MECHANISMS OF PARASITE IMMUNE-MODULATION AND EVASION

by

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ABSTRACT

A parasite is an organism that depends on another organism, its host, for food and shelter. In this parasite-host relationship, a parasite gains benefits from its host while the host may suffer from diseases. The stress put on the decreased resources available to the host can affect its growth, reproduction, and survival. This stress can sometimes lead to the host's premature death. Parasites, and the diseases they cause and transmit, have been responsible for tremendous human suffering and loss of life throughout history. It is known that in parasite-host interactions, parasites manipulate the host's immune system. In an effort to survive and replicate, parasites have evolved multiple mechanisms to counteract or evade the immune system of the host. In this project we will identify and describe the specific ways parasites manipulate the host's immune system. An extensive review of the primary literature will be performed. At the end of this project, a review paper that summarizes the literature will be generated.

I. INTRODUCTION TO PARASITES

What is a Parasite?

The word parasite comes from the Greek word *parásitos* which literally means "one who eats at the table of another" (Online Etymology Dictionary). From this description it is clear parasites cannot fulfill their nutrient requirements themselves. Parasites are eukaryotic organisms that depend on another organism in order to survive (Combes, 1997). Parasites are unable to grow and reproduce on their own but rather utilize the nutrients from their host. Parasites that require the host in order to complete their life cycle are called obligate. Parasites that can survive on their own but can take advantage of a host when they encounter one are called facultative (Combes, 1997). Often the parasite is detrimental to the host and causes them damage such as mechanical damage (mosquito bites) or chemical damage such as nutrient depletion in pregnant mothers (Weeks, 2018). Despite the damage to the host, parasitism is an effective way of living. It is estimated that of all organism characterized so far 40% are parasitic, and the other 60% are free living organisms, this means there are about 2,400,000 known species of parasites in the world (Avise, 2008). Parasites are ancient organisms that have depended on other organisms throughout time. This lifestyle means that parasites must have resided on and within ancient organisms before vertebrate even evolved. Parasites have survived in a variety of hosts and for so long that they possess more diversity than we see in them today (Sibley, 2011). Parasites often use humans as hosts. Parasites have caused numerous illnesses throughout human history ranging from a mere annoyance such as head lice to life threatening like *Trypanosoma brucei rhodesiense*. This review will focus on human parasites and their interaction with the human host.

Types of Parasites

Parasites can be divided by whether they reside inside or outside the body of the host. Ectoparasites are those on the outside of the host such as mosquitoes or bed bugs and endoparasites are those that live inside their hosts. Endoparasites can be further divided as to whether their habitat is inside the cells of their host organism or more generally in the body tissues outside the cells. Intracellular parasites are those residing within the cells of parasites such as *Plamsodium spp* the parasite that causes malaria and extracellular parasites such as *Giardia duodenalis*. Helminths is a term used to describe parasites that are commonly known as worms, these are often endoparasites that reside within the body such as in the gastrointestinal system.

Intracellular

Intracellular parasites are parasites that are capable of growing and reproducing inside the cells of a host (Sibley, 2011). Being intracellular gives the parasite many advantages, most importantly, potentially hiding from immune response (Sibley, 2011).

An example of an intracellular parasite is *Toxoplasma gondii* which causes toxoplasmosis and has the potential to cause encephalitis in immunocompromised individuals (Yarovinsky, 2014). It's estimated that 30% of the world's population is infected with the *Toxoplasma gondii* but infection in healthy individuals is often asymptomatic (Schlüter, 2014). In the human host, *T. gondii* can invade many different cell types including muscle and nerve cells ((Yarovinsky, 2014).

Leishmania spp is another intracellular parasite that is transmitted by sandflies and infects macrophages of the human host. In the macrophage the parasite survives and reproduces inside the human host. *Leishmania spp* causes the disease leishmaniasis which leads to ulcers on the skin of the host but can also damage the cutaneous and subcutaneous tissues in more serious infections (Alamilla-Fonseca, 2018). *Leishmanis spp* can also cause a visceral infection which is often fatal (Sibley, 2011). Leishmaniasis is an ancient disease that has been documented in writings by Spanish missionaries and documented by sculptors in the 5th century (Manson-Bahr, 1996).

Perhaps the master of all intracellular parasites is *Plasmodium falciparum*. The intracellular parasite that causes malaria in humans. Malaria is probably one of the most well-known parasitic diseases. To complete its life cycle, *P. falciparum* utilizes the *Anopholes* mosquito as its intermediate host. Malaria causes 429,000 deaths annually, usually in children under the age of five. Malaria is the deadliest of all parasitic diseases (Brancucci, 2017). In the human host, *P. falciparum* invades hepatocytes (liver cells) and emerges in a new form capable of invading red blood cells. It is during the erythrocytic state that the human host will experience the symptoms associated with malaria, such as cyclic fevers, tiredness, vomiting, and headaches (Carabello, 2014).

Extracellular

Extracellular parasites are parasites that live within their hosts. Unlike intracellular parasites, extracellular parasites do not invade cells, instead, these parasites reside in the blood stream or in the lumen of different human organs (Halliez, 2013). Existing within the host provides shelter and provides nutrients readily available from surfaces like the intestines.

Giardia duodenalis is an extracellular parasite that causes the disease giardiasis which causes gastroenteritis and fatty diarrhea in humans, and affects both the developing and developed worlds (Spotin, 2018). Giardiasis is often passed through non filtered drinking water (Prystajecky, 2015) by the ingestion of infected cysts or the fecal oral route. In the host, the cyst releases trophozites which then stick to the epithelial surface of the intestine. At this point, they are growing and extracting nutrients from the host's digestive process. This leads to malabsorption in humans and can lead to absorptive cells in the intestinal lining, enterocytes, to commit apoptosis due to the lack of nutrients (Halliez, 2013). This poses a problem to children who get this disease because their growth and development will be stunted if the parasite is not properly treated.

Trypanosoma brucei rhodesiense, the parasite responsible for African trypanosomiasis, or sleeping sickness is also extracellular (Lamour, 2017). This parasite causes a number of symptoms including anemia, wasting and lethargy, and is one of the few parasites that can pass the blood-brain barrier leading to coma and death. *Trypanosoma brucei rhodesiense* is transmitted by tsete fly to humans. The parasite spreads to its human host when the fly feeds and enters the human lymphatic system. The parasite then moves to the bloodstream where they multiply and mature. The mature forms of *Trypanosoma brucei rhodesiense* are able to move into the blood vessel endothelium and extravascular tissues, like the central nervous system (Kato, 2017).

Intracellular and Extracellular

Some parasites fluctuate between being intracellular and extracellular. Such a parasite is *Trypanosoma cruzi.* The parasite *Trypanosoma cruzi* causes Chagas disease. Chagas disease presents with the symptoms of swollen bites, swollen lymph nodes, and headaches. This disease is passed by the feces of the bug, hematophagous triatomines, which is commonly called the kissing bug because it tends to bite the face and lips of humans and drink the hosts blood (Ribeiro, 2013). The disease infects a new host when the kissing bug's feces are then rubbed into a bite. This disease has two phases, an acute phase where the parasite is present in the bloodstream of the host and a chronic phase where the parasite can impede the cardiovascular system of the host. The parasite is both extracellular and intracellular, with some early developmental stages found in the bloodstream and later stages replicating in the macrophages and muscle cells of its human host (Carabarin-Lima, 2013).

Ectoparasites

Ectoparasites are parasites that live on but not within their hosts such as attached to their skin. These include the more common parasites such as head lice and mosquitoes (Ghandali, 2017). Ectoparasites have adapted to spread from host to host and thus live on surfaces such as the head that are directly in contact with the outside environment. Some ectoparasites can burrow in the host's skin and remain there for weeks or months. Others come and go, and use the human host as a source of food, particularly blood (Della Torre, 2017) . While parasites in their own right, ectoparasites can lead to more serious illnesses as they can harbor other parasites and serve as a vector for them. Many ectoparasites, are intermediate hosts for other parasites. Ectoparasites can carry bacteria, viruses, as well as parasites already described here such as *Plasmodiun falciparum* and *Leishmania spp* (Ghandali, 2017).

An example of a common ectoparasite is the head louse *Pediculus humanus capitis,* which lives on the surface of the human scalp and feeds on the blood of the underlying tissue (Al-Sharani, 2017). Six to twelve million people are infected with lice every year, particularly children aged 3-12 (Epidemiology & Risk Factors). The parasite itself is a 6-legged, blood sucking, wingless insect that lives on human scalp (Della Torre, 2017). The female head lice lay its eggs on the hair shaft where they can hatch and feed on the blood of the host that lays under the scalp. Symptoms of head lice are minor and include itching and loss of sleep from the irritation these bugs cause (Ghandali, 2017). Despite terrorizing school grounds and childcare facilities, head lice do not serve as vectors for other diseases (Al-Sharani, 2017). That is the role of the body lice, *Pediculus humanus humanus*. Body lice diverted from human lice presumably at the onset of human clothing some 100,0000 years ago (Kittler, 2003). The body lice can serve as a vector for deadly diseases such as endemic typhus, relapsing fever, trench fever (Bonilla, 2017).

Cimex lectularius is the common bed bug Bed bugs climb onto their human hosts (Hinson, 2017) and feed on their blood (Zha, 2017) at night while the host is sleeping and unaware. Bed bug's bites can cause itchiness and a rash (Goddard, 2012). Although not vectors of disease, bed bugs stigmatize those afflicted and often isolate them from society (Hinson, 2017).

Perhaps the most important ectoparasite of humans is the mosquito. Mosquitoes belong to the family Culicidae which pierce the skin of their hosts and consume their blood. Considered to be the deadliest animal of humans, mosquitoes serve as a vector for many parasitic diseases. Mosquito-borne disease kill over 700, 000 humans annually (Gatenotes, 2014). Mosquitoes are often found in more humid, tropical climates though global warming threatens to extend the mosquitoes habitat, and with it the spread of more parasitic disease (How the Mosquito Spreads Disease, 2017).

Helminths

Helminths infect billions of people each year (Palmas, 2003). Adult worms can survive 1 to 30 years in the human body (Jirillo, 2014). It is estimated that there are between 75,000 and 300,000 helminth species that use vertebrates as hosts. Relatively about 3.125-12.5% of parasites are helminths (Avise, 2008). Most helminths are gastrointestinal and extracellular. Helminths cause disease that can lead to premature mortality and morbidity and is particularly detrimental to pregnant mothers (Ritler, 2017).

The species *Trichnella spiralis* is the smallest human helminth and causes the disease trichinosis which leads to diarrhea, abdominal pain, and vomiting (Brodaczewska, 2017). *Trichnella spiralis* is an intracellular, microscopic parasite. *Trichnella spiralis* has adapted in order to survive in the harsh, acidic conditions of the gastrointestinal tract and never leaves its host (The life cycle of Trichnella spiralis, the parasite which causes trichinosis, 2017). Humans become infected with *T. spiralis* by eating pork infected with the encysted larvae, it's hypothesized that this might have had something to do with the Mosaic and Islamic traditions of avoiding pork (Bundy, 1996).

In contrast to *T. spiralis,* members of the class Cestoda can be as large as 50 feet. Commonly known as tapeworms, *Taenia solium* and *Taenia saginata* (pork tapeworms and beef tapeworm, respectively) are cestodes that live in the digestive tracts on the small intestine of their hosts and cause mild symptoms such as diarrhea and vomiting to their human host. Cestoda attach to the small intestine of their hosts using their head, called the scolex, and absorb nutrients from the gastrointestinal tract (Ritler, 2017). Humans can be infected by consuming undercooked meat (Ritler, 2017).

Filiarial nematodes, such as *Wucheria bancrofti,* infect the lymph node of its host (Uni, 2017) and lead to lymphatic diseases in humans such as elephantitis. *Wucheria bancrofti* is a parasite that is transmitted by mosquitoes (Patwardhan, 2017). Larval filarial worms have adapted to reside in the peripheral blood to allow transmission to other hosts by their mosquito vector while the adult filarial worms live in the tissues below the skin (Patwardhan, 2017).

The large roundworm *Ascaris lumbricoides* is a member of the so called soil transmitted helminths (STHs). *A. lumbricoides* is a Nematode with a prevalence of approximately one billion people around the world (Cockburn, 1998). This parasite has existed since the time of Linnaeus himself and has been found in old Egyptian mummies dating back to 45 B.C (Cockburn, 1998). When an unsuspecting human consumes food contaminated with infected eggs, the larvae emerge in the intestine. These larvae circulate in the body where they reach the lungs. Here they are coughed up and re-swallowed by the host where they mature to adults in the host's intestine. The adults lay eggs in the intestine which are excreted in feces and ready to begin the process again when deposited in the environment (Cockburn, 1998). Surprisingly, this helminth infection is mostly asymptomatic (Cockburn, 1998).

II. THE HUMAN HOST

Human body as the parasite's environment

Human parasites will reside on or within the human host. However, the human body has mechanisms to protect against such invasion. This section will concern the immune system of a healthy human host and the branches and components that it consists of. The human immune system operates to defend the human host from attack due to the infection of foreign bodies (Beutler, 2004). These foreign bodies are organisms such as viruses, bacteria, and pathogens that include parasites as well as allergens that the host may not be able to tolerate such as peanuts or pollen (Koudon, 2011). In a healthy host and in the absence of parasite modulation of the immune response, the immune system acts quickly to allow the host to survive in an environment filled with potential hazards such as viruses, bacteria, and parasites. In this section, we will take a look at the two branches in the tree of the immune system, adaptive and innate, and the various components present in both that allow them to carry out their functions of protecting the body and eliminating foreign objects and organisms. These components of the innate and adaptive immune systems work together cohesively like intertwining branches. They are not separate and aid and assist each other – a common theme we will see throughout this section. The first step in immune response is to detect the foreign body. Then the host will mount its immune response. This can be categorized as either adaptive or innate. Following the immune response, the immune system take measure to be on guard against re-infection. The innate response is the first response to detection of a pathogen or foreign body and is nonspecific (Mahla, 2013). Next, the adaptive immune response will take over to ensure long lasting immunity. The innate and adaptive immune systems are made up of cellular components and humoral components. Cellular components are cells that act to decrease and eliminate pathogens. Immune cells are carried in lymphatic vessels. These vessels join together in the lymph nodes of the body. These lymph nodes tend to become swollen during an infection due the increased amount of immune cells during an infection (Loo, 2017). Humoral components of the immune system are molecules that circulate through the body in extracellular fluids like lymph nodes and blood stream to combat infection such as antibodies and complement proteins. Cellular and humoral components work together to ensure total elimination of the pathogen. The adaptive immune response is more long term and retains the memory of previous infections. The adaptive immune system is also specific and able to customize its attack to an individual pathogen. With further infection, memory B cells and memory T cells will be able to more effectively take care of the pathogen (Restifo, 2013). In this section we will take a closer look at the innate and adaptive branches of the immune system and their components.

Innate Immune System

When the host is infected by a pathogen or detects a foreign body inside, it enacts the innate immune response. The innate immune system is the first line of defense when the host is infected by a pathogen and thus serves to quickly and efficiently take care of an infection while alerting the adaptive immune system for long term protection (Beutler, 2004). In this first section we will look at the innate branch of the immune response and its various components. The innate immune system is nonspecific and reacts to each pathogen or anything detected as non-self in the same way. It doesn't have memory and thus isn't able to detect a repeat infection (Kawai, 2007). The innate immune response is important to the well-being of the host because it quickly identifies and eliminates a foreign body or pathogen. This immediate reaction is crucial to ensuring the pathogen doesn't cause irreversible or especially detrimental damage to the host or replicate further causing an extensive infection. The first step in the innate immune response is detection of the foreign body or pathogen and Pattern Recognition Receptors serve to do this.

Pattern Recognition Receptors

The first step that needs to happen when the host is infected with a foreign body or pathogen is detection of the foreign body or pathogen. Pattern Recognition Receptor's (PRR's) serve to identify self from non-self for the host and alert the body to a foreign body or pathogen. PRR's thus detect the non-self-object and alert the immune response. PRR's are important because they serve as the crucial first step that begins the entire immune system's response. Pattern Recognition Receptors are surface proteins that are expressed on the cells of the innate immune system such as dendritic cells, macrophages, monocytes, and neutrophils (Mahla, 2013). Different immune cells express different PRR's and are specialized to detect different Pathogen associated molecular patterns (PAMP's) and damage associated molecular patterns (DAMP's). PAMP's are a common component of pathogens that invade the human host such as its genetic material. DAMP's are related to signals released from the host by damage caused by the pathogens (Kawai,2007). Pattern Recognition Receptors can present on the membrane surface of the cell such as Toll-like Receptors (TLR). TLRs are able to detect a wide variety of invading pathogens by recognizing pathogen-associated molecular patterns (PAMPs) (Zheng, 2017). PAMP's that TLR's can detect include the lipopolysaccharide (LPS) layer of bacteria, double stranded RNA of viruses, as well as surface proteins of most pathogens (Fukata, 2013). When TLRs recognize their particular ligand, they form dimers with another TLR and initiate a signaling pathway that will lead to beginning of an innate immune response (Fukata, 2013).

Cytokines

After pathogen recognition by PRRs release of cytokines is a crucial second step for alerting and kick-starting the innate immune response. Cytokines are a group of signaling proteins that are created and released by host cells in response to the presence of pathogens (Horst, 2013). As molecules, cytokines are a humoral component of the innate immune system. Cytokines also serve to alert neighboring cells to infection (Chokkalingam, 2013). This allows connection of the cells in the body; if one cell is infected, then others can come in to help out. The infected cell won't have to deal with the infection alone. The neighboring cells can also then heighten their protection as they know there is potential infection present nearby in the host's body. Cytokines also activate immune cells, such as natural killer cells and macrophages. By activating other immune cells, cytokines kick-start the host's defense against pathogens (Chokkalingam, 2013). Cytokines released in response to PRR activation include interleukins (IL)-1, IL-6, and IL-8, along with tumor necrosis factor (TNF)-alpha. Together, these cytokines are associated with the classic inflammation response of pain, heat, redness, and swelling (Dinarello, 2018). If not regulated, cytokines can also have detrimental effects and play a strong role in disease. Interleukin-8 or IL-8 increases the cell division and growth of tumors and is expressed in cancer cells (Elhefny, 2017). The potential of eliciting damage by pro-inflammatory cytokines is counteracted by anti-inflammatory cytokines. Cytokines such as IL-4, IL-10, IL-13, and transforming growth factor (TGF)-beta suppress the intensity of the inflammatory response (Dinarello, 2018). Therefore, the type of cytokine and how long the cytokine is released in response to a particular pathogen will have an important role in determining pathogenicity.

Histamine

The innate immune response serves to quickly and non-specifically eliminate pathogens. As we've seen above the first steps include identification of the pathogen and alerting the other components of the immune system to the infection. In order for the innate immune response to properly function, the various components of the immune system need to be properly directed to the site of infection. Histamine is a humoral component of the innate immune system and is an organic nitrogenous compound that does just that. Histamine is produced by cells of the innate immune response such as basophils and mast cells in nearby infected tissues and spreads through the tissue (Nieto-Alamilla, 2016). Thus, the components of innate immune system collaborate in order to eliminate the pathogen from all angles. This collaboration and interaction allows the immune system to coordinate its response to a pathogen ensuring its removal from the host. Histamine serves to create inflammation in the host leading to increased permeability or vasodilation of capillaries to leukocytes (Anderson, 2015) which will be discussed later in this section. This increased permeability of capillaries facilitates movement of these leukocytes to the site of infection and allows them to eliminate the pathogen. Thus, we see the interaction between components of the innate immune system. The inflammation created by histamine, a humoral component of the innate immune system, and the accompanying vasodilation aids the

cellular component of the innate immune system, the leukocytes that move into the region of infection in order to phagocytose or eliminate the pathogen. This cooperation is important to the immune response because the other components of the innate system need to be accurately directed to the site of infection if they will be able to quickly eliminate the pathogen or foreign body.

Complement System

Another component of the innate immune system is the complement system. We've seen the process so far of the immune system in response to infection; identification of the foreign body, alerting the rest of the immune system, and direction of immune system components to the site of infection. Next comes marking the pathogen for destruction. The complement system is important because it marks the pathogen and makes it easier for the cellular components and humoral components of the innate immune system to eliminate the pathogen (Degn, 2013). Thus, the job for other components of the immune system such as phagocytes and assembly of the membrane attack complex are made easier by the complement system labelling the pathogen. The complement system is another example of a humoral component of the innate immune system. The complement system works with antibodies and complement proteins that bind to sugars on the outside of invading pathogens (Noris, 2013). This binding triggers the activation of other complement molecules that are proteases. This in turn activates more proteases and turns on peptides that activate the recruitment of immune cells to the marked invading pathogen. Proteases serve to degrade or "chew up" the proteins of the pathogen (Noris, 2013). Results of complement activation include phagocytosis of the pathogen, inflammation to attract more cells to the site which is created by histamine as discussed in the previous section, and assembly of a membrane attack complex of cells. These cells increase the permeability of blood vessels and interfere with the plasma membrane of the invading pathogen (Degn, 2013). Phagocytosis includes leukocytes that "swallow" the pathogen while inflammation caused by released cytokines serves to direct more immune cells to the site of infection. There are three pathways to the complement system in the innate immune system, the classical pathway, the alternative pathway, and the lectin pathway.

- Classical Pathway - The complement classical pathway is begun by the activation of the C1 complex and serves to recruit cellular components of the immune system in order to target pathogens and foreign bodies. C1 is the complement protein and a humoral component of the innate immune system. The C1 complement complex includes the C1 protein, and the antibodies IgM or IgG that are complexed with antigens (Noris, 2013). The classical pathway involves components of the innate such as complement and adaptive immune systems such as antibodies and antigens. Thus it's easy to see that the two sides of the immune system work together to ensure a comprehensive and efficient immune response. Activation of the C1 Complement Complex occurs when C1 binds directly to the surface of the pathogen (Noris, 2013). This binding leads to conformational changes which are changes in shape in the C1 molecule. This shape

change of C1 then leads to the activation of two C1r molecules (Zhang, 2007). C1r molecules are serine proteases which means they chew up proteins. The C1r proteases then cleave C1s which is another serine protease. These cleaved proteins come together to create C3 Convertase (Vignesh, 2017). C3 Convertase then cleaves the C3 complement protein (Noris, 2013). Part of the cleaved C3 complement protein then binds to C3 Convertase to generate C5 Convertase, which next cleaves the C5 complement protein. The cleaved products of C5 and C3 attract phagocytes to the site of infection and tags target cells for elimination by phagocytosis. In addition, the C5 convertase leads to the assembly of the membrane attack complex (Vignesh, 2017). The membrane attack complex creates a pore on the target cell's membrane, causing cell lysis and death. Thus, the complement system serves to trigger cellular components of the immune response such as phagocytes and eliminate the pathogen by phagocytosis or through the Membrane Attack Complex.

•Alternate Complement Pathway – The alternate complement pathway differs from the classical pathway in that it begins in the blood plasma specifically. The alternative pathway also utilizes different complement proteins such as C9 and does not use C1. It does however, lead to activation of the membrane attack complex and recruitment of phagocytes like in the classical pathway. The alternate complement pathway is triggered when the complement C3 protein binds a microbe. This pathway can also be started by foreign materials and damaged tissues (McHarg, 2015). The first step is the spontaneous hydrolysis of C3, which is numerous in blood plasma. The change in shape after hydrolysis allows the binding of plasma protein Factor B, which allows Factor D to cleave Factor B. This complex is also known as a fluid phase C3 – convertase. This convertase is made in small amounts but can cleave multiple C3 proteins (McRae, 2005). The complex is unstable until it binds to properdin, which is a serum protein. The addition of properdin makes the complex stable. This stable complex then binds an extra cleaved C3 to form alternative pathway C5-convertase. The C5-convertase cleaves C5 which then binds to C6, C7, C8 and multiple molecules of C9 to form the membrane attack complex (Grossman, 2015).

•Lectin Pathway - The lectin pathway is very similar to the classical pathway, but utilizes mannose binding lectin instead of C1 for initiation of the pathway. The Lectin pathway is activated by binding of the mannose binding lectin (MBL) to mannose residues on the surface of a pathogen (Degn, 2009). This binding activates MBL-associated serine proteases called MASP-1, and MASP-2 which cleave complement proteins C4 and C2. Cleaved portions of C4 and C2 then bind together to form the C3-convertase, which is seen in the classical and alternate pathways (Wallis, 2010). C3 Convertase cleaves C3 and cleaved C3 binds to the Convertase to create C5 convertase which then cleaves C5 which then attracts phagocytes with cleaved C3. The C5 Convertase then serves to help with the assembly of the membrane attack complex which then eliminates pathogens by creating pores in them.

Cells of the Innate Immune Response

Cells of the innate immune system have multiple roles. These different cells can be seen in figure 1 below along with their respective functions. We've seen the innate system identify pathogens, alert the rest of the immune system to their presence, and direct the other components to the site of infection along with marking the pathogen. The cells of the innate immune system compose the final step of the innate immune response – elimination of the pathogen. Cells of the innate immune response are crucial because they carry out the final and most important step of the innate response, elimination of the pathogen. The whole goal of the innate immune system is quick and efficient elimination of a foreign body or pathogen and the cellular component does just that. Further, the cells of the innate immune system serve to alert the adaptive immune system of infection ensuring the pathogen will be taken care of long term via its "memory" which is one of adaptive system's main goals (Purcell, 2016). Thus as the final step of the innate immune system the cellular component initiates action of the adaptive immune system for the second leg of combating foreign bodies and pathogens.

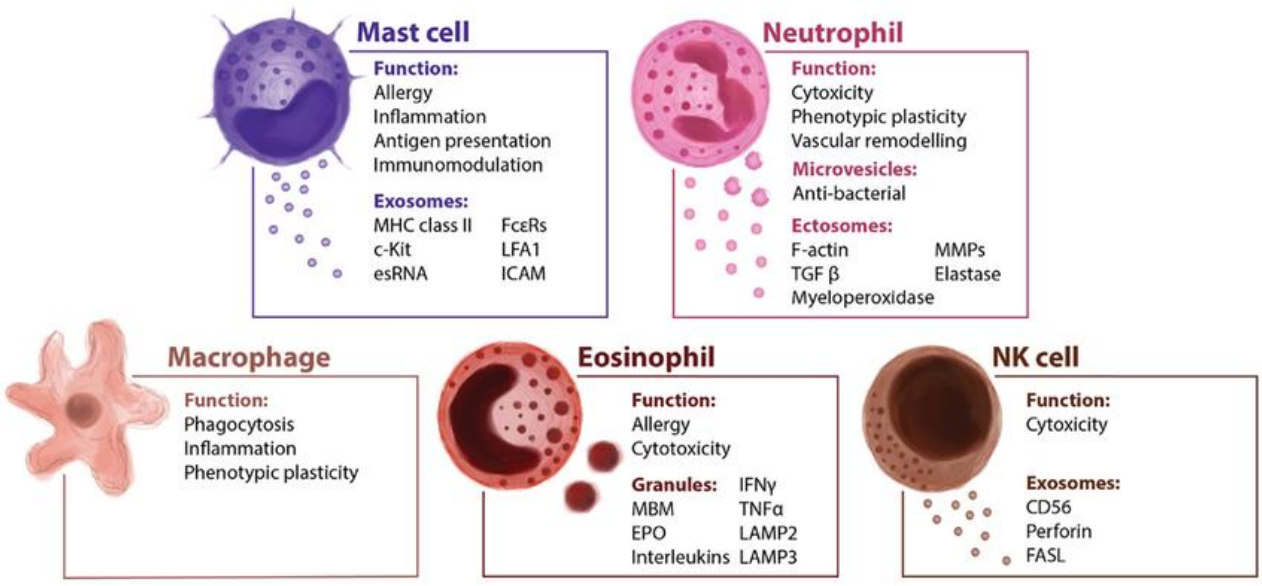

Figure 1: The various cells involved in the innate immune response. Benito-Martin, Alberto & Giannatale, Angela & Ceder, Sophia & Peinado, Hector. (2015). The New Deal: A Potential Role for Secreted Vesicles in Innate Immunity and Tumor Progression. Frontiers in immunology. 6. 66. 10.3389/fimmu.2015.00066. .

Pro – Inflammatory Cells

Neutrophils are normally found in the blood and they consist of 50% to 60% of the total circulating leukocytes (Stvrtinová, 1995). During inflammation, neutrophils are drawn toward the site of inflammation in a process called chemotaxis. This means the neutrophils are drawn to the high concentration of cytokines in the infected location. Thus we see the collaboration between components of the immune system yet again, a common theme throughout the immune response. Chemotaxis is very effective because as the first line of defense of the innate immune system, as it's important for neutrophils to be right at the center of the infection. Neutrophils are drawn to the inflammation by cytokines and are usually the first cells to arrive at the scene of infection (de Oliveira, 2016). Neutrophils are important because they are the first cells to combat an infection. If they properly take care of the foreign body or pathogen, then the rest of the immune response will be easier and put under less pressure. It's also likely that less damage will be done and the pathogen won't have time to replicate and cause an extensive infection. Neutrophils eliminate pathogens with an extracellular mechanism that releases neutrophil extracellular traps (NETs) in a process known as NETosis. NET's include a respiratory burst which is characterized by high levels of oxidative stress created by elevated NADPH oxidase activity. This oxidative stress can lead to inflammation. Other components of NET's include a decondensation of chromatin caused by histone modification and NET's are directed in the increasing concentration of inflammation and cytokines (Arumugam, 2018). NET's are effective because they hinder the DNA of pathogens preventing them from replicating and furthering replication while also creating oxidative stress which destroys the pathogens all together. Thus, Neutrophils are a powerful component of the innate immune system and target foreign bodies and the first to target foreign bodies and pathogens.

Phagocytic Cells

Leukocytes make up the majority of the cellular component of the innate immune system (Purcell, 2016). Leukocytes are white blood cells that act independently to attack foreign bodies. All leukocytes are derived from stem cells in bone marrow called hematopoietic stem cells (Purcell, 2016). Leukocytes are found circulating throughout the body in the bloodstream and lymphatic system. Thus, leukocytes circulate and monitor for foreign bodies. Should they encounter one, they spring into action and take out the pathogen. They also serve to alert the adaptive immune system of pathogens. Leukocytes include phagocytes such as macrophages, neutrophils, dendritic cells, and eosinophils. These cells operate in various areas of the body in order to destroy pathogens (Withers, 2016). Leukocytes like dendritic cells and macrophages also play a role in activating the adaptive immune system and connect the two divisions of the immune system, the adaptive and innate systems, in response to a pathogen. Leukocytes present fragments of the phagocytosed pathogen to cells of the adaptive immune system activating them and prompting them to take action (Purcell, 2016). When the human host is infected, levels of leukocytes are elevated. The normal level is about 1% of the blood volume in a healthy adult

(Vital and Health Statistics Series, 2005). This makes sense because as a component of the innate immune system, leukocytes will immediately be in action and replicate in response to infection and try to fight the pathogen.

Phagocytes destroy pathogens by engulfing the pathogen completely, almost like the cell is eating the pathogen in a process called phagocytosis (Withers, 2016). Phagocytes usually monitor the body searching for pathogens, but can be drawn to specific locations by cytokines which are released by damaged cells. Thus, we see cytokines, a humoral component of the innate system, aiding the cellular component of the innate system in order to make its job quicker and easier. Once a pathogen has been engulfed by a phagocyte, it becomes trapped in an intracellular vesicle called a phagosome. This phagosome then fuses with the lysosome to form a phagolysosome. The lysosome of cells is the organelle that has a low pH and destroys molecules with hydrolytic enzymes (Mindell, 2012). The pathogen is killed by the activity of digestive enzymes or following a release of free radicals into the phagolysosome. Neutrophils and macrophages which will be discussed below are phagocytes that move through the body searching for invading pathogens.

Macrophages are cells that reside within tissues and produce a wide array of molecules such as enzymes, complement proteins, and cytokines. Macrophages can also act as scavengers that eliminate old cells and other debris. Macrophages and other phagocytes phagocytose pathogens and then present the broken up pieces in order to activate the adaptive immune system (Rua, 2015). Thus, these cells serve to connect the innate and adaptive immune systems in the host to best manage an infection or foreign body inside the host.

Cells with Connection to Adaptive Immune System

Dendritic cells are phagocytes in tissues that are in contact with the external environment like skin, nose, lungs, stomach, and intestines. Dendritic cells serve as the connection between the innate and adaptive immune systems, as they present antigens to T cells, one of the key cell types of the adaptive immune system (Guermonprez, 2002). Dendritic cells are important in order to alert the adaptive immune system of an infection and trigger it into action. Without dendritic cells, only the innate immune system would respond to pathogens and the adaptive system wouldn't be activated in order to provide long term and specific immunity for the host.

Natural Killer Cells (NKCs) are a type of lymphocyte and a cellular component of the innate immune system. Natural killer cells don't attack the invading pathogen directly but rather eliminate cells of the host that may have been compromised during the course of infection (Gabrielli, 2016). Natural killer cells can identify infected cells by the makeup of their exteriors. All cells have a marker on their surface called Major Histocompatibility Complex 1 (MCH1). Invading pathogens have the potential to alter or decrease the expression of these MHC molecules. The natural killer cells are programmed to kill cells that don't have normal MHC expression. They leave intact cells with normal levels of MHC expression. Natural Killer Cells have a receptor called the Killer Cell Immunoglobulin Receptor which they use to attach to the MHC

antigen (Rajalingam, 2016). NKCs are important because they account for pathogen modulation of the immune response. A cell that doesn't express MHC is out of place and if the NKC didn't kill this cell, it would remain undetected allowing the pathogen to wreak havoc on the cell and host.

Adaptive Immune System

In this section, we will look at the second branch of the human immune system the adaptive immune system. The innate system as discussed above provided for quick and non-specific elimination of the pathogen. Next, the adaptive immune system will come in to target specific pathogens and retain knowledge of previous infections. The adaptive immune response is characterized by an immunological "memory" meaning that the immune system will remember a pathogen that has previously infected it and will be able to mount a quicker and better response the second time around (Purcell, 2016). Memory T cells and B cells with antibodies serve to remember pathogens and mount a more efficient response the second time a pathogen emerges (Weinstein, 2012). T cells once activated also then activate B cells to ensure the pathogen is taken care of and remembered by the host immune system (Casane, 2016). This also exhibits the collaboration between different components of the adaptive immune system in responding to a pathogen. The adaptive immune system is also specific via the antigen – antibody system and can recognize a pathogen if it were to re-appear (Casane, 2016). While it takes longer to react to initial infection, the adaptive immune system thus serves to protect the human host against further infection and endure long term immunity against pathogens. The adaptive immune system thus differs from the innate immune system discussed above in that it is able to remember a pathogen that the host was previously infected with and customize its immune response to that pathogen. This type of reaction is slower than that of the innate immune response but the phrase "slow but steady wins the race comes to mind". Despite being slower, the adaptive immune response efficiently targets specific pathogens and is specific so won't target other foreign bodies or host cells. The adaptive immune system works with the innate immune system to eliminate a pathogen and coordinate the immune response throughout the body in order to prevent against further detrimental infection from the same pathogen. The various components within the adaptive immune system also work together in order to eliminate the pathogen and target it immediately and protect the host from the pathogen long term. The first step of the adaptive immune system is loading of the antigens created in the innate response to MHC molecules to be displayed to the cellular components of the adaptive system.

Antigen Presentation

Antigen presentation is the first step that connects the innate response with the adaptive immune response. This process starts with the generation of antigens during the innate response through phagocytosis. Now, we will see the adaptive immune system take over and utilize these antigens. Antigens are important to the adaptive response because they are what elicit a- specific

immune response in the adaptive immune system. Antigens are expressed on the outside of host cells and pathogens. When a pathogen infects the host, the host cells can present fragments of the pathogen's proteins as antigens on the outside of their cells on MHC molecules in a process called antigen presentation (Purcell, 2016). During the innate immune response, phagocytic cells such as macrophages phagocytose pathogens in order to eliminate them. The remaining peptide antigens from these pathogens that have been phagocytosed are saved for presentation with major histocompatibility complex (MHC) class I or class II molecules. These antigens are attached to their MHC molecule on the antigen presenting cell in order to present to antigen-specific T cells (Mantegazza, 2013). The adaptive immune response is thus able to remember previous infections due to antigens and antigen presentation with MHC to T cells. Processing and presentation of antigens from phagosomes of innate immune serves to allow immune cells to be aware of infections from previous pathogens and customize the immune response. Antigens which are bound to their respective MHC receptor are then recognized by T cells (Purcell, 2016). MHC molecules are divided into two categories, MHC 1 and MHC 2. MHC 1 molecules present peptides that are from inside host cells present in their cytosol, while foreign peptides presented outside the host cell are endocytosed and presented on MHC 2. Figure 2 above shows the process involved in acquiring the antigen and presenting it to the outside of the cell. With the two types of MHC, antigens are able to be collected from within the cell and outside the cell in order to be displayed outside the cell. All cells with a nucleus in the human body express MHC 1 while only cells of the immune system express MHC 2 such as macrophages, B cells, and dendritic cells (Janeway, 2001). Each MHC molecule can present numerous different antigens. Next, we will look at the differences between the two routes of antigen presentation.

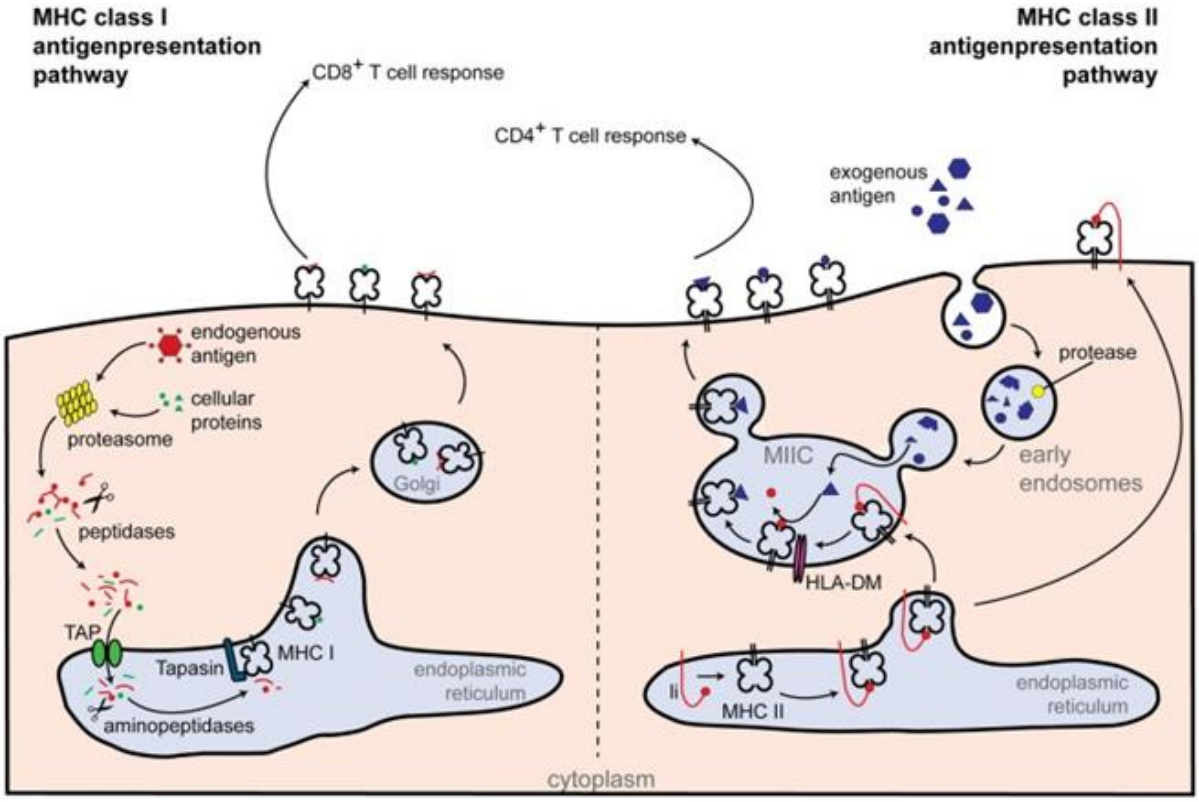

Figure 2 Comparison of MHC 1 and 2 antigen presentation and loading. Source: Neerincx, A., et al. "Nlrc5, at the Heart of Antigen Presentation." *Frontiers in Immunology* 4 (2013): 10. Print.

MHC 1

During the MHC 1 presentation process of antigens, foreign pathogen proteins from inside the host cell cytosol are degraded into small peptides by proteases in the host proteasome. This differs from MHC 2 where the peptides are outside the antigen presenting cell originally. Then, the peptides are sent to the endoplasmic reticulum by the transporter associated with antigen processing (TAP) which moves the cytosolic peptides into the ER. This requires the use of energy through ATP. Peptides are attached to MHC 1 molecules by binding to them. Then the peptide and MHC 1 complex exit the ER and are transported to the cell surface by exocytosis (Sei, 2015). Once on the exterior of cells, the antigen bound to the MHC 1 receptor can then be presented to CD8 T cells. CD8 T cells are called cytotoxic T cells and as the name implies they serve to kill any cell that presents the antigen from a pathogen (Guermonprez, 2002).

MHC 2

MHC 2 receptors are only expressed on the outside of antigen presenting cells such as macrophages, B cells, and dendritic cells as opposed to MHC 1 which were expressed on the outside of all nucleated cells. These immune cells that express MHC 2 were components of the innate immune system discussed above in the innate immune section and thus we see yet again how the innate and adaptive immune systems work together in order to detect and eliminate pathogens and foreign bodies. In antigen presentation process of MHC 2, foreign proteins are brought inside the host cell by endocytosis as opposed to beginning outside the cell like in MHC 1. Here the foreign proteins are inside endosomes. The endosomes go through three stages, early endosomes containing the foreign protein, endolysosomes where the endosome fuses with a lysosome, and finally lysosomes. In the lysosome there is a gradual decrease in pH where hydrolytic enzymes called cathespins break down the protein into peptides. In the ER the MHC 2 molecules are transported out to the Class 2 Loading Compartment where it meets the peptides and are attached. The Peptide-MHC-II complex is transported to the plasma membrane displayed to CD4 T cells. CD4 T cells are called helper T cells and release cytokines when they are activated (Stern, 2016). This serves as another point of connection between the adaptive and innate immune systems as T cells, a cellular component of the adaptive immune system, can activate production of cytokines, which are a humoral component of the innate immune system. The result of the MHC2 antigen and CD4 T cell interaction is to allow other cells to detect the infection and serve to recruit more immune cells to take care of the infection (Stern, 2016).

T Cells

T cells are a cellular component of the adaptive immune system and are activated once they are presented with an antigen bound to a MHC molecule on an antigen presenting cell (Purcell, 2016). The first step in the adaptive immune system was loading of antigens to MHC molecules.

Antigen presentation is discussed above and results from the presentation of fragments of peptides from pathogens that have been phagocytosed by cells of the innate immune system. T cells are important to the immune response because they both eliminate the pathogen directly with cytotoxic T cells and coordinate the immune response throughout the body with helper T cells that activate B cells as discussed in the next section and release cytokines to attract other immune cells as discussed in the innate immune system earlier (Purcell, 2016). Prior to being activated, T cells are called naïve T cells. Once they encounter their antigen and MHC receptor they are active and become mature T cells called effector T cells (Purcell, 2016). Thus, it's important that T cells are appropriately activated from their naïve state in order to customize the immune response once an antigen from a particular pathogen arises. This also seems to make the immune response more efficient in that there aren't excess and unnecessary cells floating around the body. These T cells then divide quickly. After infection, some T cells will remain and are called memory T cells because they are already activated and ready to go should the pathogen re-arise (Purcell, 2016). There are two types of T cells divided by what type of receptor they express on their exteriors. Cytotoxic T cells express a CD8 receptor and like the name implies, serve to kill other cells. These T cells circulate through the body and monitor for foreign pathogens. When they encounter an infected cell presenting an antigen they are activated and can kill those infected cells. First they multiply rapidly in order to have numerous cytotoxic T cells going after the pathogen (Sei, 2015). Cytotoxic T cells kill the infected cells through the release perforin and granulysin. These are compounds that form holes in the infected cells plasma membrane. This makes the cell burst because water and ions can flow into the cell. Cytotoxic T cells also release a protease called granzyme that enters infected cells via the holes created by perforin and granulysin and causes the cell to apoptose, or kill itself. Helper T cells express a CD4 receptor and serve to recruit other immune cells by releasing T cell cytokines (Stern, 2016) which are discussed above. Thus the title of helper is fitting because these cells coordinate the immune response and attract other immune cells. By releasing cytokines, they create the concentration gradient that alerts the other immune cells of the location of the infected cell. Helper T cells also help mature B cells into plasma B cells and memory B cells and activate other cytotoxic T cells and macrophages (Weinstein, 2012). Thus, the T cell component of the immune response works with humoral components of the adaptive immune system to activate them and alert innate immune cells of the infection. No one component of the immune system is isolated but rather all work together to ensure the pathogen is eliminated and ensure that future infection is dealt with quickly and efficiently. Next we will look at B cells and how antigens and T cells can further trigger activation of other cells in the adaptive immune system.

B Cells and Antibodies

B cells are another cellular component of the adaptive immune system. Once antigens are loaded to MHC in the first step of the adaptive immune system, T cells can be activated and then can either help to activate B cells or they can be independently activated allowing immunological

"memory" of the infection (Weinstein, 2012). B cells are responsible for creating antibodies which are a humoral component of the adaptive immune system (Weinstein, 2012). This is important to the adaptive immune system and the human host's immune system in general because B cells are able to circulate throughout the body to monitor for pathogens should they re-arise (Weinstein, 2012). This gives the immune system it's "memory" allowing the second infection to be dealt with more efficiently and specifically than the initial infection. B cells express a unique receptor which is a membrane-bound antibody molecule. All the B cell receptor antibodies present on one individual cell are identical and can bind to only one particular antigen. As discussed above, antigens are created from the phagocytosis of pathogens by immune cells such as macrophages and then presented on antigen presenting cells with MHC molecules to T cells which can then lead to the activation of B cells. Antigens can also be detected directly by B cells and lead to the activation of the B cells (Weinstein, 2012). The various components of the adaptive immune system work together seamlessly to provide total and comprehensive protection for the host from foreign bodies and pathogens. Antibodies circulate through the body through lymph vessels and the blood stream and can recognize foreign bodies in the host (Cooper, 2015). The human immune system has several different types of antibodies: IgA, IgD, IgE, IgG, and IgM. There are different types of antibodies to handle the different types of pathogens and antigens created from these pathogens. This variety of antibodies gives the adaptive immune system it's specificity that is lacking in the innate immune system (Cooper, 2015. IgA functions in mucous membranes such as in the gastrointestinal tract (Brandtzaeg, 2005). IgM and IgD are coexpressed in B lymphocytes. They serve to activate B cells when they encounter their partner antibody. IgE is made in blood plasma cells and plays a role in allergies and immunity to parasites. IgG is the most common antibody circulating in the blood. It monitors for pathogens such as viruses, fungi, and other pathogens (Khodoun, 2011). IgM is the largest antibody and is one of the first antibodies to appear during an infection (Capolunghi, 2013). When an antibody recognizes an antigen, the B cells it's bound to can specialize further to become an effector B cell (Castiblanco, 2017). These effector cells like the name implies create an effect on the pathogen such as agglutination, activation of complement, which creates inflammation and cell lysis, opsonization, cytotoxicity, and neutralization (Cooper, 2015). Agglutination serves to clump the infectious agents together and make it easier for the immune system to take care of at once. This seems to make the immune attack more efficient rather than the immune system going after individual pathogens that are freely moving throughout the body. Opsonization means the antibodies coat the antigen in order to mark it for phagocytosis and then elimination of the pathogen. This seems to alert the cells of the innate immune system of the pathogen making it easier for them to find and phagocytose the coated pathogen. Similarly, the antibodies can attach to the target infected cell to be killed by other immune cells such as macrophages, eosinophils, and natural killer cells (Cooper, 2015). Thus we see yet again how the adaptive immune system coordinates with the cells of the innate immune system to eliminate pathogens. Neutralization serves to prevent the pathogen from attaching or residing within mucosa of the host (Weinstein, 2012). It can also lead to the production of memory B cells which can circulate and recognize the antigen in the future (Airoldi, 2004).

III. PARASITE EVASION OF IMMUNE RESPONSE

Introduction

In this section we will take a look at the specific methods used by parasites to evade the human immune response. Earlier, we looked at different types of parasites and what distinguishes them. Then we looked at the human immune system and how it is able to combat what it perceives to be threats. Here, these two concepts come together in parasite modulation of the immune response. Parasites modulate the immune response to remain undetected by the immune system and continue to proliferate as well as spread to new hosts (Avise, 2008). Parasite modulation of the immune response will differ based on the type of parasite, such as intracellular, extracellular, ectoparasites, and helminths as discussed in the first section. Extracellular parasites reside outside the cells of their host while intracellular parasites reside inside the host's cells. Ectoparasites live outside the body of their hosts, choosing to reside on the surface of the host or come and go as needed. Helminths are parasitic worms that reside within the body of their hosts (Combes, 1997). With such a wide variety of environments within the host, it's no wonder that parasites customize their modulation of the host immune system based on their environment within the host. Some parasites trigger inflammation and itching in order to feed such as ectoparasite *Pediculus humanus capitis.* Further, some parasites like intracellular *Leishmania* need to be phagocytosed in order to enter their host cells (Mindell, 2012) while others such as extracellular *Trypanosoma brucei rhodesiense* are at risk of being eliminated from circulating macrophages monitoring for pathogens and must modulate the immune system to avoid being detected. The helminth *Trichnella spiralis* directly suppresses the host immune system by secreting Th2-likecytokines in order to progress its infection. Similarly, the type of parasite will determine what components of the immune system are triggered such as innate components versus adaptive components and cellular components versus humoral components as reviewed in the second section of this paper. Innate components are the first defense to initial infection and non-specific, thus if parasites are detected early then they need to combat the innate immune system (Mahla, 2013). The adaptive immune response is more long term and remembers particular pathogens (Restifo, 2013). A parasite that remains in tissues will need to combat the adaptive immune system that circulates throughout the body monitoring for a future infection. First, we will look at how an intracellular parasite modulates the host's immune response.

Intracellular

Leishmania

Leishmania, an intracellular parasite that infects macrophages, modulates the human hosts' immune system in order to continue and extend its infection of macrophages. *Leishmania* causes the disease leishmaniasis which leads to ulcers on the skin of the host but can also damage the cutaneous and subcutaneous tissues in more serious infections (Alamilla-Fonseca, 2018). In the hosts macrophage cells, *Leishmania* reproduces and is transferred to its intermediate host, the sand fly when the sand fly feeds on the host. Macrophages are a cellular component of the innate immune system and serve to phagocytose pathogens that have been identified. They then present the broken up pieces as antigens in order to activate the adaptive immune system (Neerincx, 2013).

Leishmania must penetrate the macrophage and avoid antigen presentation in order to carry out a fruitful infection. Thus the first step for *Leishmania* is successful penetration of the macrophage. In order to do this, *Leishmania* expresses a surface protein called lipophosphoglycan (LPG) that is recognized by the macrophage's PRRs and brings the pathogen inside the host cell (Lodge and Descoteaux, 2014). Therefore, *Leishmania* is phagocytosed by the macrophage in the first step of intracellular infection. Once *Leishmania* has been engulfed by a phagocyte, it becomes enclosed in an intracellular vesicle called a phagosome. Traditionally during phagocytosis, this phagosome then fuses with the lysosome to form a phagolysosome. This could be hazardous to *Leishmania* as the lysosome has a low pH and destroys molecules with hydrolytic enzymes or release of free radicals into the phagolysosome (Mindell, 2012). Thus to avoid being killed by the activity of these digestive enzymes or free radicals, *Leishmania* must avoid the fusion of the phagosome with the lysosome. *Leishmania* accomplishes this by utilizing lipophosphoglycan (LPG) in order to inhibit fusion of the phagosome, which contains the parasite, with the lysosome, which would degrade the parasite. During this step, the *Lesishmania* parasite utilizes LPG to displace the host protein Syt V. Syt V is involved in phagolysosome biogenesis. Syt V must recruit cathepsin D and vesicular proton-ATPase (V-ATPase) to fuse the lysosome with the phagosome and to acidify the newly made phagolysosome. Insertion of LPG into lipid microdomains of the phagosome membrane excludes Syt *V* from phagosomes, enabling the parasite's survival inside the macrophage's phagosome (Vinet, et al., 2009).

This method is usually successful, but if the phagosome does fuse with the lysosome, then *Leishmania* has a backup plan in place. *Leishmania* utilizes a surface protease, gp63, in order to prevent the macrophage's phagolysosomal enzymes from degrading the pathogen inside the phagolysosome. The parasite's gp63 prevents the fusion of vesicles destined to the lysosome by degrading the vesicle's V-SNARES (Duque, 2016). But the phagolysosome also utilizes free radicals in order to kill pathogens in addition to the hydrolytic enzymes. To combat the release of free radicals inside the phagolysosome, *Leishmania* once again utilizes LPG to prevent the

oxidation of the pathogen. LPG has several oxidizable units in its structure that it uses to collect oxygen intermediates in the phagolysosome (Duque, 2016). Thus, the oxygen intermediates are used up by oxidizing LPG and are unable to accumulate and cause the damaging release of free radicals that is necessary in order to kill the pathogen.

The parasite *Leishmania* is now successfully inside the macrophage, but more hazards to the parasites vitality remain. Once inside the macrophage, *Leishmania* must prevent the macrophage from collecting any particles from the pathogen and presenting these antigens to T cells via MHC in order to alert the adaptive immune system. During traditional antigen presentation, foreign pathogen proteins are degraded into small peptides by proteases in the host proteasome. Then, the peptides are sent to the endoplasmic reticulum and are attached to MHC 1 molecules. Following this, the peptide and MHC complex exit the ER and are transported to the cell surface by exocytosis (Sei, 2015).

Once on the exterior of cells, the antigen bound to the MHC receptor can then be presented to T cells, which will either kill the cell that presents the antigen or recruit other components of the innate and adaptive immune systems to combat infection (Stern, 2016). In order to prevent fragments of *Leishmania* being presented to T cells, the parasite utilizes glycosylinositolphospholipids to inhibit the expression of the MHC Class 1 and 2 molecules (Assis, 2008). This renders the entire antigen presentation process as obsolete and allows the parasite to remain undetected. Further, the protease gp63 that we saw above aid in parasite survival inside the macrophage comes into play here in preventing activation of T cells. T cells rely on CD4 or CD8 receptors to bind to MHC 2 or MHC 1 molecules in order to activate the T cell. *Leishmania* uses the gp63 protease to cleave the CD4 receptor molecules thus making the interaction between the MHC 2 molecule and T cells unsuccessful and preventing activation of the helper T cell (Resvan, 2014). In order to be comprehensive, parasites inside the macrophage serve to bring MHC molecules on the outside of the macrophage inside the cell and then degrade the MHC Class 2 molecules to prevent any sort of functionality (Parashar, 2017).

Thus, *Leishmania* is able to modulate the host's immune system by utilizing various proteins and proteases to prevent formation of the phagolysosome and several molecules to decrease MHC expression. Next, we will take a look at the extracellular parasite and its method of immune evasion.

Extracellular

Trypanosoma brucei rhodesiense

We earlier looked at how a parasite that resides within the human host's cell alters the immune response of the host. Next we will look at how an extracellular parasite modulates the immune response. As noted above, extracellular parasites are parasites that reside outside the cells of their host but still live inside the host's body in tissues.

The parasite *Trypanosoma brucei rhodesiense* causes the disease African Trypanosomiasis and is caused by an extracellular parasite. The disease is characterized by a number of symptoms most notably fatigue, lethargy, and wasting (Lamour, 2017). The parasite *Trypanosoma brucei rhodesiense* is transmitted by the tsete fly to humans through a bite. Once inside host the parasite enters the human lymphatic system followed by the bloodstream where the parasite will multiply and mature. The parasite circulates through the blood, as an extracellular parasite, where it can be transmitted back to the fly through feeding again (Kato, 2017).

The *Trypanosoma brucei rhodesiense* parasite is at risk for being removed by macrophages as the parasite resides in extracellular tissues that macrophages monitor. *Trypanosoma brucei rhodesiense* parasites that are not removed by macrophages can avoid activating B cells via antigens by antigenic variation of Variant Surface Glycoprotein (VSG) (Theodos, 1990). Each parasite in the human host has a number of genes encoding different VSG's but will only express one for a certain period of time before moving to a new one (Lenardo, 1986). This allows the parasite to continuously change its glycoproteins on its exterior (Grisso, 1995). Thus, the parasite is able to keep changing disguises and difficult to identify by the immune system.

Further, the parasite is able to alter and then activate CD8 T cells and macrophages in order to change the pattern of cytokines that the cells will release (MacLean, 2006). These manipulated cytokines will switch the adaptive response to one more suited to intracellular parasites and not be effective in clearing the extracellular infection allowing it to continue and progress in the host (Maina, 2004). Thus the *Trypanosoma brucei rhodesiense* parasite is able to avoid the immune response by both adjusting the glycoproteins on its exterior to avoid antibody mediated destruction and impair the ability of the macrophages in clearing infection of the parasite through modification of pattern of cytokine release.

Trypanosoma cruzi

Another example of an extracellular parasite's modulation of the human immune system is *Trypanosoma cruzi*. The extracellular parasite *Trypanosoma cruzi* causes Chagas disease in Latin America, the US, Canada, and parts of Spain. Chagas disease presents with the symptoms of swollen bites, swollen lymph nodes, and headaches. The disease can progress from an initial infection into a full blown chronic infection and is passed when the feces of the kissing bug, hematophagous triatomines, are rubbed into a bite when the bug drinks the hosts blood (Ribeiro, 2013). This disease has two phases, an acute phase where the parasite is present in the bloodstream of the host and a chronic phase where the parasite can impede the cardiovascular system of the host. The parasite is both extracellular and intracellular, replicating in the macrophages and muscle cells of its host and circulating through the blood. (Carabarin-Lima, 2013). This extracellular portion of the parasite's life cycle is what we will focus on.

Since it circulates through the blood, the *Trypanosoma cruzi* parasite is vulnerable to elimination by antibody mediated destruction and thus needs to find a way to protect itself from this. Antibodies were discussed above and act as a receptor on B cells and activate the B cells when the antibody binds to its respective antigen. The antigen is bound via MHC molecules to an antigen presenting cell after a pathogen is phagocytosed and generates antigen peptide fragments (Weinstein, 2012). In order to protect itself from antibody mediated destruction, *Trypanosoma cruzi* creates an overproduction of IgM antibodies. IgM is the largest antibody and is one of the first antibodies to appear during an infection (Capolunghi, 2013). These IgM antibodies bind to the exterior of the parasite and prevent IgG antibodies from binding and leading to elimination of the pathogen (Brodskyn, 1989). IgG is the most common antibody circulating in the blood. It monitors for pathogens such as viruses, fungi, and other pathogens (Khodoun, 2011). Thus, the antibodies produced by the pathogen serve to protect it against being eliminated by the host's antibodies. This is a brilliant way for the pathogen to avoid the immune response of the host.

Further, the parasite uses this method to produce molecules that mimic host cells that will be activated by antigens that belong to the host. This leads to the immune system not being able to recognize the pathogen and destroy its own cells creating autoimmunity (Bonney, 2010). As the disease progresses throughout the body, the autoimmunity creates a more severe, chronic infection. In combination, *Trypanosoma cruzi* utilizes an over generation of antibodies to hide from host antibodies in the blood and generates faux host molecules to evade the immune response. Next we will take a look at ectoparasites and the methods they utilize to alter immune response.

Ectoparasites

Pediculus humanus capitis

Following our look at extracellular and intracellular parasites we will shift our focus to ectoparasites and how they modulate immune response. Ectoparasites differ from endoparasites such as intracellular and extracellular parasites in that they reside on the outside surface of their host such as the scalp or skin. *Pediculus humanus capitis* is an example of an ectoparasite and is more commonly known as head lice. *Pediculus humanus capitis* lives on the scalp of the human host and feeds on the host's blood. The parasite solely feeds on the blood of its host feeds 2-5 times a day and depends on the host's blood for all its nutrition (Al-Sharani, 2017). Thus the parasite can't live without its host for long periods of time and must ensure it gets enough blood from each feeding. Further, the host needs to have adaptations to find a new host should its current host no longer be viable or detect the parasite and remove it.

Pediculus humanus capitis requires the human host's blood in order to survive. However, feeding on the host can trigger the host's immune system to release histamine and lead to itching from the human immune system (Nieto-Alamilla, 2016). This itching can lead to detection of the host on the body surface and removal of the host. Histamine as discussed above is a humoral component of the innate immune system and is an organic nitrogenous compound that creates inflammation in the human host. Histamine is produced by cells of the innate immune system like basophils and mast cells in infected tissues and spreads through to other tissue (Nieto-Alamilla, 2016). Histamine serves to create inflammation in the host leading to increased permeability or of capillaries to leukocytes (Anderson, 2015) which facilitates movement of these cells to the site of infection and allows them to eliminate the pathogen. This inflammation and histamine also leads to itching which can then allow the host to detect the parasite and remove it. Thus, the parasite must have methods to quickly find a new host in the case host itching can remove the parasite from the host. Lice have co-evolved with humans to do just that; they have adapted to have six legs that each terminate in a claw. This allows the lice to move rapidly and to transfer to new hosts (Ghandali, 2017).

Pediculus humanus capitis lives on the scalp of the human host and feeds solely on the host's blood usually around 2-5 times a day (Al-Sharani, 2017). Thus, the parasite must ensure that it gets a steady supply of blood when it feeds. In order to ensure sufficient amounts of available blood, *Pediculus humanus capitis* injects biological proteins into the host in its bite during feeding. These proteins include an anaesthetic that provokes histamine release and inflammation in the host. Further, this leads to redness and scratching which leads to itching. The act of itching the bite is beneficial to the parasite because it exposes fresh blood for *Pediculus humanus capitis* to easily find and feed on (Ghandali, 2017). Thus, the *Pediculus humanus capitis* parasite has evolved to modulate the human hosts immune system to gain enough nutrition and jump to a new host in the case of detection and removal by scratching.

Helminths

Trichnella spiralis

Next, we will take a look at helminths and the role they play in altering the immune response. As reviewed above, helminths are parasitic worms that infect billions of people each year (Palmas, 2003). The helminth *Trichnella spiralis* lives in hosts such as humans and causes the disease trichinosis. Trichinosis is characterized by diarrhea, abdominal pain, and vomiting (Brodaczewska, 2017). The *Trichnella spiralis* parasite is transferred to hosts that consume undercooked meat and causes diarrhea through which the parasite's offspring is excreted. It can then contaminate food and infect more hosts utilizing the fecal – oral route of transmission. Helminths are usually often larger in size than ectoparasites and can be seen by the naked eye but *Trichnella spiralis* is a microscopic parasite that resides in gastrointestinal tract of its host as an adult and burrows its larvae in the host's muscle cells.

Inside the host's gastrointestinal tract, the parasite must be able to remain under the radar and suppress the extracellular immune response in order to continue and progress its infection. In contrast, the parasite's intracellular stage must shift the immune response towards targeting intracellular components of the immune system (Sofronic-Milosavljevic, 2015).

Trichinella spiralis exert immunomodulatory effects on the host immune response through excretory-secretory products (ES L1) released from the encysted muscle larvae. These ES products interact with naïve T-cells activating them and enhancing a Th2 response. While Th1 cells often create responses against intracellular parasites, Th2 cells produce immune responses against helminths and other extracellular parasites (Shepherd, 2015).

This shift in the immune response allows the survival of the intracellular larval stage of the parasite (Gruden-Movsesijan, *et. al*, 2011). As an adult worm *Trichnella spiralis* secretes multiple serine proteases at different stages of infection. These proteases are involved in parasite survival and establishment of infection by aiding in evasion of the host immune system (Todorova, 2000). Serine proteases contribute to immune evasion by modulating nucleotide levels in the host during infection. These secreted serine proteases lead to an enzymatic cascade which then catalyzes the degradation of extracellular nucleotides (Gounaris, 2002). A decrease in extracellular nucleotides is significant because extracellular nucleotides are signaling molecules that are involved in the immune response of inflammation when they bind to their receptor. The immune responses such as can be modulated by the availability and local concentrations of nucleotides via nucleotide receptor signaling. Thus, by decreasing extracellular nucleotide levels, serine proteases are able to dampen inflammation (Xu, 2017). As stated earlier, the humoral compound histamine serves to create inflammation in the host which leads to increased permeability of capillaries to leukocytes (Anderson, 2015). This increased permeability of

capillaries facilitates movement of these leukocytes to the site of infection and allows them to eliminate the pathogen. So by decreasing nucleotide levels and inflammation, the host is less able to direct cellular components of the innate immune system to the location of the parasite.

Helminths Excretory-Secretory Molecules

Collectively, helminths release immunomodulatory components known as excretory-secretory products (ES). ES not only explain why most helminth infections are asymptomatic, but also provide a source for potential therapies against autoimmune disorders (Shepherd, 2015). These secreted products are composed of a mixture of proteins, peptides, glycans, lipids and some small organic molecules (Shepherd, 2015). Together, the secretion has a low molecular weight and the components are all produced from a single gene (Shepherd, 2015). ES leads to a modified Th2 cytokine response in humans. Often, a normal Th2 immune response leads to the expulsion of the extracellular helminth from the host and inflammation in the host's body (Shepherd, 2015). Thus, by modulating this response, helminths are able to remain in the body and evade the human host's immune system. Th2 cells often produce immune responses against helminths and other extracellular parasites while Th1 cells usually create a response to intracellular parasites. Modification of this Th2 response allows the helminth to remain in the human and progress infection as well as preventing inflammation (Shepherd, 2015). This allows the helminth to remain largely asymptomatic in the host. An example of this can be seen in the whipworm, *Trichuris trichiura,* which infects the large intestine of humans. During infection, the normal Th2 immune response leads to chronic diarrhea and protein loss as well as, eventually, expulsion of the helminth (Shepherd, 2015). The modified Th2 immune response cause by the whipworm is characterized by expansion of Th2 cells, alternatively activated macrophages, and suppression of the Th1 response and decrease of inflammation (Shepherd, 2015). This modification of the immune response allows the helminth to remain in the host and avoid expulsion as well as continue a largely, asymptomatic infection. As discussed above, inflammation aids the immune response by aiding movement and directing immune cells to the site of infection and elimination of the pathogen (de Oliveira, 2016). Thus, the anti-inflammatory properties of ES make them a viable option for developing drugs to combat other human diseases.

IV. **CONCLUSION**

As we have already seen in the sections above, parasites are a diverse group of eukaryotic organisms that utilize many different strategies to evade the human host's immune response. The interaction of the parasite with the immune system within the human host is a constant back and forth, but overall this seems to be an exchange the parasite has the upper hand in. We've seen the extensive mechanisms the immune system uses to combat pathogens such as antibodies and antigen presentation as well as T cells and macrophages. However, the customization and comprehensive attack of the immune system seems to do little to parasites when compared to pathogens such as bacteria and viruses. This is in part due to the nature of parasites, as they are eukaryotic while viruses and bacteria are prokaryotes. Eukaryotes have cells with membrane bound organelles and DNA contained within a nucleus while prokaryotes do not (Adl, 2012). As humans are also eukaryotes, this makes it more difficult for the human immune system to distinguish between human and parasite. Further, parasites have co-evolved with humans and this makes them all the more adapted to our immune systems and bodies. This identification of pathogen from human is an underlying principle that the human immune system relies on to plan and carry out its response to pathogens and helps explain why parasites are so successful in modulating the human immune response. The immune system looks for patterns and differences between human and parasites and as we saw with parasites, they are adapted to evade what the immune system is looking for. Parasites are able to change what they look like with as we saw with Trypanosoma brucei continuously changing the glycoproteins on the exterior of its cells in order to prevent the human immune system from getting into a groove of what to look for and use to eliminate the parasite (Theodos, 1990). Moving forward, the traditional treatments that we use for viruses and bacteria will not be as fruitful since parasites operate in such a different way and perhaps we need to look at adjusting it or developing a new plan of attack in the war against parasites.

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