The immune response to parasitic helminths: insights from murine models

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Helminth parasites are a large group of multicellular organisms that affect vast numbers of humans and are a major cause of disease. Several relevant experimental murine models, representing the spectrum of human diseases, have been helpful in analyzing and characterizing the host immune response to the different helminths. Although this response is largely defined by type-2 immunity, recent observations have identified important differences regarding the development and function of T helper and other effector cells that can mediate immunopathology and protection in response to infection with these important pathogens.

Helminthic parasites affect literally billions of people, causing great morbidity, increased susceptibility to other infectious agents and, in some cases, death. Although effective health care and sanitation can eliminate most helminthic parasite infections, immunological intervention could become an important treatment where parasitism remains endemic. As yet, vaccines or other effective immunotherapies have not been developed and our understanding of the immune response to these important pathogens remains at a rudimentary stage, although, recently, several significant advances have been made.

The host immune response evoked by the invading parasite is one product of a long and dynamic co-evolutionary confrontation in which we view a brief snapshot in time. The invading parasite occupies a specific niche, as free-living species do, in this case in a microhabitat of the host. The ecology of the parasite differs from that of free-living species in that its environment, the host, is also reacting adaptively in an attempt to control infection [1]. The host and parasite endeavor to optimize their reproductive potential, and although each requires host survival, there is a constant struggle for limiting resources. It is to the advantage of the host to produce an immune response that will control the parasite but limit damage to self and preserve the ability to effectively respond to other pathogens. From the standpoint of the parasite, it is advantageous to keep the host alive long enough to complete its lifecycle, possibly by suppressing the host immune response or alternatively subverting it into producing an ineffective response.

Helminth infections are characterized by their ability to induce Th2-cell responses that generally result in eosinophilia, goblet and mucosal mast-cell hyperplasia and the production of non-complement fixing antibodies. Despite these general common trends, however, it is becoming increasingly clear that the immune response differs considerably between different helminths. In this Review, we will specifically focus on the factors that regulate the immune responses and the immunopathology in certain well studied intestinal nematode parasites and schistosomes, emphasizing the findings in experimental murine models.

Intestinal nematode parasites

Human intestinal nematode infections (Table 1) are associated with characteristic features of a Th2 response and there is evidence that strong type 2 responses are correlated negatively with infection intensity; however, as yet few studies have been performed on T-cell reactivity [2,3]. Two rodent intestinal nematode parasites within the Trichostrongylidae superfamily, Nippostrongylus brasiliensis and Heligmosomoides polygyrus, are widely used models for gastrointestinal roundworm infections. They can trigger strong, highly polarized Th2 responses with elevated interleukin-4 (IL-4) and IL-13 levels that mediate CD4 T-cell-dependent host-protective effects. Eosinophilia, mastocytosis and marked elevations in serum IgE and IgG1 are also observed [4]. Although N. brasiliensis infection is resolved acutely within two weeks after inoculation, primary inoculation with H. polygyrus leads to a chronic infection; however, if the worms are cleared with an anti-helminthic drug and the mice are again inoculated, a host protective memory response develops, resulting in worm expulsion after about twelve days. N. brasiliensis infection is thus an excellent model for examining the acute Th2 primary response whereas the response to H. polygyrus is well suited for studying a functional CD4 Th2 memory response. The H. polygyrus...
immune response is also a direct outcome of host–parasite co-evolution because the parasite is native to mice. By contrast, *N. brasiliensis* is a mouse-adapted parasite, whose natural host is actually the rat. The acute host-protective response to *N. brasiliensis* might be a consequence of this rat parasite not being well adapted to the murine environment. Nevertheless, the response in rats is also short-lived but can be prolonged by low level and frequent ‘trickle’ infections or when neonates are infected. The fecundity of *N. brasiliensis* is also much higher than that of *H. polygyrus*, accounting for the differences in biological requirements for propagation of the infection in nature.

In the murine model, *N. brasiliensis* host exposure begins with subcutaneous inoculation of third stage larvae (L3) under the skin, the site of natural infection [5] (Fig. 1). This infection and migration pattern is similar to that of several human intestinal roundworm infections, including *Ancylostoma duodenale* (Old World hookworm) and *Necator americanus* (New World hookworm) [2]. Both systemic and mucosal immune responses to *N. brasiliensis* thus occur, although most studies have focused on the mucosal response in the lung and small intestine. Recently, it has been shown that *N. brasiliensis* also triggers a strong, highly polarized Th2 response in the draining cervical lymph node following intracutaneous injection in the ear, demonstrating that the parasite, not the mucosal environment, is responsible for the development of a Th2 response [6].

*H. polygyrus* infection is strictly enteric and follows ingestion of free-living L3 in soil, which can also occur with some livestock and human trichostrongyloid infections. Experimentally, L3 are orally inoculated and move into the Draining cervical lymph node following intracutaneous injection in the ear, demonstrating that the parasite, not the mucosal environment, is responsible for the development of a Th2 response [6].

The whipworm, *Trichuris muris*, is also a natural murine parasite, and it has a life cycle similar to the human whipworm, *T. trichiura* (Fig. 3). A spectrum of responses develop in different mouse strains, ranging from a strong Th2 response associated with worm expulsion (BALB/c), to a mixed Th1 and Th2 response and delayed expulsion (BL/6), to finally a Th1 response resulting in chronic infection (AKR) [3,5] (Fig. 3). A similar spectrum of responses is observed in humans infected with *T. trichiura*; IgE elevation is associated with host protection [9]. The reason that *H. polygyrus* triggers primarily a Th2 response, whereas *T. muris* evokes either a Th1 or Th2 response is unknown. *T. muris* is more adversely affected by the Th2 response than *H. polygyrus* and it might have adapted to this harmful host environment by developing mechanisms that promote interferon-γ (IFN-γ) production. Some studies suggest that *T. muris* can secrete a molecule with IFN-γ-like properties [10]. Alternatively, given that the Th1 response is IL-12-dependent [11] (D. Artis, pers. commun.), it is conceivable that *T. muris* might express factors that activate pattern recognition receptors (PRRs), analogous to pathogen associated molecular patterns (PAMPs) expressed by many bacteria and viruses that promote Th1 responses. It is also possible that IFN-γ could be at least partially induced by secondary microbial infection in the bacteria-dense region of the colon. The strain dependence of Th1 versus Th2 commitment is similar to that observed with *Leishmania*, except that in BALB/c mice the Th2 response is associated with host protection in the case of the whipworm and chronic infection with the intracellular protozoan parasite.

**Table 1. Classification of selected human parasitic helminths of medical importance**

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Class and order</th>
<th>Family</th>
<th>Genus and species</th>
<th>Disease</th>
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<tbody>
<tr>
<td>Nematoda</td>
<td>Adenophorea;</td>
<td>Trichinellidae (muscle worms)</td>
<td>Trichinella spiralis</td>
<td>Trichinosis</td>
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<td>Enopliida</td>
<td>Trichuridae (whipworms)</td>
<td>Trichuris trichiura</td>
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<td>Strongyloidae (threadworms)</td>
<td>Strongyloides stercoralis</td>
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<td>Ancylostomatoidae (hookworms)</td>
<td>Ancylostoma duodenale</td>
<td>Hookworm disease</td>
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<td>Necator americanus</td>
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<td>Secernentea;</td>
<td>Rabditidita</td>
<td>Ancylostomatoidae (hookworms)</td>
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<td>(filariida)</td>
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<td>Ascaris lumbricoides</td>
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<td>Wuchereria bancroftii</td>
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<tr>
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<td>(filariida)</td>
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<td>Brugia malayi</td>
<td>Filariasi</td>
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<td>Trematoda;</td>
<td>Schistosomatidae</td>
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<td>Strigeotida (flukeworms)</td>
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<td>Taenia solium</td>
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*Partial listing and classification of helminths capable of infecting and causing serious disease in humans. Murine models of helminthic disease examined in this Review provide important clues about the nature of the host immune response to these parasites.*

**Immune response to nematodes**

In many Th1 responses, innate immune cells are activated through PAMPs binding Toll-like receptors (TLRs), inducing the development of Th1 cells. By contrast, there is no direct evidence that innate immune cells drive Th2-cell differentiation. In some cases, the Th2 response might simply develop as a default response when TLR signaling is blocked, as observed in *Toxoplasma gondii* infection [12]. However, it also possible that parasites that naturally induce potent Th2 responses have structures that actively polarize the response [13]. Recent studies have shown that naive T cells, specific to a non-parasite antigen, can rapidly develop in *vivo* into IL-4 producing T cells when recipient mice are immunized with the antigen and *N. brasiliensis*...
but not the antigen or the parasite alone [6]. This finding, and others [14], is consistent with the parasite acting as a Th2 microbial adjuvant. Studies of the T-cell-independent innate response have shown elevations in IL-5 and IL-9 in *H. polygyrus*-inoculated Nude and SCID (severe combined immunodeficient) mice [15] (W.C. Gause and J.F. Urban, unpublished) and IL-4 expressing eosinophils have recently been shown to develop in SCID mice following *N. brasiliensis* infection [16]. Although these studies suggest that a type 2 innate cytokine response can develop, it remains uncertain whether this innate response influences Th2-cell differentiation. In fact, Th2 cells still develop following inhibition of eosinophils by IL-5 blockade during nematode parasite infections [4]. More studies are required to clarify whether nematodes actually express PAMPs that can drive Th2 responses.

The differentiation of an IL-4 producing T cell is an important step in the development of an effective host-protective response. IL-4 can directly mediate worm expulsion mechanisms, and it is required for the amplification of Th2 cells, which also produce IL-5, IL-9 and IL-13; *in vivo*, IL-10 is not elevated in the *H. polygyrus* response [15] and is normally only slightly elevated in the *N. brasiliensis* response [17]. Elucidation of the factors that regulate the development of IL-4 producing Th2 cells is thus essential to understanding the development of protective immunity. In infectious diseases, Th2 responses are generally more dependent on B7-1–B7-2 costimulatory signals than Th1 responses [13]. B7-1–B7-2 blockade during the primary immune response to *H. polygyrus* inhibits the development of the Th2 cytokine response but an alternative Th1 response is not observed [18]. By contrast, B7-1–B7-2 blockade of the primary immune response to *T. muris* not only inhibits the Th2 response but triggers an alternative Th1 response in BALB/c mice [19], as is also observed in the immune response to *Leishmania major* [20] and *Schistosoma mansoni* [21]. Interestingly, in the *T. muris* response, although IL-4 production is inhibited by B7-1–B7-2 blockade, IL-13 production remains elevated and, if IFN-γ is also blocked, protective immunity, mediated by IL-13, is restored [19]. The *N. brasiliensis* Th2 response is currently unique in that CD4 T cells, producing IL-4 and IL-13, can develop that mediate worm expulsion when B7-1–B7-2 costimulatory molecules are inhibited [6,22]. Thus, considerable variability is observed in the role of B7-1–B7-2 costimulation in T helper-cell differentiation between different nematode parasite infections.

Other costimulatory molecules, including inducible costimulatory molecule (ICOS), CD40 ligand (CD40L)
and OX40, have also been implicated as preferentially important for Th2-cell development. Effects of blocking B7-related protein-1 (B7RP-1)–ICOS interactions on protective immunity in intestinal nematode infections are not yet reported. CD40L interactions are required for humoral immunity but not the development of IL-4-producing T cells [23]. OX40–OX40L interactions have been implicated in Th2-cell survival [24] and also in CD28-dependent Th2-cell migration to the B-cell follicles [25]. However, the effectiveness of the Th2 response to *N. brasiliensis* was not impaired in OX40 knockout (KO) mice [26]. By contrast, optimal IL-4 production and humoral and protective immunity are impaired in *H. polygyrus*-inoculated OX40LKO mice [27]. However, the effectiveness of the Th2 response to *N. brasiliensis* was not impaired in OX40 knocko

![Diagram of the life cycle and immune response to *Heligmosomoides polygyrus*](http://treimm.trends.com)

**Fig. 2.** The life cycle and immune response to *Heligmosomoides polygyrus* is primarily restricted to the enteric region. Third stage larvae (L3) are orally inoculated and by the third day after infection they have already penetrated the intestinal wall and migrated into the muscularis externa beneath the mucosa, where an associated inflammatory response develops. There is no evidence of a true cyst but a deformation of muscle tissue and a largely eosinophilic cellular infiltration surround the larvae. Adults emerge at eight days in the lumen, mate and produce eggs at nine days post-inoculation for several months. The primary response is associated with chronic infection whereas secondary challenge results in acute worm expulsion. A highly polarized Th2-cell response develops that is dependent on B7-1–B7-2 and, to a lesser extent, on OX40 ligand (OX40L) interactions. Although the host protective mechanism is not known, worm expulsion is particularly dependent on interleukin-4 (IL-4), which along with IL-13, can directly increase luminal fluids and contractility. This response is thus a useful model for examining the functional Th2 memory response and for examining localized host–parasite interactions during the Th2 response. Thickness of arrows represents relative importance of individual Th2 cytokines in mediating expulsion of adult viable worms. Abbreviations: B, B cell; DC, dendritic cell; T, T cell.

**Protective immunity**

Effector Th2 cells mediate protective immunity to intestinal nematodes through IL-4, IL-5, IL-9 and IL-13. IL-4 and IL-13 can directly bind type-2 IL-4 receptors expressed by many non-lymphoid cell types in the enteric region. IL-4 receptor-dependent effects of the *H. polygyrus* memory response include, increased mucosal epithelial-cell permeability, decreased sodium-dependent glucose absorption and increased smooth-muscle contractility, all of which could contribute to an inhospitable environment for the parasite, leading to expulsion of viable adult worms from the lumen [28]. IL-5 and IL-9 are also of some importance in mediating host protection against nematode parasites but have more of an additive role as recently demonstrated in studies comparing *N. brasiliensis*-inoculated mice deficient in IL-4 and IL-13 with mice also deficient in IL-5 or IL-9 [29]. Interestingly, intestinal self-cure of *N. brasiliensis* is mediated by IL-13 in the absence of IL-4, suggesting that effective Th2 responses might develop in the absence of IL-4 [30]. Production of reactive oxygen intermediates that damage the worm and changes in mucous quality that facilitate mucous entrapment could also contribute to viable worm expulsion [4]. IL-10, although not generally elevated during the trichostrongyloid responses, is elevated in the *T. muris* responses and is important in maintaining host protection, probably through the downregulation of the Th1 inflammatory response [31], as in schistosomes [32]. Tumor necrosis factor-α (TNF-α) might also have a role in accelerated worm expulsion, either through direct effects on gut epithelial cells or through enhancement of the Th2 response [33]. The role of B cells in mediating protective immunity remains unclear because the response in B-cell knockout mice inoculated with either *N. brasiliensis* or *H. polygyrus* has not been reported. However, in B7-1–B7-2
double KO mice, effective host protection against *N. brasiliensis* [6], and against *H. polygyrus*, in the memory response [34], persisted despite inhibition of serum antibody elevations. B cells could still have a role in the initiation of the Th2 response, either as antigen-presenting cells (APCs) or as additional sources of Th2 cytokines [35]. Recently, the *T. muris* Th2 response was shown to be markedly impaired in B-cell KO mice, suggesting that B cells are important in priming Th2 cells following whipworm infection [36], which has also been observed following schistosome infection [37]. Mast cells, elevated in Th2 responses to all three parasites, have not yet been shown to have a major role in their host protection, although there is some evidence for a role in protection against other parasites, including *Trichinella spiralis* [38] (Table 1).

**Schistosomes**

Schistosomes (Table 1) have a complex life cycle involving an intermediate host, a fresh water snail, which sheds the infectious forms known as cercariae, which penetrate the skin of the definitive vertebrate hosts. Each schistosome species is programmed to parasitize a specific host and to reside for long periods of time (years) within a particular region of the vascular bed of the host. In the case of *S. mansoni*, the habitat is the portal-mesenteric venous plexus, where sexual mating results in oviproduction. The parasite eggs escape the vascular bed to gain access to the intestinal lumen and thereby to bodies of fresh water, where the hatched miracidia search for the specific snail that enables the completion of the life cycle. However, many eggs fail to emigrate and instead embolize into the liver, where they die and precipitate a local immunopathological reaction. *S. mansoni*, together with *Schistosoma japonicum* and *Schistosoma hematobium*, is the major cause of human schistosomiasis. Although preventable and treatable, schistosomiasis still causes considerable morbidity and mortality in tropical regions of the world (more details can be found reviewed in Refs [39,40]). *S. mansoni* also lends itself easily to experimental infection of mice, and much of our understanding of the
The immune response of the host to schistosomes comes from studies with this model.

**Immune response to schistosomes**

Remarkably, a primary schistosome infection is met with practically no resistance from the immune system of the host. In fact, throughout their development from schistosomula to adult worms, schistosomes actively hinder immune recognition by a variety of mechanisms, which include the induction of anti-inflammatory molecules [41], the incapacitation of lymphoid-cell function [42] and the coating of their surfaces with host antigens [43]. Despite their initial evasion strategies, the immune system eventually reacts against the worms but fails to destroy them. However, it will offer protection against subsequent re-infection, an observation that has long sparked the idea of a vaccine. The immune response is also variably pathogenic and sometimes lethal to the host; oddly, schistosomes depend on this immunopathology because it results in the production of molecules essential for their development [44] and in inflammation necessary for their migration through the gut [45].

The main adaptive immune response against schistosomes is mediated by MHC class II-restricted CD4⁺ T cells [46]. An initial proinflammatory Th1-polarized response lasts into the period of early oviposition at around five weeks post-infection, at which point periovular granulomatous inflammation gets underway. However, within the next one to two weeks, granuloma formation rises amid a dramatic change in the cytokine environment, which under normal circumstances becomes dominated by anti-inflammatory Th2-type cytokines [47] (Fig. 4). IL-4 itself [48] and several T-cell costimulatory systems, including the B7–CD28 [21], the CD40–CD40L [49] and the B7RP-1–ICOS pathways (L.I. Rutitzky et al., unpublished), amid a changing APC phenotype from ‘classical’ to ‘alternative’ activation [50], variably contribute to this conversion; B cells also facilitate the switch [37]. The evolving cellular response is gradually accompanied by abundant production of mainly non-complement fixing IgG and IgE antibodies. CD8⁺ T-cell responses [51,52] are also induced, although their effects are less clear, and the role of γδ T cells or CD1-restricted NKT cells, if any, is not apparent [46,53].

A Th1 to Th2 conversion is vital for the host because its absence is associated with a lethal disease characterized by severe hepatic inflammation with hepatocellular injury and necrosis [21,49]. Moreover, a well-established Th2 response is also necessary to precipitate, within the subsequent 2–3 infection weeks, a gradual overall down-regulation of CD4⁺ T-cell function and associated immunopathology, known as immunomodulation [54] (Fig. 4). Several mechanisms have been proposed to explain the loss of T-cell responsiveness; these have included CD8⁺

![Fig. 4](http://treimm.trends.com)
regulatory T cells [51,52], regulatory idiotypic networks [55] and the induction of CD4+ T-cell anergy by means of a mechanism that involves IL-10 [32]. In support of a crucial role of IL-10 in immunomodulation, and in contrast to another study [56], we found that IL-10 deficient mice fail to shut off T-cell proliferative and cytokine responses and persistently exhibit splenomegaly as well as large, poorly circumscribed egg granulomas and enhanced hepatocellular necrosis up to week 15 of infection [57]. Studies in human schistosomiasis mansoni [58,59] and hematobia [60], as well as in filariasis, caused by nematodes residing in lymphatic vessels [61] (Table 1), further link IL-10 with the downmodulatory process.

The CD4+ T-cell response is directed against numerous peptide antigens. Interestingly, several of these are schistosome housekeeping enzymes. Based on host protection from re-infection afforded by previous exposure to irradiated cercariae [62], some antigens, including glutathione-S-transferase 28 (GST-28) and triose phosphate isomerase (TPI), are being evaluated as vaccine candidates [63], whereas others, such as the egg antigens Sm-p40, phosphoenolpyruvate carboxykinase (PEPCK), and thioredoxin peroxidase-1 (TPx-1) [64], are choice immunogens for pathogenic T cells. Schistosome antigens also induce antibodies. Curiously, a substantial proportion of these antibodies, possibly as a consequence of a subverted response, are directed against carbohydrates and glycolipids [65] that express a unique set of schistosome-specific fucosylated glycan determinants present mainly on egg antigens, such as lacto-N-fucopentaose III (Lewisα), fucosylated LactoNacpentaose (LDNFP) and GalNacβ1–4(fucα1–2fucα1–3)GlcNac (LDN-DF) [66,67]. These glycan determinants can boost Th2 cytokine responses to schistosome [64] and other [68] protein antigens; they can also elicit cytokine responses in human monocytes [69] and probably instruct dendritic cells (DCs) to induce Th2-polarized responses in vivo [70].

Immunopathology of schistosomiasis

The granulomas are aggregates of inflammatory cells attracted to eggs trapped in the tissues. Although ultimately dependent on activated egg antigen-specific CD4+ T cells, granuloma formation is the immediate product of complex cellular interactions with the participation of adhesion molecules, cytokines and chemokines. Granulomas contain T and B cells, as well as macrophages and DCs, but the most frequent cells are eosinophils. Eosinophils are themselves a source of cytokines [71], however, amazingly, they have yet to reveal an essential role or function. With time, granulomas acquire an increasingly fibrous extracellular matrix, and following death of the egg, they transform into scars; in the mouse, the Th2 cytokine IL-13 significantly contributes to the accomplishment of this process [72,73]. Controlled fibrogenesis is useful because it serves to confine granuloma contents, thereby preventing hepatocellular injury from the spread of inflammation and toxic egg products. However, excessive fibrosis can be a serious complication because the impaired blood flow through the liver can give rise to portal hypertension. In humans, this occurs in a small percentage of patients with severe ‘hepato-splenic’ schistosomiasis, characterized by splenomegaly, ascitis, gastro-intestinal hemorrhage and death. Cytokine analysis in these patients revealed a Th1-biased profile [74], which differs with a study in the mouse, in which IL-12–IL-10 double-deficient animals exhibited detrimental fibrosis associated with a Th2 environment [75]. These seemingly contrasting findings between the two species suggest that fibrogenesis can occur in either a Th1 or a Th2 environment, possibly using different pathways that might involve cytokines other than, or in addition to, IL-13. Regardless, it is noteworthy to point out that wild type mouse strains that achieve full Th2 polarization, such as BL/6 and BALB/c, do not exhibit such pronounced pathology [76,77], and in humans there is at present no study suggesting that a Th2-dominant profile is associated with, or conducive to, severe schistosomiasis.

From several observations it is evident that, despite comparable infection rates, there are significant variations in the outcome of schistosomal disease, both in humans as well as in mice. In humans, the severe ‘hepato-splenic’ schistosomiasis contrasts with the milder, often symptomless, ‘intestinal’ form of the disease. The reasons for these considerable differences are not clear but are presently addressed by studies focusing on host genetic factors; for example, severe hepatic fibrosis has been linked to a locus on chromosome 6 [78]. In mice, the infection results in a different level of disease expression in each inbred strain, that is, C3H and CBA strains develop more severe lesions than BL/6 and BALB/c strains [76,77]. Interestingly, we found the level of CD4+ T-cell apoptosis in granulomas and mesenteric lymph nodes to be significantly higher in BL/6 than in CBA mice, suggesting that this mechanism contributes to reduce the magnitude of pathology (L.I. Rutitzky et al., unpublished). Moreover, egg antigen stimulation of T cells in the high pathology CBA mice reveals strong mixed cytokine responses with a lingering Th1 component [79]; this could at least in part be a result of their unusually large T-cell repertoire against the Sm-p40 egg antigen and its immunodominant epitope peptide, which preferentially elicit Th1 responses [79,80]. The association between increased pathology with a Th1 phenotype is reinforced by the marked exacerbation of hepatic immunopathology and death observed in BL/6 mice following immunization with a Th1-inducing regimen [81]. Additional support comes from the cited evidence in human schistosomiasis, and also from filariasis [82], where severe lymphatic pathology tends to run parallel with a Th1-biased response.

Conclusions

In this Review, we have briefly examined several experimental mouse models for human helminth infections that have greatly contributed to our understanding of the host immune response. Each of these parasites triggers distinct and characteristic reactions inherent to their own life cycle and anatomic location within the host. Nonetheless, they have in common the induction of a host-protective Th2-type immune response, which mediates worm expulsion in
Intestinal nematode infections and largely dampens harmful immunopathology caused by schistosomes, filariae, and cestodes. Factors that might influence the establishment of the Th2 response, and that might vary between parasites, include the T-cell costimulatory molecules, the glycan residues and the absence of Th1-inducing PAMPS. Despite the ultimate common Th2-dominant cytokine profile, the mechanisms used to achieve host protection can vary considerably among the different parasites. N. brasilensis and H. polygyrus generate highly polarized Th2 responses with IFN-γ at low to undetectable levels throughout the course of the infection in mucosal and non-mucosal tissues. By contrast, the type of response that develops after infection with T. muris and certain tissue helminths, including the schistosomes and filariae, is more strain dependent and generally of a mixed Th1–Th2 type. Interestingly, infections with T. muris, schistosomes and filariae are also characterized by pronounced increases in IL-10, suggesting that this cytokine is induced in response to, and for the purpose of dampening, harmful inflammatory Th1 responses. Future studies are required to further understand the development of a Th2 response and the mechanisms leading to host resistance and reduced morbidity in helminth infection.

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