated. Unfortunately, one reason we know so little about dendritic cells is that they are extremely hard to isolate, which is often a prerequisite for the study of the functional qualities of specific cell types. Of particular issue here is the recent finding that dendritic cells bind high amount of HIV, and may be a reservoir of virus that is transmitted to CD4+ T cells during an activation event.

The Immune Response

An immune response to foreign antigen requires the presence of an antigen-presenting cell (APC), (usually either a macrophage or dendritic cell) in combination with a B cell or T cell. When an APC presents an antigen on its cell surface to a B cell, the B cell is signalled to proliferate and produce antibodies that specifically bind to that antigen. If the antibodies bind to antigens on bacteria or parasites it acts as a signal for pmns or macrophages to engulf (phagocytose) and kill them. Another important function of antibodies is to initiate the "complement destruction cascade." When antibodies bind to cells or bacteria, serum proteins called complement bind to the immobilized antibodies and destroy the bacteria by creating holes in them. Antibodies can also signal natural killer cells and macrophages to kill viral or bacterial-infected cells.

If the APC presents the antigen to T cells, the T cells become activated. Activated T cells proliferate and become secretory in the case of CD4+ T cells, or, if they are CD8+ T cells, they become activated to kill target cells that specifically express the antigen presented by the APC. The production of antibodies and the activity of CD8+ killer T cells are highly regulated by the CD4+ helper T cell subset. The CD4+ T cells provide growth factors or signals to these cells that signal them to proliferate and function more efficiently. This multitude of interleukins or cytokines that are produced and secreted by CD4+ T cells are often crucial to ensure the activation of natural killer cells, macrophages, CD8+ T cells, and PMNs.

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Immunity

The specific defense of the Immune system is to provide immunity, which is the capacity to resist certain types of organisms and toxins (poisons) that will damage tissues and organs. There are two major types of immunity:

I. **Natural (innate) immunity** - one's own ability to fight off disease
II. **Acquired immunity** - the body develops specific immunity (antibodies and cells) against invading agents such as lethal bacteria, viruses, toxins, and even foreign tissues from other organisms.

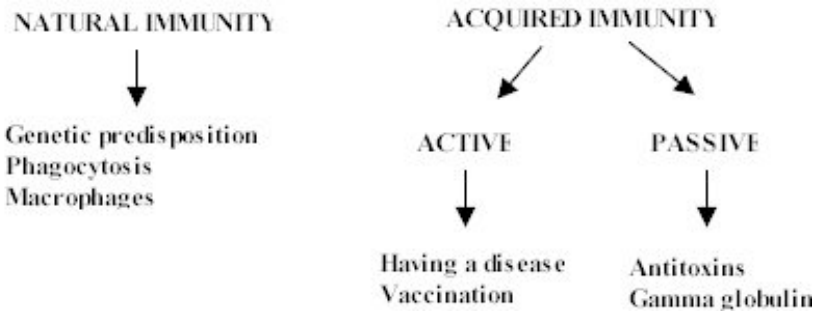
Acquired active immunity occurs in two ways

1. By having a disease There are many diseases that, if you catch them once, you will never catch again. Measles is a good example, as is chicken pox. What happens with these diseases is that they make it into your body and start reproducing. The immune system gears up to eliminate them. In your body you already have B cells that can recognize

the virus and produce antibodies for it. However, there are only a few of these cells for each antibody. Once a particlular disease is recognized by these few specific B cells, the B cells turn into plasma cells, clone themselves and start pumping out antibodies. This process takes time, but the disease runs it course and is eventually eliminated. However, while it is being eliminated, other B cells for the disease clone themselves but do not generate antibodies. This second set of B cells remains in your body for years, so if the disease reappears your body is able to eliminate it immediately before it can do anything to you.

2. Receiving a vaccination containing a modified pathogen or toxin, which stimulates production of antibodies (see vaccination section below)

Acquired passive immunity - Passive Immunity may be acquired naturally by a fetus through the passage of antibodies from the mother through the placenta or through breast milk to a nursing infant. Another way to acquire passive immunity is when the patient receives immune serum containing antibodies produced in another animal (e.g., Antitoxins or Gamma globulin). Antibodies are temporary (e.g., maternal antibodies will protect the infant for up to 6 months or longer if the mother continues nursing)



Vaccinations

A vaccine is a weakened form of a disease. It is either a killed form of the disease, or it is a similar but less virulent strain. Once inside your body your immune system mounts the same defense, but because the disease is different or weaker you get few or no symptoms of the disease. Now, when the real disease invades your body, your body is able to eliminate it immediately.

A vaccine is given by an injection or liquid by mouth. An alternative needle-free route is the use of inhalation by aerosol and powder.

A. Types of Vaccines
   1. Live organisms - used must be nonvirulent for humans or treated in the lab to weaken them so they are not as pathogenic to humans.
   2. Attenuated - an organism that has been weakened.
   3. Killed - vaccination with a toxoid occurs when the toxin produced by an organism is altered with heat or chemicals to render it harmless, but still allow the body to make antibodies against it.

Vaccines exist for all sorts of diseases, both viral and bacterial: measles, mumps, rubella, pertusis, tuberculosis, smallpox, polio, typhoid, Meningococcal, Influenza, etc.

Many diseases cannot be cured by vaccines, however. The common cold and Influenza are two good examples. These diseases either mutate so quickly or have so many different strains in the wild that it is impossible to inject all of them into your body. Each time you get the flu, for example, you are getting a different strain of the same disease.

Immunity may or may not be life-long with vaccines. To help keep the antibody levels high enough to prevent a disease sometimes "booster shots" are needed.

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