The Immune System

Structures of the Immune System

- **Innate Immunity** consists of defenses that are always active against infection, but do not have the ability to target specific invaders. **Nonspecific Immunity**
- **Adaptive or Specific Immunity**: defenses that target a specific pathogen. Is slower to act, but maintains a memory of an infection so that it can more quickly attack subsequent infections.

Anatomy

- **Bone Marrow** produces all **leukocytes** that participate in the immune system. Are created through hematopoiesis.
- **Spleen**: location of blood storage and activation of **B-cells**, which turn into plasma cells to produce antibodies as part of adaptive immunity.
  - When B-cells leave the bone marrow, they are mature but naïve since they have not been exposed to an antigen.
  - These antibodies dissolve in the blood and not in the cell, because of this, they are a division of adaptive immunity called **humoral immunity**.
- **Thymus**: location of maturation for **T-cells**.
  - Agents of **cell-mediated immunity** since the T-cells coordinate the immune system and directly kill virally infected cells.
- **Lymph Nodes**: Provide a place for immune cells to communicate and mount an attack.
  - B-cells can also be activated here.
- **Gut-associated lymphoid tissue (GALT)**: immune tissue found close to the digestive system. Have a higher chance of potential invasion.
  - **Tonsils, adenoids** in the head, **Peyer’s patches** in the small intestine, and lymphoid aggregates in the **appendix**.
- Leukocytes produced through hematopoiesis and can be divided into **granulocytes and agranulocytes**. Granules contain toxic enzymes and chemicals and are effective against bacterial, fungal and parasitic pathogens.
  - **Granulocytes**: include neutrophils, eosinophils and basophils
  - **Agranulocytes**: **Lymphocytes** which are responsible for antibody production, immune system modulation and targeted killed of infected cells. And **Monocytes** which are phagocytic cell in the blood.
    - Monocytes become **macrophages** in tissue and some names are specific to the tissue they reside in. (microglia for CNS, Langerhans cells in the skin, Osteoclasts in bone)

Classification

- **Nonspecific immune response** includes antimicrobial molecules, phagocytes. Also triggers an inflammatory response which triggers an influx of immune cells through the increased blood flow.
- **Specific Immune Response** is adaptive and can be further divided:
  - **Humoral immunity**: driven by B-cells and antibodies
  - **Cell-mediated immunity**: provided by T-cells.
The Innate Immune System

Noncellular Nonspecific Defenses

- First line of defense is the skin (integument). It provides a physical barrier to the outside world. Stops pathogens from entering body and internal organs freely
  - **Defensins:** antibacterial enzymes that are found on the skin.
  - **Sweat also has similar properties**
- **Respiratory Passages:** mucous membranes are lined with cilia to trap particulate matter and push it towards the oropharynx.
  - **Mucus:** helps to trap smoke and dirt particulates, but also prevents bacteria and viruses from entering the lung tissue.
  - Other mucous membranes a bacterial enzyme called lysozyme. This is found in a variety of location, notably the eye and in the oral cavity. Is secreted through tears and saliva.

Gastrointestinal Tract

- Stomach secretes acid which eliminates most pathogens.
- Bacteria in the gut are non-harmful and take up space so that other invaders cannot occupy.

Complement

- **Complement System:** number of proteins in the blood that act as a non-specific defense against bacteria.
  - **Classical Pathway:** Is how most complements are activated and requires the binding of an antibody to a pathogen.
  - **Alternative Pathway:** Does not require antibodies.
  - Complement molecule punches holes in the cell walls of bacteria and make them osmotically unstable. Is a noncellular defense since it cannot be modified to target specific organisms.

Interferons

- Cells that have been infected by a virus produce **interferons.** These are proteins that prevent viral replication and dispersion.
  - Causes nearby cells to decrease production of both viral and cellular proteins. Also cause cells to decrease permeability, which makes it harder for viruses to infect.
  - Upregulate MHC class I and class II molecules. This increases the amount of antigens in the bloodstream and makes it easier to detect infected cells.
  - Are responsible for many “flu-like” symptoms such as malaise, tiredness, muscle soreness and fever.

Cells of the Innate System

Macrophages

- Reside in tissue and come from monocytes within the blood. These become resident population which means that they become a permanent stay within the tissue.
  - Activate when bacterial invader enters a tissue
  - Phagocytizes the invader through endocytosis
  - Digests invader using enzymes
- Presents little pieces of invader to other cells by using the protein major histocompatibility complex (MHC).
  - This binds to the antigen and carries it to the cell surface so that it can be recognized by the cells of the adaptive system.
- Macrophages also release cytokines which stimulate inflammation and recruit additional immune cells to area.

MHC Class I molecules
- MHC class I molecules are displayed in all nucleated cells. This allows the immune to monitor the health of these cells.
- Endogenous pathway: since it only binds antigens from inside the cell, i.e. – only the cells that are infected are detected.
- Those cells that are marked can be killed by cytotoxic T-lymphocytes.

MHC Class II molecules
- Displayed by professional antigen-presenting cells like macrophages, dendritic cells in the skin, some B-cells, and certain epithelial cells.
- Antigen is a substance (usually pathogenic protein) that can be targeted by an antibody.
- Exogenous Pathway: antigens originate from outside the cell. This is since the phagocytic cells pick up pathogens from the environment and process them and then present them on MHC-II.
- Pattern Recognition Receptors (PRR): special receptors in Macrophages and dendritic cells. Able to recognize the category of the invader (virus, bacteria, fungus, parasite) and then secrete the appropriate cytokines to attract the necessary immune cells.

Natural Killer Cells
- Are able to detect the downregulation of MHC cells by viruses. These cells then induce apoptosis in the virally infected cells.
  - May occur with cancer cells as well.

Granulocytes
- Neutrophils are most abundant in blood and are short-lived. These are phagocytic and target bacteria.
Chemotaxis: ability of neutrophil to follow bacteria through the sensing of certain products

Opsonized: cells which are marked with an antibody from B-cells can be detected by neutrophils

Pus: dead collections of neutrophils are responsible for this

- **Eosinophils**: contain bright red-orange granules and are involved in allergic reactions and invasive parasitic infections.
- **Histamine**: released upon activation and is an inflammatory mediator. Which results in vasodilation and increased leakiness of blood vessels, which allows additional immune cells to move out of the blood stream and into the tissue.
- **Inflammation**: useful against extracellular pathogens (bacteria, fungi & parasites)

- **Basophils**: large purple granules and are involved in allergic responses. The least abundant in blood.
  - **Mast Cells**: related to basophils but have smaller granules and exist in the tissue, mucosa and epithelium.
  - **Release large amounts of histamine which leads to inflammatory response.**

### The Adaptive Immune System

#### Cells of the Adaptive Immune System
- All cells created in bone marrow. T-cells mature in thymus while B-cells stay in bone marrow.

#### Humoral Immunity
- Involves the production of **antibodies**, and may take as long as a week to be effective.
  - Antibodies are specific to the antigen of the invading microbe and are produced by B-cells.
  - Activation of B-cells come in the spleen or lymph node.
- **Immunoglobulins [Ig]** is another name for antibodies. These can be present on the surface of a cell or secreted into body fluids.
- If antibody is in a body fluid, there are three main possibilities for when an antibody binds to a specific antigen:
  - **Opsonization**: May attract leukocytes to phagocytize the bounded antigens.
  - **Agglutinate**: cause antigens to clump together which forms a large insoluable molecule that can be phagocytized easily.
  - Can block the ability of a pathogen to invade tissues
- For cell-surface antibodies, the binding of an antigen to a B-cell causes its activation which results in proliferation and formation of plasma and memory cells.

#### Antibody Structure
- Antibodies are made up of two heavy chains and two light chains. These chains are linked by disulfide and noncovalent interactions.
- **Antigen Binding Region**: is located the end of the variable region (at the tips of the Y).
  - There are specific polypeptide sequences that will bind to only one specific antigenic sequence.
o **Hypermution:** humoral immunity takes longer because each B-cell undergoes this change in its antigen-binding region in an attempt to find a best match for the antigen.

 o **Clonal Selection:** Only those B-cells with a high affinity for an antigen will survive.

• **Constant Region:** natural killer cells, macrophages, monocytes, and eosinophils have receptors for this region of an antibody.

• Each B-cell can only make one type of antibody, but there are many B-cells within the body and each B-cell can also have five different isotopes. These isotypes can be used at different times or in different locations during the adaptive immune response.

 o **Isotype Switching:** is the ability of the cell to change which isotope of an antibody they are producing. Stimulated by specific cytokines.

• **Naïve B-Cells:** wait in the lymph node for their particular antigen to come along. Upon exposure to the correct antigen, a B-cell will activate and produce two daughter cells:

 o **Plasma Cells:** produce large amounts of antibodies

 o **Memory B-Cells:** stay in lymph node and may last a lifetime

• **Primary Response:** when antigen is first encountered, takes 7-10 days for antibodies to be produced.

• **Secondary Response:** If same antigen carrying microbe is encountered again, memory cells will quickly begin producing the specific needed antibodies. This response is much more rapid and robust.

**Cytotoxic Immunity**

• T-cell undergo both positive and negative selection as they mature in the thymus:

 o **Positive Selection:** maturing cells that can only respond to the presentation of antigen on MHC. Other cells undergo apoptosis.

 o **Negative Selection:** causing apoptosis in cells that are self-reactive (Are activated by antigens present in the organism itself)

• **Thymosin:** A peptide hormone that facilitates the maturation of T-cells. Once mature, the T-cells are naïve. Once exposed to an antigen, only those that have a high affinity for a given antigen will proliferate (called clonal selection).

**Helper T-Cells (T_H) or CD4+ T-Cells**

• Coordinate the immune response by secreting chemicals called **lymphokines.**

 o These cells are capable of recruiting other immune cells such as plasma cells, cytotoxic T-cells and macrophages, and also increasing their activity.

 o If these cells are lost (as in HIV), it prevents the immune system from mounting an adequate response.

  ▪ If advanced such as acquired immunodeficiency syndrome (AIDS). Small pathogens can cause devastating effects

• These cells respond to antigens that are present on MHC-II molecules. Since they are exogenous antigens present, these cells are most effective against bacterial, fungal and parasitic infections.

**Cytotoxic T-Cells (T_C or CTL) or CD8+ T-Cells**

• Capable of directly killing virally infected cells by injecting toxic chemicals that promote apoptosis into the infected cell.
- Respond to antigen present on MHC-I molecules. As such, they are most effective against viral (and intracellular bacterial or fungal) infections.

**Suppressor or Regulatory T-Cells (T_{reg})**
- Also express CD4, but can be distinguished from helper t-cells due to presence of Foxp3.
- These cells control and tone down the immune response once the infection has been contained.
- **Self-tolerance:** turn off self-reactive lymphocytes in order to prevent autoimmune diseases.

**Memory T-cells**
- Are very similar to memory B-cells and result in a more robust and rapid response.

**Activation of the Adaptive Immune System**
- Five types of infectious pathogens: bacteria, viruses, fungus, parasites and prions.

**Bacterial (Extracellular Pathogens) Infections**
- Macrophages act as guards of the body since they are always on the lookout for potential invaders.
- If bacteria enter the body, first macrophages engulf the bacteria and then release inflammatory mediators. These cells also digest bacteria and present their antigen markers on their surface (MHC-II).
- Cytokines released attract the inflammatory cells (neutrophils and macrophages)
  - Mast cells are activated by the inflammation and degranulate to release histamine.
  - Histamine increases the leakiness of the capillaries and allows the immune cells to leave the bloodstream and go to the affected tissue.
- Dendritic Cells then leave affected tissue and travel to nearest lymph node, and antigen is presented to B-cells.
  - B-cells, which produce correct antibody, proliferate to create plasma cells and memory cells.
- Antibodies then travel through bloodstream to the affected tissue where the bacteria are tagged for death.
- At same time, Dendritic cells also present antigen to T-cells. CD4+ is activated in two types: T_{h}1 and T_{h}2
  - T_{h}1 Cells release interferon gamma which activates macrophages and increases their ability to kill bacteria.
  - T_{h}2 cells help activate B-cells and are more common in parasitic infections.

**Viral (Intracellular Pathogen) Infections**
- Virally infected cells produce interferons which reduces the permeability of nearby cells, reduces the rate of transcription and translation in these cells, and cause systematic symptoms.
- These infected cells also present intracellular proteins on their surface (MHC-I). At least some of these proteins will be viral proteins.
- CD8+ T-cells will recognize the MHC-I and antigen complex as foreign and will inject toxins into the cell.
If virus downregulates production of MHC-I molecules, then natural killer cells will recognize this and cause apoptosis of the cell.

**Recognition of Self and Non-self**

- **Self-antigens** are present on the surface of every cell of the body. These antigens signal to immune cells that the cell is not threatening and should not be attacked.
  - If immune system fails to recognize the cells as the body’s own, this is known as **autoimmunity**.
- **Hypersensitivity Reactions**: allergies and autoimmunity are apart of this group. Where it misidentifies harmless molecules as foreign and potentially harmful.
- Body attempts to prevent autoimmune diseases through the maturation process of T-cells and B-cells.
  - Negative Selection: B or T-cells that react to self-antigens are eliminated before they leave the bone marrow.
  - Can be treated with administration of **glucocorticoids**

**Immunization**

- **Active Immunity**: immune system is stimulated to produce antibodies against a specific pathogen. Means of exposure may be natural or artificial.
  - For natural, antibodies are generated by B-cells when individual is infected
  - Artificial (vaccines) also develop antibodies, but individual is never infected.
    - Antigen may be weakened or a killed microbe form or part of protein structure
- **Passive Immunity**: transfer of antibodies to an individual. Only the antibodies and not the plasma cells are transferred.
  - Transfer of antibodies across placenta or through breast milk

**The Lymphatic System**

**Structure**

- Type of circulatory system that is made up of one-way vessels that become larger as they move towards the center of the body.
- Vessels carry lymphatic fluid (**lymph**) and most join to comprise a large **thoracic duct** (located in the posterior chest). The fluid is then delivered to the left subclavian vein
- **Lymph Nodes** are small, bean-shaped structure along the lymphatic vessels. These contain a lymphatic channel as well as an artery and a vein.
  - These provide a space for cells of the immune system to be exposed to possible pathogens

**Function**

**Equalization of Fluid Distribution**

- Since net pressure at venule end is less than net pressure at arteriole end, there is a small amount of fluid that remains in the tissue after this exchange. Lymphatic vessels drain these tissues and subsequently return the fluids to the bloodstream.
- This provides some protection against certain pathologies. This can prevent **edema** (swelling) from occurring if the Lymph nodes are not blocked or overwhelmed.
**Transportation in Biomolecules**

- Also transports fat from digestive tissue into bloodstream.
- **Lacteals** are small lymphatic vessels that are located at the center of each villus in the small intestine.
- Fats enter the lacteal for transport after being packed into chylomicrons
  - Lymphatic fluid with a lot of chylomicrons appears milky white (called **chyle**)

**Immunity**

- Place for antigen presenting cells and lymphocytes to interact.
- B-cells proliferate and mature in the lymph nodes in collection called **germinal centers**