Macrophages and Our Immune Response

**Macrophage Background:**

A **macrophage** is a cell that is found inside of the immune system that will phagocytose bacteria that infiltrates the system. The macrophages are long-lived, unlike other bodies found in the immune system. They must be activated in order to kill bacteria through phagocytosis. By definition, **phagocytosis** is the process that is used by many different types of cells where they will ingest other cells/particles by engulfing them in their entirety.

Macrophages were discovered by Elie Metchnikoff who won the Nobel Peace Prize (along with Paul Ehrlich) for this discovery. Metchnikoff was interested in the field of immunology, and this is what led him towards his study of macrophages and their role in the human and animal bodies. From a young age, he was very interested in animal biology and he pursued it in his future studies at many universities throughout his scientific career. The discovery of the macrophage forever changed science and definitely changed the way that the scientific community views immunology. Today, our macrophages serve as a line of defense from debilitating diseases and have been explored on a much deeper level.

Overall, the function of the macrophage extends from phagocytosis to many others. They are a defense mechanism, they also regulate lymphocyte activation and proliferation while being essential in the process involving T and B lymphocytes by antigens. These lymphocytes both share their own responsibilities in the immune system. T lymphocytes, also commonly referred to **T cells**, function to produce antibodies and antigens while also containing memory in the immune system. These T cells are developed inside of the thymus, and have two prominent functions to respond to foreign antigens. These two functions are one, to control the immune and inflammatory responses via cell to cell contact and cytokine release, and then two is to kill the foreign cells, infected cells and cancer cells that are infected by viruses directly. The T cells compose up to eighty percent of your entire peripheral blood which is the red and white blood cells as well as platelets. There are three different groups of T cells, helper T cells, cytotoxic T cells, and memory T cells. Each group has its own function and surface antigen which is used to create a bacterial attachment. The B lymphocytes, also known as **B cells**, have a major function in making antibodies for the immune system. These B cells are created in the bone marrow.

This all plays a major role in immunology as a whole, so background on the subject of immunology should be explored as well. The immune system works day in and day out to protect the body from outside pathogens as well as inside invaders that become detected. It is composed of cells, tissues, and molecules that function to seek, find and eradicate pathogens. There are two major portions of the immune system, the innate and the adaptive immune system. In brief, the **innate immune system** is the first response that acts quickly and without past memory. The **adaptive immune system** is opposite of that and will act in a slower manner and will use memory and “learn” to attack the pathogen that is present. Of these types of immunity, the next in the hierarchy of levels in the immune system is a **cell-mediated** response or a **humoral response**. With macrophages, their involvement is considered cell-mediated. This is because the cell-mediated immunity includes the production of cytotoxic T lymphocytes, macrophages and cytokines.

So in all, the macrophages follow three basic functions: mainly for phagocytosis, for antigen presentation to T cells to expand specific immune responses, and then the secretion of specific cytokines to activate and promote innate and immune responses. Their overall significance to the immune system is very important, and without them there would not be many other ways to evoke an immune response.

**Structure and Function:**

The structure of the macrophage is very important to its function as well. The macrophage will completely cover, or engulf, its target organism which is very unique to the macrophage. If one wanted to differentiate the macrophage from another cell, it would be important to use techniques like **density gradient centrifugation** and **adherence separation**. Density gradient centrifugation is defined as a method in which the components of a specific sample are separated by their observed density, in a dense medium or density gradient, inside of a centrifuge. Adherence separation is defined as adherence that occurs due to separation. The plasma membrane of the macrophage will have to be purified to be able to be identified. In this plasma membrane, there are markers for sodium, potassium, and ATPase that are present in the attached bead fraction. This differentiates the plasma membrane because these markers in other things like lysosomes, mitochondria, the cytoplasm are non-existent or much lower in concentration. So as far as differentiation of cells you can use the plasma membrane of the macrophage. This plasma membrane is also the first portion of the macrophage to recognize the environment around the cell. It has been studied that the plasma membrane will recognize as well as act on foreign materials through cell surface receptors.

Phagocytosis has been explored often through this chapter, but this function has to be explored on both a surface and a deeper level. The macrophage itself will not carry out phagocytosis without having a successful binding that occurs on that cell surface receptor. Once this binding does occur from the macrophage and an invading bacteria or virus, it begins the engulfing process where it draws the invader into the macrophage. It does this engulfing not by surrounding it with the plasma membrane, but by using its own extensions of the cytoplasm, called **pseudopods**, which will surround the invading bacteria or virus and then encapsulate it inside. The macrophage cell is very flexible as well as fluid in its composition. All of this is completed without harming the plasma membrane of the macrophage, and done around it as well. After being surrounded by the pseudopods the invader becomes enclosed in a **phagosome**, which is a vacuole inside of the cytoplasm of the macrophage. This phagosome then becomes fused with a lysosome, creating a new “phagolysosome”. This **phagolysosome** is important because without the lysosome portion, it would be unable to break down the contents of the phagolysosome. Inside, the breakdown begins and the pH is lowered. This low in pH creates a very acidic environment, which is an environment that is ideal for killing the contents of the phagolysosome. After this neutralization, the phagolysosome creates a residual body made up of the waste products that were created.

Macrophages have different functions depending on the type of virus or bacteria it is up against. This is not because it will go through phagocytosis in a different way, but it is because when certain viruses and bacteria are phagocytosed into the macrophage different things happen. Not only can the viruses and bacteria survive inside of the macrophage, but they can also thrive inside. This can mean a lot of different things for the immune system. It could mean that a virus or bacterial invader can evade the macrophage or could be engulfed in the macrophage but stay inside and replicate.

**Virus and Bacteria Interactions:**

There are many different interactions that occur between viruses, bacteria, and the macrophage. Each interaction though depends on the type of virus and bacteria that are present. Some viruses, bacteria and pathogens can evade the macrophage, and some can prevent the macrophage from doing its own job effectively. Pathogenic Microbiology explores all of these in detail, but there are a few that can be seen most in everyday life that have common interactions like this with macrophages. Pathogens that have adverse reactions include, but are not limited to, *Staphylococcus aureus*, *Streptococcus* strains*, Haemophilus influenza,* and *Shigella.*

*Staphylococcus aureus* can be seen as a manifestation of infections like MRSA and VRSA. Both MRSA and VRSA are predominantly seen in places like hospitals since there is a high concentration of immunocompromised individuals as well as the connection of infected fomites (which are bed linens, clothes, etc.). Known as a “staph” infection, which is the most commonly found form of *Staphylococci*. The *Staphylococcus aureus* organism has a capsule, slime layer, peptidoglycan, and coagulase present and *S. aureus* is the main contributor to the “staph” infections. The **capsule** is what prevents phagocytosis by the macrophage. This is a common defense against the human immune system’s innate immunity. Th**e slime layer** will help with adherence to the foreign bodies which will prevent the phagocytosis. **Peptidoglycan** will also prevent phagocytosis due to the osmotic stability that it provides and how it stimulates the production of endogenous pyrogen. **Coagulase** is the last portion of phagocytosis prevention in this organism and it will convert the fibrinogen to fibrin, which will create a blood clot or a fibrin clot preventing phagocytosis. These are important to note when studying macrophage phagocytosis and *S. aureus* as a whole.

The *Streptococcus* is mostly associated with infections like strep throat, which is a very common type of infection in many different individuals. **Pharyngitis** is a likely cause of this strep throat and it is classified as a reddened pharynx causing pain and discomfort for the individual. It can also cause things like **Scarlet Fever**, which is a much more serious disease that caused trouble throughout history but is hardly seen in current times. There are other diseases caused, but their relevance in today’s medical field is not as notable. *Streptococcus* infections have similar methods to evade phagocytosis, like a capsule present. This capsule as stated previously allows evasion of the immune response in macrophages involved in immunity. Therefore, it will create the *Streptococcus* infections that are normally seen in all types of *streptococcus* even with the immune responses.

The *Haemophilus influenza* organism is another that uses different methods to avoid phagocytosis by macrophages and other immune responses. Its method is to use the capsule as well to prevent phagocytosis by macrophages. There are strains that are **encapsulated** as well as strains that are **nonencapsulated**, but the encapsulated tend to cause more pathogenicity inside of the body as well as outside of the body. Encapsulated strains can cause symptoms like septicemia, septic arthritis, meningitis, osteomyelitis, cellulitis, pericarditis, pneumonia, and epiglottis. Septicemia is the most invasive and problematic of these, and is a blood poisoning, specifically caused by a bacterial toxin. Septic arthritis is similar to this, in the fact that the joints are infected via the blood but different because there is a presence of arthritis. Arthritis is inside of joints causing inflammation. The other symptoms are also important, and can also become very life-threatening in many different ways. Nonencapsulated strains can causes otitis media with effusion, conjunctivitis, sinusitis, bacteremia and pneumonia. In comparison, the symptoms of the nonencapsulated are much milder than those of the encapsulated strains. These issues are much more treatable. For example, **conjunctivitis** is an inflammation that occurs in the conjunctiva of the eye. Conjunctivitis can be treated with the use of antibiotics and no real invasive or painful measures. The encapsulated strains are more effective at evading the immune system, therefore can reach and effect more portions of the body as a whole. This is why the macrophage cannot prevent these kind of issues that could stem from the *Hemophilus influenza* strain when they do contain a capsule.

The *Shigella* are the last to be spoken about in this chapter, but also have interesting ways that they deal with macrophages and phagocytosis in the immune system. *Shigella* will produce toxins called **Shiga toxins**. One is called stx-1 and the other stx-2. Stx-2 is 60% homologous to the stx-1 toxin. These Shiga toxins will inhibit protein synthesis, and will be the main reason for the pathogenicity of the organisms that contain them. *Shigella,* in general, will lyse the phagocytic vacuole and will also replicate inside of the host cell in the cytoplasm. This is not a common practice, but being inside of the cell further allows the *Shigella* to avoid the immune system’s defenses. Once inside the cell, the *Shigella* will induce cell death and eventually apoptosis of the macrophage itself. *Shigella* also causes diseases like shigellosis and bacterial dysentery when it invades the human system. **Shigellosis** is a certain form of gastroenteritis, and is considered the most common form of the disease. Initially it will start with watery diarrhea which will then progress within one to two days into abdominal cramps and tenesmus. This can be with, or without blood in the stools present. **Bacterial dysentery** is similar to shigellosis as far as symptoms are concerned but overall is more severe. This specific disease is from the *Shigella dysenteriae* and people can be carriers for this disease without showing any symptoms for a long period of time. The disease itself is self-limiting, and will usually resolve itself in the body within five to seven days without the use of antibiotics. However, there are severe cases that the infection may last over 3 weeks but not up to six weeks.

Though the human immune system and the macrophages associated are a great defense system for the body, there are times where the system is evaded or can be used to the pathogens advantage. Therefore, it is important to know why pathogens do the things that they do to avoid it and exactly how their mechanisms work. Each is very similar, but also slightly different depending on the needs of the pathogen, virus or bacteria that is invading. With an understanding of this, scientists can discover and use ways to assist the body in finding these organisms in the body and help prevent them from wreaking havoc in the body.

**Recent Studies and Practical Application:**

In the recent scientific studies done, there has been new information discovered on both macrophages and the human immune system as well. Just like the entire subject of science, what the world knows about the topic of immunity and immune mediators is ever changing. The information that was known even as few as ten years ago can be considered “outdated”. In collecting this research there were a few studies that stood out and could break new ground in these subjects.

The first of these subjects is that an article published in late 2019 that explores the role of macrophages in atherosclerosis regression. This research was conducted by Tessa J. Barrett in the cardiology department at New York University’s medical department. As a background, atherosclerosis is a cardiovascular disease that will encompass coronary artery disease, peripheral artery disease, cerebrovascular disease, and aortic atherosclerosis. The macrophages will contribute to maintaining the local inflammatory response of the cells, spread plaque development and will also act to promote thrombosis. These characteristics of macrophages make them a great option when attempting to stabilize existing atherosclerosis. There are multiple forms of macrophages (M1 and M2 macrophages) that are appealing for this type of therapy treatment for atherosclerosis. This treatment option is still being explored in medicine but has a very promising looking outcome for treatment. Anything having to do with the heart is of upmost importance, and having multiple treatment options means saving more lives in the long run.

Another important subject in science that has a lot of influence on the immune system is organ donation. Organ donation plays a major role in saving patients’ lives after trauma has occurred to the vital organs. Organs like the lungs, kidneys, liver, heart and many others are subjects that can be transplanted to others. The biggest threat though to these organs is the immune system of the person who is receiving them. If the organ is not technically “of themselves” the immune system will not recognize it as its own and instead of using it will eventually reject the organ and start to attack it with the immune response. Transplant immunology explores this topic of rejection, and provides great understanding of how to notice rejection and correct it as well. Many measures are taken to prevent rejection, but in the body it is simply taken as either self or non-self. The receptors that decide to trigger or not trigger an immune response are the human leukocyte antigen (or HLA) complex. These proteins can be seen on the surface of cells and will act as “self-markers” for the immune system response. Every individual has different HLA proteins, making it hard for transplant organs to be recognized as self. This is why when matching tissue, the HLA antigens must be compared and the closer that they are the more chance of recognition. The immune system makes many different decisions twenty-four hours a day, protecting the organism as a whole from its own environment. The macrophages play a huge role, but also need the support of other aspects of the immune system.

Our immune system will continue to be explored as long as individuals continue to become sick, and that is seemingly never going to go away. Since sickness is inevitable scientist and doctors will continue to research our immune system and its important components like macrophages that were focused on during this chapter. This means that the world of the immune system and its own immune response will be ever-changing, but hopefully all of these discoveries and studies will better the understanding of how sicknesses work and what is best to combat them. Sometimes, invisible enemies are the ones that society has to look out for most and biological warfare is a real threat. Those who use and also respond to this type must also comprehend the effects certain bacteria or viruses have on the human body. This again is an important role of immunology today, tomorrow and forever into the future.

Citations:

Barrett, Tessa J. “Macrophages in Atherosclerosis Regression.” Arteriosclerosis, Thrombosis, and Vascular Biology, 14 Nov. 2019, [www.ahajournals.org/doi/full/10.1161/ATVBAHA.119.312802](http://www.ahajournals.org/doi/full/10.1161/ATVBAHA.119.312802).

“Conjunctivitis.” Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 4 Jan. 2019, [www.cdc.gov/conjunctivitis/about/treatment.html](http://www.cdc.gov/conjunctivitis/about/treatment.html).

“Density-Gradient Centrifugation.” Royal Society of Chemistry, [www.rsc.org/publishing/journals/prospect/ontology.asp?id=CMO%3A0002017&amp;MSID=b603595g](http://www.rsc.org/publishing/journals/prospect/ontology.asp?id=CMO%3A0002017&amp;MSID=b603595g).

Hirayama, Daisuke, et al. “The Phagocytic Function of Macrophage-Enforcing Innate Immunity and Tissue Homeostasis.” International Journal of Molecular Sciences, MDPI, 29 Dec. 2017, [www.ncbi.nlm.nih.gov/pmc/articles/PMC5796042/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5796042/).

Lutter, Erica. “Lecture Notes.” MICRO 4053. Class, 2020, Stillwater, Oklahoma State University.

“The Nobel Prize in Physiology or Medicine 1908.” NobelPrize.org, [www.nobelprize.org/prizes/medicine/1908/mechnikov/biographical/](http://www.nobelprize.org/prizes/medicine/1908/mechnikov/biographical/).

“Overview of Immunology.” Cell Signaling Technology, [www.cellsignal.com/contents/\_/overview-of-immunology/overview-of-immunology](http://www.cellsignal.com/contents/_/overview-of-immunology/overview-of-immunology).

“Septic Arthritis.” Mayo Clinic, Mayo Foundation for Medical Education and Research, 1 Dec. 2018, [www.mayoclinic.org/diseases-conditions/bone-and-joint-infections/symptoms-causes/syc-20350755](http://www.mayoclinic.org/diseases-conditions/bone-and-joint-infections/symptoms-causes/syc-20350755).

Shibata, Yasuo, et al. Macrophage Membrane: Structure and Function. Springer Science and Business Media. <https://page-one.springer.com/pdf/preview/10.1007/978-1-4757-9531-8_8>

“Transplant Immunology.” | British Society for Immunology, [www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/transplant-immunology](http://www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/transplant-immunology).