

## MINIREVIEW

### Immunology of Parasitic Helminth Infections

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Parasitic helminths, or worms, comprise a diverse group of metazoan organisms that infect billions of people and their domesticated animals worldwide (22). In large part, helminthiasis are caused by members of the phyla Nematoda and Platyhelminthes (59, 68). Species belonging to both phyla occupy numerous niches within their mammalian hosts, ranging from intestinal lumen to intravascular and even intracellular sites. While the majority of individuals infected with parasitic worms experience relatively minor symptoms compared to those infected with organisms that typify more acute viral or bacterial infections, a small percentage suffer severe life-threatening consequences. Since the overall prevalence of helminthiasis is so high, relatively low frequencies of severe disease nevertheless equate to large numbers of people experiencing infection-associated morbidity. Owing to the control of insect vector populations, the safe disposal of human excrement, and the availability of efficacious drugs, helminth parasites have been largely eradicated as a public health concern in developed countries. Unfortunately, however, in developing countries, where these types of control measures are often not yet practical, helminths remain a significant biomedical problem. One consequence of this geopolitical segregation is that most of the world's pharmaceutical industries do not support active research and development programs on helminth parasites that cause human disease. The financial burden of scientific advancement in this area of research is therefore carried primarily by philanthropic and government-funding agencies.

Many of the parasitic worms have complex multistage life cycles that involve several hosts. Within their mammalian hosts they often undergo extensive growth and differentiation with the ultimate goal of producing stages intended for transmission to the next intermediate host. Usually, the life stage responsible for infecting the mammalian host is the larva, and the larva must migrate within the host to its appropriate niche where it can grow and reproduce. Since the offspring are intended for transmission to another animal, they must necessarily be ca-

pable in some way of entering a site from which they can leave the host. How all this is accomplished varies from one helminth to another. Nevertheless, despite this extensive organismal complexity, in the majority of cases the immune responses of the hosts to worm infection are remarkably similar, being Th2-like with the production of significant quantities of interleukin-4 (IL-4), IL-5, IL-9, IL-10, and IL-13 and consequently the development of strong immunoglobulin E (IgE), eosinophil, and mast cell responses. This inherent ability of helminths to induce Th2 responses has led to interest in them from both the perspective of elucidation of the underlying mechanisms that lead to Th2 response development and in terms of understanding Th2 response function.

This review attempts to integrate data from experimental systems and human studies and to highlight developing areas of particular interest and importance.

#### IMMUNOPATHOLOGY

Many helminth parasites are long-lived and cause chronic infections. The immune response that develops during this time often proceeds to cause pathologic changes that in many helminth infections are the primary cause of disease. A well-studied example of this is the granulomatous reaction that sequesters schistosome eggs. Adult *Schistosoma mansoni* parasites live within the portal vasculature, where female worms lay eggs that are intended for transmission across the intestinal wall into the gut lumen and from there to the outside of the host. However, because blood flow in the portal system is towards the liver, many of the eggs are carried to that organ where they become lodged in the sinusoids. Antigens (Ag) released from eggs induce a marked Th2 response that orchestrates the development of granulomatous lesions in the liver (18). The host-protective nature of these lesions has been demonstrated by work in a mouse model of infection with the human parasite. Infected mice that lack CD4 cells are incapable of making granulomas and die due to the toxic effects on hepatocytes of certain egg proteins (4, 33). By surrounding the egg, the granuloma essentially segregates it from the hepatic tissue and allows continuing liver function. In the long term, as the eggs die and the granulomas resolve, fibrosis can develop (18). This can lead to increased portal blood pressure and the development of portal varices. Bleeding from varices is the most common cause of death due to schistosomiasis. Analysis of the role of Th2 cytokines during infection using the mouse model of human schistosomiasis has revealed that IL-13 plays a role of central importance in the development of fibrosis (18,

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19, 37). Treatment with soluble interleukin-13 receptor (IL-13R), which inhibits the effect of IL-13 (19), or immunization prior to infection with egg Ag plus IL-12 to induce a Th1 response and thereby minimize production of IL-13 (107), significantly ameliorates fibrosis and morbidity. The situation in humans is less clear, but segregation analysis applied to the severe fibrosis associated with portal hypertension phenotype revealed the effect of a major gene that mapped to 6q22-q23, close to the gene that encodes the alpha chain of the gamma interferon (IFN- $\gamma$ ) receptor (29). This result is consistent with findings in murine schistosomiasis where IFN- $\gamma$  and the Th1 response can protect against severe fibrosis by preventing alternative macrophage activation and thereby limiting the fibrosis-enhancing effects of the Th2 response (51, 52). As a whole however, these findings remain to be integrated with the report by Mwatha et al. (83) that the immune responses of individuals suffering most-severe hepatosplenomegaly, usually considered to be indicative of severe fibrosis, were more Th1-like, whereas infected individuals with less-severe disease mounted Th2 responses. Perhaps hepatosplenomegaly is not always indicative of fibrosis during schistosomiasis?

Filarial parasites cause significant pathology either through obstruction and damage of the lymphatic system by adult parasites, as is the case with *Brugia* spp. and *Wuchereria bancrofti*, or through cutaneous and ocular irritation by larval transmission stages (microfilariae) of *Onchocerca volvulus*. Clearly there is a physical component to this pathology caused by highly motile parasites living within the lymphatic system or actively migrating through the skin and conjunctiva, but more intriguing are the role of the immune response in the disease process (27, 31, 61, 73) and the growing possibility that the *Wolbachia* symbionts of filariae may be playing a role in the induction of destructive inflammatory reactions (for further discussion, see reference 100).

Not everyone infected with lymphatic filariae develops hydrocele or chronic lymphedema, and there is a general although incomplete association between the ability of an individual to clear microfilaremia (presumably by immunologically killing microfilariae or suppressing microfilarial production by adult parasites) and apparent clinical symptoms. In contrast, individuals who are microfilaremic have been considered pathology free, although ultrasound and lymphoscintigraphy have revealed that these individuals do experience subclinical pathologic changes (27). Whether Th1 responses play a pivotal role in the development of severe pathologic change has yet to be fully determined, although it is clear that the microfilaremic state is associated with a Th2 response. Of concern is the possibility that immune responses capable of preventing microfilaremia and/or killing adult parasites are also those that cause most pathology. Detailed experimental analysis has been hampered by the fact that neither *Wuchereria* nor *Brugia* will complete its full developmental cycle in mice.

Infection with *O. volvulus* leads to debilitating cutaneous inflammation and blindness. A mouse model has allowed detailed investigation of the immunopathologic changes that lead to loss of vision (90). When mice are sensitized to adult *O. volvulus* Ag by intraperitoneal injection and then challenged by injection with the same Ag into the corneal stroma, they develop ocular opacification and neovascularization, conditions that mimic the human disease. Dissection of this system has

revealed that disease correlates with the development of a strong Ag-specific Th2 response and that both IL-4 and CD4 cells are necessary for the ocular pathology (90). The effector mechanism that leads to opacification and neovascularization is neutrophil mediated and CXC chemokine receptor 2, PECAM-1, and antibody dependent (48, 49, 56).

An important, and often underappreciated, point is that in addition to specific pathologic changes, there are less clear but nevertheless well-documented and very important effects of helminth infections on child growth and mental and sexual development (88, 99). The contribution of the immune system to these facets of disease is poorly understood, although interactions between the endocrine system and IL-6 in chronic cysticercosis due to *Taenia crassiceps* has been recently reported (81).

### IMMUNOREGULATION

A dominant theme with chronic helminthiasis is the necessity for the host to modulate its immune response appropriately. Evidence suggests that a response dominated by the production of Th2 cytokines, such as IL-4 and IL-10, may play a crucial role in reducing the severity of acute disease and allowing survival. Despite evidence that IL-13 plays a central role in the development of fibrosis during infection with *S. mansoni*, the absence of IL-4 (a cytokine most commonly coproduced with IL-13 by Th2 cells) allows the development of a severe, lethal inflammatory condition in which mice become cachectic prior to death (13, 37). The absence of IL-10 exacerbates this condition (54). In this model, pathologic changes that occur in the absence of IL-4 appear to be related to the dysregulation of NO production during infection and the subsequent production of damaging levels of peroxynitrite (64). Thus, while Th2 responses are clearly implicated in immunopathology during helminth infections (18), they can also permit survival in the face of continuing infection while simultaneously protecting against superinfection (see below).

An additional facet of immunoregulation during filarial as well as schistosome infections is that the marked T-cell responsiveness that follows initial infection is, in the majority of patients, dampened as the infection becomes chronic (61, 84, 108). This diminution of responsiveness is believed to be in the best interest of the host, as it is not apparent in infected individuals exhibiting the most-severe forms of disease (73, 108). For example, peripheral blood mononuclear cells taken from microfilaremic individuals fail to proliferate to filarial antigen *in vitro* but are still able to respond in an Ag-specific manner as measured by cytokine production. Conversely, individuals with chronic lymphatic pathology, who rarely exhibit blood microfilaremia, generally mount stronger filarial-specific cellular proliferative responses. The underlying mechanisms behind down-regulation of cellular proliferative responses during helminth infections remain unknown, although recent studies have suggested that host macrophages may be alternatively activated by the parasite to effect suppression via a contact-dependent mechanism (69, 71), via the production of NO in response to parasite glycoconjugates (8), or through IL-10 production (72, 87). Indeed, it is clear that IL-10 plays a major role in the regulation of the intensity of both Th1 and Th2 responses during helminth infections and in so doing plays a

principal role in minimizing immunopathology (40, 53, 62, 98) and in suppressing the expression of the allergic-like symptoms that might otherwise be expected in helminth-infected individuals who are producing large amounts of IgE (103). There is an important additional role for idiotypic regulation of immune responsiveness in disease severity in schistosomiasis (80).

### IMMUNE RESPONSES THAT PREVENT INFECTION WITH HELMINTHS

A pervasive theme of resistance to helminths is that of pre-munition or concomitant immunity, a state wherein the host is protected from further infection with a given species by ongoing persistent infection with the same organism (5, 16, 45, 73, 101). There are at least two explanations for this type of immunity. In one scenario, parasites of the primary infection induce an immune response that, while incapable of killing them, is nevertheless able to kill incoming parasites that may cause a superinfection. This requires that the adult parasites, but not invasive larval stages, express immune evasion mechanisms and that common Ag be shared between the different stages. A second explanation is that the primary infection alters the anatomy or physiology of the host in such a way that it becomes more difficult for incoming larval organisms to establish infection in the appropriate niche (106). In some cases, immunity can persist, or is only fully apparent, following drug clearance of the primary infection, when the host is resistant to further infection. These themes are well illustrated, and in fact were partly defined, by findings from immunoepidemiological studies of individuals living in areas of endemicity for *Schistosoma* spp. In such areas, individuals who have passed their midteen years generally have significantly less-intense infections than younger children, despite similar exposure to infectious parasites, suggesting that concomitant immunity develops with age in this case (16). Following treatment, the older individuals are resistant to reinfection whereas children exposed to the same degree of infectious challenge become as heavily infected as they were prior to treatment.

The immunological basis of resistance to reinfection with schistosomes has been examined by comparing the parasite-specific immune responses of older (resistant) versus younger (susceptible) individuals following treatment. This type of study has indicated that antiparasite IgE levels closely correlate with resistance (32, 46, 93), and segregation analysis of Brazilian pedigrees provides evidence for the effects of a major gene on the ability of individuals to resist infection (1, 28). Data from a genome-wide scan of individuals from informative families revealed linkage to a region on chromosome 5q31-q33 that contains several Th2 response genes, reinforcing considerably the view that Th2-mediated effector mechanisms play a pivotal role in resistance to schistosome infection (78). Experimental analysis of the role of Th2 responses in concomitant immunity in mice supports the view that this type of response is crucially important for naturally acquired resistance to *S. mansoni*. In contrast to infected wild-type animals, which are partially resistant to superinfection, infected IL-4<sup>-/-</sup> mice are incapable of mounting a strong Th2 response and exhibit no resistance (15).

Individuals infected with filarial parasites may also exhibit concomitant immunity against incoming infectious life forms

(L3 larvae) of a secondary infection and against the transmission stage of the parasite (microfilariae, which are produced by the resident adult parasites). Additionally, some residents in areas of endemicity, the so-called "endemic normal" or putatively immune individuals, remain uninfected despite repeated exposure. Mechanisms responsible for these patterns of immunity in humans remain unclear and have been difficult to address experimentally due to the absence of a widely available experimental model. Recent rediscovery of the mouse filarial parasite *Litosomoides sigmodontis* as a viable organism for immunological studies (3) has opened the way for new developments in this important area.

It has become apparent over the last 10 years that the ability of hosts to expel intestinal nematodes is closely linked to their ability to mount a Th2 response against the parasite. In the case of *Trichuris muris*, which is a natural infection of mice and a close relative of the human parasite *Trichuris trichuria*, a survey of different inbred mouse strains revealed that the majority of strains (analogous to the majority of individuals in an outbred population) are initially susceptible to infection but with varying kinetics expel the parasites (104). In contrast, a few strains are unable to expel the parasites (104). Comparison of the immune responses of different mouse strains following infection revealed that susceptibility correlated with the development of a Th1 response and that expulsion was associated with the ability to induce a Th2 response (36). Manipulations of the immune system to prevent the development of Th2 responses in expeller mice and of Th1 responses in resistant mice converted them to susceptible and resistant animals, respectively (35). Similarly important roles for Th2 responses in resistance and Th1 responses in susceptibility have been documented for the intestinal nematodes *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis* (38, 39), and it seems likely that the same will be true for intestinal trematode parasites (14). Current efforts are aimed at understanding the components of the immune system that are responsible for immune response skewing during these infections (an area that will be discussed below) and at identifying the effector functions that mediate worm expulsion. Interestingly, the latter studies have failed to clearly identify a universal protective effector mechanism, and it is fair to say that in most cases the nature of the response that ultimately expels the parasite is unknown (39). Moreover, it seems likely that despite similarities associated with being members of the same phylum, different nematode parasites will be expelled by different effector mechanisms. For example, while expulsion of both *Trichinella spiralis* and *N. brasiliensis* is dependent upon the ligation by IL-4 or IL-13 of the IL-4R $\alpha$ -containing receptor and activation of STAT6 via this receptor, expulsion of *T. spiralis* does not occur if mast cells are absent, whereas these cells are not necessary for *N. brasiliensis* rejection (102). Moreover, the injection of IL-4 alone into mice that lack T cells, B cells, or mast cells is sufficient to cause expulsion of *N. brasiliensis*, whereas T cells as well as mast cells are essential for exogenous IL-4-promoted rejection of *T. spiralis* (102). The implication of these findings and others showing that expulsion of *H. polygyrus* and *T. muris* is also dependent upon the signature Th2 cytokines IL-4 and IL-13, is that the mammalian host possesses an arsenal of effector mechanisms that can be blanket triggered by IL-4 and/or IL-13 and mediate protection against a panel of related

pathogens (9, 38, 39, 75). Understanding these effector mechanisms is an area of considerable current interest.

Killing of helminths by eosinophils via antibody-dependent cellular cytotoxicity (ADCC) is an attractive and widely cited mechanism for resistance to parasitic worms. Although this mechanism was initially based on *in vitro* assays in which eosinophils were shown capable of killing a wide variety of Ab and/or C-opsonized helminths, and on immunoepidemiological data (17), it has nevertheless been difficult to show a widely important role for eosinophils in protection against helminths. However, important recent reports have established a role for the Th2 cytokine IL-5, the central regulator of eosinophilia, in resistance to the nematodes *Strongyloides stercoralis* and *L. sigmodontis*, (50, 66) and have strongly implicated the eosinophil as a killer cell against the tissue-traversing larval stages of this type of parasite (12) and surprisingly as helper cells for protective Ab production (12, 50). In most other settings, despite clear and decisive evidence that eosinophils can kill helminths (17, 44), their importance for resistance to infection against most helminths remains to be proven.

### VACCINE DEVELOPMENT

There have been attempts to systematically fund research for vaccine development against certain helminth parasites, with schistosomiasis perhaps receiving most attention. This program has led to the development of several defined vaccines against schistosomes that have been tested in animals and at least one of which is now in human trials (11, 47). While this represents a significant step forward, it is important to note that there is no certainty that any of these vaccines will reach the market and, moreover, that during development these vaccines have been shown to be only partially effective. The real challenge remaining is to renew momentum for continued work on vaccine development. The hope is that, in conjunction with a greater appreciation of immune response induction mechanisms, our understanding of basic helminth biology will improve sufficiently in the coming years and allow the rational development of more efficacious vaccines. Basic research on model vaccines continues and the reader is directed to an excellent recent article on this subject (76).

Intriguingly, the application of antihelminth vaccines is more advanced in veterinary medicine than in human medicine, with a history of the use of attenuated vaccines against certain nematode parasites and more recently the development of recombinant protein and DNA vaccines against the sheep tapeworm *Taenia ovis* (30, 55, 67). This probably reflects a combination of factors including the greater commercial potential of veterinary vaccines that can be sold in the developed world and the less stringent safety requirements for products intended for veterinary versus human use.

### IMMUNE RESPONSE EVASION

The long-term survival of helminth parasites within mammalian hosts indicates that they have developed sophisticated mechanisms to evade the cytotoxic effects of the immune response (89). Early work provided some clues as to how this could occur. For example, antibodies in the sera of schistosome-infected hosts fail to bind to the surface of the living

parasites and yet bind strongly to dead parasites or parasites extracts, indicating that living parasites are able to modulate their surface structure in a way that prevents recognition (100). Recent studies have begun to provide mechanistic explanations for evasion (6, 74). For example, serpins made by the microfilariae of *B. malayi* are able to inhibit neutrophil serine proteases (110), and a cystatin homologue from the same parasite can inhibit class II major histocompatibility complex-restricted Ag processing (77). Deeper understanding of the basic requirements of metazoan life have revealed areas in which interactions between helminths and their hosts that could influence immune effector functions are likely to occur (74). Prominent among these is the expression of transforming growth factor  $\beta$  receptor family members by helminths (26, 43), and, in the case of nematodes at least, a homologue of transforming growth factor  $\beta$  itself (41, 42).

### COINFECTION, AUTOIMMUNITY, AND ALLERGY

Since so many people are infected with helminth parasites, there is little doubt that many individuals become exposed to nonhelminth pathogens while harboring chronic helminth infections. How the presence of an underlying Th2 response-inducing infection affects the host's ability to mount an appropriate immune response to the new infection is a subject of growing interest (10, 23, 24, 94). It is clear from existing reports that helminth infection can make mice far more susceptible to certain pathogens against which Th1 responses are protective (e.g., *Toxoplasma gondii*) and more resistant to pathogens against which Th2 responses are protective (e.g., *T. muris*) (25, 79). Ongoing studies are examining the impact of schistosomiasis and other helminthiases on the outcome of human immunodeficiency virus infection. For more information on this important area, see references 57, 58, 65, 84, 96.

Another important issue is that of how the presence of ongoing helminth infection affects the likelihood of the development of immunological disorders, such as autoimmunity and allergy. Data from studies addressing the issue of autoimmunity are still descriptive but nevertheless tantalizing. Weinstock and colleagues have argued that a failure to acquire helminthic parasites predisposes one to Crohn's disease and have correlated increased hygiene in westernized countries with the decreased prevalence of helminthiases and the increased prevalence of autoimmune intestinal diseases and other forms of autoimmunity (34). The relationship between immune responsiveness to allergens and/or allergic symptoms and helminth infections is fascinating and has puzzled immunologists for decades. Helminth infections induce strong IgE responses, which in combination with high Ag levels would be expected to lead to allergic symptoms and possibly anaphylaxis (63). However, helminth-infected individuals rarely have allergic reactions to these parasites and, moreover, appear to suffer less from allergic disorders in general than do helminth-free individuals (e.g., see reference 7). There are several possible explanations for this paradox, including the production of IgG antibodies that block access of allergenic Ag to specific IgE (61, 109), but in an exciting recent development, studies have correlated increased IL-10 levels resulting from chronic schistosomiasis hematobium with reduced expression of house mite allergy in African children (103, 109).

## TH2 RESPONSE INDUCTION

An exciting but yet-unanswered issue is that of how the mammalian host is able to recognize helminth Ag and respond with a Th2 response. It has become clear over the past decade that IL-4 produced early in the response plays an important role in Th2 response consolidation and amplification (85). One school of thought is that accessory cells, innately responsive to helminth Ag (and other Ag that induce Th2 responses), make IL-4 at the inception of the response and in so doing dictate the phenotype of the subsequent Th response (21). Discrimination of helminth pathogens could be based on recognition of parasite glycoconjugates, which contain unusual sugars (60, 82, 91) that have been implicated in Th2 response development (86). It seems likely that Toll receptors and/or other pattern recognition receptors (2) capable of identifying these and/or other features of helminth Ag exist.

An alternative view of Th2 response development, probably with more support, is that autocrine IL-4, derived from the naïve Th cell itself, is of central importance (20, 21, 85). The circumstances under which Th cells are activated to make and/or retain responsiveness to IL-4 are not completely clear, and there is a growing interest in the role of dendritic cells, the initiators of immune responses, in this process. Clearly, these cells play a central role in Th1 response induction by producing IL-12 following recognition of certain microbial pathogens (92, 97). However, recent reports indicate that dendritic cells are not activated by helminth Ag to make either IL-4 or IL-12, or to undergo any of the phenotypic changes that occur following exposure to Th1-inducing pathogens, and yet acquire the ability to induce strong Th2 responses (70, 105). Helminths can also inhibit dendritic cell migration (6) and prevent their activation by Ag that normally would promote IL-12 production (95).

## SUMMARY

Helminths remain a major cause of morbidity and mortality, especially in developing countries (22). While excellent drugs are available to treat many helminth infections, they remain relatively expensive and/or difficult to administer systematically in situations where so many other vital needs compete for limited resources. The absence of vaccines, the amenability of several mouse models of helminth infection to experimental analysis, the suitability of helminth infections for studying the immunobiology of chronic infection and of Th2 response development, the possibility of molecular cross-talk between helminths and the mammalian immune system, and the developing realization that helminth infections affect the ability of an individual to mount immune responses against other Ag (self or nonself) make the immunology of helminth infection an important, challenging, and exciting choice for investigation.

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