Immunity to Parasites

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Abstract: Parasites such as protozoa or helminths currently account for greater morbidity and mortality than any other class of infectious organisms, particularly in developing countries. The structural and antigenic diversity of pathogenic parasites is reflected in the heterogeneity of the adaptive immune responses that they elicit. Protozoa that live within host cells are destroyed by cell-mediated immunity, whereas helminths are eliminated by IgE antibody and eosinophil-mediated killing as well as by other leukocytes.

The principal innate immune response to protozoa is phagocytosis, but many of these parasites are resistant to phagocytic killing and may even replicate within macrophages. Phagocytes also attack helminthic parasites and secrete microbicidal substances to kill organisms that are too large to be phagocytosed. Some helminths may also activate the alternative pathway of complement.

The principal defense mechanism against protozoa that survive within macrophages (e.g. *Leishmania* spp., *Toxoplasma gondii*) is cell-mediated immunity, particularly macrophage activation by TH1 cell-derived cytokines. Protozoa that replicate inside various host cells and lyse these cells stimulate specific antibody and cytotoxic T lymphocytes (CTL) responses (e.g. *Plasmodium* spp.).

Defense against many helminthic infections is mediated by the activation of TH2 cells, which results in production of IgE antibodies and activation of eosinophils and mast cells. The combined actions of mast cells and eosinophils lead to expulsion and destruction of the parasites.

Most parasitic infections are chronic because of weak innate immunity and the ability of parasites to evade or resist elimination by adaptive immune responses Parasites evade the immune system by varying their antigens during residence in vertebrate hosts, by acquiring resistance to immune effector mechanisms, and by masking and shedding their surface antigens.

Keywords: Protozoa, helminths, innate, Th1/Th2.

1. INTRODUCTION

Currently, parasitic infections affect more than 3 billion people worldwide and in absence of adequate treatment, they result in high morbidity and mortality, especially in developing countries. In recent years developed countries have witnessed a significant boom of parasitic diseases because of various factors such as immigration, increase of opportunistic diseases in immunocompromised patients, etc. The magnitude of this public health problem has contributed to the great interest in the setting up of vaccines against parasites and the development of immunoparasitology as a well-defined branch of immunology.

Parasitic infections induce different immune responses due to the structural and antigenic heterogeneity of the parasites. Thus, protozoa that penetrate inside host cells require an adaptive immune response mediated by cells for its elimination, while adult worms are extracellular and in general of greater size and require the production of specific antibodies. The complexity of the life cycle of parasites, the developmental stage and the stage of infection, which determine the anatomical location of the parasite in the host also influence the immune response triggered. On this way, the ingestion of *Taenia solium* eggs by humans results in a disseminated infection (cysticercosis) in which the contact with the immune system and the response are different to that ocurred when larvaes (cysticerci) are ingested and infection is located in the gut. Moreover, in the case of parasites with different stages of development in humans, the expressed antigens can change depending on the stage, leading to phase-specific immune responses, as in the case of antibodies produced against sporozoites of *Plasmodium* spp., which are not reactive to the erythrocytic stages. Finally, it´s noticeable that parasitic infections are usually chronic because the immune response is not powerful enough to eliminate such pathogens and, especially, due to the mechanisms of evasion and modulation of the immune system that parasites have developed along its evolution as a way to survive in their host.

This review summarizes the general mechanisms of innate and adaptive immune defense against protozoa and helminths, incorporating new findings, as well as the different ways that parasites use to avoid elimination by the immune system.

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2. INNATE IMMUNITY TO PARASITES

2.1. Recognition of Parasite Pathogens

Innate immunity is the first line of defense against pathogens that invade human´s organism and it´s mediated at the cellular level by phagocytic cells including macrophages and granulocytes, but also by antigen presenting cells (APCs), like dendritic cells, some lymphocytes, epithelial cells and phagocytes themselves. The innate immune system can recognize certain structures of microorganisms that are not found in mammalian cells called pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs) encoded by the germline. The binding of PRR(s) to its specific ligand(s) is required for the initiation of the immune response to invading organism, since it induces, through various signaling pathways, the activation of the innate immune system cells and the development of effector functions against the pathogen, such as phagocytosis, secretion of cytokines that determine the type of adaptive response, etc. [1]. Several PAMPs have been reported among human parasitic pathogens that are recognized by PRR of different types, although none has been described that is unique to parasites, ie those receptors are also used by other organisms [2, 3]. Within the diversity of PRR, some extracellular classical human receptors have been associated with the recognition of parasites. For example, among collectins, the mannose-binding lectin (MBL) [4] binds mannose-rich lipophosphoglycan (LPG) from *Leishmania* [5, 6], *Plasmodium falciparum* proteins on infected erythrocytes [7, 8], *Trypanosoma cruzi* amastigotes [9, 10], *Schistosoma mansoni* [11] and all *Trichinella spiralis* developing stages [12]. Pentraxins that belong also to classical human receptors function as opsonins when fixed to their ligand. One member of the pentraxin family, the C-reactive protein (CRP), binds to molecules of *Leishmania* LPG and facilitates through opsonization the penetration of the parasite within macrophages [13]. In addition, CRP binds to *Plasmodium* sporozoites, thus protecting the host against its hepatocyte invasion [14]; and, as well, CRP is involved in natural resistance to *S. mansoni* infection [15]. Different C-type lectins expressed on the surface of macrophages and dendritic cells have been associated with parasite recognition. Among them, the macrophage mannose receptor (MMR) has been shown to facilitate the permissive entry of *T. cruzi* amastigotes into macrophages; and the dendritic cell-specific intracellular adhesion molecule (ICAM)-3-grabbing non-integrin receptor (DC-SIGN) on dendritic cells binds with high affinity to schistosomes through Lewis x [16] and amastigotes and promastigotes of *Leishmania* through mannose-capped LPG [17-19]. Other C-type lectins, the calcium-dependent galactose-binding proteins, known as intelectins, are expressed by paneth cells and goblet cells and have also been implicated in the recognition of gastrointestinal helminths, as well as in the interaction with the surface of parasites to prevent attachment to host surfaces [20]. Of the scavenger receptors (SR), CD-36, a type B-SR, by means of the binding to PfEMP1, allows the phagocytosis of *P. falciparum*-infected erythrocytes by macrophages and it has been shown that this binding modulates the function of DCs [21, 22]. Complement receptor CR3, which has a multifunctional role in the innate immune response like other members of its PRR family, is the gateway to several intracellular pathogens, such as *Leishmania major*, where it was recently described as essential in preventing the progression of lesions during the course of infection [23].

Furthermore, Toll-like receptors (TLRs) represent an important family of PRR involved in innate immunity against pathogens [24]. There are few studies related to the role that TLRs play in the recognition of parasites, but they have been involved in various responses to parasites, such as TLR-2 on dendritic cells and its binding to lysophosphatidylserine from *S. mansoni* and Tc-52 or glycophosphatidylinositol (GPI) anchors from *T. cruzi*. In the first case, the interaction induces a Th2 response and in the second case a Th1 response; this dicotomous response is probably due to the cooperation of TLR-2 with TLR-1 and TLR-6 [3]. GPI anchor proteins from *T. cruzi*, *P. falciparum* and *T. gondii* also appear to stimulate production of tumor necrosis factor (TNF)-α by macrophages *via* TLR [25]. The intracellular receptor TLR-9 recognizes unmethylated CpG motifs present in bacterial DNA in phagosomes, and it has been shown that protozoal DNA containing CpG motifs is sufficient to elicit a TLR9-response of host cells [26]. It has also been postulated that activation of TLRs could be responsible for some consequences of immunopathology associated with parasitic infections, such as anemia and nephritis caused by autoantibodies in malaria [27]. As far as the nucleotide-binding oligomerization domain proteins (NOD) are concerned, there is nowadays no clear relationship with parasites, but, given their nature, they may be involved in intracellular recognition of intracellular parasites, as Finney *et al.* [28] predict in the analysis of the inflammatory function mediated by NOD receptors in cerebral malaria.

2.2. Initial Immune Response and Modulation of the Th1/Th2 Response by Dendritic Cells

Once the parasite interaction with host receptors occurs, the innate immunity is triggered. Macrophages and neutrophils phagocyte small-size parasites and release cytotoxic factors to destroy large parasites, although these functions will exhibit full capacity upon activation of adaptive immunity cells. Moreover, once activated, macrophages and neutrophils release a series of pro-inflammatory molecules such as TNFα, interleukin (IL)-1, chemokines, and other mediators that promote growth and differentiation of other immune cells, such as IL-12, which activates the cytotoxic function of natural killer (NK) cells and stimulates interferon (IFN)-γ synthesis by T cells and NK (triggering in this case Th1 responses). Particularly, production of TNFα, IL-1, chemokines and IL-12 is typical of macrophages, while neutrophils secrete IL-12, TNFα in smaller quantities as well as some other cytokines. In addition, phagocytes act as antigen-presenting cells (APCs) like dendritic cells and, to a lesser degree as DCs do, apart from stimulating an adaptive response, they exert influence on its type (Th1/Th2). When DCs recognize a pathogen, they undergo maturation, usually characterized by (i) expression of adhesion and co-stimulatory molecules such as CD40, CD80 and CD86; (ii) increased expression of MHC-II molecules; and (iii) cytokine production like IL-6, IL-12, IL-23 and TNFα. DCs also migrate to lymph nodes and present

captured and processed antigens *via* MHC-II molecules to naïve T cells. There is increasing evidence that parasite-DC interaction plays a crucial role in triggering the type of adaptive response [29, 30]. It has been previously demonstrated that stimulated DCs present antigens associated with MHC-II molecules to $CD4^+$ naïve T cells, but, to conduct their maturation into differentiated Th1 or Th2 effector cells, costimulatory signals on DCs surface and other signals, such as IL-12, are required [31]. DCs can be activated by (i) parasite direct invasion, as *Leishmania* promastigotes invade dermal and myeloid DCs [32]; (ii) parasite-derived antigens or products, like soluble *S. mansoni* egg antigens (SEA) known for its potent induction of Th2 responses [33]; or (iii) other parasite-infected cells or cells that have contacted with it, as Denkers *et al.* [25] describe in their article, where DCs interact with *Toxoplasma* tachyzoites-infected neutrophil. There is evidence supporting that DC-protozoa interaction usually leads to the stimulation of IL-12 production, a cytokine that induces a Th1 response, whereas in the case of helminths, DCs release less IL-12, thus triggering a Th2 response through mechanisms that have not been clearly identified. For example, it has been shown that Th1 responses to *Leishmania* are associated with protective immunity, while the development of Th2 responses leads to disease progression [34]. Several studies have determined that the Th1 response is initiated by the *Leishmania* amastigote-DC interaction, probably through DC-SIGN, resulting in DC activation and IL-12 production, while the interaction of *Leishmania* amastigotes and promastigotes with macrophages promotes the inhibition of IL-12 release and seems to stimulate IL-10 secretion, triggering a Th2 response [35-37]. In addition, it has also been described that human myeloid DCs activation is dependent on *Leishmania* species: *L. major* promastigotes, but not those of *L. donovani* or *L. tropica*, efficiently stimulate the IL-12 release by DCs, and this fact can be related with the outcome of infection in these different species, since *L. major* causes limited infections while *L. donovani* and *L. tropica* spread to viscera or other cutaneous sites, respectively [38]. Mechanisms by which intracellular protozoa trigger Th1 response-induction by DCs are better known than those for helminths, because of similarity with other intracellular organisms. Albeit some studies show that the release of IL-12 by DCs is not essential for the naïve T cells polarization onto Th1 cytokine production [39], MyD88, an adapter molecule of the TLR signaling pathway in DCs, plays an essential role in the generation of Th1 responses [40, 41]. It is noticeable that IL-12, independently of its cellular origin, is required at the onset of Th1-responses [40].

The occurrence of Th2 responses are of more interest in immunity to parasites since they are unique to these pathogens (immediate hypersensitivity reactions are considered as pathological responses). The mechanisms by which DCs induce Th2 responses have not been well defined, but it is increasingly clear that DCs are able to process helminth-derived antigens converting them into signals that trigger naïve Th cell maturation towards a Th2 phenotype. Like for IL-12 production by DCs, MacDonald *et al.* [39] conclude in their work that DCs´ production of IL-4 is not strictly necessary for the emergence of a Th2 response, although it seems that IL-4 is essential in the development of Th2 responses, and that other cells also participate in its synthesis. Another way to explain how DCs would determine a Th2 response upon contact with helminth antigens has been proposed: the low IL-12 production by DCs in this situation leads to a low stimulation of responses Th1, thus favoring a Th2 response [33]. Moreover, this is associated with the fact that during helminth infection, DCs do not seem to mature in the sense of expressing some molecules such as CD80 or CD86 on their surface, producing detectable amounts of IL-4, IL-10 or IL-12 and significantly upregulating MHC-II molecules. However, these features appear to be indispensable for the correct development of Th1 responses [42]. But, for the same reason that a characteristic maturation of DCs is necessary for induction of Th1 phenotype, it is likely that an alternative maturation of DCs exists that triggers the Th2 phenotype. Furthermore, despite the apparent lack of maturation, DCs are able to induce Th2 responses under stimulus that influence Th2 polarization like SEA, even in the presence of stimuli that activate Th1 responses [43, 44]. In addition, various molecules expressed sometimes by DCs have been proposed as costimulatory signals for activating naïve T $CD4^+$ cells to produce Th2 cytokines, such as CD40, that interacts with CD154 on the surface of Th cells, apparently triggering a Th2 phenotype [45, 46], although some studies do not indicate the same [47, 48]. Another molecule recently linked with the turnout of Th2 responses is OX40L, a TNF superfamily member expressed on activated DCs, which interacts with the OX40 receptor on T $CD4^+$ lymphocytes performing a costimulatory function [49]. However, the key for explaining how DCs influence on naïve Th cell differentiation into Th1 or Th2 effector cells is the DCs differential expression of Delta (also called, "Delta-like" ligands or DLL) and Jagged ligands of Notch receptors, which induce Th1 and Th2 responses respectively [50]. Hence, the interaction of DLL expressed by DCs with the Notch3 receptor of Th cells leads to the activation of the transcription factor T-bet that promotes Th1 maturation through stimulating the expression of different genes, like *Ifnγ*, that results in IFNγ production [51, 52]. Furthermore, when activated by Th2 antigenic stimuli, DCs express Jagged ligands, which bind to Notch1 and Notch2 receptors, thus initiating a signaling cascade in $CD4^+$ T cells where the effector molecule RBPJk induces *Gata3* expression, leading to the production of GATA3, a transcription factor indispensable in Th2 maturation [52-56]. Apparently, GATA3 activates *Il4* expression resulting in the production of IL-4 by Th cells [52, 54, 56].

2.3. Role of Other Cells in Innate Immunity to Parasites

2.3.1. Granulocytes

Other innate immune system cells also bias the activation of the adaptive immune response, either through interaction and activation of DCs and other immune cells or by producing cytokines and other mediators. Thus, granulocytes such as basophils, eosinophils and mast cells have been implicated in the initial production of Th2 cytokines such as IL-4 and IL-13 [57]. For example, Reese *et al.* [58] demonstrate that eosinophils and basophils are recruited in the lung as a primary source of IL-4 when intranasal administration of chitin, a polymer found in nematodes. It

has also been shown that basophils are capable of producing IL-4 rapidly after the invasion by a parasitic pathogen without relying on binding to IgE [59, 60] in response to activation by various parasite antigens, like proteases secreted by several helminths [61] or IPSE, IL-4 inducing principle from *S. mansoni* egg [59, 62]. Furthermore, it has been suggested that basophils are capable of producing thymic stromal lymphopoietin (TSLP), normally excreted by epithelial cells, which is a cytokine that increases DCs´capacity to induce a Th2 maturation [63, 64], possibly through the expression of OX40L [65] and other molecules. Even though basophils have been revealed as APCs able to induce by themselves the maturation of naïve T $CD4^+$ into Th2 effector cells [66, 67]. New endogenous inflammatory mediators called "alarmins" have been described that function as chemokines and promote DCs´ maturation. This group includes defensins, cathelicidins, eosinophil derived neurotoxin (EDN) and high-mobility group box protein 1 [68]. Interestingly, EDN, produced by eosinophils, is a ribonuclease recently implicated in DCs´ activation to promote a Th2 response [69].

2.3.2. Natural Killer (NK) Cells

Other cells involved in innate immunity are natural killer (NK) cells. NK cells are important in immunity to intracellular pathogens, therefore its function has been mainly studied in protozoal infections. These cells have two essential functions: (i) to destroy abnormal or infected cells by cytotoxic mechanisms similar to those used by cytotoxic T lymphocytes [70], and (ii) to release proinflammatory cytokines and chemokines, especially IFNγ [1, 71]. IFNγ activates macrophages and neutrophils, enhances antigen presentation by APCs *via* increasing MHC molecules expression, induces IgG subclass changes in B lymphocytes, but principally, stimulates the differentiation of Th naïve cells to Th1 [72]. Invasive pathogens that trigger Th1 responses, including intracellular protozoa, are captured by DCs or macrophages, which produce NK-activating cytokines, like the most potent NK inducer IL-12 [73-75]. Furthermore, NK cells can be activated by direct binding to infected or altered cells, since they have different inhibitory and activating receptors with different specificities, like Ig superfamily receptors (e. g. KIR) and C-type lectins [76]; but they also express TLRs [77] which have been shown to interact with protozoa, such as *Leishmania* that activates NK cells by TLR-2 binding [78]. The role of NK cells has been studied in various protozoal infections, and, while their cytotoxic function in these infections appears to be needless, their IFNγ secretion is critical [79-81], especially in *T. cruzi* [81-83]. Although IL-12 and in lesser extent IL-18 [84] production by macrophages and DCs is the most studied signal for NK cell activation, the role exerted in this activation by NK direct recognition of parasite antigens is increasing its importance. Hence, in *P. falciparum* infection, contact between NK cells and *P. falciparum*-infected erythrocytes is necessary for optimal IFNγ production by NK (though dependent on IL-12) [85, 86]. Finally, the fact that IL-4, IL-10 and TGF-β release inhibits NK cells activation [87], suggests that during helminth infection when the response is primarily Th2 and IL-4 is abundant, these cells could play a less important role. Despite this assumption, some studies have been carried out that demonstrate an increase of NK cells in helminth infections, denotating somewhat the participation of NK in immune responses to helminths [88-91]. Several observations explain this fact. On the one hand, helminths life cycles are complicated and they develop Th1 and Th2 responses depending on the stage of infection [92, 93]. On the other hand, two NK subsets have been described, NK1 and NK2, which, by homology to Th1 and Th2, would be producing Th1 cytokines such as IFNγ, and Th2 mediators, including IL-5 and IL-13, respectively [94]. To conclude, the involvement of NK cells in helminth infections could be both directing a Th1 response and a Th2 response. Anyway, there are still many mechanisms to be elucidated in the understanding of how NK cells participate in parasitic infections, especially in regard to helminths.

2.3.3. Natural Killer T Cells (NKT Cells)

Other cells involved in innate immunity are natural killer T cells (NKT) that are cells which recognize glycolipids in association with CD1d molecules presented by APCs, such as DCs or intestinal epithelial cells [95]. NKT cells are characterized by expressing specific markers of T lymphocytes (CD3) and NK (NK1.1) and they are divided into two subtypes: (i) invariant or classical NKT cells (iNKT), which express a highly restricted T cell receptor (TCR) with an invariant α chain -in mice, $Vα14^+$ and in humans, $Vα24^+$- and actively respond to the glycosphingolipid α-galactosylceramide (αGalCer); and (ii) the variant or non classical $Vα14^-$ NKT cells (non-iNKT), which express more TCR and do not respond to αGalCer [96-99]. A third subtype of NKT cells has been described subsequently: CD1d-independent NKT cells [99]. NKT cells have been suggested as an early source of Th1 and Th2 cytokines [95, 100], being therefore candidates to trigger the later adaptive immune response [101]. Several publications have related NKT cells with the primary immune response to diverse parasites: on the one hand, with protozoa, such as *Leishmania* spp. [102], *Toxoplasma* [103] or *Plasmodium* liver stage [104] and on the other hand, with helminths, such as *Schistosoma* [105]. Despite these findings, there are diverse opinions regarding the role of NKT cells in immune responses to pathogens, maybe due to the variability in the definition of NKT cells among studies [106] or to the difficulty of differentiating non-iNKT from other cells in the absence of specific markers [107]. Thus, while Ishikawa *et al*. [102] concluded that NKT cells are essential in the initial protective response to *L. major* in mice -they detect the parasite in regional lymph nodes- because they are associated with the production of HSP65 which prevents apoptosis of *Leishmania*-infected macrophages; there are other studies that disparage NKT cells function, at least in terms of its protective role in the onset of *Leishmania* infection in subcutaneous tissue [108]. In that case, it has been proposed that NKT cells present a needless participation in response to the parasite at the organic level, like the spleen, where the infection is disseminated. Furthermore, Wiethe *et al.* [109] have reported that CD1d-dependent NKT cells activated by DCs rather mediate non-protective Th2 responses to *Leishmania*. In *T. gondii* infection, a damaging role for NKT cells has been proposed: in some cases, by lack of control of the Th1 protective response in which they take part [103], in others by interfering with the protective response associated with γδ T

cells [110]. In *Plasmodium* spp. murine infection, CD1d-dependent NKT cells seem to participate in the protective response to the sporozoite in the liver but not in the subsequent erythrocytic stages [104], although their occurrence is not indispensable [111, 112]. Furthermore, CD1d-independent NKT cells have been proposed to play a potential protective [112] or damaging [113] role in *Plasmodium* infections, evidencing once again the controversy regarding NKT cells role in immunity to parasites. The relationship between CD1d-dependent NKT cells and the development of Th2 responses is also interesting, and has mainly been studied in murine schistosomiasis in the egg stage, known as a potent activator of Th2 responses [105, 107]. Moreover, it has recently been shown that iNKT cells and non-iNKT may exert an opposite influence on the type of immune response to schistosome eggs, suggesting that the former contribute to the differentiation of Th1 cells and the latter to the Th2 response [107]. In conclusion, given the disparity of opinions, it is necessary to continue research in this field.

2.3.4. B-1 and MZ ("Marginal Zone") Lymphocytes

B-1 and MZ ("marginal zone") lymphocytes seem to act as intermediates between innate and adaptive immunity and they are usually found in the peritoneal cavity and in marginal areas [114], like the pleural space. They differ from B-2 lymphocytes, which are characteristic of adaptive immunity, in (i) different cell markers expression, (ii) low affinity, non-specific antibodies production, mostly of IgM class, and (iii) not usually undergoing somatic hypermutation or heavy chain isotype switching [115, 116]. Furthermore, they do not require Th cells intervention to proliferate and survive for months [116] and they are capable of producing reactive oxygen species and proinflammatory cytokines to directly eliminate pathogens [114]. Their situation allows them to directly contact with pathogens dwelling in the gastrointestinal tract and it is not surprising that they have been shown to intervene in the immune response to intestinal parasites, especially helminths, including *S. mansoni* [117, 118]. Moreover, in this context, B1 cells producing IgE have been detected [119]. B1 cells also appear to be essential to *Brugia* spp. infection control, probably due to their ability to produce antibodies, to act as APCs and to release IL-10, which could trigger a protective Th2 response [120]. However, B1 cells have also been associated with the suppression of immune response to helminths, through induction of Th cells apoptosis [121]. Again, further investigations are needed to clarify the role of these cells in the immune response to parasite pathogens.

2.3.5. γδ T Lymphocytes

γδ T lymphocytes, as defined by their TCR, play a role analogous to that of B-1 lymphocytes. This type of T cells has a reduced diversity of antigen receptors and is found mostly in the gastrointestinal mucosa as part of intraepithelial lymphocytes [122, 123]. γδ T cells are generally considered part of the early immune response, participating in (i) the rapid release of cytokines such as TNFα, IFNγ -phenotype Th1- and IL-4 -phenotype Th2- [124], (ii) the secretion of cytokines to lyse damaged or infected cells [125], (iii) the presentation of antigens acting as APCs [126], and also (iv) the regulation of the immune response [123, 127, 128]. It was initially noticed that γδ T cells level in peripheral blood increased in responses to different types of parasites, including *Toxoplasma* [129], *Leishmania* [130, 131], the nematode *Onchocerca volvulus* [132] or the trematode *Schistosoma* [133], suggesting that these cells are somehow involved in immune response to parasites. Subsequently, they have been assigned a protective role in infection by certain protozoa. Hence, in *T. gondii* infection, γδ T cells are associated with induction of HSP-65 expression and nitric oxide (NO) production by macrophages [134, 135], and in *T. cruzi* liver infection they may contribute to the production of IFNγ [83]. However, there is also evidence that γδ T cells are related to the exacerbation of immune response and the subsequent immunopathology [136] like the intestinal disease produced during *P. vivax* malaria [137], or the cardiac and skeletal muscle infiltration by inflammatory cells during *T. cruzi* acute infection [138, 139]. Although the latter work [139] suggests the existence of different subsets of γδ T cells with different immune functions, and, in this particular case, only $V\gamma1^+$ cells produce the pathology. The existence of different subtypes would explain as well the association of γδ T cells with immunoregulatory functions [136]. The immunopathologic role could be explained by the ability of γδ T cells to release IL-17, a proinflammatory cytokine also related to autoimmune diseases [140].

With regard to helminths, the role of γδ T lymphocytes in the immune response is still not clear. Their presence in mucous membranes, especially in the gastrointestinal tract, suggests their implication in the response to pathogens that reside in that niche [123], like many adult worms do. This assumption is strengthened by the fact that γδ T cells are able to produce IL-4, a cytokine involved in Th2 responses. In murine *T. spiralis* infection, the increase of γδ T cells within the population of intestinal intraepithelial lymphocytes has been associated with worm expulsion from the gastrointestinal tract, whereas in spleen and peripheral blood these cells showed a different kinetic [141]. Furthermore, the contribution of γδ T cells in granuloma formation around *S. mansoni* egg has been studied and, despite their presence and apparent activation [142], they do not seem to be indispensable [143]. Therefore, the role of γδ T cells in response to different parasites apparently depends on the type of parasite, given the different roles that these cells assume in each case.

There have been major advances in the understanding of the innate immune response to parasites, but further research is needed to elucidate the mechanisms by which interaction occurs between these pathogens and actors of the innate immune response, and how it affects in the response later developed. Moreover, it remains to clarify the role played by the different cells of the early response against invasion by parasites.

3. ADAPTIVE IMMUNITY TO PARASITES

T and B lymphocytes are the most representative cells of adaptive immunity to pathogens, and therefore also to parasites.

T lymphocytes expressing the αβ TCR are roughly divided into three subsets: $CD4^+$ or T helper (Th) cells, $CD8^+$

or cytotoxic T lymphocytes (CTL) and $CD4^+$ regulatory T cells (Treg) [2, 144-147], although the division is greater with the inclusion of Th17 lymphocytes [148, 149]. As seen previously, the differentiation of naïve $CD4^+$ T cells in response to stimulation by APCs can lead to two phenotypes depending on the stimulus, Th1 and Th2, characterized by the type of cytokines produced in each case. These cytokines stimulate various effector cells depending on the Th phenotype, which in turn release more cytokines and chemokines also Th-response specific [150-153], which are molecules that allow the guidance and communication of immune system components. Immune responses are usually not only categorically Th1 or Th2, but a balance is established that tends toward one or the other depending on the cytokines produced. The Th response developed influences the outcome of parasitic infections, as it happens with other pathogens. However, in the case of parasites, the Th response depends on the stage of infection and the type of parasite. A dogma has been setted according to which Th1 responses are established to eliminate intracellular pathogens while Th2 allow the elimination of extracellular pathogens. Thus, in general, the protective responses against protozoa, many of them being intracellular, are usually Th1 and are mediated primarily by IFNγ; while helminths, that are extracellular organisms, need Th2 responses to be expelled and the key cytokines are IL-4, IL-5 and IL-13.

3.1. Adaptive Immune Response to Protozoa

In Th1 responses to protozoa, IFNγ production by $CD4^+$ T cells, but also by $CD8^+$ T cells leads to the activation of effector mechanisms to effectively eliminate parasites, such as macrophages stimulation to destroy phagocytosed parasites, like *T. cruzi* [154]. This feature is important because many protozoa escape from humoral immunity by penetrating inside macrophages, like *Toxoplasma* [155] or *Leishmania* [156, 157]. It has been stated that cellular immune response rather than antibody production is important for resistance to protozoa with intracellular stages, like the *Plasmodium* pre-erythrocytic stage [158, 159]. Furthermore, IFNγ activates Th1 cells differentiation by stimulation of the transcription factor T-bet generation, and inhibits Th2 cytokine production through suppression of the transcription factor GATA-3 expression by T-bet [160]. IFNγ also increases the expression of MHC-I molecules to facilitate recognition and elimination by $CD8^+$ cytotoxic T cells, and MHC-II molecules to promote the presentation of antigens to $CD4^+$ T cells [157]. IFNγ also stimulates the switch to certain classes of Igs, such as IgG2a, and inhibits isotype switching to IL-4 dependent Igs, such as IgE and IgG1 [161]. As noted previously, the most typical example of the protective role of Th1 responses at the expense of Th2 is *Leishmania* infection, but while that´s true for cutaneous leishmaniasis, this fact remains unclear in visceral leishmaniasis [162]. Th1 responses are characterized, in addition to IFNγ production, by the activation of CTL-mediated cell lysis, although the importance of these cells in the defense against protozoa is due apparently to their ability to produce IFNγ rather than to its lytic activity, like in toxoplasmosis (reviewed by [163]). However, $CD8^+$ T cells plays a protective role in malaria by destroying *Plasmodium* sporozoites-infected hepatocytes; and Overstreet *et al.* [164] show that memory $CD8^+$ T cells unable to produce perforin, FasL or IFNγ separately can protect against the liver stage in any of the three cases, concluding that the effector function of memory $CD8^+$ T cells is due to a combination of the cytotoxic/cytolytic mechanisms and IFNγ production but any of them is indispensable in the presence of the others. The role of $CD8^+$ T cells is apparently essential for the immune response to *Plasmodium* sporozoites [158, 159, 165-167]. Cellular responses against the erythrocytic stage of malaria have also been described [168, 169], but, while the role of $CD4^+$ T cells is manifestly important, it is not yet clear whether $CD8^+$ T cells are indispensable or not [170], and even, $CD8^+$ T cells have been associated with the pathogenesis of cerebral malaria [171]. The participation of $CD8^+$ T cells in Chagas´ disease is also relevant for controlling infection [172], to the point that *T. cruzi* infection has been proposed as a model for $CD8^+$ T cells-mediated vaccine development against intracellular pathogens [173]. In fact, knowledge of the importance of $CD8^+$ T cell response in protozoan infections is leading to the investigation of parasite epitopes that potently stimulate the activation of $CD8^+$ T cells in order to develop protective vaccines [172-175].

Although antibodies are not apparently the main control mechanism in parasitic infections with intracellular stages, they are produced in response to all protozoal infections: *Leishmania* [176-178], *T. cruzi* [179, 180], *T. gondii* [181, 182], *Plasmodium* [170, 183], etc. However, B cells´ productions of antibodies do show a central role in African trypanosomiasis, probably for the reason that *T. brucei* is an extracellular parasite [184]. In African trypanosomes the importance of various immunoglobulins has been determined. Hence, IgGs play a more critical role than IgMs in infection control, although IgM levels are high. Moreover, it has been shown that different subclasses of IgGs are generated at each stage of infection and depending on the recognized antigen [184-186], although the immunodominant antigen is possibly the variable surface glycoprotein or VSG [187-189]. Thus, although the production of immunoglobulins is not always the main effector mechanism, they display a relative importance in response to different parasitic protozoa. The roles of antibodies in response to protozoa are diverse. On the one hand, direct lysis by antibodies has been described, like for *T. cruzi* infection [190] or complement-mediated lysis, like it occurs, for example, in the destruction of *Plasmodium* gametocytes [191] or *T. cruzi* trypomastigotes [192]. Moreover, antibodies cooperate in phagocytosis by macrophages and other phagocytes that express Fc receptors, resulting in better elimination of parasites if the complement also takes part; this happens for example in macrophage phagocytosis of african trypanosomes which is mediated by IgM and IgG2a in the murine model [193], phagocytosis of *P. falciparum*-infected erythrocytes [194, 195] as well as in the destruction of *T. gondii* by macrophages [196]. Finally, antibodies inhibit the binding of parasite antigens to the surface receptors that enable their penetration into host cells, thus neutralizing the infectivity of the parasite; in this manner, specific antibodies to the merozoite surface protein-1 (MSP-1) inhibit *P. falciparum* invasion of erythrocytes [197], as well as antibodies to the surface protein SAG-1 prevent *T. gondii* penetration into mouse host cells [198].

Furthermore, the detection of different types of antibodies is useful as a tool for the diagnosis of these parasitic diseases, allowing the performance of serologic profiles that are related with various stages of the infection [176-178, 180, 181, 199-201].

3.2. Adaptive Immune Response to Helminths

Helminths are usually large and extracellular parasites, and the adaptive immune response normally developed to these pathogens is characterized by the differentiation of Th2 cells, which release IL-4, IL-5 and IL-13, but also other cytokines such as IL-9 and IL-10. IL-4 is the main cytokine in Th2 responses [202], although it has been shown that IL-13, which also binds to IL-4 receptor, IL-4Rα, performs similar functions to IL-4 and can compensate or substitute IL-4 in various helminth infections [203, 204]. IL-4 stimulates the development of Th2 cells, thus acting as an autocrine growth factor [205, 206]. Moreover, IL-4 is the main promoter of Ig class switching to IgE, which is the characteristic Ig of Th2 responses [207, 208]; and also, IL-4 inhibits the maturation of naïve $CD4^+$ T cells into Th1 and Th17 lymphocytes. Furthermore, both IL-4 and IL-13 induce macrophages to transform into a phenotype different from classical macrophages, termed alternatively activated macrophages [209, 210], whose role will see later. Meanwhile, IL-13 has different functions in addition to those shared with IL-4, as mediating resistance to intestinal helminths through direct action on intestinal smooth muscle and enteric nerves resulting in increased peristalsis, which favors helminths expulsion, or stimulating mucus production and bronchial hyperresponsiveness in the lungs (reviewed in [211]). Then, IL-5 is the primary stimulus for eosinophil activation [212, 213], which are important effector cells in Th2 responses to parasitic helminths [214, 215].

Immune responses to helminths are characterized by parasite antigen-specific IgE production by B cells in response to stimulation by IL-4, mainly released by Th2 cells. Circulating IgE binds to tetrameric ($\alpha\beta\gamma_2$) high-affinity Fc receptors specific for ε heavy chain, called FcεRI, which are essentially expressed by mast cells and basophils [216]. It is noticeable that tissue mast cells in all individuals are normally coated with IgE, which is bound to the FcεRI. Thus, when IgE-FcεRI complex interact with parasites, ie with multivalent antigens, there is a cross-linking of Fc receptors that leads to activation of mast cells [217] and, in the same way, to basophils. Once activated, these cells release the preformed contents of their granules by exocytosis: histamine, which exerts a vasoconstrictor role, and proteases such as tryptase or chymase, are some of the most important molecules of mast cells granules. In addition, mast cells synthesize in response to stimulation proinflammatory cytokines and lipid mediators. Thus, mast cells are involved *via* their released mediators in the expulsion of some gastrointestinal helminths through increased intestinal peristalsis and mucus production [178, 203], as for *T. spiralis* [218-220], although the involvement of IgE in this process is still controversial [220]. Basophils produce, in addition to IL-4, proteases and other enzymes [221]. Notwithstanding FcεRI expression by eosinophils, they are not activated when binding to IgE because their Fc receptor lacks the β-chain -ie, their receptor is trimeric- [216, 222], and β-chain is essential for initiating the signaling pathway that leads to cellular activation. Apparently, the binding of IgEs to helminths allows eosinophils, once they are at the site of infection and have been activated through other mechanisms, to secrete cytotoxic substances intended to destroy the neighbouring parasites coated with IgEs, preventing these substances to act on surrounding self tissue. This mechanism is called IgE-mediated cytotoxicity [1]. Eosinophilia is a typical sign of helminth parasitic disease [223, 224], although the exact role of eosinophils in these infections is not yet clarified. It has been demonstrated that eosinophilia is more persistent in helminth infections which include tissue migration in their life cycle, such as *Ascaris lumbricoides* or *T. spiralis*, than in those where worms stay in the intestinal lumen, such as taeniosis, or inside of cysts, like hydatid cysts [224]. This is easily explained by greater exposure of the former to the components of the immune system [224]. Eosinophils circulate in the blood and are attracted to sites of parasitic infection by IL-4 and IL-13 [225, 226], and other chemokines, including eotaxin [227, 228] and RANTES [229]. Eosinophil degranulation is activated, in addition to IL-5 -which by itself is capable of causing eosinophilia-, by other cytokines such as IL-3, TNFα and GM-CSF [230]. Moreover, other immunoglobulins apart from IgE, like IgG or IgA, acting as opsonins, can also bind to Fc receptors on eosinophils promoting degranulation [231-234]. It has been shown that *in vitro*-activated eosinophils are capable of destroying opsonized parasites through substances contained in their granules, like lysosomal hydrolases, eosinophil peroxidase or specific eosinophil proteases such as major basic protein (MBP) and eosinophil cationic protein [235-241]. However, there are animal models that question the role of eosinophils in helminths destruction, proposing rather for them a role in innate immunity [242-244], as discussed above. This remains controversial. Thus, while Swartz *et al.* [244] argue that in eosinophil-ablated mice, *S. mansoni* infection does not differ from that which occurs in normal mice; other studies defend the protective role of eosinophils in *S. mansoni* infection and reinfection in humans [245]. Therefore further analysis over the status of eosinophils in helminth infection has to be achieved in order to clarify the situation.

Another characteristic of Th2 responses to helminths is the induction of a macrophage phenotype different from classical (caMΦ), resulting in "alternatively activated macrophages" (aaMΦ) [246]. It has been demonstrated that IL-4 and IL-13 produced in within a Th2 response induce different maturation of macrophages to a phenotype characterized among others by: (i) up-regulated mannose receptor expression, (ii) inhibition of nitric oxide-synthase (iNOS), (iii) production of arginase-1, chitinase-like molecules (Ym1/2 or AMCase), resistin-like molecules (RELMα) and protein Fizz as well as (iv) collagen deposition [209, 247-253]. Shift from caMΦ to aaMΦ is apparently due to the IL-4Rα-dependent induction of arginase activity in macrophages [254]. Arginase and NOS produce by L-arginine hydrolysis an increase of L-ornithine, which stimulates proline and polyamines production, molecules that direct cell proliferation and collagen deposition [255, 256]. This change results in macrophages that promote cell growth and tissue repair, a fact also

evidenced by up-regulated mannose receptor, which generally recognize damaged cells [257]. There are other molecules that stimulate the differentiation of this macrophage type referred by some authors as M2 macrophages [258] in contrast to the classical type or M1, and different subpopulations of these macrophages have been proposed in terms of the different mediators that induce their appearance [258, 259]. Thus, it has been suggested dividing aaMΦ in M2a, M2b and M2c, each representing macrophages stimulated by IL-4 and IL-13 only (real aaMΦ), immunocomplexes and TLR-ligands (or MΦ type II) [260] and IL-10 or TGF-β (or inactivated MΦ), respectively. These macrophages, especially M2c, apparently show an anti-inflammatory function, as determined by low production of proinflammatory cytokines and high secretion of IL-10 and TGF-β, involved in reducing inflammation and activating regulatory T lymphocytes. This fact and the inhibition of iNOS demonstrate that aaMΦ counteracts and inhibits caMΦ, which are mostly related to Th1 responses. This feature explains partially why aaMΦ appearance is associated with poorer immune protection against protozoa, such as *Leishmania* [261], african trypanosomes [262-264] and *T. cruzi* [265]. Moreover, apart from prolonging protozoa survival, aaMΦ apparently counteract the immunopathology associated with an excess of Th1 responses to these parasites [266]. In helminths infection, the benefit of aaMΦ activation under Th2 responses has been proved. Thus, in *S. mansoni* infection, the granuloma formation around the egg during Th2 protective responses is necessary for egg´s expulsion in faeces [267], and the emergence of Th1 responses disrupts ganuloma formation and egg´s expulsion, what is lethal [268]. In this context, Herbert *et al*. [269] showed that mice deprived of aaMΦ have a 100% of mortality during *Schistosoma* trematode infection associated with lower expulsion of eggs in faeces, thus attributing an essential role of these macrophages in protection against this parasite. Furthermore, they demonstrated that mortality in these mice is also related to high intestinal damage, with extravasation of its contents and septic shock, which can be explained by the lack of tissue repairing by aaMΦ. With regard to intestinal nematodes, it was not possible to identify a similar function of aaMΦ in parasite expulsion during primary infection, although it does have a protective role in Th2 cell-mediated memory [270]. In the context of nematode infections, there are molecules produced by macrophages, such as those belonging to the families of chitinase and Fizz (ChaFFs) that could be involved in wound repair at the site of infection [271]. Finally, aaMΦ have been proposed to play a protective role in cestode chronic infections. During *Taenia crassiceps* infection in mice, acute infection is characterized by a Th1 response dominance, and when it progresses to chronicity, response turns to Th2 type, where aaMΦ intervention is beneficial: they inhibit $CD4^+$ T cells proliferation through programmed death ligand (PD-L), thereby reducing tissue damage due to inflammation [246, 272]. Therefore, aaMΦ are effector cells in helminth infection and are apparently essential in the protective immune response to these pathogens.

Other cells that participate significantly in the intestinal elimination of helminths are intestinal epithelial cells and goblet cells, which are increasing in importance by the fact that the way of expelling intraluminal parasites has not been since now clarified. Thus, a wide range of mechanisms by which these cells are actively involved in the effector phase of the adaptive immune response to helminths have recently been described. It has been shown that during the immune response to intestinal helminths, epithelial cells turnover is accelerated in order to contribute to parasites´ elimination [273] and there is also a goblet cell hyperplasia that produce greater amounts of mucin which may contribute to worms expulsion [274, 275]. Furthermore, several studies have been carried out to identify genes that are upregulated in helminth infection models compared to controls, and it was found that many of the upregulated genes are specific of intestinal epithelial cells [276] and goblet cells [277]. The most frequently expressed genes were those related to the wall function, ion exchange, tissue repair and metabolism of epithelial cells [277]. Genes encoding intelectins, that are calcium-dependent galactose-binding proteins described previously [278], 3 calcium-activated chloride channel 3 and pancreatic lipase-related protein 2 [279]. According to these studies, intelectins are secreted in large amounts in the intestinal lumen and, through binding to parasite surface residues, contribute to their expulsion. The presence of resistin-like molecules or RELM, which, as discussed above, are found in aaMΦ and therefore seem to be associated with Th2 responses, has also been demonstrated in the gastrointestinal tract during nematode infections [280]. Thus, RELMβ, produced mainly by goblet cells, is apparently involved in the intestinal helminth expulsion, although its role remains unclear [280]. Consequently, it appears that local cells contribute to the effector response to gastrointestinal parasites. Moreover, similar mechanisms have been described in relation to the respiratory tract, including the involvement of intelectins [281], although more researchs are needed in this field.

Recently, new Th cell subsets, like Th17, have been described [282]. The differentiation of naïve Th in Th17 cells is due to antigen recognition in the presence of TGF-β and IL-6; and furthermore, IL-23 appears to be essential for the survival of these cells [283]. Th17 cells are characterized by the production of IL-17, a cytokine family related to the promotion of inflammation at the site of infection through granulocyte recruitment and cytokines and proinflammatory chemokines release [283]. IL-17 is also produced by other lymphocytes such as NK, T and T CD8 + γδ [284]. This cytokine family consists of six members [285], but IL-17A and IL-17F are the most specifically produced by Th17 cells and the instigators of the proinflammatory state. Furthermore, these lymphocytes have been related with the pathogenesis of various chronic inflammatory and autoimmune diseases such as psoriasis or rheumatoid arthritis [282, 286-288]. In regard to parasitic infections, the participation of Th17 cells has been described in liver damage exacerbation due to *S. mansoni* egg, suggesting that these cells are responsible of the immunopathology associated with this infection [289, 290]. Th17 cells have also been linked to inflammation and intestinal dysfunction during murine *T. spiralis* infection through the promotion of intestinal hypermotility [291]. Another member of the IL-17 family, IL-17E, also known as IL-25, which is produced by activated Th2 lymphocytes, mast cells and a non-T non-B lymphocyte population -a new Th25 subpopulation has been

proposed [292]- has been associated with Th2 responses because it promotes apparently the production of Th2-related chemokines. IL-25 also appears to be associated with the protective immunity to parasites, as denoted by the study with *Nippostrongylus brasilensis* performed by Fallon *et al.* [293], where IL-25 induces Th2 response and is necessary for parasite expulsion. It has also been proposed for IL-25 a role in limiting the intestinal pathology associated to *Trichuris* infection in mice due to the decrease of IL-17 production (the other family membersy) and IFNγ [292]. Therefore, IL-25, despite of belonging to the same family, presents an opposite function in comparison to the other members of the IL-17 family, and also appears to inhibit their production, showing a protective role against autoimmune diseases [294]. Therefore, helminths parasitization has been proposed as a beneficial factor to prevent autoimmune inflammatory diseases [295].

Another T cell subpopulation that has recently gained importance is that of regulatory T cells (Treg). A characteristic of chronic helminth infections is their ability to produce Th2-restricted responses, which decrease over time, leading to the regulation of tissue damage caused by the initial exacerbated Th2 response, thus permitting parasite protection from host but at the same time allowing host survival [296]. It has been shown that an important part of this immunoregulatory process is due to a T cell subpopulation different from Th1/Th2/Th17: Treg cells. Within these regulatory T cells that control the intensity of effector responses, two main types can be differentiated: the natural $Foxp3^+CD4^+CD25^+$ Treg cells that develop in thymus, and inducible Treg that are differentiated from $CD4^+$ T cells (such as Th3 or Tr1) [297]. The first type acts through cell-to-cell contact with other T cells, probably through cell surface expression of TGF-β molecules [298] and CTLA-4 [299]; and the latter acts through TGF-β and IL-10 production [297]. It seems that TLR-stimulated dendritic cells influence the onset of the second Treg cells type [31, 296, 300]. The two Treg cells types appear to be important in several parasitic infections. Natural Treg cells are apparently involved in controlling the pathology caused by Th2 immune responses to parasites, both in helminths, including *S. mansoni* [301], and protozoa, like *Leishmania* [302, 303]. Thus, Treg cells control the pathological immune response, but allow as well the parasite survival and persistence, as it has been demonstrated in a murine model of the filaria *Litomosoides sigmodontis* infection; in the latter case, the suppression of $CD25^+$ Treg cells with subsequent decrease in CTLA-4 allowed parasite elimination [304]. Moreover, IL-10 influence in immunoregulation during parasitic infections has been demonstrated, both in helminth, such as filariasis [305] or schistosomiasis [306], and in protozoa infections, such as leishmaniasis [307] or toxoplasmosis [308], through the control of immunopathology and inflammation. While IL-10 is produced by natural Treg and other cells, such as DCs, or conventional T and B lymphocytes, Tr1 cells are a major source of this cytokine during parasitic infections, as it happens in infection with *O. volvulus* [309-311]. Furthermore, Th3 cells have also been implicated in parasitic infections as a source of IL-10 and TGF-β [309]. Like natural Treg, inducible Treg cells have been implicated in lethal responses to parasites due to an excess of immunoregulation, as it has been noticed in *Plasmodium* infection in mice [312, 313]. Finally, due to the relationship between helminth infection and the development of a Treg-limited Th2 response, it has been proposed that helminth parasitization has a protective role promoted by the Treg-mediated immunoregulatory response in allergies characterized by abnormal and exacerbated Th2 responses [314, 315].

To conclude, it has been proposed that parasitic infections result in diverse adaptive immune responses that move between two crossed axes that define immune responses: the Th1/Th2 responses and the inflammatory/anti-inflammatory responses (see Fig. **1**). Each of these responses is characterized by a T cell subset and an effector cell type and the response status in each of these axes will determine the final infection outcome [316].

4. MECHANISMS OF IMMUNE EVASION BY PARASITES

Most of the parasites cause chronic infections, with symptoms of low intensity, in order to generate a lasting parasite-host relationship and maximize the chances of transmission or adapt the time to the biological process of its life cycle. These pathogens have developed a variety of mechanisms to adapt to the host, either by evasion or modulation of the immune system.

4.1. Mechanisms of Innate Immunity Evasion

When parasites enter the host, they confront a first line of defense: the innate immune system. In many cases, the first contact occurs for extracellular parasite forms with soluble factors existing in the host, where the main effector is the complement system. The strategy mostly used by parasites to avoid complement-mediated destruction is the inactivation of the alternative pathway of the complement at different enzyme levels. One of the ways by which parasites achieve complement inactivation is the acquisition of complement regulatory proteins that are anchored to their surface, such as glycoproteins that accelerate the dissociation of the C3/C4b convertase similarly to DAF proteins in host cells. Thus, the production of DAF homologues, such as gp72 and gp160 by the *T. cruzi* metacyclic trypomastigote, allows this parasite stage to survive within humans, whereas the epimastigote form present in the vector can be destroyed by the complement [317]. Another way to avoid the complement lysis is by blocking membrane attack complex or MAC proteins (C5-C9) or preventing the pore formation which results in complement-mediated cell death. Host cells protect themselves from complement action by expression of different molecules such as a molecule called CD59 [318]. There are parasites that mimic this protein function, like *Entamoeba histolytica*, wich is able to activate complement but at the same time, is resistant to it. This pathogenic amoeba produces a galactose-specific adhesin which is binds monoclonal antibodies to CD59 protein and presents structural similarity with it, suggesting that this adhesin is responsible for complement evasion by *E. histolytica* [319]. Besides, *S. mansoni* adopts a similar strategy by producing a

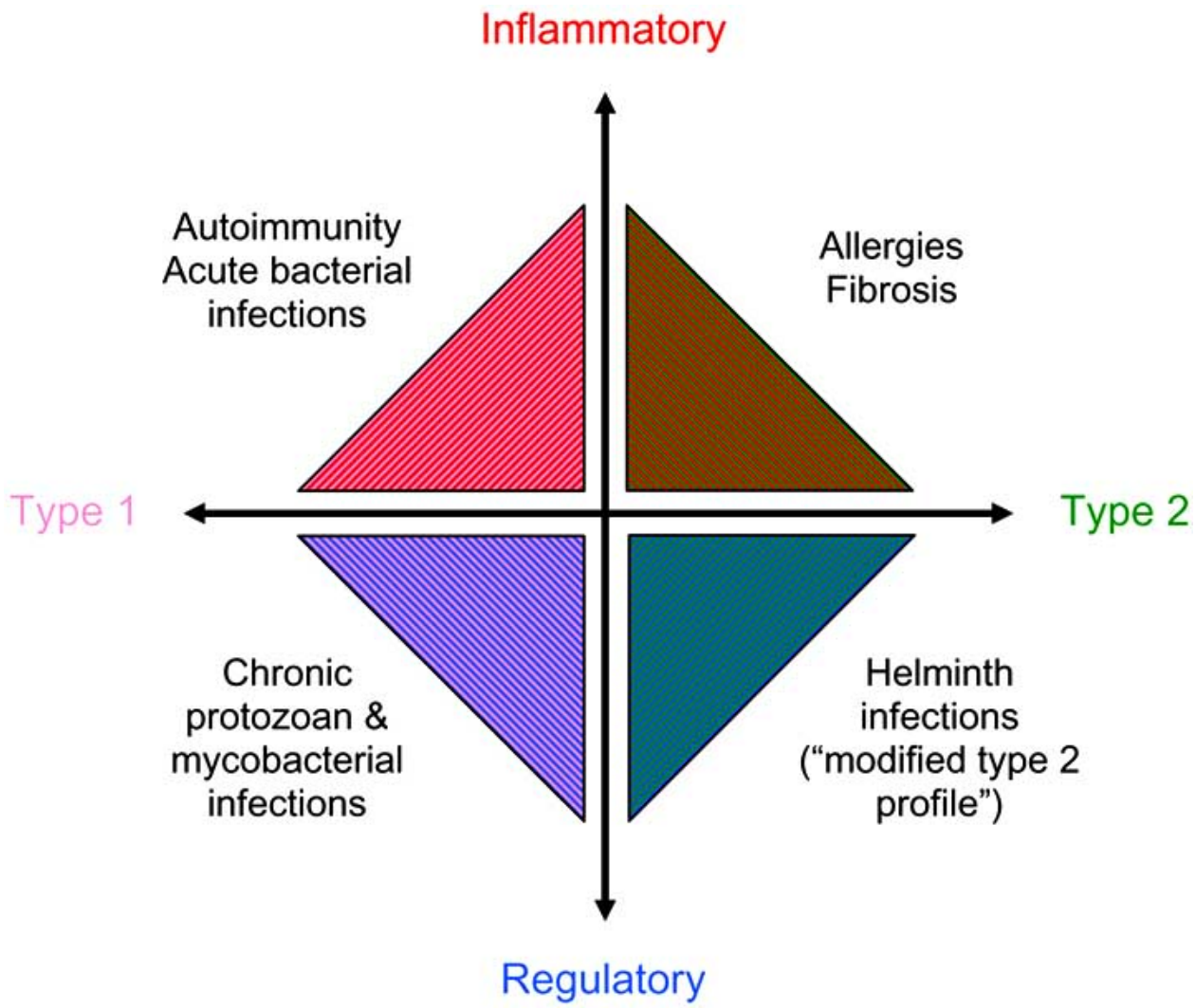

Fig. (1). A two-dimensional map of immune responses. It has been proposed that immune responses can be summarized in a two-dimensional map defined by type 1-type 2 and inflammatory-regulatory axes. Thus, both type 1 and type 2 responses can combine with regulatory and inflammatory responses. Each response direction can be targeted to foreign as well as self antigens, but the responses to self in healthy individuals are mainly regulatory responses. The central elements of type 1, type 2, inflammatory and regulatory are Th1, Th2, Th17 and Treg cells, respectively [316].

94 KDal-protein called SCIP-1, which, in addition to bind to anti-CD59 antibody, presents structural homology to paramyosin, a molecule expressed by muscle cells that inhibits the polymerization and incorporation of C9 on the cell surface [320]. Another widely studied soluble mediator that parasites should avoid when penetrating hosts, is the trypanosome lytic factor (TLF) or trypanolytic factor of human serum, which prevents infection by *T. brucei* in primates. The structure of this factor includes an HDL particle attached to (i) apolipoprotein A-I (like all HDL particles), (ii) apolipoprotein L-I (ApoL-I) and (iii) a serine protease, the haptoglobin-related protein (HPR) [321, 322]. Two TLF have been described: TLF1, which is rich in lipids, and TLF2, which has a few number of lipids and circulates in the blood forming immunecomplexes with polyclonal IgMs [323, 324]. Trypanosomes recognize and endocytose these particles through an unknown specific receptor. Once inside a trypanosome endolysosome, due to the pH acidification, apoL-I dissociate from the particle and form pores in the lysosome wall resulting in its gradual swelling leading to cell death [325]. There are studies that associate HPR with the trypanolytic activity, but it seems that, rather than intensifying the toxic activity of apoL-I, HPR allows the particle binding to parasites [326]. One of the two *T. brucei* subspecies capable of infecting humans and causing the sleeping sickness disease, *T. brucei rhodesiense*, has a gene called SRA (serum-resistance associated) gene, which is involved in a transcriptional change (R-ES) that leads to the truncated expression of the major antigen, the variable surface glycoprotein or VSG, thus conferring resistance to TLF [327].

Another important mechanism is the adaptation to intracellular life into host cells to avoid recognition by serum components, like intracellular protozoa do. Many protozoa are capable of penetrating macrophages, as described above. To avoid elimination by the lysosome hydrolytic

environment, parasites have developed different mechanisms. Among them is the ability to change cellular compartmentalization to prevent the union of the parasitophorous vacuole (PV) with endosomes or lysosomes. This is important in *T. gondii* infection, which is able to penetrate into both phagocytic and nonphagocytic cells. In that case, it has been reported that after active endocytosis, the membrane of the PV where the parasite is, contains a high percentage of parasite proteins, accompanied with a decrease of host cell membrane proteins and opsonization-related proteins which are promoters of the PV-lysosome fusion [328]. *Leishmania* promastigotes are primarily phagocytosed by macrophages and once inside the PV they transform into amastigotes, which resist acid pH and enzymatic hydrolysis, probably due to their production of protector glycoconjugates. It has been proposed that the *Leishmania* lipophosphoglycan (LPG) can delay phagolysosome maturation to allow the promastigote to transform into a more resistant form, the amastigote [329]. Furthermore, the adaptation of *Leishmania* to intra-macrophage life implies the existence of other mechanisms to ensure a prolonged parasitism of infected macrophage. Hence, *Leishmania* expression of macrophage migration inhibitory factor (MIF) orthologous genes, such as Lm1740MIF, has been described, thus suggesting that they are able to inhibit macrophage apoptosis [330]. Other mechanisms by which intracellular parasites inhibit phagocytic functions consist of disrupting reactive oxygen species-mediated destruction, through, for example, inhibition of kinases involved in activating the signaling cascade that enhances phagocytosis. Thus, the malarial pigment hemozoin has been shown to act as a potent regulator of macrophage oxidative phagocytic function through inhibition of enzymes involved in the process [331]. Finally, DCs regulation by parasites for their own benefit should be mentioned, since, as discussed previously, the subsequently adaptive response is influenced by mediators released by these cells. Many parasites have been reported to inhibit DCs activation, such as *T. cruzi*, whose DC penetration leads to a worsening of their activation determined by a decrease in TNFα and IL-12 and a poorer response to microbial LPS [332]. Furthermore, it has been suggested that Th2 responses to helminth parasites mediated by DCs´ recognition of certain antigens previously described, constitute a mechanism by which parasites modulate the immune system to their advantage [316].

4.2. Mechanisms of Adaptive Immunity Evasion

Parasites are able to avoid the effector mechanisms of humoral and cellular adaptive immunity. One mechanism by which parasites evade the humoral response is through antigenic shift, which prevents its recognition by circulating antibodies. Antigenic shift can occur among different parasite stages, as it occurs with *P. falciparum*, and at the same parasite stage, like in African trypanosomes. On the one hand, *P. falciparum* cytoadherent antigens expressed on the surface of infected erythrocytes suffer continuous changes that let them avoiding antibody recognition, besides promoting the capture of infected erythrocytes into capillary circulation and their adhesion to uninfected erythrocytes forming rosettes that prevent their removement from circulation in the spleen. The subtelomeric region of the *P. falciparum* genome contains several families of variant or polymorphic genes encoding some variant proteins: PfEMP1 (*var* gene), Rifin (*rif* gene), Stevor (*stevor* gene) y Pfmc-2TM (*Pfmc-2TM* gene), which are sequentially expressed during ring (PfEMP1), immature trophozoite (Rifin) and mature trophozoite (Stevor and MCSP-2TM) stages. There are approximately 60 *var* genes, 149 *rif* genes, 28 *stevor* genes and 11 *Pfmc-2TM* genes and only a gene from each family is expressed every time, giving as changes as parasite cycles (reviewed in [333]). On the other hand, african trypanosomes are able to express in each generation a different VSG, which is the immunodominant antigen and activate T and B cells, so that every time, the parasite completely evades the immune response mediated by Th1 cells and antibodies. VSG molecules present three hypervariable regions (HV) involved in this change, and it appears that the extracellular HV-1 and 2 are responsible of avoiding recognition by antibodies, while the HV-3 region would be the Th1-differentiation inducer [334]. Another way to prevent the role of Igs is the release of antigens or "capping" characteristic of *E. histolytica*. When the amoeba leads to disseminated infections, the surface antigens are recognized by circulating antibodies. To avoid the consequences of this union, *E. histolytica* actively moves opsonized antigens toward its posterior pole, a region called uroid, where the antigens are expelled from the parasite. A rhomboid protease, EhROM1, was described that seems to be actively involved in the formation and detachment of uroid through the rupture of adhesion molecules [335, 336]. Furthermore, schistosomes persist in blood vessels over a long period, so they should be unnoticed by the immune system. A classic mechanism by which these parasites prevent their destruction is the incorporation of host proteins on their surface. The tegument structure has yet been described and several studies are trying to identify how antigens provided by red cells are located to prevent parasite´s recognition and which are these antigens, although apparently most of them are components of the complement [337]. Furthermore, penetration stage, their larval stages are capable of destroying IgE by secreting elastase [338].

Finally, as it has been seen throughout this review, the mechanisms recently highlighted in immune system evasion are those that allow the modulation of the immune response. Many mediators secreted by parasites are capable of interfering with host immune function, from the initial interaction to the effector mechanisms. Thus, it was reported that many worms release enzymes like proteases that degrade host chemokines, such as eotaxin destruction by helminth-produced metalloproteases [339]. Through the development of genomics, helminth proteins have systematically been analyzed, leading to a profound description of the proteins most frequently secreted by helminths, as mentioned proteases, but also protease inhibitors, glycolytic enzymes, lectins and venom allergen/ASP-like or VAL proteins. An example that illustrates this type of molecules is described below. Two of the most helminth-expressed protease inhibitors are cystatins and serpins. The former have been described in *Brugia malayi*, *O. volvulus*, *N. brasiliensis* and functions at least by two ways: on the one hand, inhibition of cysteine proteases required in antigens processing and presentation by APCs,

thereby decreasing activation of T cells; and on the other hand, induction of IL-10 production, inhibiting the proliferation of T cells and decreasing the expression of costimulatory molecules by APCs. Serpins are inhibitors of serine proteases and one of them, the SPN-2, is the most abundantly product secreted by *B. malayi* microfilariae; it is still unknown which is its exact role, but apparently SPN-2 inhibits neutrophil-produced enzymes (reviewed by [340]). Another example of molecules secreted by helminths are those that mimic functional host molecules such as the cytokine homologues, as in the case of filariae, which secrete MIF homologues [341] that appear to influence, together with IL-4, in the activation of aaMΦ [342].

CONCLUSION

Parasites are complex organisms that have co-evolved with their hosts, which have enabled them to develop unique mechanisms to survive within them and cause chronic infections. Although many points remain to be elucidated in regard to the immune response to parasites, the effort made in recent years has paid off and has permitted to describe many of the mechanisms by which immune system reacts to invading parasites and how parasites defend themselves. Thus, a new branch that studies the relationship between the immune system and the different parasites has been created: immunoparasitology. With its development, the details that characterize the immune response to parasites are being better understood and implemented in order to create vaccines for the protection of populations, especially those that are more affected by these pathogens. Although it remains to be determined whether the elimination of the parasites will lead to the rise of other pathologies, given the protective role against some diseases in which these organisms are being involved, particularly helminths.

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