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Immune Response against Helminths

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5.1 Introduction

Numerous diseases that are hazardous to humans are transmitted by helminths, often known as worms. Parasitic worms can be divided into two major phyla: nematodes (or roundworms) and platyhelminthes (or flatworms), which are further subdivided into trematodes (flukes) and cestodes (tapeworms). Soil-transmitted helminths infect around 25% of the world's population, or more than 1.5 billion people. Some of the most common nematode species that infect people are *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, and *Ancylostoma duodenale*. Even exposure to a small number of these species greatly increases the risk of developing a condition that may persist for up to 20 years [1].

Macro-pathogen helminths produce compounds that act as modulators of phagocyte activation during infection by altering the microenvironment in which these cells engage in the induction and training of innate and adaptive immune responses [2]. An immune response of Type-2 is the norm in humans in the face of any pathogenic helminth. Although the protective components of the T helper (Th)-2-type response vary between parasite species and between phases of infection with the same helminth species, this response is effective against a wide range of helminths. Helminths, as a group of parasites, invade a specific ecological niche that encompasses the microenvironment in which the parasites appear and the ensuing host-parasite interactions at different points in the parasite's life cycle [3]. When it

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comes to helminth infections, the symptoms might range from completely absent to debilitating chronic illness depending on the degree of the infection. Subtle symptoms, like anaemia, malnutrition, and slow physical or mental development, are experienced by the majority of people living in endemic areas [4]. The purpose of this chapter is to learn about the immunological reactions that occur in response to helminth infections, and then to use those molecular targets to find new immunomodulatory treatment drugs.

5.1. Variables Related to the Host that Play a Role in the Regulation of the Immune System

The production of cytokines such as interleukin-4, IL-5, IL-9, IL-10, and IL-13 as well as antibody isotypes such as immunoglobulin IgG1, IgG4, and IgE, and as increased populations of eosinophils, basophils, mast cells, type 2 innate lymphoid cells, and alternatively activated macrophages are hallmarks of the T helper immune response to all helminths [5].

Although the helminths parasite-induced Th2 response is well known, its initiation, development, and interaction with a wide range of cells, including epithelial cells, innate immune cells, lymphoid cells, dendritic cells, eosinophils, basophils/mast cells, neutrophils, T and B cells, is not as well understood. These cells include: epithelial cells, innate immune cells, lymphoid cells (Figure 5.1).

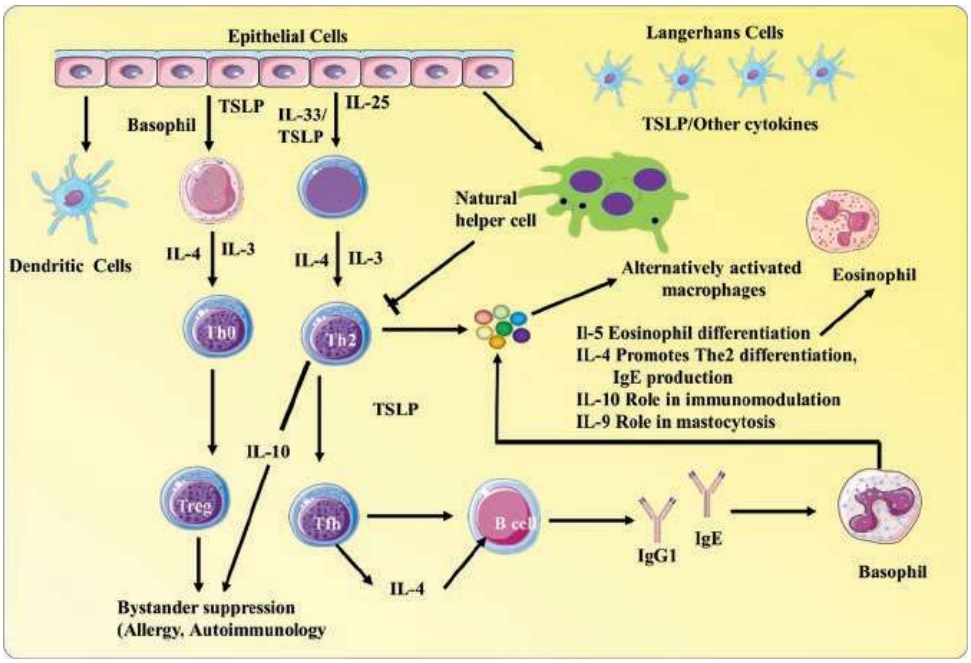

Figure 5.1 Host-related variables in the control of the immune system.

5.1.1.1 Helminths and Epithelial Cells

The bulk of helminths enter the body through the epithelial cells, which are the first barrier layer to be compromized or exposed when the barrier is broken [6]. In addition to IL-25, IL-33, thymic stromal lymphopoietin (TSLP), and IL-33, these cells are responsible for the production of the alarmins uric acid, ATB, HMGB1, and S100 proteins. They also interact with helminth parasites through nucleotide oligomerization domain-like receptors or toll-like receptors.

Intestinal epithelial cells, for example, are in continuous touch with the gut bacteria; this places them in an advantageous position for immunological monitoring within the digestive system. In addition, it has been found that epithelial cells, which can be found anywhere in the body, can send tolerogenic signals to T cells and B cells [7]. Mucus production and the bioactive compounds associated with mucus, such as mucin 5AC, trefoil factor-2, and resist in like molecule (RELM), are also factors that contribute to improved resistance to helminth infections of the digestive tract (Figure 5.1).

5.1.1.2 Helminths and Innate Lymphoid Cells

Innate lymphoid cells, also known as ILCs, are a recently discovered kind of hematopoietic effector that plays a protective role in both the homeostasis of tissue stromal cells and the innate defences against pathogenic microorganisms [8, 9].

The ILC family consists of three different members: ILC1, ILC2, and ILC3. Among these are the ILC2 cells, which are recognized for their ability to produce IL-5, IL-13, IL-9, IL-4, and IL-10. In spite of the fact that there are some similarities between ILC2s and Th2 cells, there are also variations between the two in terms of the developmental complexity, tissue tropism rules, and the specificity of the immune stimuli to which they respond [10]. Eosinophilia, the creation of goblet cell mucus, the activation of alternative activation of macrophages (AAM), muscle contraction, macrocytosis, and the repair of tissue can all be efficiently triggered by these cytokines (Figure 5.1) [11].

In addition, although their effect is not as strong as that of DCs, ILC2 have the ability to directly influence the activation of T cells by generating MHC class II molecules as well as the support molecules CD80 and CD86. In conclusion, recent studies have shown a connection between ILC2 and metabolic balance, obesity, and nutritional stress, which suggests that helminths may indirectly influence host metabolic function.

5.1.1.3 Dendritic Cells and Other Parasitic Helminths

Dendritic cells, also known as DCs, play a significant role in the detection, collection, processing, and presentation of helminth early signs (ES) to T cells, which act as mediators between innate immunity and adaptive immunity. Antigen-presenting cells, also known as DCs, are cells that are responsible for presenting antigens to T cells and initiating immune responses. DCs are also known

as APCs. Despite the fact that it is known that DCs have a role in the initiation of Th1, Th17, and Treg responses, it is still uncertain how DCs influence Th2 responses. However, a number of studies have shown that DCs are essential for an appropriate Th2 response in vivo. It has been proven that the in vivo depletion of DCs places a barrier in the way of the activation of Th2 responses in response to either *Schistosoma mansoni* or *Heligmosomoides polygyrus*. Helminth products can prepare DCs for the beginning of Th2 immune responses by interacting with pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), and C-type lectin receptors (CLRs). This interaction, which is based on TLR and CLR signalling, has the potential to improve Th2 responses by lowering the amount of antigen presentation, co-stimulation, and/or the synthesis of cytokines that support Th1 responses by directly blocking these pathways. DC are hampered in their capacity to respond to a wide variety of pathogenic stimuli since it has been demonstrated that helminth antigens inhibit DC activity (Figure 5.1).

5.1.1.4 Macrophages and Other Types of Helminths

Macrophages, which are the most prevalent type of tissue-resident mononuclear phagocyte, provide a significant boost to the immune response that is mounted against helminth infections. They produce nitric oxide and other mediators, which allows them to function as effector cells in the body's defence against bacterial and protozoan infections. These macrophages are classified as alternatively activated macrophages due to their capacity to upregulate arginase, YM1, YM2, and RELM-(AAMs). It has been hypothesized that these AAMs can assist in the recovery process of wound injury brought on by the tissue migration of helminth parasites. They are known for accelerating the healing process after an injury. Because these AAMs express regulatory molecules including IL-10, TGF-, and programmed cell death, it is possible that they have a role to play in the regulation of helminth infections. 1 ligand 2. These anti-inflammatory macrophages make use of the enzymes arginase-1 and PDL2, as well as the triggering receptor expressed on myeloid cells 2 (TREM2) and RELM, in order to reduce the amount of T-cell activation, recruitment, and traditional macrophage inflammation.

When macrophages are activated in response to an infection caused by a pathogen, both pathogen-associated molecular patterns (PAMPs) and cytokines play a role in the process. For more than twenty years, based on in vitro research conducted on murine macrophages, macrophages have been classified as belonging to one of two activation phenotypes (Figure 5.1).

5.1.1.5 Both Helminths and Eosinophils are to Blame

A sizeable body of evidence lends credence to the theory that the principal function of eosinophils is to protect hosts from infection by relatively big organisms, such as parasitic helminths. This hypothesis has been backed by the aforementioned body of evidence. It succeeds in achieving the following: large numbers of eosinophils

are regularly detected in close contact with both intact and injured helminths in vivo; eosinophils obviously degranulate around or onto the surfaces of helminths.

IL-5 is the factor responsible for eosinophilia in the blood and tissues, which is an indication of helminth infection. When an experimental helminth infection is carried out, eosinophils begin to migrate to the site of the infection as early as 24 hours after the initial exposure. ILC2 appears to be responsible for regulating both the accumulation of tissue following helminth infection and the basal eosinophil levels. Eosinophils are known for their ability to eliminate helminth parasites, but they are also known to play a role in tissue remodelling, metabolic balance, and anti-inflammatory cell activity by releasing cytokines that have already been generated. This is despite the fact that eosinophils are best known for their ability to eliminate helminth parasites [12]. In contrast to T and B cells, eosinophils are able to rapidly release cytokines in response to stimulation within a matter of minutes. This is possible due to the fact that the vast majority of cytokines are stored in secretory vesicles in a predetermined manner (Figure 5.1).

5.1.1.6 Mast Cells and Basophils, Helminths

Basophils play an important role in the immune system's response to infections caused by helminths [13]. Histamines, cytokines, and lipid mediators are only a few examples of the Th2 response-stimulating mediators that basophils are capable of releasing. Basophils in both humans and mice, whether they are IgE-dependent or IgE-independent, produce significant amounts of the cytokine IL-4. Basophils appear to play a vital role in the resistance to secondary infections caused by *N. brasiliense*, *H. polygyrus bakeri*, and *L. sigmodontis* (much like eosinophils do), and they also contribute considerably to the resistance to primary infections caused by *T. muris* and *T. spiralis* (via the production of IL-4 and IL-13). In addition, it has been found that basophils play a significant role as anti-parasitic cells (APCs) in helminth infection models for the purpose of triggering the development of Th2 cells. IL-4 and IL-13 are two of the most important effector cytokines, and they are responsible for mediating the defence against helminths through a variety of mechanisms [14]. In spite of the widespread belief that Th2 cells are the principal source of both cytokines, recent research has shown that basophils may also release comparable levels of IL-4 (approximately 10 femtograms per cell under a stimulation with ionomycin for 24 hours) (Figure 5.1) [15].

5.1.1.7 Helminths and Neutrophils

Despite the fact that there is evidence to suggest that neutrophils and macrophages can work together to control or remove helminth parasites, neutrophils are more commonly connected with bacterial and fungal infections [16]. However, neutrophils play a significant role in the treatment of helminth infections. When the larvae first enter the lung, local TCRgd T cells become activated and release IL-17, which attracts neutrophils to the location [17]. The acute lung damage that these

neutrophils inflict is controlled and partially reversed by the type 2 immune response, which does this by lowering the amounts of IL-17 and simultaneously increasing the number of neutrophils infiltration [18]. Neutrophils also differentiate in the context of developing type-2 responses, which results in an upregulation of the expression of genes linked with type-2 responses such as IL-13, IL-33, Renta, and Chi3I3, amongst other genes. Neutrophils have an essential role in the promotion of the activation of M2 macrophages, which then contribute to tissue repair and acquired resistance during the early phases of the immune response. In conclusion, it was discovered that the absence of neutrophils led to decreased lung immunity, which ultimately resulted in greater worm burdens even during the initial infection stage. Because of this, neutrophils appear to play a role in helminth immunity that was not anticipated, and this finding warrants additional research (Figure 5.1).

5.1.1.8 B Cells and Other Head Lice

Autoimmune illnesses were the impetus for the discovery of the role of B cells in the regulation of the immune system. Helminths can interact with B cells in two different ways: by stimulating the generation of B cell cytokines, and by stimulating the creation of antibodies. Cellular interactions, most likely triggered by the stimulation of IL-10, are the primary cause of the activation of B cells, which then leads to the production of cytokines. According to the findings of a number of research, B cells enhance and sustain Th2-type immune responses during helminth infections. This is done in order to successfully combat Th-1-type immune responses. Their production of IgE is a symptom that is unique to helminth infections, as is the degranulation of mast cells and basophils, as well as the release of soluble components, which are all side effects of immunoglobulin [19].

It has been demonstrated that other antibodies, in particular IgM and IgG, are advantageous, although IgE appears to have only a limited role in the production of protective immunity. It has also been proven that maternal IgG specific for parasites, and antibodies-mediated passive immunity, protect offspring from *Trichinella spiralis* and *H. polygyrus* in a number of different helminth models. In schistosome infections, a decrease in B cells leads to a rise in immunopathology that is dependent on Th2 cells. On the other hand, B cells are essential for the generation of antibodies in conditions involving helminth infections. In the absence of B cells, a person infected with *Litomosoides sigmodontis*, *S. mansoni, T. muris*, or *Heligmosomoides polygyrus bakeri* is more likely to develop a secondary infection [2]. B cells, on the other hand, in addition to creating antibodies that are critical to the immune system's defence, also serve as regulators and effectors, present antigens, and co-stimulate the immune system in ways that are not dependent on antibodies [20]. Recent studies have concentrated on determining the part that regulatory B cells play in dampening the immune response to infections caused by helminths. Similar to the function of B cells, which involves the

synthesis of IL-10 and IL-35, the regulatory activity of B cells in autoimmune diseases is identical to the role that B cells play (Figure 5.1).

5.1.1.9 T Cells and Other Helminths

Helminth-mediated immune control works on numerous fronts, preventing the development of adaptive immunity, the activation of effector mechanisms, and the sensitization of innate immune cells to antigens. One of the most important methods of parasite immunomodulation is the presence of regulatory T-cells (Tregs) In addition to the existence of a number of surface indicators that are important to their function, such as Tregs, which may be recognized by their expression of CD25, CTLA4, ICOS, and T-cell immunoreceptor with Ig and ITIM domains, are the cells that produce the transcription factor FOXP3, which is known as FOXP3 in humans (TIGIT). In most cases, infections caused by helminths cause a powerful Th2 reaction, which is distinguished by an increase in the synthesis of interleukin-4, interleukin-5, interleukin-9, interleukin-10, and interleukin-13 occurs in response to live parasites, parasite antigens, or mitogens [21].

In addition, the production of IL-4 and IL-13 within the Th2 cell compartment is spatially segregated. Tissues exhibit a majority of IL-13 expression, whereas lymph nodes show a predominance of IL-4 expression. In conclusion, it has been demonstrated that activating GATA-3 and lowering the expression of T-box in T cells (T-bet) are necessary steps in the transition from T-resist in-like molecular cell phenotypes to Th2 in helminth infections. Despite the fact that tissue-resident memory (TRM) T cells play a crucial role in the fight against bacterial and viral infections, relatively little is known about how they influence helminth infections. On the other hand, it has been discovered that tissue-resident Th2 cells, in response to the appropriate stimuli, engage in innate activity that is TCR-independent and IL-33-dependent. This activity acts as a defence mechanism against helminth infection. In addition, it is known that helminth infections are associated with an antigen-dependent rise in both mono- and dual-functional Th2 cells, as well as their reversal after therapy. This is the case despite the fact that multifunctionality in Th2 cells, which is defined as the capacity to create two or more cytokines, is not fully understood. In animal models of helminth infection, it has been shown that a persistent subset of parasite-induced T-bet+, GATA-3+, and Th1/Th2 hybrid T cells develops from naive progenitors and contributes to the reduction of severe inflammation. These cells come about as a result of helminth infection and develop from naive progenitors. It is believed that these cells help the parasite live longer while also protecting the host from a potentially harmful immune response. Regulatory T cells are essential for preventing autoimmunity and other types of immunological dysregulation. It is believed that these cells help the parasite survive longer. Because of this, many people who are infected with helminths do not

mount an inflammatory reaction to the parasite, which is the type of reaction that would normally induce "collateral harm" in the tissues that are being impacted. It was recently demonstrated in human infections, where it was found that children who have pathology due to *S. haematobium*, exhibit stronger Th17 responses than children who do not have pathology related to *S. haematobium*. It has also been demonstrated that there is a significant association between Th17 responses and pathological responses in lymphatic filariasis. In conclusion, a subgroup of CD4 cells known as Th22 cells is responsible for the continual secretion of IL-22. Very few researchers have looked into the role of Th22 cells in helminth infections [22]. It was discovered that IL-22 was induced in the intestinal mucosa of humans after infection with *T. trichura* or *Nector americanus*. Both of these pathogens cause infections in people. In addition, it was discovered that individuals suffering with filaria had a higher number of Th22 cells compared to the healthy endemic controls. In addition, T cell clones from onchocerciasis patients that release IL-10 and TGF- have been discovered (Figure 5.1) [23].

5.2 Effector Immune Mechanisms against Helminths and Their Regulating Mechanisms

Infections caused by helminths typically show themselves through hypereosinophilia, significant production of IgE, mucosal mastocytosis, and goblet cell hyperplasia [14]. Depending on the location of the helminth, these immunological characteristics play an important part in a variety of different effector pathways.

5.2.1 The Effector Defense Mechanisms against Tissue-Dwelling Parasites and the Parasite-Developed Escape Mechanisms

There are several different types of defences that have been described in order to combat parasites that reside in tissues. Typically, these tissue-moving parasites are the larval stages of nematodes or trematodes.

Effector cells in antibody-dependent cellular cytotoxicity (ADCC), which can be mediated by IgE, IgG, or IgA antibodies, can be eosinophils, neutrophils, macrophages, or platelets. The parasitic entities that are guarded by antibodies are eliminated by cells that carry Fc fragment receptors (RFc). After being stimulated by the attachment of the antibodies to the RFc, these cells let off poisonous chemicals, which cause the worm to sustain damage (major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, reactive nitrogen intermediates). Nematode larval stages can also be immobilized by ADCCs when they travel through the intestinal mucosa as they develop [24–27]. Nitric oxide (NO), which is a gas that is toxic to the worm, is finally released by the macrophages that had

been stimulated by IFN and TNF earlier in the process. This process has been documented in the most significant way in relation to trematodes (*Schistosoma* species, *Fasciola* species) during the acute infection stage, prior to egg development in *Schistosoma mansoni* [28–30].

Tissue-dwelling parasites have devised a variety of techniques during the course of evolution in order to circumvent the effector response of their hosts. For example, *Fasciola* sp. is able to steer clear of immune responses by avoiding them in the following ways:

i) The superoxide dismutase that is produced by *Fasciola gigantica* is capable of neutralising the superoxide radicals that are damaging to young people [31, 32].
ii) *F. hepatica* is responsible for the release of chymotrypsin L-protease, an enzyme that degrades the IgE and IgG that are involved in ADCC [33].
iii) It was shown that IgM is present in flukes that are still in their juvenile stages [34]. Even though eosinophils do not have the Fc receptor, the accumulation of IgM on the fluke's tegument may inhibit eosinophils from attaching to the fluke. IgG2, which is produced during fasciolosis in susceptible sheep [35], is thought to be able to operate as an ADCC-inhibiting immunoglobulin.

5.2.2 Effector Defences against Parasites Discovered in the Duct Lumen and the Escape Mechanisms Evolved by the Parasites Themselves

Intestinal anaphylaxis with IgE-induced mast cell degranulation causes changes in the physiology of the intestine, as well as the structure and chemistry of the gut epithelium. These changes can be traced back to the immune response. Involvement of eosinophils or mast cells in the recruitment process, improvement in vascular and epithelial permeability, smooth muscle contraction, activation of fluid, electrolyte, and mucus secretion, and smooth muscle contractility are all components of these changes [36].

It is possible that this will cause the adult to be expelled, and the gastrointestinal larvae will need to be removed as rapidly as possible before they can locate their tissue niche [37]. In addition, IgA that is present on the surface of the gut mucosa helps to neutralize the metabolic enzymes that are released when strongyles are digested, which impedes the capacity of the worm to consume food [38].

When it comes to parasites that reside inside of living tissue, those that are discovered in the duct lumen have the ability to produce immunomodulatory substances, which allows them to avoid being destroyed by the immunological reactions of the host. For example, *Nector americanus* produces a metalloprotease that is responsible for the breakdown of eotaxin, which is a component of eosinophil chemotactic activity [39]. In addition, gastrointestinal nematodes are responsible for the production of the enzymes superoxide dismutase and glutathione S-transferase, both of which are capable of scavenging potentially damaging

oxygen radicals [40]. A cystatin produced by *H. contortus* and *N. brasiliensis* changes the manner in which an antigen is delivered to T cells. This is accomplished by inhibiting the cysteine proteases that are utilized by antigen-presenting cells to breakdown the antigen [41, 42].

5.2.3 Controlling the Immune Response to Helminths

All of these pathways are controlled, with the exception of the ones involving traditionally activated macrophages, by cytokines that are similar to Th2 and cell types that are immunomodulatory. Interleukin-4 is responsible for influencing the isotype-switched IgE responses in B-cells. Interleukin-5 is responsible for influencing eosinophil production, and interleukin-13 is primarily responsible for influencing the development of fibrosis. Interleukin-13 has roles that are comparable to those of interleukin. T regulatory cells are responsible for producing suppressive cytokines like IL-10 and TGF. These cytokines have anti-inflammatory properties and are produced by T regulatory cells. The Th2-like responses may be the result of these cytokines. The growth of a population of Th2-activating dendritic cells, which may be induced by excretory-secretory antigens from *N. brasiliensis* [43] or soluble schistosome egg antigen, may also contribute to immunological deviation [44]. Last but not least, activated anti-inflammatory macrophages (AAMps) with powerful anti-inflammatory capabilities, accelerated Th2 cell differentiation, and the IL-4 and IL-13 cytokines can all work in concert to induce fibrosis and healing at the site of damage [45]. Because of this, an individual who is infected with helminths will experience a condition characterized by downregulation of proinflammatory reactivity, active damage repair mechanisms, and controlled development of Th2-like anti-parasite effector responses [46].

5.3 Immune Regulation and Spectrum of Disease

Immune control by parasites weakens immunity while also protecting the host from potentially harmful immunopathological reactions to the presence of parasites. This is especially true in tissue settings where the severity of the infection does not always positively correlate with pathology, such as in the cases of lymphatic filariasis, onchocerciasis, and schistosomiasis. In contrast, patients with lower levels of infection who have immunologically reactive responses and chronic pathology may not exhibit any symptoms in those with high parasite numbers and stronger regulatory responses. Long-term filaria-exposed populations provide the best examples of the disease's spectrum, with infection outcomes ranging from those who appear immune and uninfected (endemic normal) to those who range from a minority who have chronic pathology in the form of lymphatic inflammation and elephantiasis to microfilaremic (Mf), with bloodstream microfilariae,

who have a large percentage of asymptomatic instances with patient infections [47, 48]. The absence of symptoms is associated with elevated levels of the immune-regulatory cytokine interleukin-10 (IL-10) [49], a suppression of key Th2 components such as IL-5 [50], as well as Th1 inflammatory cytokines such as gamma interferon (IFN), and higher concentrations of circulating T lymphocytes that express the inhibitory marker CT (cytotoxic T lymphocyte antigen 4) [51].

In contrast, cases that develop lymphatic pathology have higher levels of potent Th1 and Th17 effector components, which may be responsible for causing lymphatic inflammation against resident adult worms. However, these cases also have lower levels of regulatory T cells, which are an essential cell type (Treg). The fact that Th17 cells are also more prevalent in patients who have had their bloodstream Mf cleaned raises the intriguing question of whether Mf indirectly inhibits Th17 responses and enhances their survival as a result of shed levels of another immunosuppressive mediator, transforming growth factor (TGF), in nodules surrounding parasites. This question is raised due to the observation that nodules surrounding parasites contain shed levels of TGF [52]. It is likely that parasites and/or their released products are actively inhibiting the immune system. This is because the degree of an infection and immunological responsiveness are connected. Because a sustained granuloma formation takes place around implanted eggs in schistosomiasis and because persistent liver fibrosis is common, it might be difficult to differentiate between infections that are asymptomatic and those that have caused pathology. However, the degree of the inflammatory response to infection can vary along a continuum from mild to severe. When visitors who have not been exposed to schistosomes in the past become infected with the parasite, they experience an acute inflammatory immune reaction, with enormous granulomatous responses surrounding the parasite's implanted egg. However, persistent infection greatly reduces inflammatory cytokine responses to *Schistosoma* soluble egg antigens (SEAs). On the other hand, Th2 cytokines, such as IL-10, are enhanced [53]. Additionally, only a very small percentage of patients experience severe hepatosplenic disease.

Patients with acute schistosomiasis and severe pathology cases demonstrate considerably stronger T cell proliferative responses to SEA as compared with chronically infected individuals with minimal pathology [54]; nevertheless, the group with low pathology exhibited higher frequencies of CD4(+)CD25high [55]. Even while it is necessary for resistance, the production of Th2 cytokines, in particular IL-13, can also cause detrimental effects. This is due to the fact that it is essential for the formation of fibrosis, and chronic schistosomiasis causes damage to the liver and the spleen [56]. In the asymptomatic Mf condition, the production of IgG4 rather than IgE antibodies against filariasis antigens reaches levels that are significantly higher than typical [57, 58]. It is interesting to note that IL-4 and IL-13 promote B cells to create IgE; yet, when IL-10 and TGF- are present, it is

more likely that B cells will flip to producing IgG4 [59]. As a consequence of this, it was argued that the extraordinarily powerful immune reactions could potentially be explained by studies indicating an increase in immune responses to parasite antigens following drug-induced clearance of the parasites. Immunological response to the relevant antigens is regained after treatment with medication for filaria infection [60] or individuals who have been infected with schistosomes [61]. In addition, an increased Th2 responsiveness following the administration of the medication is positively connected with infection resistance [62].

These findings reveal that helminth parasites have the ability to powerfully generate a regulatory environment that is precisely tuned to maintain a suppressed, nonresponsive condition in effector T cell levels. It is essential to note that the host's immunological competence can be restored if parasites are removed or if there is an increase in the immune response [63]. Therefore, the suppression that is generated by parasitic infection is active, and the release of mediators produced by helminths may serve as the starting point for various different pathways [64]. The hypo-proliferative condition that is seen in tissue helminth infections may be caused by a suppression of the number of antigen-presenting cells (APCs). Filarial infection has an effect on the function of monocytes as well as antigen-presenting cells (APCs): in Mf patients, there is a preponderance of circulating CD11c-CD123lo monocytic dendritic cells (DCs), which have down-regulated CCR1 and may as a result be impaired in their ability to migrate. In addition, there is a preponderance of circulating CD11c+CD123lo [65] and when compared to the norm, the production of inflammatory cytokines from microfilariae (Mf) donor monocytes is greatly suppressed by lipopolysaccharide. This is due to the fact that lipopolysaccharide acts as an immune checkpoint (LPS) [66].

After stimulation, there is a general decrease in the expression of the TLR (Toll-like receptor) family of innate pattern recognition receptors upregulated by APCs; this deficiency was also observed in B cells from Mf patients. In addition, filarial infections cause a decrease in TLR expression levels, which is part of the larger pattern of reduced TLR function that occurs during helminth infection [67]. An intriguing question that has to be answered is whether or not certain APC populations only impair their function or change into active regulatory and suppressive cell types.

5.4 Protective Immunity against Helminths

Helminths, in spite of the Th2-like immune response that is generated against them, are often able to live inside their host for an extended length of time, which might result in a chronic infection. On the other hand, premature immunity and partial immunity are also types of immunity that have been described. These types of immunity are measured by the host's resistance to reinfection and the

partial clearance of established parasites. The manner in which helminth protective immunity operates is determined, in large part, by the location of the helminth infection [14]. T cells are a crucial component in the process of resisting parasites, playing a critical role in the process that mediates the expulsion of gastrointestinal (GI) nematodes. For example, mice that are deficient in T cells are unable to eliminate *T. muris*, but the T cells from mice that have immune systems that are functioning normally can be used to reestablish resistance.

The ability of mice with severe combined immunodeficiency (SCID) to receive protective immunity from the CD4 T cells of infected mice is further evidence that CD4 T cells, and not CD8 T cells, are essential for protective immunity. This evidence was provided by the fact that SCID mice were able to receive protective immunity from infected mice's CD4 T cells (lacking both B and T cells). It has also been proven that T cells are required for ejection in *N. brasiliensis* infection. Nude mice, who lack only T cells, and SCID mice, are susceptible to infection with Brugian parasites. However animals that lack CD4 T cells or CD8 T cells are not susceptible to infection with Brugian parasites. The formation of host-protective granulomas around the schistosome eggs produced by the mouse liver requires the participation of T lymphocytes. When worms are infected, the host's immunological response to the helminths may be able to control the infection; but this response may also result in tissue lesions and other symptoms, which are frequently the major causes of disease. The immunopathologic effects of *Schistosoma* infections have been the topic of a significant amount of research in recent years. Similar to what was discussed before in relation to *F. hepatica* infection, acute schistosomiasis is associated with Th1-like responses directed towards adult parasites. The Th2-like responses that are triggered as a result of the release of egg antigens are responsible for the downregulation of the production and effector activities of Th1-like mediators [68]. When Th2-like responses to the eggs were artificially repressed, a higher granuloma that was driven by Th1 and Th17 cells resulted in hepatic injury and death. This was due to the fact that Th1 and Th17 cells were overactive [69]. The function of cytokines in protective immunity has been extensively researched using mice models of both gastrointestinal helminths and tissue-invasive helminths [70].

Type 2 cytokines are responsible for activating a wide variety of downstream effector pathways. Tuft cells are a type of intestinal epithelial cell that promote the formation of goblet cells, enhance mucus secretion, and produce RELM, which is an innate effector molecule that functions directly as an anthelmintic. Mucins that can form gels are one of the most important macromolecular components of the mucus barrier, and goblet cells are able to release mucins. Two of these mucins, known as Muc2 and Muc5AC, have been proved to be necessary for the protection of the intestines against infection by nematodes. In addition, activation of IL-4R leads to increased intestinal smooth muscle hypercontractility as well

as rapid epithelium turnover. These two factors, when combined with epithelial secretions, contribute to the elimination of intestinal helminths. Mast cells in the mucosa are responsible for producing proteases as part of the "weep and sweep" reflex. These proteases have the ability to breakdown epithelial tight junctions and improve fluid flow. It is also possible for AAMs in the gut to ensnare intestinal worms, which diminishes the chances of worm survival and ultimately ends in the death of the worms. Although it is common knowledge that Th2 cytokines have a role in the resistance to gastrointestinal helminth infection, considerably less is known regarding their function in the protection against tissue-invasive helminths. It is possible to establish protective immune responses in mouse models of schistosomiasis by immunising mice with irradiated cercariae and observing their subsequent behavior. This resistance is based on a Th1-mediated immune response, which is made up of endothelial cells and macrophages that are activated by TNF and IFN- and create nitric oxide. Additionally, this resistance is reliant on the fact that there is a presence of a Th1 cell. In addition to this, it is reliant on the antibodies IgG2a and IgG2b, both of which are associated with the Th1 immune response. On the other hand, studies conducted on rats as well as epidemiological study conducted on humans suggest that protective immunity is predominantly assumed to be mediated by eosinophils, IgA and IgE antibodies, as well as Th2-mediated effector pathways. It is primarily the Th2 responses in mice that are responsible for the protective immunity that mice have against filarial infections. Mice that are deficient in IL-4, IL-4R, or Stat6 are susceptible to infection with the Brugian parasite because of this. Antibodies can protect against helminth infections in some cases, although this is not the case in other instances. Passive immunity mediated by antibodies has been demonstrated in animal models of *Ascaris suum*, *A. caninum*, *Schistosoma* species, *Taenia* species, *S. ratti*, *T. muris*, *N. brasiliensis*, and *H. polygyrus bakeri*. In addition, IgM monoclonal antibodies (mAbs) that are specific for *B. malayi*, IgG or IgA mAbs that are specific for *T. spiralis*, and IgG monoclonal antibodies (mAbs) that are specific for *Fasciola hepatica* and *S. mansoni* have all been utilized to demonstrate passive immunity. IgM's significance in the host defence mechanism against *B. malayi* and *S. stercoralis* has been proven once more with the assistance of genetically modified mouse models. This protective axis seems to rely significantly on B1B cells, which are a subset of B cells that are responsible for the production of IgM. It is possible for antibodies to limit tissue damage by collecting larval helminths as they move through tissue thanks to their ability to trigger an IL-4R-independent alternative macrophage differentiation that is dependent on CD11b and FcR1. Granuloma formation, which is dependent on a Th2-like immune response, can also be observed in patients with gastrointestinal worm infections. In a recent study, the researchers found that when the Th2-like response to *Nippostrongylus brasiliensis* was experimentally downregulated, the

animal's resistance to pulmonary granulomatous inflammation, fibrosis, and gastrointestinal nematode infection was significantly reduced [70]. A similar pattern can be seen with the signs of bovine ostertagiosis, which include diarrhea, loss of appetite, and weight loss. These clinical symptoms may be brought on by a contraction of the smooth muscle, an increase in the production of mucus, immediate hypersensitivity responses mediated by IgE that cause the degranulation of mast and goblet cells, the loss of specialized cells in the abomasal epitheliums, and the release of inflammatory mediators [71].

5.5 Immune Reaction-Related Pathology in Parasitic Helminth Infection

Even while certain pathological responses are the direct result of the host's response, the fact that the majority of pathological results are tied to the presence of the parasites in the tissues of the host is what differentiates one parasitic infection from another.

5.5 Immune Complexes

Immune complexes play a significant role as potent mediators of localized inflammatory processes in many diseases caused by parasites. This is most likely as a consequence of the constant low-dose antigen release that is characteristic of parasitic infections. Immune complexes can be found circulating in the blood of humans and animals infected with both filarial and schistosomal parasites. It has been proven that due to their deposition, they produce lymphatic inflammation as well as vasculitis in filarial infections. In addition, the outcomes of kidney biopsies performed on patients with schistosomiasis and filarial infections have revealed immune complex glomerulonephritis (ICGN), which is a common sign of immune complex-mediated illness. In patients suffering from helminth infections, two additional signs of immune complex-mediated harm have been reported. These symptoms are reactive arthritis and dermatitis.

5.5.2 Autoantibodies and Molecular Mimicry

Molecular mimicry is one of the key mechanisms that can be used by infectious organisms or chemical irritants to set off an autoimmune response. It takes place when an antigen obtained from a foreign source causes the activation of self-reactive T or B cells in a susceptible individual. This happens because foreign and self-peptides share similarities with one another. Infections with a variety of helminths, such as filarial infections, schistosomiasis, and hookworm illnesses, have

been linked to autoantibodies, which are presumed to represent the polyclonal B cell proliferation that frequently follows these infections. Autoantibodies have also been linked to schistosomiasis [72]. The majority of people who have chronic schistosomiasis have autoantibodies that target nuclear material, while the majority of people who have onchocerciasis have antibodies that target human calreticulin and defensin.

5.5.3 Granulomatous Reactions

Granuloma growth is an essential part of the immune system's defence against some helminths; nevertheless, it can also have negative implications in the form of the disease if it is not controlled. Granulomatous reactions can be seen in a number of different helminth disorders, such as toxocariasis, infections caused by angiostrongyliasis, and lymphatic filariasis; however, parasitical granulomata have been studied the most in *S. mansoni* infections. In these infections, CD4 T cells are responsible for coordinating granulomatous and fibrosing reactions against tissue-trapped eggs; the fibrosis that develops as a direct result of the cellular response is the primary factor that contributes to morbidity. It has been shown that responses from Th1 and Th17 cells are associated with more severe forms of illness, whereas responses from Th2-dominant cells are associated with less severe forms of pathology. This finding holds true for both human patients and animal models used in experimental research [73]. Studies conducted with animal models of granuloma development demonstrated that TNF and IL-13 play critical roles in the development of the tumor.

5.5. Fibrosis

There is a strong correlation between fibrosis and repeated helminth infections, which are known to produce persistent inflammation and slow wound healing [5]. By stimulating macrophages and fibroblasts, these infections lead to the production of TGF-, platelet-derived growth factor (PDGF), and IL-1, among other chemicals. Macrophages contribute to inflammation in a number of different ways, including drawing in and boosting neutrophils and monocytes, as well as drawing in and stimulating CD4 T cells. In addition, the activation of fibroblasts results in the production of tissue inhibitors of metalloproteinases and matrix metalloproteinases (MMPs), both of which contribute to the process of fibrosis and remodelling of the extracellular matrix (TIMPs). Another impact of chronic schistosomiasis is pulmonary arterial hypertension, which has been linked to TGF-induced pulmonary vascular disease and type 2 inflammation, which is mediated by IL-4 and IL-13. In a manner that is analogous to the way in which IL-10 and IL-12 are known to govern IL-13-mediated fibrosis, IL-13–dependent fibrosis in chronic schistosomiasis

patients who are deficient in IL-10, IL-12, and IL-13R advances rapidly toward cirrhosis, which is a condition that is fatal. *Wuchereria bancrofti*, one of the agents that are responsible for generating lymphatic filariasis, is associated with comparable fibrotic reactions.

Wolbachia, an endosymbiotic *Rickettsia*-like bacteria, has been connected to immunopathology in lymphatic filariasis.

5.5.5 Toll-Like Receptors

Wolbachia has been linked to immunopathology in lymphatic filariasis. It is well established that *Wolbachia* stimulates immune cells by using the proinflammatory cytokines and vascular endothelial growth factors (VEGFs) that are generated as a result of TLR2 and TLR4 interaction. as well as possibly being a contributor to lymphatic illness [74]. In addition, it has been established that the primary factor causing ocular inflammation in onchocerciasis is an interaction between *Wolbachia* and TLR4, and it has also been established that the development of pathogenic Th17 cells in *S. mansoni* infections is regulated by the TLR signalling protein IL-1 receptor-associated kinase-2. Both of these findings have implications for the treatment of onchocerciasis (IRAK-2).

5.5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions are associated with the first and/or acute stage of invasive helminth parasite infections, such as those caused by *Ascaris*, hookworm, schistosomes, or filariae. These infections can cause a variety of symptoms, including itching, hives, and rashes. Patients do show indicators that point to an allergic reaction, such as wheezing and urticaria. IgE-mediated reactions are also believed to be the cause of the signs and symptoms of clinical syndromes connected to tropical pulmonary eosinophilia, larval treatments for strongyloidiasis, and *Loa loa* infection (with associated angioedematous Calabar swellings). These syndromes include tropical pulmonary eosinophilia, larval treatments for strongyloidiasis, and *Loa loa* infection [75].

5.5. The Healing Process

Recent research has shown that responses of the type 2 cytokine have a close relationship with numerous aspects of the process of wound healing and tissue repair [76, 77]. Because infections caused by helminths are tightly connected to damage to tissues, according to one school of thought, the type 2 cytokine response first came into being in order to mediate resistance to helminth infections and then to initiate the wound healing mechanism in order to repair and reconstruct

damaged tissue. It should come as no surprise that AAMs are involved in this process given that they are responsible for the production of MMPs, Arginase-1, insulin-like growth factor 1 (IGF1), VEGF, and TGF-. These are all factors that, when combined, promote myofibroblast activation, angiogenesis, epithelial cell turnover, and extracellular matrix deposition.

5.5 Lymphangiogenesis

According to the anatomical changes in the architecture of the lymphatics, which range from lymphangiectasia and granulomatous reactions to the creation of collaterals, it is possible that active lymphatic remodelling caused by early lymphatic filarial disease, which involves the growth, migration, and proliferation of endothelial cells, is a key factor. Live filarial parasites, along with their excretory and secretory secretions, have been demonstrated to stimulate lymphatic endothelial cells (LECs) to activate, proliferate, form tubes, and develop into tubelike networks.It is generally accepted that TLR-mediated pathways are the key drivers of the angiogenic and lymphangiogenic process that occurs in filarial illness [78].

5.5.9 arcinogenesis

Infections caused by *Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma hematobium* are examples of biological carcinogens that belong to Group 1. (i.e., definitive causes of cancer).

While the latter is associated with cancer of the bladder and urinary tract, the former (liver fluke) is linked to cancer of the bile duct as well as cancer of the liver (cholangiocarcinoma) (carcinoma). In addition to other cancer-causing pathways, chronic inflammation, persistent cellular proliferation, altered redox and glucose signalling, genomic instability, tumor protein destabilisation, angiogenesis enhancement, apoptosis resistance, and helminths can promote invasion and metastasis [79].

5.5.10 Epileptogenesis

In some endemic areas, neurocysticercosis is responsible for almost thirty percent of all cases of epilepsy. This condition is caused by the larval form of *Taenia solium*, which is the most common preventable risk factor for epilepsy in the entire world. The symptoms, as well as the severity of the inflammation that is caused by cyst disintegration, calcification, and/or perilesional edoema, all have a role in determining the size of the cysts, the number of cysts, and the locations of the cysts that are found in the central nervous system.

5.6 onclusion

Helminths are able to modulate the immune system, which is now recognized as an essential survival strategy due to the passage of time and the major host–parasite relationship that is emerging. The investigation of helminth parasites is leading to a number of exciting immunological findings as well as potential therapeutic applications. Both in-depth field research and thorough laboratory testing have revealed epidemiological evidence that various diseases that are common in the industrialized world are protected against. With this new information, we can now offer methods for the management of infectious and immunopathological illnesses. These strategies can take advantage of the broad ideas that have been clarified as well as the specific modulatory mediators that have been found. Helminths are powerful agents that inhibit type 1 immune responses, which can be triggered by inflammatory diseases, secondary infections, or a combination of the two. It is currently difficult to understand the mechanisms behind this interaction and to discover possible biological targets in order to develop new methods that can prevent or postpone allergic, inflammatory, autoimmune, or metabolic illnesses in humans. This presents a challenge for the creation of new treatment options.

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