**The Immune System**

**Introduction:**

 In this chapter, we will learn the overview of how the human body is able to defend itself against foreign pathogens and remember that invader in subsequent infections. Ancient medicine was focused on balancing the four humors, that is, blood, yellow bile, black bile, and phlegm. The balancing of these four was rather extreme interventions or palliative care for one about to die from infection or injury. Interestingly, since the 1400s, it was known that if one ingested the product of illness, protection from that illness would occur. With the advancement of technology and knowledge over time, Edward Jenner was known to be the founder of Immunology due to his smallpox vaccination strategy via the cowpox that occurred two months later, protected against smallpox, a deadlier disease. This principle laid the foundation for the study of Immunity and its respective field: Immunology. The Immune system differs from the majority of the human anatomy in that it is not defined by a localized organ, tissue, or one cell type. The collective effort of **pluripotent** **hematopoietic stem cells** into three different lineages, other organs and tissue systems, and even the use of **commensal organisms** on our skin contributes to the immunity that allows our body to continually function and recover from illness and disease.

**Innate vs. Adaptive Immune Response**

 Before diving into how our bodies are able to fight off infection, it is important to differentiate how Immunologists define response in what they study. The innate immune system is a non-specific and readily available response to begin healing itself. This system is split between its physical and chemical barriers and the phagocytic response. The cells that comprise the innate immune system are closely intertwined with those of the adaptive immune response. First, they are able to recognize foreign cells by having **pathogen-associated molecular patterns (PAMPs)** via the **pattern recognition receptors (PRRs)**, which are receptor proteins that interact with the environment to sample for pathogens. The cells of innate immunity specialize in a non-specific response to a pathogen. Once in contact with a pathogen and becoming activated, these cells can begin digesting and destroying the pathogen and/or secrete **cytokines** which are chemicals used to communicate with other immune cells or have an effect on other cells. One of the effects of these cytokines is triggering inflammation, a common symptom for many illnesses with redness, swelling, and increased temperature, eventually becoming a fever. The adaptive immune response begins when these prior processes cannot contain the infection, or a pathogen is able to hide within cells evading the innate immune response. These B and T cells produce specific **antibodies** and **killer T cells** that recognize and actively search for that pathogen. While the adaptive immune response provides a specific response, it does take a significantly longer time to heal the body and clear the infection due to immunological memory of the pathogen’s **antigen**. Another key difference between the innate and adaptive immune response is that the innate response is localized to one specific area of the body, whereas the adaptive response is systemic and includes significantly more cells, tissues, and organs to provide healing.

**Innate Immune Response**

**1-1 Physical and Chemical Barriers Provide Protection**

 The body is constantly exposed to microorganisms every second of the day. If we are continually exposed all the time, how are we not sick all the time? Remember, not all cells are harmful to the body. Only certain diseases and illness-causing ones are **pathogens** which can either be viral, bacterial, fungal, or parasite infections. The first layer of protection against these pathogens is an anatomic barrier. First, our skin is coated in commensal organisms that compete with pathogens for space on your skin. Commensal organisms are ones that benefit themselves and their host by occupying a **niche**. In this case, it is competing for space to attach to your skin. The collection of these microorganisms within the human body are known as the **Microbiome**. These organisms live and not harm you if they do not leave their respective home, where they could become an **opportunistic pathogen**. Next, mucosal sites (mucus membranes that link the mouth, nose, eyelids, trachea, lung, intestinal tract, and reproductive tract) also aim to get rid of pathogens by their respective fluid or phlegm production to secrete these pathogens or other invaders out, such as coughing, sneezing, tears and mucus secretion. These are known as the chemical barriers that either eject (coughing or sneezing) or breakdown (stomach acid and saliva with its digestive **enzymes**) materials that come into contact with it. At a stage after the physical and chemical barriers, the **complement** system and antimicrobial proteins are the innate response's intermediate steps. Complement activation occurs in three specific and detailed steps of the lectin, classical, and alternative that we will not go in-depth. Ultimately complement activation results in the aggregation of proteins to form a **membrane attack complex (MAC)** that creates a massive pore in the pathogen’s membrane. On top of complement activation, antimicrobial peptides are secreted by the commensal organisms in the skin and mucosal sites to provide an additional step of protection.

**1-2 Immune Cells from the Pluripotent Hematopoietic Stem Cell**

 Before introducing the process of how the immune system responds to foreign invaders, a brief overview of the cells of interest is necessary. The immune system is a large and complex system that has organs, vessels, and cells coordinating the healing of the body. There are **primary and secondary lymphoid organs** of the immune system. The primary lymphoid organs include the **Thymus** and **Bone Marrow**. Within these organs, lymphocytes come from the pluripotent hematopoietic stem cell from the bone marrow and differentiate into the **common myeloid progenitor (CMP)** as well as the **common lymphoid progenitor** **(CLP)**. The CLP then differentiates into **B cells**, **T cells**, **Natural Killer cells**, or immature **dendritic cells**. The lymphocytes (B and T Cells) migrate to the Lymph nodes or Thymus, respectively, and develop until they are immature. They are considered immature until exposure to an antigen that they can uniquely bind. These lymphocytes' migration occurs in the lymphatic vessels to the secondary organs, the lymph nodes, spleen tonsils appendix and Peyer's patches. After becoming immature, these cells are able to either stay within their respective organ or migrate to local tissues for potential exposure to their respective antigen. The CMP cell lineage ends with red blood cells, platelets, **macrophages**, **dendritic cells**, **neutrophils**, eosinophils, basophils, and mast cells. The cells we are particularly interested in are the dendritic cells, macrophages, and neutrophils. Eosinophils and basophils are known to have roles in parasitic infections, while mast cells are known to have key roles in allergic responses. Now with this knowledge on key players intervening infection, we can begin following the process of how our body

**1-3 Phagocytic and Inflammation Response**

 Within two branches below the lineage of the pluripotent hematopoietic stem cell, there resides three cell types: macrophages, neutrophils and natural killer cells. These innate immune cells are known as sensor cells and have the ability to detect foreign cells with PRRs that bind to PAMPs of the pathogenic cells. Pathogenic, cancerous, and toxic antigens stimulate an innate response to a localized area. Once bound, these cells have different responses to binding a pathogen and its antigen. Macrophages have the ability to completely engulfs the pathogenic cell with an extension of its plasma membrane and digest that cell. This is known as **macropinocytosis**. Neutrophils recognize the pathogen and are only able to digest it once before being completely degraded. Dendritic cells are the third phagocytic cell that links the innate to the adaptive system. We will explore this linkage later. For now, dendritic cells are localized with the other innate responders to constantly sample antigens in the healthy state and infection state of their respective areas. Natural killer cells are tasked with surveying our own body’s cells that are displaying a **Major Histocompatibility Complex I protein** **(MHC1)**. When this protein is no longer presented or issues in the protein's expression, this marks the cell for **apoptosis** via the natural killer cell inserting degrading enzymes within that cell.

 When these cells encounter a pathogen, their respective response is initiated as well as the production of pro-inflammatory signals. PAMP **Inflammation** is a common symptom that occurs from infection and is accompanied by redness, swelling, and an increased temperature at the site, and ultimately a fever results from a prolonged response. This state of inflammation with increased cytokines and **chemokines** recruits more sensor cells to the site of infection from the bloodstream. The infection site's inflamed state recruits more natural killer cells that are closely related to cells of the adaptive system, both arising from the common lymphoid progenitor (CLP). What makes them different from their other lymphocytes is that they lack the receptors for antigen-specific binding. When these powerful mediators defending us constantly cannot contain a pathogen, specific and more powerful means are required to heal our body.

**Adaptive Immune Response**

**1-4 Innate Response Needs Reinforcements**

**Humoral Response**

 While innate immune response provides fast and non-specific mediated phagocytosis, some invading pathogens are particularly evasive or persistent beyond the innate response scope. This is when specific **humoral** and **cell-mediated** **immunity** via the adaptive immune system is required. Humoral immunity is responsible for antibody production to a specific pathogen. A major difference in the innate and adaptive immune response is that the specific recognition of a pathogen is retained over time to provide protection in subsequent infection. This was the common concept of immunity that has existed since the 1400s across the world and scientifically proven by Edward Jenner.

 When pathogens are evading the innate immune response or overwhelming it by sustaining through the inflammation process, pathogens will run into the free-floating B cells. Remember, these cells arise from the CLP just as natural killer cells; however, they are able to recognize a unique pathogen with its abundant antibodies present on the cell surface. These cells came from the Bone Marrow, migrated to the Thymus for development. Each B cell has its own unique (genetically varied sequence of antibody structure) antibody that recognizes one antigen on a pathogen. This interaction activates the B cell to transform from a naïve B cell to an effector B cell as a plasma cell or effector cell and proliferate to produce numerous clones of itself for the mass production of that one specific antibody. The production of the secretion of these antibodies is only possible through the **effector** function of the B cell, known as a plasma cell. The other B cell differentiation is the preservation of this antibody via memory B cells.

 Antibody response to the pathogen acts in two ways. The antibodies are free-floating in the body to encounter its antigen via the blood and lymph vessels randomly. These antibodies were mass-produced by the plasma cells to directly bind to the pathogen and inactive the ability of the pathogen to bind to its target. This is known as neutralization. An interesting characteristic of antibodies is their ability to **polymerize**, where two molecules can bind to each other and form ordered units of themselves called polymers, more specifically dimers, trimers, etc. Once the antibodies have attached and neutralize their respective target, the phagocytic cells, particularly macrophages, can recognize the antibodies' constant region to engulf and digest both pathogen and antibodies.

 The premise of vaccination occurs from B cells' ability to encounter the pathogen and produce the humoral response. As we learned, vaccines introduce a portion of a pathogen for the body to recognize as foreign; however, not elicit an extreme immune response to cause illness or a disease state. Vaccines can introduce antigens via inactivated (dead) pathogens, live-attenuated (alive, non-disease causing pathogen), toxoid, subunit (specific antigen only), and mRNA (messenger ribonucleic acid molecule to induce pathogen protein production from the ribosome). When the body encounters a pathogen for the first time, the memory B cells are the crucial component of vaccines that prevent a significant illness from occurring when exposed to that antigen. The vaccine itself does not prevent infection; however, the second response is already primed and ready to respond in subsequent infections when the body has learned to fight the infection from the first exposure.

**Cell-Mediated Response**

 Dendritic cells have a unique role in linking the innate and adaptive immune response. These cells are a part of the phagocytic cells by digesting pathogens and sampling antigens with macropinocytosis; however, dendritic cells migrate to the most regional lymph nodes after macropinocytosis. Upon their arrival to the regional lymph node, they are non-phagocytic and now activate naïve T cells. These T cells are derived from the CLP just as B cells; however, they migrate specifically to the Thymus's primary lymphoid organ. Here, the T cell undergoes development to selectively recognize antigens without binding to own our bodies ' molecules and cell receptors. Antigen-presenting cells contain both the MHC I and MHC II receptor protein. The Helper T cell is an essential cell for the function of the adaptive immune response binding to the MHC II receptor on the antigen-presenting cells of dendritic cells and macrophages. Upon activation from macrophages and dendritic cells, the helper T cell is able to proliferate into its effector and memory cell lines.

 The effector function of Helper T cells is responsible for activating naïve Cytotoxic T cells (referred to as Killer T cell) and activating macrophages to active more Killer T cells and naïve B cells to produce antibodies. This communication is accomplished with the production of cytokines. Upon activation from the helper T cell, Killer T Cells can recognize that specific antigen presented on the MHC I protein on infected or cancerous cells (interestingly, some cancers evade this MHC I presentation). Killer T cells function to bind to the specific MHC I protein and target that specific cell for apoptosis. Apoptosis is the induced cellular death; in this case, the Killer T cell introduces holes into the cell as well as degrading enzymes through the holes made by the T cell. Many subsets of T cells respond to infection, and similar to B cells, T cells have memory T cells that remain in the body in preparation for subsequent infection. Upon activation in subsequent infections, these cells proliferate into effector and more memory cells just as the Helper T cell did upon activation.

**1-5 The Unique Development of B Cell Antibodies and T Cell Receptor**

 Antibodies and T Cell receptors must have the ability to recognize an antigen. There is an incredible amount of antigens possible through the genetic variability in protein development. How does our body continue to develop unique antibodies and receptors? Antibodies contain two portions to their Y-shaped structure: the variable and constant regions. The varying receptor is the alpha and beta varying regions on the top half of its tetramer shape for T cells. The constant region is what macrophages are able to recognize as antibodies and begin digesting it and the pathogen bound to them. The variable region is responsible for the amazing property of binding to a numerous variety of antigens. Recall that before a protein exists, it was made from the DNA sequence into an mRNA transcript. The various combinations of the variable (V), diversity (D), and joining (J) gene segments on a DNA sequence is responsible for the variability of these antibodies and receptors. This recombination ability is unique to these lymphocytes and their ability to recognize numerous amounts of antigens.

**Summary**

 The immune system is an anatomically wide-spanning and complex system that helps us fight infection each and every day. The innate immune system is the first line of defense if the physical and chemical barriers fail to contain pathogens or an injury occurs that can be infected. The innate immune response relies on non-specific recognition and containing the infection as well as initiating the inflammation process. The adaptive immune response is specific in its recognition of pathogens and retains the memory of the infection for an indefinite time in the future. The key link between this response is primarily the dendritic cells migrating from peripheral tissue to the lymph node. The activation of the T cells, which in turn active more T cells as well as B cells is crucial in responding to infection. The key recognition sites of immune cells are the MHC I and MHC II receptors. Remember that MHC I is present on all nucleated cells to indicate health or a disease state. If they are in a disease state, then natural killer cells represent the innate response, and T cells are the adaptive response for this protein. MHC II receptors are for antigen-presenting cells only, such as macrophages, B Cells, and dendritic cells. This receptor is key for activating the helper T cell to recruit the other subset of T cells and B cells for the adaptive response.

**References:**

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