

To repel all the bacteria, viruses, and fungi that make a daily attempt to invade and colonize, the body relies on the immune system.

**Immunity** is the ability to resist damage from foreign substances (microorganisms, harmful chemicals). Immunity is categorized as being **innate** or **adaptive**.

Innate immunity provides the basic means for the destruction of foreign organisms. It recognizes and destroys certain foreign substances, but the response to them is the same during each encounter. It consists of **mechanical barriers** as well as certain **cells** and **chemical mediators**. The main barriers are skin and mucosae. Cells and chemicals include granulocytes, monocytes, macrophages, antimicrobial proteins, etc. A characteristic response of the innate system is **inflammation**.

The adaptive immune system consists of cells that attack particular antigens in a particular way. It improves and enhances the efficiency of the innate mechanisms and remembers the infection the next time it is encountered. Specificity (the ability to distinguish pathogens) and memory (the ability to respond more rapidly to a previously encountered pathogen) are characteristics of adaptive immunity, but not of innate immunity.

**Skin** helps repel pathogens in many ways. It's highly **keratinized**, which provides a physical barrier to pathogens. The acidity of **sweat** can kill some pathogens. **Sebum** is bactericidal.

**Mucous membranes** are another major barrier to pathogens. They line the digestive, respiratory, urinary, and reproductive tracts - all of which are potential entrance points for pathogens. They are often covered in sticky, pathogen-trapping **mucus**. Respiratory mucosa is also ciliated. **Cilia** sweep bacteria-laden mucus upward to the pharynx where it can be swallowed. Coughing and sneezing also assist in expulsion.

A variety of body fluids also provide innate defense. Tears, saliva, and urine wash away microorganisms. Saliva, intestinal fluid, and tears contain **lysozyme**, an enzyme that destroys bacteria. The acidity of certain mucosal secretions (gastric and vaginal) can impair pathogens.

Growth of disease-causing organisms is inhibited by the growth of **non-pathogenic bacteria** in the gastrointestinal and urogenital tracts. These bacteria successfully compete w/ the pathogenic ones for nutrients and resources.

WBCs and derivatives are the most important cellular component of the innate immune system. Recall that WBCs can exit blood vessels (**diapedesis**), converge upon areas of infection/damage (**positive chemotaxis**) and move over, btwn, and through other cells. **Neutrophils** are small phagocytic cells that are usually the first to enter infected tissues. They function primarily as bacteria killers. **Macrophages** are large phagocytic cells derived from monocytes. Macrophages may be **free** (able to move thru tissue spaces) such as the **alveolar macrophages** in the lungs or **fixed** (permanent residents of a

particular organ) such as the **microglia** of the CNS. Macrophages perform **phagocytosis** whereby they ingest something (a bacterium, particulate matter, etc.) and enclose it within a membrane-bound vesicle. The process begins with the adherence of a microbe to the phagocyte. The probability of this occurring is increased when **antibodies** or **complement proteins** have already bound to the microbe (a process called **opsonization**). The phagocyte then extends membrane “arms” that wrap the microbe and engulf it, forming a membrane-bound vesicle containing the pathogen. This vesicle is known as a **phagosome**. The phagosome then will fuse with a **lysosome**, an organelle that contains digestive enzymes. The enzymes will then destroy the engulfed material. Whatever indigestible material remains is then exocytosed. **Basophils** are motile WBCs that release histamine and other inflammatory chemicals when stimulated innately (by complement proteins) or by chemicals of the adaptive immune system. **Mast cells** are nonmotile cells that perform a function similar to that of the basophils. **Eosinophils** act to contain the inflammatory process and are extremely adept at killing certain parasites.

**Natural killer cells** are another innate cellular defense. They’re a specialized type of lymphocyte that attacks and destroys virus-infected cells and cancer cells.

Innate defense is also provided by a variety of **antimicrobial proteins**. One class is the **interferons**. There are several types of interferons. We’ll discuss one particular brand. These interferons are proteins produced by cells that have been infected with a virus. The interferons then diffuse to nearby cells and stimulate them to synthesize a protein that prevents viral replication. This prevents copies of the original virus from taking over neighboring cells. Interferons thus do not save the infected cell but prevent nearby cells from being infected. The same interferons can act against many different types of viruses.

**Complement** refers to a group of about 20 plasma proteins synthesized by the liver. They’re normally found in the blood in an inactive state. They may be activated by interacting directly with a pathogen or by members of the adaptive immune system. Activation of complement results in 4 things:

1. **Chemotaxis** – activated complement proteins attract WBCs.
2. **Opsonization** → binding of activated complement proteins to bacteria increases the likelihood of their phagocytosis.
3. **Inflammation** → activated complement proteins bind to basophils and mast cells and stimulate histamine release. This results in vasodilation and increased capillary permeability and inflammation.
4. **Lysis** → activated complement proteins can form a “**membrane attack complex**,” which is a tube that pierces the bacterial cell membrane. This allows salt and water to flow in and results in cell lysis.

The **inflammatory response** occurs whenever tissues are damaged. It helps to prevent pathogen spread, disposes of pathogens and debris, and sets the stage for repair. The signs of inflammation include *heat, redness, swelling, pain, and loss of function*. It begins when damaged tissues release inflammatory chemicals (**histamine, prostaglandins, leukocytosis-inducing factor**, etc.). These chemicals act to: increase

WBC count, increase local capillary permeability, cause local vasodilation, attract WBCs to the injury site, and stimulate pain-sensitive neurons. The increase in vasodilation and capillary permeability yields an increase in blood flow and capillary fluid loss. This results in swelling, heat, redness, and increased access to the injury site by WBCs, complement proteins, antibodies, and clotting proteins.

**Fever** is a systemic response to infection associated with an abnormally high body temperature. Many WBCs and macrophages release chemicals called **pyrogens** in response to pathogen exposure. Pyrogens act on the body's hypothalamic thermostat to raise body temperature. A mild increase in temperature can accelerate WBC function; impair bacterial metabolism; and cause the liver and spleen to sequester **zinc** and **iron**, 2 minerals necessary for bacterial survival. A major increase in body temperature can result in severe protein denaturation and possible loss of life.

The **adaptive immune system** responds in strong ways tailored to particular antigens. It differs from the innate system in that it's specific, systemic, and improves its efficiency each time it encounters the same pathogen.

**Antigens** are substances that can provoke the adaptive immune system and cause a response. Most are large, complex molecules not normally found in the body. Thus they are **non-self** or **foreign antigens**. **Self-antigens** are molecules produced by the body that stimulate the adaptive immune system. They can result in **autoimmune disease**.

The principal cells of adaptive immunity are the **lymphocytes**. There exist 2 main types of lymphocytes: **B lymphocytes** and **T lymphocytes**. Both are formed initially in the red bone marrow. B lymphocytes gain **immunocompetence** (i.e., mature) in the **bone marrow** while T lymphocytes gain immunocompetence in the **thymus**.

Immunocompetent B and T cells are composed of small groups of identical lymphocytes called **clones**. Each clone has many copies ( $10^4$ - $10^6$ ) of a **receptor** on its cell surface. The presence of one specific type of receptor allows each clone to bind/recognize and interact with 1 specific type of antigen. There are more than a million different varieties of clones, giving the lymphocytes a large variety of antigens to which they can respond. Once a B or T cell has become immunocompetent, the naïve cells will travel to the lymph nodes, spleen, or other lymphoid organs to await antigens.

Another cell type that plays a critical role in adaptive immunity is the **antigen-presenting cell**. The main APCs are the **dendritic cells** in connective tissue, and the macrophages. They function by engulfing antigens and then presenting antigen fragments on their surface as a signal to **Helper T cells** (a type of T lymphocyte). They are basically identifying the invading antigens and then displaying it the specific appropriate lymphocyte and saying – *“Hey these guys invaded us. Find them, build an army, and kill ‘em!”*

There are 2 main components to the adaptive response: **antibody-mediated immunity** and **cell-mediated immunity**. The antibody-mediated response (a.k.a. the **humoral**

**response**) is the body's response to **extracellular antigens**, i.e., those antigens found within plasma, ISF, or lymph. Cell-mediated immunity refers to how the body deals with microorganisms that have invaded cells (e.g., viruses, certain bacteria and fungi). Bear in mind that these 2 branches will overlap and work together.

Let's suppose a pathogen has invaded the body and is somewhere in the extracellular space (i.e., plasma, lymph, tissue fluid, etc). The 1<sup>st</sup> step in the body's response is for an APC (i.e., a macrophage or dendritic cell) to engulf it. Once engulfed, the pathogen will be destroyed. Then resulting pieces (which we can consider antigens) will be displayed on the surface of the APC by a molecule known as a **class II MHC protein**. The antigen will be recognized by and stimulate a Helper T cell that contains the specific receptor matching the particular antigen. The Helper T cell must also receive a confirmation signal from the APC before it proceeds. This confirmation signal is called **costimulation**. The Helper T cell will now proliferate to form many more Helper T cells, which also respond to the same original antigen. These Helper T cells can release **cytokines** (which are chemicals that will stimulate the body's innate defenses). The Helper T cells will also help activate B cells and/or **Killer T cells**.

Now let's suppose that the same pathogen runs into a B cell that carries the specific receptor for it. The B cell will then engulf it, kill it, and display antigenic fragments on its own MHC II proteins. Once the antigen has been displayed to the previously mentioned Helper T cells, those Helper T cells will stimulate the B cell to begin dividing. Most of the resulting cells will be **plasma cells**. Plasma cells secrete up to 2000 **antibodies** per second. Each antibody will specifically bind to the original antigen and mark it for destruction. A small percentage of the clones will be **memory cells**. These memory cells have the ability to mount an almost immediate humoral response if the same antigen appears again in the future. NB: this entire process is referred to as **clonal selection**.

Antibodies are also called **immunoglobulins**, **gamma globulins**, or **Ig's**. Each consists of 4 polypeptide chains that combine to form a Y-shaped structure known as an **antibody monomer**. Each antibody monomer has 2 **variable regions** (the ends of the 2 arms of the Y) and a **constant region** (the stem of the Y). The variable regions contain the **antigen-binding sites**. All antibodies released from the same plasma cell will have the same antigen-binding sites. Thus they will all be specific for the same antigen. The constant region binds to other immune chemicals or cells and *determines the mechanism by which the bound antigen will be destroyed*. The constant regions also determine the **antibody class**. There are 5 antibody classes: **IgM**, **IgA**, **IgD**, **IgG**, and **IgE**. Antibodies of each class have different constant regions and different roles and locations in the body.

Antibodies have 4 main mechanisms of action: **precipitation**, **lysis**, **agglutination**, and **neutralization**. Precipitation occurs when antibodies bind soluble antigens into clumps. This increases the likelihood of phagocytosis. Lysis occurs when antibodies activate complement. This results in the formation of a membrane attack complex, and bursting of the bacterial cell. Agglutination occurs when antibodies bind cell-bound antigens into

clumps. This increases the likelihood of phagocytosis. Neutralization occurs when antibodies bind to and mask the dangerous portions of antigens, toxins, and viruses.

Now let's suppose that the original pathogen has begun invading the body cells. Antibodies are only effective against extracellular antigens. They're useless against pathogens that have slipped inside body cells. This is where cell-mediated immunity comes into play. Fragments of intracellular proteins are displayed on the surface of every nucleated body cell by molecules known as **class I MHC proteins**. This gives a "window" into a cell, that T lymphocytes can "look in" to see if everything is ok. The combination of our original antigen and the MHC I protein displaying it will bind to and stimulate a Killer T cell that contains the specific receptor matching the original antigen. With a little stimulation from our aforementioned Helper T cells, the activated Killer T cell will begin to divide. This results in both **mature killer T cells** and **memory killer T cells**. Memory killer T cells will persist in case of a subsequent infection by the same pathogen. Mature killer T cells will set about to kill those body cells displaying the same specific antigen as the original one that began the activation process, e.g., cells infected by the same type of virus. Killer T cells release lethal chemicals that are capable of causing cell death.

It should be noted that Helper T cells are sometimes referred to as **CD4 cells**, while Killer T cells are sometimes referred to as **CD8 cells**.

**Suppressor T cells** are another class of T lymphocytes. They release cytokines that suppress the activity of B cells and certain T cells. This helps prevent runaway or unnecessary immune activity.

Let's take a look at another aspect of antibody-mediated immunity. The initial encounter with a particular antigen is termed the **primary immune response**. It typically has a **lag period** of 3-6d btwn the time of exposure to the antigen and the appearance of antibodies specific for that antigen in the plasma. During this lag period clonal selection and antibody production both take place. Plasma antibody levels peak at about 10d and then decline. B/c the primary immune response results in memory cell production, it will differ from future responses. In the **secondary response**, the presence of memory cells primed for the original antigen will result in:

- 1) A shorter lag time.
- 2) Plasma cells that remain alive and functioning for a much longer time.
- 3) Achievement of higher antibody levels in a shorter time.
- 4) Higher efficiency of binding between antibodies and antigens.

A similar form of immunological memory will occur with T cells.

Immunity can be achieved into basic ways. **Active immunity** is the result of memory cell production by the body in response to a foreign antigen. **Passive immunity** occurs when antibodies from another person (or animal) are transferred to a non-immune individual. Active immunity can be **naturally adaptive** in response to **infection**. It can also be **artificially adaptive** due to **vaccination** – the injection of dead or weakened pathogens into the body. This results in memory cell production, but spares the body of

symptoms. Active immunity lasts for as long as the memory cells remain alive in the body. Truly long lasting immunity may require continual exposure to the pathogen. Passive immunity, since it does not involve memory cell production, has a much shorter duration than does active immunity – lasting only as long as the antibodies remain in the circulation. Passive immunity can be **natural** when antibodies cross the placenta and travel from the maternal bloodstream to the fetal bloodstream, or when antibodies are excreted in breast milk. It can be **artificial** when antibodies are given by injection.