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Induction of Immune Responses and Inflammation to Parasitic Infections

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2.1 Introduction

Senescent multimorbidity, which is the co-existence of numerous chronic pathologies including the principal diseases of advanced age, is mostly caused by aging. Slowing down the aging process can simultaneously avoid the onset of a number of age-related disorders [1]. Worm therapy is a form of immunotherapy that treats immunological problems and autoimmune diseases by purposefully contaminating a patient's body with parasites in any of their developmental stages, including eggs, larvae, or adult worms. Studies showing that individuals who routinely contract parasitic worms have low rates of autoimmune illnesses, so all parasitic worms cannot be damaging to the body [2]. In affluent nations, the prevalence of autoimmune inflammatory illnesses has dramatically increased over the past three decades. Just a few examples include type 1diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis (RA), and Crohn's disease. An immune-mediated attack on a target organ that causes the immune system to no longer identify itself is the hallmark of autoimmune disease. Both antibody and cell-mediated elements can contribute to autoimmune disease [3].

Various age-related diseases, such as cardiovascular disease, dementia, cancer, chronic obstructive pulmonary disease (COPD), osteoporosis, and age-related macular degeneration, are made worse by this inflammation [4]. Gut dysbiosis, an

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imbalance in the composition of the intestinal microbiome, is one factor contributing to inflammatory aging. Such an imbalance, which is aggravated by pro-dysbiotic components of contemporary life like antibiotic use and the so-called Western diet, can show up as a decrease in immunomodulatory microbial species [5].

When considered collectively, the studies reviewed here propose multiple methods for triggering an immune response and inflammation in response to parasite infections.

2.1 Induction of Immunity to Parasite Infections

Immune responses must be induced by the immune system's innate components, which react quickly and relatively non-specifically, and other specialized components, which detect specific epitopes on an antigen. Dendritic cells (DCs), which operate as "professional antigen-presenting cells", are a crucial component of this relationship. In combination with major histocompatibility complex (MHC) molecules, DCs endocytose and process the antigen to create the peptide that is displayed on the cell surface. The issue with many infectious diseases is that the immune system only responds after the organism has been invaded, at which point disease symptoms have already shown. Vaccination with a harmless form of the disease-producing agent, which is nevertheless capable of imitating the immune system, circumvents this issue and benefits the immune system. This method produces immunological responses that shield the body from further pathogen attack. After crucial interactions between the two main components of the immune system – innate and specific – immune defenses are formed. Natural killer (NK1) cells, granulocytes, macrophages (Ms1), and dendritic cells are the cellular elements of innate defenses (DCs1) [6]. Specific immune responses take longer to develop, but they are more lasting and specific. These particular defenses must interact with intrinsic components to become effective. The critical interaction between the innate and specific parts of the immune system involves the role played by antigen-presenting cells (APCs1), which include monocytes, MS, endothelial cells, fibroblasts, fibrocytes, and DCs [7]. B-cells can also serve as APCs from the specific immunological component, but not for primary immune responses that require activating naive lymphocytes. DCs are referred to as "professional APCs" since they are at the center of antigen presentation for both primary and recall immune responses. Despite the fact that DCs are particularly significant APCs, not all monocytes exhibit APC characteristics. Due to their "scavenger" phagocyte activity they are frequently more active in effector immune responses and they can even block the emergence of antigen-specific responses [8]. The aim of the chapter deals with the immunity response and inflammation to parasite infections with special emphasis on the different treatment regimens for parasite infections.

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Many parasites such as *Blastomyces dermatitis* and *Staphylococcus aureus* elicit a ferocious immunological response from the host; unfortunately, this response may be ineffectual or may interfere with a normal immune response due to generations of contact and genetic modification. Furthermore, parasites can migrate away from an inflamed location to avoid being trapped, some have tough body walls, and most are relatively large. Due to these distinctions, parasite infection differs from the majority of viral and bacterial infections, in which the immune system typically provides protection. One author stated that there is now "no coherent explanation of immunity in any parasite disease" due to the intricacy of the host response to parasitic infection [9].

Recent research has shown that basophils, a rare form of white blood cell, are important participants in type 2 inflammation, although it is still unclear how basophils work in this setting [10]. A potential possibility for regulating basophil responses after parasite infection is the Notch signaling pathway, a molecular lock-and-key that may quickly transmit messages of inflammation to a range of cell types [11].

2.2 Defense Systems

2.2 Innate Immune Defenses

Innate immune defenses are composed of numerous and variable components. The skin, mucosal secretions, stomach, and intestinal pH are physical/chemical barriers that form the first line of innate defense. Phagocytic cells (neutrophils and macrophages), the complement system, natural killer cells, antimicrobial peptides, and sentinel cell production of innate defense cytokines are among the main innate defense systems. Different stressors have the tendency to decrease the effectiveness of innate defense mechanisms, increasing infection vulnerability. The development of adaptive (or acquired) immunity (antibody and T cell-mediated immunity) to a particular pathogen by the animal increases the activity of all of these innate defense mechanisms. The only aspect of innate immunity to be covered in detail will be the function of sentinel cells in the early detection of microbial invasion, activation of innate defense mechanisms, and induction of acquired immunity.

2.2.2 Production of Pro-Inflammatory Cytokines by Sentinel Cells

Sentinel cells play key roles in the early detection of microbial invasion and the stimulation of the immune response including mast cells, dendritic cells, and macrophages. These cells have receptors known as toll-like receptors (TLRs),

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which can bind chemicals that are specific to infectious pathogens. They are concentrated at or beneath epithelial surfaces. These substances include bacterial DNA (which is rich in CpG motifs), flagellin, bacterial lipoproteins, and bacterial lipopolysaccharide (endotoxin). These microbial compounds are seen as danger signals, and the sentinel cells respond quickly by secreting pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF), interleukin-1 (IL-1), and IL-6. These substances cause a localized inflammatory response at the site of their creation and stimulate the neutrophils, macrophages, natural killer cells, and endothelial cells to generate more of the proteins needed to effectively clear a local infection. The pro-inflammatory cytokines will start to circulate in the bloodstream if they are secreted in sufficient quantities. When they get to the hypothalamus, they cause fatigue, appetite loss, and fever. They cause the liver to create a lot of acute-phase proteins and stimulate neutrophilia in the bone marrow. These act to improve the body's natural defensive mechanisms' capacity to contain an infection. The animal interacts with other members of its species less due to lethargy and loss of hunger, which lessens the spread of infection. The replication of some viruses is slowed down by fever, and some inherent defenses that work to destroy viruses are strengthened.

2.2.3 Role of Dendritic Cells, Macrophages, and B Cells in Antigen Processing and Presentation to T-lymphocytes

Only peptide antigens displayed on major histocompatibility class II (MHC II) molecules are recognized by T-helper (CD4+) cells. These peptides originate from endocytosis proteins that are subsequently broken down into brief peptides by enzymes and attached to MHC II molecules. These molecules are then transported to the cell surface and presented to T-helper cells. Only peptide antigens shown on MHC I molecules are recognized by T-cytotoxic (CD8+) cells. These peptides are made from proteins that are produced in the antigen-presenting cell's cytoplasm. A proteasome in the cytoplasm processes a sample of all proteins made within a cell before being transferred into the endoplasmic reticulum, where brief peptide fragments are linked to MHC I molecules. Because the healthy animal is tolerant of normal self-proteins, there are no cytotoxic T cells that can detect them. Cytotoxic T cells will be exposed to peptides from foreign proteins if a cell contracts a virus or mutates and starts generating such proteins in its cytoplasm. The cell that is generating an alien protein will be killed in response by the cytotoxic T-cell. After initial exposure, it takes the cytotoxic T cells 7 to 10 days to become proficient at controlling viral infection. On a second encounter with the virus, they react very quickly.

Both killed and live vaccination antigens can be endocytosed, digested, and presented to T-helper cells on MHC II molecules. However, the creation of pathogen

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proteins in the cytoplasm of infected cells can only be induced by live vaccinations. As a result, live vaccines are often thought to be more successful at stimulating the production of cytotoxic T cells after vaccination. Researchers have created techniques to transfer vaccination antigens into the cytoplasm without utilizing conventional modified live vaccines now that this endogenous channel of antigen presentation has been identified. To transfer protein antigens into the cytoplasm for processing and presentation on MHC I molecules to cytotoxic T cells, one technique is to use adjuvants, such as ISCOMS (immune stimulating complexes), which fuse with the cell membrane. Utilizing recombinant virus vectors, which have one or more pathogen-specific genes inserted into their genetic material, is an additional strategy. When the vector infects a cell, this genetic material triggers the production of pathogen proteins in the cytoplasm, which is then processed and displayed on MHC I molecules. Instead of utilizing a standard modified live virus to deliver the protein, a viral vector may be more cost-effective or less dangerous to use overall than the MLV vaccination. It might also be less likely to be blocked by maternal antibodies (Figure 2.1).

2.2.4 Stimulation of Specific Immune Responses

2.2.4.1 T Lymphocytes

The bulk of specific immune responses, including antigen-activated B lymphocyte antibody generation and antigen-specific cytotoxic T cell (Tc) effector activity, depend on CD4+Th lymphocytes for effective execution. The fact that not all Th lymphocytes detect the same peptide and that only unique Th cell clones can recognize specific

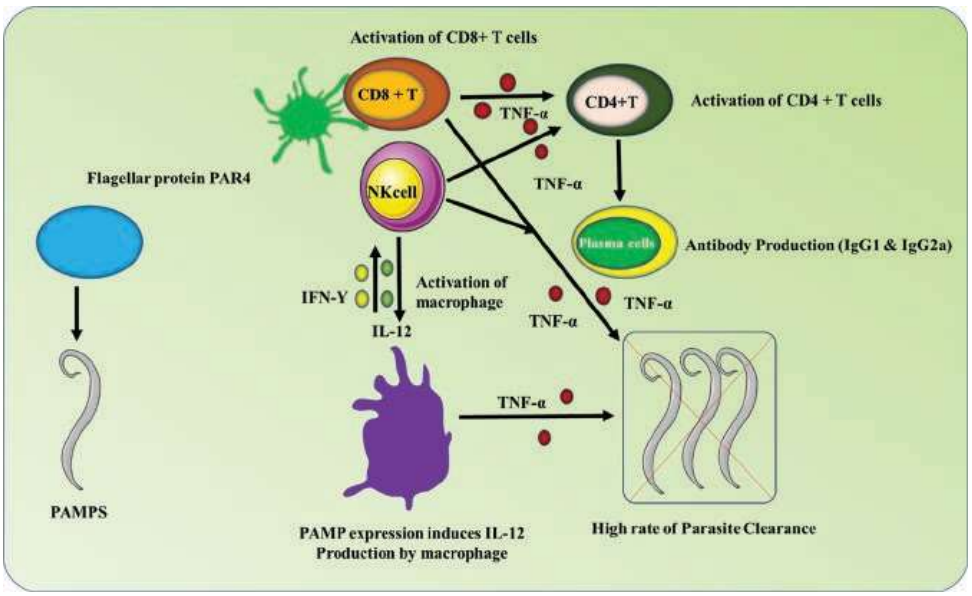

Figure 2.1 Role of dendritic cells, macrophages, and B-cells in antigen processing.

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peptide sequences is a crucial factor to consider. This specificity derives from the APCs' digestion of the antigen, which yields a number of peptides that can stimulate the target Th cells. The conversion of antigen-stimulated B and Tc lymphocytes into effector and antibody-producing cells, respectively, is mediated by cytokines. Of course, proper cognate contacts are necessary for such cytokine signaling.

2.2.4.2 B Lymphocytes

Continued stimulation of the surface cytokine receptors by Th cell-produced substances as well as the membrane immunoglobulin-like receptors on B lymphocytes is necessary for B lymphocyte activation. A physical interaction between the B and Th cells is additionally necessary. As an illustration, CD40 and its ligand are essential for enabling selective differentiation. Similar to T lymphocyte responses, B lymphocyte responses are likewise limited to specific clones that can detect one of the antigen's epitopes, also known as the B cell epitopes. Although it is not necessary for APCs to process and present antigens in order to excite B lymphocytes, it appears that they do so in order to "transport" antigens to the B lymphocyte regions of lymphoid follicles. Because the epitopes recognized by B lymphocytes are frequently discontinuous and depend on the tertiary and quaternary (conformational) structure of the antigenic determinants on the antigen, this antigen must be "given" somewhat intact. A B-lymphocyte is prompted to cap its B cell receptor (BCR) in preparation for division and differentiation after it connects with the epitope for which it is specified via the BCR. The interaction with the Th lymphocytes at this time, particularly the contribution of the T cell cytokines, is crucial. The B lymphocyte returns to its resting stage, as it did before the engagement with the antigen, in the absence of this interaction. The B lymphocyte starts the process of differentiating into an antibody-producing plasma cell when there is appropriate cognate contact with T lymphocytes and the participation of T cell cytokines. The fact that several of the T cell cytokines involved were initially referred to as B cell differentiation factors is the result of this.

2.3 Identification of Important Immunoregulatory Systems Is Aided by Parasitic Worm Infection

Type 2 immune responses are related to allergic illness and helminth infection. Type 2 immune responses, in contrast to Th1 or Th17 immune responses, have the advantage of producing less collateral damage, which is often necessary for controlling parasite infections. On the other hand, type 2 reactions in allergies can result in pathology that is crippling or even lethal. The crucial significance of these responses in parasite killing/ejection, healing, metabolic alterations, and allergy disease has been demonstrated in models employing animals lacking in key components of type 2 immune pathways. Th2 cells that produce IL-4, IL-5, and IL-13 and antigen-specific IgE immunoglobulins are characteristics of type 2 immunity. Eosinophils

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are activated in response to antigen identification by Th2 cells, while primed mast cells are degranulated in response to IgE cross-linking. Allergy-related illnesses such as atopic dermatitis, asthma, and food allergies have clinical symptoms that are brought on by these effector immune cells working in concert.

It's interesting to note that in both people with chronic helminth infections and people who have repeatedly been exposed to allergens in the environment or in the therapeutic setting [12], high antigen-specific IgG4 levels have been observed, and regulatory T cells (Treg) and regulatory B cells that secrete IL-10 and TGF are more prevalent in circulation. [13, 14]. Thus, the type 2 adaptive immune response is tolerant to changes in the innate immune system that are necessary for their activation, external substances acting on adaptive immunity cells, or the cells' inherent exhaustion.

a) A population of innate immune cells called dendritic cells (DCs) is crucial for the creation of the best effector. Immune system responses in cells, including Th2 responses [15, 16]. As they are closely linked to barrier locations like the lungs, DCs can pick up antigens both inside and outside the epithelial barrier. Upon the discovery of an environmental allergy or helminth infection [17], as they get activated and go to the draining lymph nodes, DCs can potentially trigger a Th2 immune response by presenting antigens to T cells. Although it is obvious that DCs play a crucial role in Th2 formation, our understanding of the precise signals that prime a DC to produce Th2 is still lacking. Thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and IL-33 are examples of epithelial-derived cytokines that are important in the treatment of allergies and parasite infection [18]. These cytokines have the ability to directly activate type 2 innate lymphoid cells (ILC2s), causing a rapid innate type 2 response, as well as directly operate on DCs, skewing subsequent responses to Th2. Lacking antigen-specific receptors, ILC2s are innate lymphocytes that make a lot of the type 2 cytokines IL-5, IL-13, and IL-9 as well as the pro-resolving proteins amphiregulin [19] and IL-10 [20].

Additionally, class II MHC expression, peptide antigen presentation, and IL-4R signals for type 2 response initiation are all possible with activated ILC2s [21].

2.4 The Role of Regulatory Cells, Cytokine Inhibitors, and Immunoglobulins in the Modulation of Allergic Illness by Helminths

2.4.1 Immunoglobulins

Functional allergy as evaluated by skin prick test (SPT) reactivity highly corresponds with allergen-specific Ig E in high-income countries. However, this link frequently fails in helminth-endemic areas, particularly rural areas with poor

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socioeconomic status [22, 23]. Wheeze and/or atopy have also been linked positively by epidemiological research to antihelminth Ig E (ascariasis, schistosomiasis, filariasis). The cross-reactivity of antihelminth Ig E to specific allergens may be one of the causes of differences between Ig E reactivity and allergy in high-income versus helminth-endemic areas. For instance, Ig E against *Onchocerca volvulus* tropomyosin reacts with Derp10 tropomyosin from house dust mites, increasing allergic reactions to HDM. Despite the fact that IgE against carbohydrates on *Schistosoma* egg glycoproteins can react with cross-reactive carbohydrate determinants (CCDs) on peanut antigens, this Ig E has a low affinity, so cross-linking and degranulation of IgE-coated mast cells that are specific for carbohydrates do not take place. Consequently, these cross-reactive reactions could prevent clinical responses to allergens like peanuts [24]. Further research is required to determine if elevated levels of circulating CRP or carbohydrate-specific IgE play a role in causing or avoiding allergic reactions [22]. Following allergen-specific immunotherapy, the immunoglobulin isotype IgG4 is frequently linked to a tolerized allergic response; many people with helminth infections also produce more of this antibody [25,26]. IgG4 has been linked to a number of systemic disorders, although it is not yet obvious how this pathogenic role of IgG4 differs from active tolerance development to allergens or during helminth infection. Despite the growing knowledge of potential negative effects, IgG4 is still not completely understood. Despite the new reports of illnesses connected to IgG4, IgG4 antibodies are thought to be the least inflammatory of all isotypes since they do not activate IgG4 complement and, unlike IgE, do not result in mast cell degranulation. IgG4 is characterized as functionally monovalent because of its exceptional capacity to switch antigen-binding arms, which prevents immunological complex formation. Because of this, its primary role in this situation seems to be a blocking one, which may be helpful in preventing Ig E-mediated inflammation. While in a *S. mansoni* endemic area, higher levels of both Ig E and IgG4 were found in infected individuals, a higher ratio of Ig E to IgG4 predicted clinical allergic symptoms, just as in allergen-specific immunotherapy, high levels of anti-*Ascaris* IgG4 have been negatively associated with allergen SPT positivity [24]. Due to the homology of many helminth products to common allergens, IgG4 responses generated in response to helminth products may also bind and block IgE epitopes on allergens, decreasing responses to allergens and directly reducing SPT responses [27].

2.4.2 Regulatory Cells

In animal models, regulatory B cells (Bregs) and regulatory T cells (Tregs) play key roles in the regulation of allergic airway inflammation and type 2 immune responses. Levels of Tregs and Bregs are elevated and necessary for the maintenance of tolerance in those who have become tolerant to allergens through high-dose environmental exposure or allergen-specific immunotherapy [28]. The

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immune-suppressive cytokines IL-10 and TGF- may be produced by both Tregs and Bregs, which can reduce harmful inflammation [29]. The immunosuppressive effects of a variety of helminths, such as *Onchocerca*, *Ascaris*, *Trichuris*, or *Toxocara* species, are also mostly mediated by IL-10 and TGF-β [30, 31, 32] and seem to play a key role in the inhibition of allergic reactions. In fact, IL-10 was associated with a decreased likelihood of allergic skin reactions in Gabonese students who had schistosome infections [33]. In *Schistosoma haematobium*, higher concentrations of circulating FOXP3+ CD25+ Treg cells have been found [34] and in filaria-infected people [35]. Antihelmintic therapy for *S. haematobium* or geohelminth infected people results in a normalization of circulating FOXP3 Treg or PD-1 and CTLA-4-expressing CD4+ cells116 and/or later elevated in vitro cytokine responses to both helminth and bystander antigens [34]. Similar to MS patients who have helminth infections, more Breg cells have been seen in Gabonese people who have *S. haematobium* infections [36].

2.4.3 Myeloid Cells

The development of effector versus regulatory T-cells is determined by dendritic cells (DC), the vital link between innate and adaptive immunity, depending on their ontogeny, tissue location, and/or the presence of environmental cues. Conventional type 1 (cDC1) and type 2 dendritic cells (cDC2), two distinct myeloid DC subsets, can be separated by a number of surface expression markers that have recently been discovered using an impartial methodology across tissues and species [37, 38].

cDC2 can enhance both Th17 or Th2 cells depending on the environment and exhibits improved allergen absorption compared to cDC1, whilst cDC1 can create large levels of IL-12p70 and activate cytotoxic CD8 T-cell and antitumor responses. Intriguingly, cDC1 can also play a tolerogenic role in allergy models; they do this by inducing Treg cells through retinoic acid and peroxisome proliferator-activated receptor gamma (PPAR) and reducing inflammation in schistosome infections as well as in an HDM and ovalbumin model of allergic airway inflammation. More DCs are seen in the blood, induced sputum, and bronchoalveolar lavage when an allergen is introduced to asthma patients, but only cDC2 migrated into the bronchial tissue [39]. The Th2 polarization molecule OX-40L and the Fc RI are expressed more by the DCs. However, other myeloid cell types, such as monocyte-derived dendritic cells, may also be crucial to support Th2 cell formation in either allergy models or helminth infection, as type 2 responses in allergy models are substantially disrupted in the absence of DCs [40].

2.4.4 Innate Lymphoid and Epithelial Cells

It has only lately been clear how crucial early, innate, epithelial cell-derived cytokines are for the onset of type 2 responses. At barrier locations, the epithelial cell cytokines IL-25, IL-33, and TSLP activate ILC2s, which release a lot of IL-5,

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IL-13, and IL-9. ILC2s have recently been demonstrated to be capable of activation to release IL-10, establishing an immunoregulatory pathway (similar to that of T cells) that may be accessible to parasite immunomodulation [20]. Therefore, proximal epithelial cell responses are a prime candidate for intervention since inhibiting these cytokines could reduce subsequent T-cell, dendritic cell, and ILC responses. The study of the repression of these pathways, however, is still in its early stages because they have been identified only recently. The IL-33 pathway in *H. polygyrus* infection is one instance, in which numerous parasite immunomodulatory components have been found. Excretory/secretory products of *Heligmosomoides polygyrus* (HES) duplicate the suppressive effect of parasite infection in reducing airway allergic inflammation [41]. The initial ILC2 reactions to an allergen preparation from *Alternaria alternata* have been eliminated [42], a stimulation with clinical relevance. HES administration blocks the IL-33 pathway by inducing IL-1 [43], RNA-containing HES extracellular vesicles that reduce IL-33 receptor expression, and HpARI, a protein in HES that directly binds IL-33 and prevents its release. *Alternaria* allergen administration is a remarkably potent stimulus for IL-33 release [5]

2.5 Conclusion

Parasites can suppress, alter, or even trigger some immune activation pathways, which effectively but subtly control the host immune system. Our interpretations of the immune response to parasites as they were understood just a few years ago now appear to be overly simplistic, and many of the facts that have been seen have had to be reinterpreted in light of the new findings. These recent discoveries have made it possible for us to comprehend many of the observed events much more clearly. It is simplest to demonstrate these ideas using a few specific parasitic diseases and to interpret them in terms of human disorders.

It is still unclear which immunological pathways are necessary for the development, growth, and maintenance of defenses against parasite infections. As we learn more about induction of immune responses and inflammation to parasitic infections, we will also be revealing new immune pathways that are modulated by parasitic infections and looking at new options to use therapeutics to treat it.

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3

Animal Parasites

Insight into Natural Resistance

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3.1 Introduction

Food animals (cattle, poultry, and pigs) have been widely raised throughout the world, not only as a source of food but also as a source of revenue [1]. Helminths are parasitic worms that are mainly transmitted through food or feces; infection has been documented all over the world [2]. Parasite infection prevention in animals is important not only for animal welfare and the human–animal interaction, but it also minimizes the potential risk of human infection [3]. Once an infectious agent has been recognized, hosts have some options for reducing the pathogen's influence on their health. As part of their total array of defences, animals may employ three ways to protect themselves against the detrimental consequences of parasite infestations [4, 5]. Firstly, they can use infection-minimizing or infection-preventing mechanisms (qualitative resistance), such as behavioral avoidance of surroundings, conspecifics, or foods connected to diseases, or "avoidance" [5]. Once an infection or parasite has been established, the second line of defence

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consists of mechanisms that reduce the amount of growth that occurs, with both specific and nonspecific immune responses being important (referred to resistance). Third, by limiting the damage caused by parasites and repairing it, hosts can lessen the negative effects of infection known as "tolerance", allowing for infection without parasite prevention [4, 5].They can, for example, fight the expanding pathogen population directly in order to eliminate it. However, hosts can try to reduce the amount of harm produced by a given number of infections by increasing tissue healing and detoxifying pathogen by-products [6]. Animal adopt some mechanisms to resistance and remove animal pathogenic parasites. Anthelmintic resistance is on the rise in livestock in countries all around the world, including the United Kingdom, according to some reports. Control of helminth parasites is a major concern in both animal and human medicine. Individual susceptibility to various parasitic diseases varies significantly (due to genetic factors). The identification of genes that contribute to resistance variation leads to a better understanding of resistance mechanisms [7]. Some studies have found that some breeds of domestic ruminants are more resistant to parasite illnesses such as coccidian protozoa, worms, ticks, and flies than others. The phenomena of trypanotolerance demonstrated by West African humpless cattle (N'dama) and West African shorthorn cattle, which continue to exist in trypanosome-challenged environments, is perhaps the most obvious illustration of this [8]. Toxoplasmic encephalitis (TE) is mostly prevented by interferon (IFN)-dependent cell-mediated immunity. *Toxoplasma gondii* is controlled by the humoral immune system in the brain. Combining T and B cells with non-T cells that produce IFN, microglia, astrocytes, and dendritic cells results in resistance [9]. Some of the exceptional host specificity of the numerous species of *Eimeria* is one example of how many parasites do not grow at all in hosts other than their natural ones. For example, some sheep-borne larvae of the bovine parasite *Ostertagia ostertagi* undergo development in sheep but very few of them reach the adult stage [8]. As they mature, many animals have a greater resistance to developing initial infections with certain parasites. For instance, animals who are a few months old are more prone to acquire a patency in their ascarid infection. In the same way, very young ruminants and horses are most commonly observed to have patent *Strongyloides* infections. When hosts are infected later in life, the parasites stop growing or fail to stop at the larval stage in the tissues. *Nematodirus battus* is not a very dangerous parasite for sheep older than three months [8]. Among the fly-repelling tactics used by ungulates are tail flipping, head tossing, muzzle flicking, and muscle twitching. When the number of biting flies is large, the cattle repel the flies more actively, and the animals that do the best repelling have the fewest biting flies around them [10, 11]. Mast cells have been identified in abundance in fish parasitized by helminths, showing that this cell type is linked to the response to these parasites. When parasites enter the host's tissues, alarmins, also known as damage-associated molecular patterns

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(DAMPs), are generated by harmed or dead cells and start inflammatory processes. Alarmins trigger the production of pro-inflammatory cytokines and chemokines by local mast cells, dendritic cells, and macrophages, causing leukocyte recruitment into the infected area [12]. Nonspecific immune response mechanisms to also help the animal to resist against some nematodes [13]. The availability of resources may have an impact on an animal's ability to resist parasites and tolerate them. For many vertebrate host species, a better food supply lowers the amount of parasites that feed on host tissue [14].

3.1.1 Host Resistance against Animal Parasites

Once an infectious agent has been recognized, hosts have two options for reducing the pathogen's influence on their health. They can, for example, fight the expanding pathogen population directly in order to eliminate it. However, hosts can try to reduce the amount of harm produced by a given number of infections by increasing tissue healing and detoxifying pathogen by-products: "tolerance" and "resistance" [6]. Animals adopt the following mechanisms to resistance and remove animal pathogenic parasites:

1) genetic resistance of ruminants to gastrointestinal nematodes;
2) host resistance to *Toxoplasma gondii* in the brain;
3) species and breed resistance in animals against parasitic diseases;
4) resistance due to age;
5) removal strategies for biting flies;
6) avoidance and eradication strategies for ticks;
7) avoidance and removal strategies for fleas;
8) medicinal herbs used by animals for the treatment of parasites and pathogens
9) mechanism of the immune response of teleost fish to helminth parasite infection;
10) nonspecific immune response mechanisms to *Haemonchosis contortus*;
11) effector immune mechanisms against helminths;
12) the function of eosinophils against nematode infections; and
13) host resistance of gut nematoses depending on resource availability

3.1.1.1 Genetic resistance of ruminants to gastrointestinal nematodes

Susceptibility to numerous parasite infections varies significantly across individuals. Genetic factors account for some of this diversity in vulnerability. The current issue is identifying the most effective means of utilizing the variety to enhance our comprehension of parasite infection and lessen the damage caused by parasitic disease. Understanding of resistance mechanisms is improved by locating the

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genes that affect resistance variance. However, further research is required to establish if these genes, individually or collectively, account for a significant enough fraction of the diversity in resistance to support marker-assisted selection. Comparing reactions between susceptible and resistant stock offers a valuable method for separating pathological, irrelevant, and protective responses [7]. Breed differences should make understanding the mechanisms underlying resistance to such infections easier, which should help improve treatments and vaccinations or identification of resistant sheep [7] or other animals The fact that some varieties of domestic ruminants are more resistant to certain parasite infections, such as coccidian protozoa, nematodes, ticks, and flies, than other breeds has aroused the curiosity of some researchers. The phenomena of trypanotolerance exhibited by West African humpless cattle, such as the N'dama, are likely the best illustration that survives in areas of heavy trypanosome challenge. Although it is believed that immune reactions may be involved, how these cattle control their parasitaemias is still unknown. In studies on helminth infections, Red Masai sheep from East Africa are more resistant to *Haemonchus contortus* disease than other imported breeds. In contrast, South African Merinos have been less susceptible to trichostrongylosis than some other breeds [8]. Compared to Merino or European breeds, the St. Croix, Barbados Blackbelly, and Florida Native (Gulf Coast) sheep breeds. are significantly more resistant to *H. contortus*. Merino, Scottish Blackface, and Finn Dorset sheep, all homozygous for hemoglobin A, develop smaller worm burdens after infection than their hemoglobin B homozygous or heterozygous counterparts, indicating that variations in hemoglobin genotypes within breeds reflect differences in susceptibility to *H. contortus* infection. However, under severe stress, these genotypic variations in susceptibility frequently falter. According to research conducted within a single breed in Australia, individual Merino lambs can be classified as responders or non-responders based on how they reacted to *Trichostrongylus colubriformis* infection and their genetic differences are passed down to the next generation. It has been demonstrated that genetics plays a role in tick resistance, particularly *Rhipicephalus* (Boophilus) resistance, which is higher in the humped (*Bos indicus*) Zebu breeds and lower in the European (*Bos taurus*) varieties. However, where cattle have a genetic makeup that is 50% or more Zebu, a high level of resistance is still feasible, permitting a restricted use of acaricides [8].

3.1.1.2 Host resistance against *Toxoplasma gondii* in the brain

To prevent the onset of toxoplasmic encephalitis, interferon (IFN)-dependent cell-mediated immunity is crucial (TE). *Toxoplasma gondii* in the brain is likewise controlled by the humoral immune system. T and B cells, non-T cells that make IFN, microglia, astrocytes, and dendritic cells work together to generate resistance. Interactions between these cells and the activation of effector cells that

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prevent intracellular parasite reproduction are mediated by other cytokines. In mice, the Ld gene gives resistance to the development of TE. The major histocompatibility complex contains these genes, which governs immunological responses. These genes seem necessary for determining the host's resistance to this infection. *T. gondii* strains also influence TE development [9].

3.1.1.3 Species resistance in animals against parasitic diseases

Animal parasites like *Cryptosporidium parvum, Fasciola hepatica, Trichinella spiralis*, and the asexual stages of *Toxoplasma* have a vast host range. Some of the exceptional host specificity of the numerous species of *Eimeria* is one example of how many parasites do not grow at all in hosts other than their natural ones. For instance, some *Ostertagia* larvae grow in sheep but relatively few of them mature into adults. However, with these unnatural hosts, particularly parasites that migrate through tissue, there can occasionally be serious effects, especially if the migratory path becomes unpredictable. An example of visceral larva migrans in children caused by *Toxocara canis* is accompanied by hepatomegaly and sporadically involves the brain and eyes [8].

3.1.1.4 Age resistance

As they mature, many animals have a greater resistance to developing initial infections with certain parasites. For instance, animals who are a few months old are more prone to acquire a patency in their ascarid infection. The majority of patent *Strongyloides* infections in horses and ruminants are found in very young animals. The parasites either stop growing or stop at larval stages in the tissues if hosts become infected at an older age. *Nematodirus battus* is not a very dangerous parasite for sheep older than three months [8]. Similarly, dogs gradually become resistant to *Ancylostoma* infection during their first year of life. On the other hand, most parasite organisms appear to have evolved a potent counter-mechanism if age resistance is present. *Toxocara vitulorum, Toxocara canis* and *Strongyloides* spp. are affected; they remain in the host's tissues as larval stages and only become active in the late stages of pregnancy to infect the unborn child in utero or through the transmammary pathway. The key hatching conditions for the egg in the case of *Nematodirus battus*, which enabling the parasites to survive as a lamb-to-lamb infection from one season to the next. These conditions include a prolonged cold followed by a temperature above 10°C [8].

3.1.1.5 Removal strategies for biting flies

Many studies have shown the high expenses incurred by flying parasites like Tabanid flies, which are widespread in Asia, East Africa, and the US. According to a study, a horse can be bitten by as many as 4000 tabanid flies in a single day, resulting in a blood loss of up to 0.5 liters; these insects also can transmit several

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diseases. Among the fly-repelling tactics used by ungulates include tail flipping, head tossing, muzzle flicking, and muscle twitching. When the severity of the biting flies is high, cattle engage in more fly repelling activity, The lowest number of biting flies are around those who actively participate in fly repelling [10, 11]. Elephants have thick, fly-resistant skin that covers much of their body and is impervious to gigantic tabanids. Asian elephants kept in captivity in Nepal had 43% less flies on their flanks when a branch was present to serve as a fly switch than when one was not [15]. In other experiments, when branches were excessively long or bushy, elephants changed them into switch-size branches [16].

3.1.1.6 Avoidance and eradication strategies for ticks

Due to the fact that ungulates graze on grasslands, ticks prey on them. It is possible to lose a lot of blood after ingesting pregnant female ticks. A single engorging tick, for instance, has been found in studies on growing cattle to reduce a growing calf's annualized weight gain by 3 kg [17, 18].

Before making their way to the head, neck, or hindquarters, where oral grooming is ineffective, ticks climb up legs and over shoulders. The first line of defence against ticks for the majority of ungulates is to swipe the tongue or lower incisors over the shoulders and trunk. Grooming in eastern and southern African antelope has been thoroughly studied. Antelope sweep their lateral incisors over their shoulders, bellies, and flanks while grooming, likely catching the majority of flying ticks [19]. These lower incisors form a tooth comb that makes it simpler to remove mature ticks [20].

3.1.1.7 Avoidance and removal strategies for fleas

Fleas are the most common ectoparasite on cats. Fleas are difficult to get rid of and bounce around the body, in contrast to ticks which move slowly. Cats have tongues with papillae that have cornified. The papillae aid in both flea catching and maintaining the health of the cat's fine fur coat [21].

3.1.1.8 Medicinal herbs used by animals for the treatment of parasites and pathogens

Herbal medicine and modern pharmaceuticals have their roots in ancient herbal therapies for parasite and pathogen eradication, as well as preventing serious diseases in humans and animals [22]. The observation of a sick chimp extracting and consuming the bitter pith of a *Vernonia amygdalina* plant, which is known to have antibacterial qualities, provided the most persuasive proof of the use of herbal therapy for ailments in animals [23]. A special feature of animal herbal treatment is the use of anthelminthics from a "pharmacy in the woods" to remove intestinal parasites from an animal's digestive tract. The regular ingestion of full leaves of indigenous plants (*Manniophyton fulvum*) by chimps [24] and bonobos [25]

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resulted in the purging of intestinal parasites, according to studies. Chimpanzees in the wild eat plant leaves that pass through their intestines. In other instances, the plant material increases intestinal motility, removing nematodes from the intestine.

3.1.1.9 Mechanism of the immune response of teleost fish to helminth parasite infection

Environmental, hormonal, dietary, and life stage variables can all have an impact on the immune response in teleost fish [26]. One of the most important defence mechanisms of fish intestines against parasites is hyperplasia of mucus-producing cells [27]. When helminth infections induce tissue damage, innate immune cells, such as ILC2s (type 2 innate lymphoid cells), respond quickly by producing cytokines and chemokines, which deploy neutrophils, basophils, and eosinophils [28]. Depending on the type of damage a parasite does and how deeply it infiltrates a cell, different responses result from infection. Granular leukocytes called rodlet cells are only seen in teleost fish. They are typically called in when hazardous chemicals or helminth infections are present in tissues [29]. These cells support the inflammatory response when helminths are merely clinging to the intestinal epithelium; however, when penetration into the intestinal wall deepens, the presence of granulocytes and macrophages increases [30]. Mast cells have been found in significant numbers in fish parasitized by helminths, demonstrating that this cell type is connected to the defence against these parasites. Damage-associated molecular patterns (DAMPs), also known as alarmins, are released by damaged/dead cells when parasites infiltrate the host's tissues and encourage inflammatory responses. Alarmins stimulate leukocyte recruitment into the infected area by inducing the production of pro-inflammatory cytokines and chemokines by local mast cells, dendritic cells, and macrophages [12]. The local release of cytokines and chemokines is stimulated by tumor necrosis factor (TNF), which in turn enhances the presentation of antigens, phagocytosis, and co-stimulation of T cells. The transition from the inflammatory phase, which is dominated by neutrophils, to the phase, which is dominated by macrophages, appears to be mostly mediated by interleukin-6 [31].

3.1.1.10 Nonspecific immune response mechanisms to *Haemonchosis contortus*

The *H. contortus* larvae need a gastrointestinal niche that promotes development and expansion while shielding them from host barriers such as mechanical (peristaltic movement) and chemical (abomasum mucus). The larvae's motility and parasite load both contribute to parasite colonization in the host abomasum. After being sensitized by past infections, certain hosts can adjust the microenvironmental properties of their niche to expel the parasite [13]. Complement fixation is one

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of the earliest intrinsic reactions to *H. contortus* infection. Numerous studies have discovered that helminths bind certain molecules (opsonins) on their surface and activate the alternative complement pathway [32]. Vasoactive and chemotactic peptides (C3a and C5a) are produced after complement activation in larvae, and they mobilize eosinophils to the infection site without relying on particular pathways (CD4+ and IL-5). Additionally, *H. contortus* releases chemo-attractants for neutrophils and eosinophils, which intensifies the inflammatory response [33]. The thymus-independent rise in tissue eosinophils, which enhances complement activation and eosinophil cytotoxicity against larvae in the early stages of infection, is a crucial innate response in the absence of particular antibodies. Inflammation caused by the alternative complement pathway and driven by mast cells and eosinophils is linked to the rapid clearance of parasites in rats following the initial infection [32].

3.1.1.11 Effector Immune Mechanisms against Helminths

Infections with helminths are accompanied by hypereosinophilia, IgE production, mucosal mastocytosis, and goblet cell hyperplasia [34]. Depending on where the helminth is located, these immunological characteristics play a significant role in various effector pathways. There have been described a number of defences against parasites that live on tissues. These parasites are frequently the larval stages of trematodes (trematodes that move through tissue, such as *Schistosoma* species, *Fasciola* species, or nematodes). Eosinophils, neutrophils, macrophages, or platelets are examples of effector cells in antibody-dependent cellular cytotoxicity (ADCC), and IgE, IgG, or IgA are the antibodies [35–38].

3.1.1.12 The role of eosinophils in nematode infection protection

Parasite infections, especially those caused by nematodes that invade tissues, trigger a potent Th2-type immune response that raises the levels of immunoglobulin E and eosinophil in the blood and tissues. Eosinophils are effective against nematode larvae, although not all helminth infections can be treated with them. The activation of acquired immunity results in a significant accumulation and activation of eosinophils, which affects the worm larvae, when a host is infected by a nematode species that has previously been encountered. It has been demonstrated that eosinophils play a part in host defence, inflammation, and immunomodulation. Eosinophil generation and activation are mainly regulated by the innate lymphoid cells of group 2 and Th2 cells, interleukin (IL)-5.

Non-antigen-specific immune activation that defends the host by causing group 2 innate lymphoid cells and Th2 cells to produce the cytokines interleukin (IL)-5 and IL-13 in response to IL-33 stimulation. Migration of larvae from a species distinct from the one previously encountered causes this immunological response.

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Eosinophils are essential in the destruction of migratory larvae. So, both antigen-specific and non-antigen-specific mechanisms by which eosinophils support host defence [39].

3.1.1.13 ost resistance of gut nematodes depends on resource availability

Dynamics between hosts and parasites can be significantly changed by resource availability. In addition to giving hosts more resources to fight infections, an abundance of food can make hosts more tolerant of illnesses by lowering the competition for food between hosts and parasites [40]. The availability of resources may affect an animal's capacity to resist and tolerate parasites, regardless of whether the parasites consume the resources the host requires or host tissue. For many vertebrate host species, a better food supply lowers the amount of parasites that feed on host tissue [14], suggesting that these hosts are devoting additional energy to fend off their parasites and the tissue damage that goes along with them. Contrarily, greater availability of food for other animal hosts, like *Daphnia*, encourages increasing tolerance of the parasites that they share food with, may be because less competition exists when there is more food available to both the host and the parasite [41]. Contrary to what researchers predicted, a low-resource diet improved host resistance to worm formation in the stomach [42]. It was also suggested that by starving the parasite, a low-resource diet may improve host immunity and resistance to infection. For instance, the increasing consumption of glucose by domesticated animal hosts can reduce their immune system's defences against gastrointestinal nematodes.

3.2 Future Prospects

In the context of animal ecology and evolution, the study of host tolerance is still in its infancy and is being put to the test in various settings. Over the course of the infection, the life of the host, and in response to environmental cues, tolerance might change. Diversity in tolerance is a pervasive feature, just as hosts differ in resistance. Given that some theoretical models suggest that tolerance will be driven to fixation in a population, the existence of diversity in tolerance is intriguing. The idea of tolerance is proving to be valuable, but as others have pointed out before us, different research applies it in different ways. The parasite's qualities and the host's traits work together to determine the host's fitness. In fact, separating the two and determining correlation can be challenging or perhaps impossible. However, research that emphasizes tolerance has the potential to increase both general immunology and our understanding of the ecology of host–parasite relationships.

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3.3 onclusion

This chapter discussed the importance of understanding natural resistance of prospective hosts toward animal parasites, particularly their relationships. Such interactions may have a considerable impact on host–parasite evolution, which may help us predict the outcomes of future parasite–host interactions. Numerous studies have demonstrated the genetic interaction between hosts and parasites as well as the wide genetic heterogeneity in host responses to parasites. The main factor affecting a host's resistance to parasite infections is its immunological makeup. In addition to age, other factors such as resource accessibility, host avoidance behaviors, or others may enhance host resistance against animal parasite control.

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4

Immune Response against Protozoan Parasites

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4.1 Introduction

Following the entry into the host organisms, parasites first come in contact with specialized cells (antigen-presenting cells). These cells either induce phagocytosis by eating-up the whole parasitic protozoa or attack on the proteins produced by the invading protozoa. The antigen presenting cells possess intense inducible expression of major histocompatibility compounds (MHC). These compounds are involved in the presentation of engulfed proteins/antigens produced by the parasitic protozoa to the T-cells, which in turn, play important roles in immune response [1–3]. Therefore, the immune defense mechanisms, both antibody- and cell-mediated, are often stimulated by parasitic infections, and the responses that are most effective are dependent on the specific parasite and the stage of infection. Inside the T-cells, the $CD4^+$ cells, T-helper (Th) cells, display major modulatory action in the immune response. Based on the type of the invading parasitic protozoa, the $CD4^+$ cells turn into distinct subunits known as the Th1 and Th2 cells.

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This process was proposed by Mosmann and co-workers and with modification stated to be a valuable paradigm [1, 4]. The Th1 $CD4^+$ cells stimulate the cell-regulated cascade of effector mechanisms. Also, an immune system stimulus involving Th1-type is associated with synthesis of interferon-gamma (IFN-γ), interleukin-12 (IL-12), and other meditators. Th1-type immune response is also linked to potent stimulation of monocytes and macrophages, however $CD8^+$ cells are involved in fighting various parasites in cells. On the other hand, the immune response involving Th2 type is linked to the production of IL-13, IL-5, IL-4 and other mediators as well as significant production of antibody. The pathway is efficacious against invading parasites found outside of cells [1].

However, protozoans such as *Plasmodium* and trypanosome have developed a variety of ways to evade host immune systems, and their structures and metabolic processes are unique to each species. To get around specific immune reactions, some parasitic protozoans have devised new ways to provoke diverse kinds of immune responses in host organisms. In contrast to fungi, bacteria, and viruses, protozoans cause distinct immune reactions [5, 6], but certain protozoans that cannot be eaten by macrophages and can survive and even multiply inside of them. For instance, *Trypanosoma brucei*, an external parasitic protozoon that can produce an immunological reaction [7]. To protect against *Leishmania* sp. infections, the host immune system relies on $CD4^+$ T lymphocytes, which recruit macrophages as effector cells and regulate them with Th1-type cytokines. Each species of *Plasmodium* has its own unique set of defense mechanisms. These range from cell-based to humoral, depending on the antigen and the protozoan's location [8].

Cytokines, important components of the immune response in host organisms, help to maintain a proper balance between the adaptive and innate immune system responses, which are critical in managing both infectious and chronic illnesses. Interferons (IFN), a broad group of cytokines, were initially discovered as a response to a viral infection. Because of their ability to prevent viral replication in mammalian cells, these antiviral factors are known as IFNs [9]. There has been a plethora of investigations since their discovery, leading to the discovery of other chemically related substances. Inflammatory factor nuclear antigens come in three varieties: type I, type II, and a newly discovered type III inflammatory factor nuclear antigens. In terms of structural characteristics and receptor molecule affinities, they fall into distinct categories [10]. Antigen presentation and natural killer (NK) cell activity can be enhanced by IFN-1. Their management is also assumed to be facilitated by antigen-specific B cells, as well as immunological memory against a variety of diseases [11]. However, IFN-1 can exacerbate disease in some situations, and these fundamental traits are important in limiting pathogen proliferation in the great majority of the time. There are number of parasitic diseases caused by protozoans, this includes trypanosomiasis, leishmaniasis, malaria, and toxoplasma, which disproportionately impact

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people in under-developed nations [12]. The present chapter highlights the various mechanisms used by parasitic protozoans to stimulate immune responses in host organism.

4.2 Specific Immune Response to Protozoa Infections

4.2 *Plasmodium* Species-Induced Immune Responses

Diseases caused by *Plasmodium* parasites are usually deadly if not treated. *Plasmodium* parasite induced immune responses is stimulated by the release of sporozoites from bites of a mosquito on the skin of a host organism. In the outer layer of the skin (dermis), the sporozoites are acted upon by innate immune system involving macrophages, neutrophils, mast cells, dendritic cells, γδ T cells, NKT and NK cells. In other parasitic protozoans, neutrophils are among the initial immune responses to mosquito sporozoites. The neutrophils can be seen in the dermis after twenty minutes of infection [13]. But, the depletion of neutrophil seen in infection induced by sporozoite does not influence parasite development and distribution in the hepatic cells, indicating redundant compensatory actions for other types of cell [14]. In the hepatic cells, sporozoites of *Plasmodium* infect the liver and transform into merozoites. The liver macrophages (Kupffer cells) are involved in vital functions, in engulfing the parasites, and reduction in Kupffer cells elevates the sporozoite invasion of the liver cells [15]. In addition, other cells of innate system including eosinophils, neutrophils, macrophages and monocytes, all attack the hepatocyte in response to sporozoite. This attack is potently linked to BALB/c mice resistance to infection induced by *P. yeolii* and *P. berghei* [16, 17]. Once the disease progresses to the red blood cell stage, major innate system mechanisms for removal depend on the potential of macrophages and monocytes to ingest and remove the infected red blood cells [18]. CD36 is a vital receptor for the clearance of infected red blood cells. Moreover, individuals that lack CD36 are more susceptible to malaria infection [19, 20]. In addition to their actions of overwhelming and inhibiting cells infected by *Plasmodium*, the innate immune cells release cytokines including IL-12, and IFN-γ, in response to molecular patterns linked to *Plasmodium*, which include hemozoin, DNA, RNA, and glycosylphosphatidylinositol [21]. Both IL-12 and IFN-γ enhance resistance against infection induced by *Plasmodium*. Although, *Plasmodium* RNA recognition via the MDA5-MAVS cascade stimulates responses of the type 1 IFN that result to protection in certain experimental conditions, Toll-like receptor (TLR)-MyD88-controlled *Plasmodium* pathogen-associated molecular pattern recognition enhances pathogenesis of *Plasmodium* parasites. Also, MyD88 experimental mice have significantly increased resistance to *P. berghei* and *P. chabaudi*, and antagonists of TLR confer protection from malaria of the cerebrum in mice

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[21]. Both $CD4^+$ and $CD8^+$ cells are employed in vital functions in conferring protection against *Plasmodium* disease [22]. The $CD8^+$ T cells are vital for mediating and attacking the plasmodium parasite at the hepatocyte level [23–26], while $CD4^+$ T cells play an essential role at both blood and hepatic stages against the parasites of *Plasmodium* [27, 28]. However, a work indicated that $CD4^+$ T cells are vital in conferring protection while the $CD8^+$ T cells are not too significant [29]. Therefore, the organized coordination between T cells is vital for inducing protection against the malaria parasite [18].

4.2 Trypanosome-Induced Immune Responses

Innate immune cells such as monocytes, macrophages, neutrophils, dendritic cells and NK are involved in the vital role of mediating trypanosome infections such as from *Trypanosoma cruzi* in host cells. *T. cruzi* recognition by the innate immune cells is vital in the production of protective compounds such as IFN-γ, nitric oxide, tumor necrosis factor (TNF)-α, and IL-12. Experimental mice lacking IFN-γ, inducible nitric oxide synthase, and IL-12 are strongly susceptible to infection caused by *T. cruzi* [30–32]. Reduction in BALB/c mice neutrophils and macrophages is detrimental in infection caused by *T. cruzi*, showing that these mediators are vital and the same important actions for NK cells were indicated by depletion researches [33, 34]. Cytotoxic processes are not directly involved in NK cells; however, they are the main source of IFN-γ. The IFN-γ signal transduction is vital for macrophages to potently attack *T. cruzi* in cells. In another study, experimental mice deficient in MyD88 were found to be strongly susceptible to infection induced by *T. cruzi* due to defective synthesis of pro-inflammatory protein such as IL-12 and IFN-γ. Efforts to locate upstream TLRs that identify ligands of *T. cruzi* showed TLR9, TLR7, TLR4 and TLR2 as potential innate receptors [35]. TLR4 identifies glycoinositolphospholipid and TLR2 identifies *T. cruzi* glycophosphatidylinositol. Also, TLR9 and TLR7 identify DNA and RNA fragments derived from *T. cruzi* respectively. Although, TLRs deficiency leads to elevated *T. cruzi* susceptibility, the infection in such deficient experimental mice is less affected compared to $Myd88^{-/-}$ mice, indicating incomplete redundancy within the TLRs [35].

Adaptive T cells are involved in the vital role of conferring protection against infection induced by *T. cruzi*. Mice lacking either $CD8^+$ or $CD4^+$ T cells have greater susceptibility to infection caused by *T. cruzi* [36, 37]. Subsequent to activation, IFN-γ-derived T-cells ($CD4^+$ and $CD8^+$ T cells) that cause stimulation of phagocytes such as macrophages, enhance killing of the parasite [38–40]. Furthermore, $CD8^+$ T cells specifically, can phagocytize cells that are infected. However, the adaptive response of the immune system is not adequate establish a sterilizing immunity, and the parasitic organism can form potent detrimental infections in most people [18].

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4.3 Immune Evasion Mechanisms of Protozoan Parasites

Malaria, leishmania, trypanosomiasis, and amoebiasis are protozoan infections that cause some of the most lethal and frequent human diseases. The ability of protozoans to infiltrate and develop inside cells makes them change antigens found on their surface, and remove their protein coating. Also, they are able to remain undetected by the host immune system for long periods of time [41]. Antigenic mimicry, which is common in parasitic infections, can cause immunosuppression directly or indirectly. Activation of a specific subset of Th cells is one of the most difficult evasion tactics. To protect the body, the host has a vast range of defense systems, from simple barriers to highly complicated devices that can recognize and eliminate pathogens. While the humoral immune response targets parasites outside the body, the cell-mediated immune response targets parasites inside the body. Parasites can survive in the host despite the host's immune and inflammatory reaction to the parasite and its large amount of antigen. This is because parasites have evolved numerous evasion mechanisms during many years of evolution [2]. The evasion methods used by parasites differ depending on their life cycle stage, the point of entry into host organisms, and the environment they find themselves.

4.3 Malaria

Malaria infection is caused by *Plasmodium vivax*, *P. falciparum, P. ovale*, and *P. malariae*. Intracellular and extracellular stages are both part of the infection's life cycle. Due to low sporozoite density and rapid migration to the liver, the host's immune response is limited in the early stages of the disease. There are two ways for a parasite to survive: first, by infecting hepatocytes and then by becoming a merozoite. After establishing itself in the host, the *Plasmodium* parasite evades the immune response of the host organism by altering the antigens on its surface throughout its life cycle [42]. Thus, each stage is associated with the expression of species- and stage-specific proteins, many of which are introduced into the red blood cells it infects or membrane of the parasite. Stage-specific proteins are challenging to immune response because of their high polymorphism or antigenic variability. Circumsporozoite protein (CSP), an antigen on malaria sporozoite surface that is susceptible to sequence polymorphism, is just one example among several *Plasmodium* proteins. Antigens with frequent repetitions can inhibit the synthesis of high-affinity antibodies and maturation of antibody isotype as superantigens of B-cells and essentially activating a polyclonal humoral response that is dependent on the thymus [43]. Antibodies are rendered useless by plasmodia, which shed their surface CSP coat while the extracellular malaria phases are still present in the bloodstream for only a short time, for example, in mammalian cells [44]. CSP

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has been shown to inhibit RNA translation through its RNA-binding motifs. For instance, the *P. falciparum* merozoite surface protein-1 causes blocking antibodies, which bind anywhere on merozoite surface protein-1 and prevent real inhibitory antibodies from binding [45]. Aside from CD36 and intracellular adhesion molecule-1, a protein of *P. falciparum* protein known as PfEMP-1, which is produced on infected erythrocytes surfaces, enhances vascular endothelial adhesion via CD36 and intracellular adhesion molecule-1. Based on this, infected cells are not transported to the spleen for phagocytosis because of their significantly altered appearance. Because of antibody syntheses for anti-PfEMP-1, the PfEMP-1 protein is subjected to clonal variation many times [46].

Molecular mimicry, which affects cellular immune response and cytokine release, is thought to be responsible for some of the clinical characteristics of malaria. Macrophages produce more TNF and IL-1, which induces the synthesis of acute-phase proteins and malarial fevers [47]. Two *P. falciparum* proteins with sequences like 1-thymosin have also been discovered, according to a study (a hormone from thymus that regulates T cells development). These peptides, like the human hormone, altered T-cell maturation in a comparable way, suggesting that they could interfere with the development of an effective cellular immune response. People with human malaria may develop autoantibodies because of molecular mimicry and B-cell activation [48]. Autoantibodies have been discovered in DNA from erythrocytes, carbohydrate epitopes, heat-shock protein 70, and polypeptide. The relationship between autoantibodies and malaria pathogenesis has been disputed. According to recent studies, autoantibodies may play a role in protecting against malaria. Despite the wide variety of surface proteins found on *Plasmodium*, some internal antigens appear to be substantially conserved among the many *Plasmodium* species. According to research, schizont antigens appear to initiate a cytokine cascade that is associated with most of the symptoms and pathologies linked to the infection [49, 50].

Infection with acute malaria reduces the immune response temporarily. Peripheral blood mononuclear cells' lymphoproliferative response and cytokine production are both diminished when stimulated by malaria antigens [51]. The number of T lymphocytesis also lowered. Activated macrophages' prostaglandins could be to blame for this effect, which indomethacin can partially mitigate. Releasing acute-phase proteins, which cling to lymphoid cells' surfaces, slows the development of lymphocytes. Some malaria antigens, however, have been proven to cause immunosuppression in the body on their own. In experimental mice, antigen-specific responses to *P. berghei* and *P. falciparum* schizont extracts have been found to be decreased [52]. Although parasite hemozoin accumulation has been postulated to inhibit macrophage auxiliary function, the mechanisms responsible for suppression are still speculative. Certain strains of *P. falciparum* exhibit CSP variations with T-cell epitopes identical to the original CSP, according to a recent investigation of the immune response against it.

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Memory T-cell effector functions such as synthesis of lymphokine, proliferation and cytotoxicity are altered by changing T-cell epitope binding to MHC. Spirochetes need MHC-class I alleles to attach to hepatocytes during the liver stage of infection.

4.3.2 African Trypanosomiasis

Humans are infected with two strains of trypanosomes (*T. brucei rhodesiense* and *T. brucei gambiense*) that cause African trypanosomiasis, while cattle are infected with four different strains of the parasite (*T. brucei brucei*, *T. vivax*, *T. evansi* and *T. congolense*) [53]. Antibody-mediated elimination is a possibility for eradicating these trypanosomes because they are present in the circulation and do not have intracellular stages. Liver macrophages remove the vast majority of trypanosomes from the circulation. But, the remaining parasitic organisms are able to survive and spread disease because of antigenic polymorphism in the so-called variant surface glycoprotein (VSG). Many VSG genes are present on a single trypanosome, and each encodes a unique main sequence, particularly at the N terminus [54, 55]. An unexpected fact is that one VSG gene is only expressed by each parasite in turn, with the previous gene being replaced at its telomeric active transcriptional location. Thymus-independent humoral response is circumvented by trypanosomes, which can escape it through a reoccurring antigenic shift inside the VSG. This leads to a cycle of parasitemia that is similar to that of being infected by closely related but distinct diseases. As a result, it's been challenging to create a vaccine [56].

In order to understand the mechanism used by a parasitic organism to interfere with host immune system and affects cytokines and other mediators, researchers have looked into how the parasitic organism interacts with host immune system and allows the progression of the disease. B and T lymphocyte populations are changed in several ways during parasitemia. Reduction of thymus-independent humoral response against persistent *Trypanosoma* antigens, but thymus-independent humoral response against VSG surface epitopes is likely to prevent repeated parasitemias. Additionally, trypanosome products alter the pattern of cytokine release in macrophages and $CD8^+$ T cells. VSG's glycosylphosphatidylinositol group causes macrophage over-activation and the release of TNF-α by suppressor macrophages [57], which causes $CD8^+$ T cells to produce considerable IFN levels [58], which is analogous to the parasite protein T-cell-triggering factor. The proliferative T-cell response is impaired and parasite eradication is impaired when IFN levels are high enough to suppress synthesis of IL-2 and the expression IL-2 receptor. A new research shows that trypanosomes and *Leishmania* share numerous genes expressing glycoprotein 63-like proteins [59]. Even if their function is uncertain, they may be involved in a major part in the immune evasion of trypanosomes. Glycoprotein 63-like protein on the parasite's

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surface corresponds with its vulnerability to complement-mediated lysis in different stages of the parasite. Unlike procyclic trypanosomes, which are sensitive to the glycoprotein 63-like protein, blood trypanosomes are resistant to it.

4.3.3 merican Trypanosomiasis

According to recent studies, children and neonates who are infected with the parasitic organism (*T. cruzi*) that induces American trypanosomiasis (Chagas disease) usually die. Adults, on the other hand, are more likely to acquire a chronic sickness after an initial infection, leading to a syndrome known as megacardia with mega-esophagus, mega-colon, and degeneration of the peripheral and central nerve systems [60]. Antibody defense mechanisms are in action during infection, which contributes to the long-term effects on health as well as any pathological changes. An immune response suppression is often present, which becomes more apparent as the parasitemia moves through tissues and into other organs. Surprisingly, the phagocytic activity of immunosuppressed mice was significantly increased, suggesting that the inhibition of the mononuclear phagocytic system is not the source of the immunosuppression. There was a similar condition of elevated mononuclear phagocytic action and substantial immunosuppression in *P. vinckei* experimental infections [61]. *T. cruzi* also avoids harming macrophages by infiltrating non-phagocytic cells and altering the transcriptional pattern of cytokines generated. It has been shown that the glycosylphosphatidylinositol-anchored mucin AgC10 of *T. cruzi* connects to macrophages and enhances the release of IL-1, but not TNF-α or IL-12. Both proteins are crucial in the protective response to Chagas disease. Infected macrophages also produce IL-10 and transforming growth factor, which limit IL-12's induction and effects [62]. T-cell immunosuppression has been confirmed following an experimental infection with *T. cruzi*. Lymphocyte receptor expression such as IL-2R and cytokine production in the effector phase of the immune response are negatively affected by parasite chemicals. The spleen-associated non-adherent Thy-1^+ Ly-2^+ cells may be involved. A protozoal infection, like others, causes an immune system overproduction of immunoglobulin M antibodies when *T. cruzi* makes polyclonal B-cell activation. *T. cruzi* parasite eradication in mice is hampered by the attachment of these antibodies to the surface of trypomastigote and disruption of immunoglobulin G inhibitory antibodies binding. As a result, polyclonal B-cell activation can activate B lymphocytes that recognize autoantigens [63], leading to autoimmune illness in people infected. *T. cruzi* generates chemicals that are like those found in host cells, confusing the immune system, and causing autoimmune illness. It's unclear whether parasite or host antigens cause host cell death in an autoimmune reaction. To survive in vertebrate blood, *T. cruzi* utilizes anti-complement surface molecules such T-decay-accelerating factor (DAF), glycoprotein 58/68, and

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glycoprotein 160, as well as the endocytic pathway to turnover surface molecules and phospholipases to breakdown anchoring glycoproteins [64].

4.3.4 Amoebiasis

The parasite *Entamoeba histolytica* causes intestinal amoebiasis. The parasite's ability to lyse its hosts is vital. The amoebic granules' aggressive components, cystine proteases and hydrolytic enzymes, lead to host cell and tissue destruction. Antigens for immunoglobulin G and A are degraded by proteases [65]. This is critical because *E. histolytica* must overcome both secretory immunoglobulin A and serum immunoglobulin G antibodies to colonize and spread outside the intestine. When entering the host's tissues, amoeba trophozoites acquire complement-mediating substances and inactivate C5a and C3a regulators, avoiding complement's lytic action and the inflammatory response. *E. histolytica* uses a sophisticated method that guides antibodies deposited on the organism's surface toward the uroid area, where they are naturally removed as molecular clumps (capping) [66]. Amoebic liver abscesses in convalescence are thought to be associated to tissue invasion by *E. histolytica*, which has been repressed by cell-mediated immunity in the extra-intestinal amoebiasis cases including amoebic liver abscesses. *E. histolytica* affects T cells (particularly Th1 response) and macrophages in a variety of ways. Uninfected cells' IL-2 production seems to be suppressed by a soluble suppressor found in the serum of infected host organism. Phorbol myristic acid acetate or IL-2 in conjunction with ionomycin can reverse it, suggesting a problem with signal transmission [67].

The cytotoxic and cytokine-secreting abilities of macrophages are decreased during the acute phase of amoebic liver abscess. *E. histolytica* trophozoites uses monocyte locomotion inhibitory factor to suppress human macrophage respiratory burst. Direct exposure to *E. histolytica* and its products appears to inhibit macrophages for the parasite. MHC molecules related to the I region (Ia molecules) were not produced in mouse macrophages *in vitro* when amoebic antigens were present. When amoebic induction is active, *E. histolytica* or macrophages release prostaglandin E2, which was the source of the impact because cyclooxygenase inhibitors reversed it [67, 68]. When prostaglandin E2 activates the macrophage phosphokinase A pathway, it raises cAMP in macrophages, which decreases the production of Ia substances on the surfaces of macrophage and the formation of Th1 factors including IFN and IL-2 by T cells. There is no TNF-α production by macrophages in the peritoneum or the blood of people with acute lymphocytic leukemia, but there is by hepatic cells and macrophages in animals with infection. In vitro proliferation of mice-derived spleen cells injected with a 220 kDa surface protein failed, despite the presence of Th2 mediators such as IL-10 and IL-4. After the parasite has invaded the liver granuloma, *E. histolytica* may alter macrophage or T cell activity and cytokine production to aid its own survival [69].

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4.3.5 Leishmaniasis

It is possible to classify human leishmaniasis into three distinct categories: skin, mucosal and visceral. In order to infect cells, *Leishmania* relies on the host cell's ability to phagocytose it, as it lacks a specific method of penetration. Host cell attachment and uptake of promastigotes is facilitated by the surface-exposed protease glycoprotein 63 and a lipophosphoglycan, while macrophage proteolytic activity is suppressed [70]. The immune evasion activities of these chemcials appear to be complementary, which is surprising. Since lipophosphoglycan prevents parasites from merging with the cells' lysosomes, it helps promastigotes survive *Leishmania donovani* infection earlier on. It's possible that glycoprotein 63 blocks the degradation of the phagolysosome if the phagolysosome does form. They become amastigotes inside the macrophage because this stage of the parasite is more active in an acidic environment compared to non-acidic one. A lack of enzymes like catalase and super oxide dismutase means that promastigotes have to rely on their ability to prevent the cellular burst in order to survive. Glycoprotein 63 and lipophosphoglycan scavenge oxygen intermediates directly by preventing protein kinase C from undergoing an oxidative burst and decreasing its membrane translocation. Oxygen intermediates can be directly scavenged from lipophosphoglycan's structure, which contains repeating oxidizable phosphorylated disaccharide units [71, 72].

Apoptosis, MHC presentation, and cytokine responsiveness are all suppressed by the parasite, allowing it to persist within the macrophage. According to prior studies, stimulation of GMCSF and TNF-α is associated with a decrease in apoptosis. MHC class-1 and class-2 molecules, and the loading of peptides onto those few MHC molecules produced in macrophages driven by IFN-γ are all inhibited by *Leishmania* components like glycosylinositolphospholipids. *L. major* and *L. donovani* glycoprotein 63 proteins cleave CD4 structures on the surface of T cells, breaking the connection between T helper cells and antigen-presenting cells [73]. The antigen (which is heat-stable) and B7-1 are two examples of the macrophage co-stimulatory molecules that amastigotes suppress production of in addition to internalizing and degrading class II MHC molecules. *Leishmania*, like *E. histolytica*, secretes glycoprotein and transforming growth factor, which suppresses macrophage function. Lipophosphoglycan is used to inhibit neutrophil and monocyte chemotaxis as well as to modulate infected macrophage response by downregulation of TNF-α receptor expression. Perhaps the parasite's methods of avoiding complement are among the most complicated ever evolved by a living thing [67]. To tolerate complement, metacyclic promastigotes shed the membrane attack complex (C5b–C9) on their surface, which may be due to lipophosphoglycan structure elongation on the surface of those promastigotes. When C3b is transformed to C3bi on its surface, gp63 protects the parasite. C3, C5, and C9 are all components of the complement system that can be phosphorylated by *Leishmania* kinases, which

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would prevent either pathway from being activated. An immune response based on a Th1 reaction has been shown to be effective in preventing *L. major* infection, while susceptibility appears to be associated with a Th2 response. Instead of increasing IL-12 production, *L. major* metacyclic promastigotes have been reported to actively inhibit the transcription of the gene. Because interferon-gamma (IFN-γ) production is primarily stimulated by IL-12 production, and because IFN-activated macrophages can kill *Leishmania*, reducing the synthesis of IL-12 is expected to produce a significant survival benefit to *Leishmania* [74]. With these findings and their application to human patients, the future seems brighter.

4.4 Parasitic Protozoans and Their Mechanism to Induce Disruption of the Complement in Host Cells

Over the years of evolution, parasitic organisms including ectoparasites, parasitic protozoans, and helminths, have formed well-organized mechanistic actions as means of avoiding attack by the host immune system. The initial process formed was complement activation abrogation to attack the host immune clearance, mainly at the initial phases of attack. Complement system plays a vital role in the protection against infection induced by parasites, which depends on its lysis on attacking parasites via membrane attack complex formation, and serves as a connector to responses of the adaptive immune response. Parasitic organisms can execute many mechanisms that interrupt the actions of the complement in host cells as the first process to interrupt the immune attack in the host organism [75].

4.4.1 Host Regulatory Proteins Recruitment to Abrogate Complement Activation

Complement activation soluble modulator, known as C1 inhibitor (C1-INH), negatively controls the lectin and classical cascades by abrogating MBL-associated serine protease (MASP)-1, C1s and C1r, the stimulating proteases of the complement pathway [75]. *Plasmodium falciparum* (an intracellular protozoa) can aggregate and use C1-INH to abrogate activation of the complement system [76]. The invasive type of malaria (merozoites) translocate C1-INH to the surface when in-contact with human serum. pfMSP3.1 (one of the merozoite surface protein 2 family) act as a main interactive co-molecule to interact with C1-INH, to abrogate C1s, MASP2, and MASP1 [77]. Factor H (FH) from host complement system is the major inhibitor of the alternative cascade against the formation of C3-convertase. It stimulates the inhibition through promotion of the formation of iC3b from C3b. *Echinococcus granulosus* (a type of cestode that induces human cystic echinococcosis) presents a protein that aligns host FH on the wall of hydatid cyst to abrogate the complement C3b deposition [78–80]. It was later discovered that InsP6 was the binding

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molecule (which is a main part of the acellular laminated layer of the wall of the hydatid cyst) that interacts with host FH to abrogate the alternative cascade [81]. Also, cells of the epithelium found in the midgut of mosquito express 2 receptor proteins that interacted with host FH to abrogate deposition of C3b and impair the alternative complement cascade activation [82].

Another regulatory factor of the human complement system, DAF induces the increased decay of the C5 and C3 convertases by linking to C3b and C4b found on the membrane of cell [83, 84]. When incubated with human red blood cells, although not with erythrocytes lacking DAF, the blood fluke (*Schistosoma mansoni*), which induces schistosomiasis of the intestine, showed resistance to lysis of the complement system [85]. Another work indicated that the blood fluke obtained DAF from the red blood cell from host organism through glycosylphosphatidylinositol anchor expression on the worm surface. The potential of the *S. mansoni* worm to obtain DAF was decreased following treatment with trypsin [86]. Glycosylphosphatidylinositol-specific phospholipase D treatment promoted the interaction of DAF with the surface of schistosomula [87].

As a result of its action of inhibiting the cytolytic membrane attack complex, CD59 deceases the polymerization of C9 found on the surface of cell by intereacting with C9 and C8α. The CD59 glycosylation is associated with its complement-inhibitory action [88, 89]. The malarial parasite, *P. falciparum*, can obtain CD59 to impede invasion on the red blood cell that is infected. In addition, *P. falciparum* showed mannosyltransferase, which is involved in the synthesis of glycosylphosphatidylinositol, and then causes elevation in CD59 levels (which is a GPI-anchored protein) on the surface of cells, showing that the anchor with glycosylphosphatidylinositol is vital for CD59 expression on *P. falciparum*-infected erythrocyte surfaces [90]. *Trichomonas vaginalis*, which is an anaerobic flagellated parasitic organism, obtained CD59 from various cells in the host organism, including erythrocytes, during disease stage to inhibit the lysis of the parasite by the complement system of the host organism [91].

4.4.2 Expression of Homologous Proteins with Host Modulators of Complement System Activation

To prevent degradation controlled by the complement system, certain parasites show different types of surface complement regulatory proteins. As more genomes of parasites have been studied, helminths have been reported to show several mammalian-like receptor proteins for cytokines, growth hormones from host cells to control the development, reproduction, growth and signal cascade pathway of the parasite [92]. Furthermore, it was reported that parasites control the anti-parasite immune system of the host organism by showing host receptors of certain components of the immune system. The similarity of antigenicity between parasite- and

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host-expressed proteins may overwhelm the ability of the immune system of the host organism to recognize attacking parasites, and therefore prevent the elimination of the parasite [93, 94]. The host complement-orthologs are expressed by parasites to inhibit or regulate the activities of the complement system found in the host organism. A blood fluke, *Schistosoma japonicum* (which induces Asian schistosomiasis), expresses schistosome C2 receptor inhibitor trispanning (CRIT) protein that has similarities with CRIT of the host complement [95]. The expression is an indication of their presence in host organism stimulation. Furthermore, the schistosome-linked CRIT is found on the *Schistosoma* parasite tegument and it allows it to interact with C2 through a region found on the extracellular region. Subsequently, it abrogates the interaction of C2 and C4b, to disrupt the C3 convertase formation. The CRIT (a type of molecular mimicry) was showed to interact with a region that is similar to one domain found in human C4b. When C2 is interfered with, the lectin and classical complement cascade are impeded [96]. The schistosome CRIT C2 interacting region is found on 11-amino acids of the first extracellular region, which is vital in the decrease of inflammation mediated by the immune complex and classical complement cascade inhibition [97]. *T. cruzi*, the parasitic organism inducing American trypanosomiasis, also shows CRIT expression on the membrane of trypomastigotes to abrogate activation of the complement system linked to C2 [93].

Moreover, matured schistosomes show C3 receptor protein expression on the surface of their tegument. During stimulation of complement system, C3 interacts with the surface of the worm via the C3 receptor protein and activates the substitution of the tegument found on the outside region. This is then shed during the attack of the complement system [98]. The C3 receptor expression and C3-C3 receptor shedding allow parasites to consume serum C3, and then transform into non-stimulators of the alternative cascade [99, 100].

Also, the trypomastigote of *T. cruzi* expresses DAF on its virulent form to abrogate stimulation of the host complement system by C3 blocking, which is similar to DAF found in the host mammals [101–103]. Other works showed that *T. cruzi* expressed a glycoprotein gene (160 kDa) regulatory glycoprotein of the complement system on the surface of the trypomastigote. The glycoprotein 160 mRNA was found to share marked sequence of DAF gene-linked DNA homologous from the human host [104, 105]. Formation of the classical and alternative C3 convertase is inhibited by GP160 because it is part of the C4/C3 interacting group of complement mediators. The process above inhibits implication and activation of the host complement pathway on the surface of the parasitic organism [106, 107]. Another work showed that a schistosome complement inhibitor protein showed expression on the membrane of adult and larvae *S. mansoni*, and it is antigenically and functionally associated to human CD59. This protein interacts with C9 and C8 found in humans and impedes C5b-9 assembly [108]. Furthermore,

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other homologs of CD59 were discovered in the total genetic make-up of schistosome showing CCXXXCN as the consensus sequence at the C terminal region and around schistosome tegument found in the membrane fraction [109, 110]. A homolog of CD59 (FhCD59-1,2,3), was discovered on the surface membrane of tegument of *Fasciola hepatica* (a trematode). FhCD59-2 displayed a phylogenetic association with SmCD59-2 existing on *S. mansoni* membrane tegument [111]. But, isomers of recombinant schistosome CD59 in mammals indicated no abrogation of complement action in an *in vitro* study. This was proposed to be different from the activity of tegument-derived native proteins [112].

4.5 Cell-Mediated Killing Induced by Protozoans

Cell-mediated immunity serves as a key line of defense against protozoan infections. The effector cells immediately participating in the process include neutrophils, macrophages, and finally activated macrophages. There are huge differences in activity within this simple framework. To deal with a specific protozoan infection, effector cells from various animal species may be more or less effective, based on the species of animal and even the strain of the same species. Depending on the species, strain, and morphological shape of the protozoa in question, the sensitivity to cell-mediated death varies. They are the most vulnerable to attack from the vertebrate host if they are derived from insect vectors that have not yet acquired defense systems. *Trypanosoma promastigotes* and *Trypanosoma epimastigotes* are easily destroyed by antigen-presenting cells, whereas *Leishmania* trypomastigotes and amastigotes are far more resistant [18]. Microbic protozoa, such as *Leishmania amastigotes*, *Toxoplasma endozoites* (tachyzoids), and *T. cruzi* amastigotes with reticulotropic morphology, have developed extraordinary resistance to macrophage microbicidal activity, and this resistance has been passed on to the host cell. *T. cruzi* amastigotes that reside in muscle cells, in contrast to those from other strains, have not established this resistance to cell-mediated killing by macrophages. *T. brucei* and *Plasmodium* merozoites in the bloodstream are readily accessible protozoa that do not have the extensive resistance developed by reticulotropic protozoa. However, they do have some protection because phagocytic cells only attack them when a specific antibody is present, which is not always the case. This provides some protection. Neutrophils have a crucial role in granulocyte-mediated killing. Because of their small size, eosinophils don't seem to have much of an impact when they're mixed together with neutrophils. Among the protozoal species studied, only those of the *Trypanosoma stercorariana* genus have been demonstrated to be significantly influenced by eosinophilia. Eosinophils can kill parasite *T. cruzi* antibody-coated trypomastigotes, despite the fact that this has only been demonstrated in vitro. Even more strangely, this species appears to be the only one that can be infected by eosinophils, an extremely toxic immune

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system constituent that was found to be highly effective against helminth infections. Pathogens such as *Trypanosoma*, trypomastigotes of salivary, free merozoites of *Plasmodium*, promastigotes, and amastigotes of *Leishmania* are among those that neutrophils are ineffective in destroying [11].

4.6 Role of Inflammasome in Protozoan Infections

An innate immune system is critical in the quick identification and elimination of attacking organisms via various processes, including phagocytosis and the activation of inflammation [113]. Also, it is important in priming and stimulating the adaptive immunity, which leads to potent immunity. Cells of the host organism such as the myeloid and epithelial lineages, and others show several germline-encoded pattern recognition receptor proteins that identify polysaccharide, conversed protein, nucleic acid, or motifs, lipid and stimulate various inflammatory cascades. The pattern recognition receptors include TLRs, C-type lectin receptors, cytosol-based NOD-like receptors (NLRs), HIN200 proteins, and retinoate inducible gene-1-like helicase [114, 115]. To date, more than 20 NLRs in humans have been discovered. These receptors are associated with resistance to R protein of plant diseases and to apoptosis protease-stimulating factor 1 [116, 117]. They are similar to proteins with a tripartite structure containing of an N-terminal protein-protein interacting module, which can be baculovirus IAP repeat, a caspase recruitment domain (CARD), pyrin domain, and C-terminal agonist-sensing region, which in NLRs is a sequence of Leu-rich repeats, similar to TLRs [113]. The initial NLRs discovered were used determine bacterial peptidoglycan groups and stimulate inflammation by triggering MAP kinase and NF-κB cascades [118–121]. Additional work on the NLR class indicated that certain members can form inflammasome, which is a multi-protein complexes that aggregate and stimulate the activation pro-caspase-1 via adaptor proteins including apoptosis-associated speck-like protein consisting of a CARD [122].

Several inflammasomes such as members of the NLR class (NAIP5, NLRP3, NLRC4, and NLRP1) and recently, other inflammasomes such as inducible gene-1 and AIM2, have been described. Adaptor protein is needed for the recruitment of caspase-1 to the inducible gene-1 inflammasomes, NLRP3, and AIM2 whereas its action in NLRC4, NIAP5-associated complexes and NLRP1 is still speculative. After the stimulation of inflammasome, the pool of apoptosis-associated speck-like protein containing a CARD (ASC) in the cell turns into a big molecule known as pyroptosome, which is the region of activation of caspase-1. Inflammasomes are stimulated by various signals and may show redundant actions during the infective period. Impairment and or mutation or changes in mRNA encoding molecules of inflammasome were associated with human genetic diseases, such as a continuum of auto-inflammatory syndromes ranging from Muckle-Wells

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syndrome and familial cold urticarial to sepsis, Crohn's disease, neonatal onset multisystem inflammatory disorder, as well as susceptibility to infections induced by some pathogenic organisms [113, 123]. Caspase-1 processes several cellular substrates, which are requirement for inflammatory response induction. Specifically, pro-IL-18 and pro-IL-1β are converted into bioactive cytokine type's caspase-1 [124–126]. In addition, caspase-1 is necessary for the release of several pro-inflammatory mediators and they may not be required as substrate for caspase-1 [127]. Furthermore, excessive caspase-1 activation results to a type of cell death known as pyroptosis, which is characterized by necrosis and apoptosis [128, 129]. Among the several caspase-1 substrates, it has been indicated that the enzyme acts on enzymes of glycolysis, which may be the main mechanism to carry out cell death [113, 130].

4.6.1 Inflammasome and Protozoans

Malaria is caused by the *Plasmodium* genus, and it is endemic in sub-Saharan Africa and tropics [113]. The parasitic protozoa are transmitted by the bite of a mosquito into the host organism and then multiplies within red blood cells, following a period of incubation [131]. The breakdown of hemoglobin by the malaria parasite leads to heme removal from hemoglobin, which is thereafter turn into the crystalline molecule called hemozoin [132]. Recently, it was documented that inflammasome NLRP3 might be involved in a vital function of hemozoin identification. This crystalline product was shown to stimulate caspase-1 and active the release of IL-1β in a NLRP3 and ASC, however not NLRC4 in an in vitro model [133, 134]. This finding was not reproducible in the work of Griffith et al., [135]. In a more interesting way, NLRP3 deficiency and not caspase-1 or ASC elevated the survival of mice following injection with erythrocytes infected with *P. chabaudi adami*, a virulent strain found in mice [134]. Also, it was found that the mice induced with cerebral malaria using *P. berghei* showed a similar outcome that *Nlrp3*$^{-/-}$ mice, however not *Il1b*, *Casp1*$^{-/-}$, or *Asc*$^{-/-}$ mice, displayed more time to mortality compared to wild-type experimental animals [136]. Therefore, it was proposed that NLRP3 may possess harmful action in malaria of the cerebrum, and not be dependent on IL-1β and caspase-1 [113]. Consistent to this, it was discovered that mice with *casp*$^{1-/-}$ were similar to wild-type experimental mice in their response to the *P. berghei* and *P. chabaudi* malaria animal models) [137]. Contrarily, experimental mice lacking caspase-12 (inhibiting protein of NF-κB and caspase-1) displayed improved immune and inflammatory responses to the malaria parasitic organisms and were susceptible to malaria of the cerebrum. This phenotype was not dependent on caspase-1, but occurred from excessive activation of NF-κB and IFNγ synthesis [137]. Malaria parasites are among the most well-studied parasites in terms of activation of inflammasome and a detailed study of other helminths and protozoa may result in a clearer picture of the immune

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system response to these parasites and other unknown actions of the NLRs and inflammasome [113].

4.7 onclusion

Initially, the parasites and their antigens come in contact with antigen presenting cells to aid their presentation to the T-cells, resulting in immune response stimulation. This process stimulated the formation of Th1 and Th2 cells from the CD4 cells of the T-cells. Cell-regulated cascade, monocytes, macrophages, IFN-γ, IL-12 and other cytokines are stimulated by Th1 while antibodies, specifically IL-4, IL-5 and IL-13 are activated by Th2. Parasitic protozoans such as *Plasmodium*, *Trypanosoma* and others display different mechanistic actions for evading the host organisms and this depend on the stages of the lifecycles, their location in the host organism, and others. Furthermore, these organisms use various mechanisms to avoid host immunity (such as host complement activation and others) and inflammatory reactions, which are stimulated through the innate immune system of the host organisms and various unique pattern recognition receptor proteins including TLRs, and NLRs. Therefore, *Trypanosoma*, *Plasmodium* and other protozoans induce diseases in humans and animals through the invasion of various host immune systems and responses.

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