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Helminth Infections and Host Immune Regulation

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INTRODUCTION

Nearly one-third of the global population is infected with helminth parasites, rendering them among the most prevalent infectious agents in the world today, and they are responsible for many debilitating diseases and syndromes (124). Moreover, helminths are widespread in livestock and cause major agricultural losses. In both human and animal hosts, helminths establish long-term chronic infections associated with significant degrees of downregulation of the host immune response (78, 121, 181). The eradication of helminth infections remains a distant goal, due to a lack of effective vaccines, limited pharmacological efficacy, emerging drug resistance, and rapid reinfection in environments where transmission cannot be interrupted. New intervention strategies based on an understanding of the immunological basis of helminth persistence are therefore urgently needed.

Helminths are multicellular worms of three taxonomic groups: cestode tapeworms, nematode roundworms, and trematode flukes. They present a striking variety of life histories, from direct fecal-oral transmission (such as the common roundworm *Ascaris*) to development through free-living stages (such as hookworm larvae in the environment) or dependence on invertebrate vectors (such as the schistosome snail vector). Correspondingly, helminths also have various invasion routes, including through the skin (schistosomes and hookworms), by mosquito bite (filarial worms), and, most frequently, in the gastrointestinal tract.

The extraordinary prevalence of helminth infections undoubtedly reflects their ability to manipulate the host immune system, suppressing responses that could result in their ejection. Host immunity has also developed—over eons of coevolution with parasites—mechanisms to limit pathology and to best balance susceptibility, resistance, and immune pathogenesis. Hence, immune responses often permit ongoing infection in preference to complete parasite elimination and the collateral damage that would result (3). In other cases, this balance is upset, and immune dysregulation and pathology ensue, as in the instances of hepatic fibrosis in schistosomiasis or elephantiasis in lymphatic filarial infections (Table 1).

Protective immunity to helminths develops only slowly, and the effector mechanisms for eliminating parasites in humans are not well delineated; however, animal models have defined a set of Th2-dependent pathways that mediate protection (3, 6). Not surprisingly, the Th2 response is itself a major target for helminth immunoregulation, as successful parasites seek to blunt the host immune attack. In this review, we set out the patterns and pathways of helminth modulation, with the perspective that this knowledge will not only provide new avenues for eradicating parasite infections from humans and animals but also offer routes to

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TABLE 1 Human helminth infections and their rodent models

Human disease (pathogen[s])	Human pathology	Global prevalence[a] and DALYs[b]	Rodent model	Reference
Filariasis				
Lymphatic (*Brugia malayi*, *Wucheria bancrofti*)	Lymphatic incompetence, elephantiasis	LF prevalence, 120 million; LF DALYs, 5.64 million	Mouse/gerbil for *Brugia malayi*/*B. pahangi*[c] and *Litomosoides sigmodontis*[d]	158
Subcutaneous (*Loa loa*, *Onchocerca volvulus*)	"River blindness," dermatitis	Ov + Ll prevalence, 50 million; Ov DALYs, 0.99 million		
Schistosomiasis (*Schistosoma haematobium*, *Schistosoma japonicum*, *Schistosoma mansoni*)	Liver fibrosis, hepatosplenomegaly, anemia, malnutrition, bladder cancer (*S. haematobium*)	Prevalence, 207 million; DALYs, 1.76 million	Mouse for *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*[e]	220
Ascariasis (*Ascaris lumbricoides*)	Cognitive impairment, intestinal obstruction	Prevalence, 807 million; DALYs, 1.18 million	Mouse for *Ascaris suum*[f]	164
Hookworm infection (*Ancylostoma duodenale* and *Necator americanus*)	Anemia, cognitive impairment	Prevalence, 576 million; DALYs, 1.83 million	Rat/mouse for *Nippostronglus brasiliensis*[g] and *Heligmosomoides polygyrus*[h]	40
Trichuriasis (*Trichuris trichiura*)	Diarrhea, cognitive impairment	Prevalence, 604 million; DALYs, 1.65 million	Mouse for *Trichuris muris*	45

[a] See reference 124.
[b] DALYs, disability-adjusted life years (309).
[c] The full life cycle does not develop in mice; however, each life cycle stage can survive temporarily.
[d] Natural parasite of the cotton rat *Sigmodon hispidus*.
[e] Low-level infection in mice.
[f] Only larval stages survive in mice. *Ascaris suum* is a natural parasite of pigs.
[g] Truncated infection, especially in mice.
[h] Taxonomically related to hookworms but lives entirely in the gastrointestinal tract and does not ingest blood.

treat noncommunicable immune dysfunctions such as allergies and autoimmunity.

IMMUNE DOWNREGULATION IN HUMAN HELMINTH INFECTION

In human populations, the helminths with the largest burden of disease are the vascular-dwelling schistosomes, the filarial nematodes (*Brugia malayi* and *Wuchereria bancrofti* in the lymphatics and the subcutaneous *Onchocerca volvulus*), and the predominant gastrointestinal nematodes (Table 1).

The downregulation of the immune system in these infections takes effect at multiple levels. In infected populations, a large proportion of individuals may be asymptomatic carriers with depressed immune reactivity to the infecting parasite, as measured by the response of peripheral T cells to parasite antigens; as responsiveness can be rescued by curative chemotherapy, active suppression by parasites is implicated (181). Furthermore, in infected populations, responsiveness to "bystander" antigens such as vaccines, allergens, or autoantigens is attenuated in a more general manner (182). As detailed below, analyses of the cellular basis for these effects have revealed profound dysregulation across the range of innate and adaptive cell populations and pathways.

Immune Regulation and Spectrum of Disease

Immune regulation by parasites compromises immunity but also protects the host from damaging immunopathological reactions to the presence of parasites; this relationship is most evident in tissue settings, such as lymphatic filariasis, onchocerciasis, and schistosomiasis, in which the intensity of the infection does not necessarily positively correlate with pathology. Individuals harboring high parasite numbers may be asymptomatic, with stronger regulatory responses, while chronic pathology can occur in immunologically reactive patients with lower-level infections. The immunological mechanisms responsible for this are discussed below and are depicted in Fig. 1.

The spectrum of disease is best illustrated in long-term filaria-exposed populations, for whom infection outcomes range from those who are apparently immune and uninfected (endemic normal), through a large proportion of asymptomatic cases with patent infections (microfilaremic, Mf^+, with bloodstream microfilariae), to a minority who experience chronic pathology in the form of lymphatic inflammation and elephantiasis (181, 216, 223). The asymptomatic phenotype shows elevated levels of the immunoregulatory cytokine interleukin-10 (IL-10) (173), a suppression of Th1 inflammatory cytokines (such as gamma interferon [IFN-γ]) as well as key Th2 components such as IL-5 (243), and increased expression levels of circulating T cells expressing the inhibitory marker CTLA-4 (cytotoxic T lymphocyte antigen 4) (265). Conversely, those cases succumbing to lymphatic pathology have deficient numbers of a key cell type, the regulatory T cell (Treg), while expressing stronger Th1 and Th17 effector components (14); the latter may be responsible for lymphatic inflammation against resident adult worms. Th17 cells are also more numerous in patients who have cleared bloodstream Mf (10), raising an interesting question of whether Mf directly downregulate Th17 responses and extend their survival by doing so.

In the related filarial infection onchocerciasis, antigen-specific responses also decline with increasing numbers of skin Mf (35), while cases of chronic pathology (dermatitis and lymphadenitis) carry low parasite numbers. In these patients, strong immune responses against subcutaneous parasites are associated with dimin-

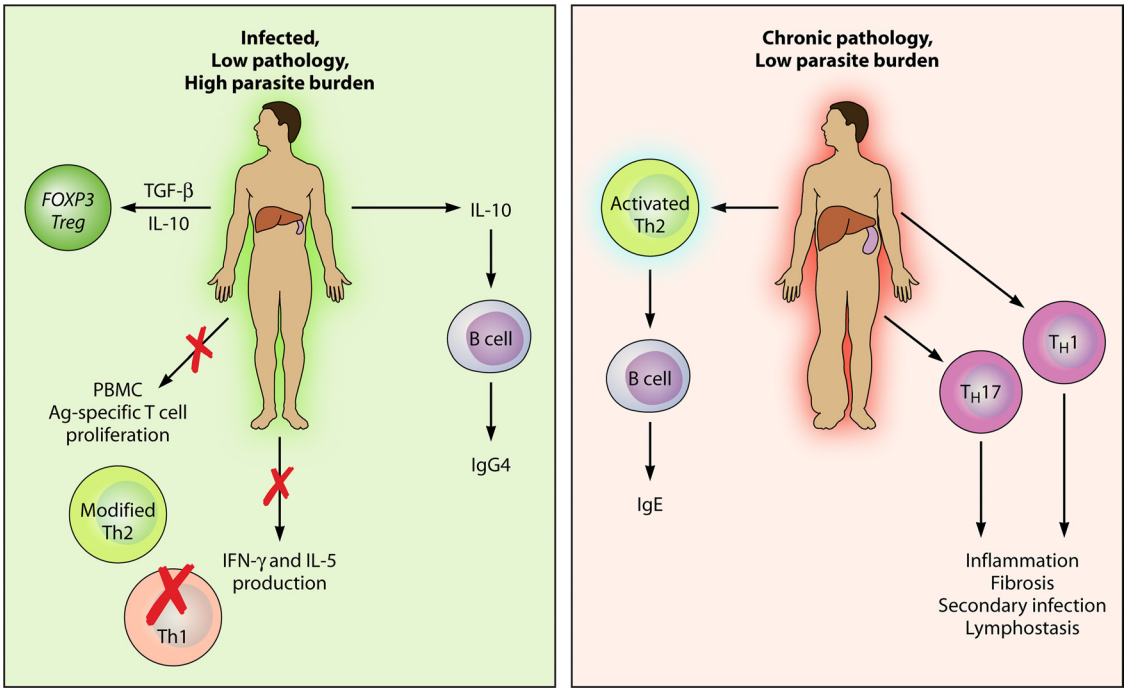

FIG 1 Spectrum of pathology in chronic tissue helminth infections. In areas where schistosome and filarial diseases are endemic, a spectrum of pathology is seen, with some individuals developing chronic debilitating pathologies and others showing a tolerant phenotype. The tolerant phenotype is characterized by the production of transforming growth factor β and IL-10 and the expansion of Forkhead box $P3^+$ Tregs. These cytokines lead to IgG4 production by B cells, suppressed parasite-specific T cell proliferation in PBMCs (peripheral blood mononuclear cells), reduced levels of Th2 cytokines, and ablated Th1 cytokines. Thus, the parasite survives productively in the host (schistosome eggs are deposited in the feces, or microfilariae circulate in the blood), with minimal collateral damage. In individuals with chronic pathology, the parasite may be killed or kept at low levels, at the cost of damaging immunopathology. High levels of Th1 and Th2 cytokines are seen, with the emergence of a Th17 response. B cells produce high levels of IgE against parasite antigens (Ag). Th1 and Th17 responses lead to inflammation and fibrosis around deposited schistosome eggs and lymph stasis, leading to secondary infections in lymphatic filariasis.

ished levels of another immunosuppressive mediator, transforming growth factor β (TGF-β), in nodules around parasites (149). As infection intensity correlates negatively, rather than positively, with immune responsiveness, it is likely that active immunosuppression by parasites and/or their secreted products is taking place.

In schistosomiasis, the distinction between asymptomatic and pathological infections is less clear, as chronic liver fibrosis is common, with sustained granuloma formation around deposited eggs. A spectrum is evident, however, in the degree of the inflammatory response to infection. When previously unexposed travelers are infected with schistosomes, they mount an acute inflammatory immune response against the parasite, with large granulomatous reactions around deposited eggs (39). However, during chronic infection, inflammatory cytokine responses to *Schistosoma* soluble egg antigens (SEAs) are much reduced (202), while Th2 cytokines (including IL-10) are upregulated (39, 63), and only a small proportion of patients progress to severe hepatosplenic disease. Both acute schistosomiasis patients and severe pathology cases mount much stronger T cell proliferative responses to SEA than low-pathology but chronically infected individuals (98); the low-pathology group, however, has higher frequencies of $CD4^+$ $CD25^{high}$ Tregs (282). The production of Th2 cytokines (especially IL-13), although required for resistance, can also have detrimental effects, as they are important for the generation of fibrosis and pathology in the liver and spleen during chronic schistosomiasis (62, 64).

In gastrointestinal nematode infections, particularly infections by the highly prevalent *Ascaris*, hookworm, and *Trichuris* species (Table 1), the pathology is less intense, and long-term infestation is common. Infection is associated with a regulatory set of cells and cytokines, as IL-10 and TGF-β are significantly linked with hyporesponsiveness and susceptibility (86, 285), and patients show a higher frequency of circulating $CD4^+$ $CTLA\text{-}4^+$ T cells (95). Thus, an immunoregulated state is a common outcome across a diverse range of helminth infections.

The profile of antibody isotypes can be a telling indicator of the regulated status of the host; in helminth infections, the relative levels of IgG4 and IgE appear to be the most important corollary of susceptibility to and protection from infection, respectively (106, 132, 179, 235). The IgG4 isotype, unlike IgE, cannot cross-link receptors on basophils, mast cells, or eosinophils and, unlike other IgG molecules, does not activate complement or act as an opsonin. It thus appears to be a canonical marker of the modified (noninflammatory) Th2 state, potentially blocking cytophilic isotypes such as IgE and preempting potentially damaging inflammation (181).

In filariasis, the production of IgG4 rather than IgE against filarial antigens is maximal in the asymptomatic Mf^+ state, reaching extraordinarily high levels (132, 152). IgG4 titers fall rapidly following curative drug treatment (11). Interestingly, IgE production by B cells is promoted by IL-4 and IL-13, but in the presence of the regulatory cytokines IL-10 and TGF-β, a switch to IgG4 is favored (246). Hence, it was suggested that the extremely high

IgG4 levels in many helminth-infected patients reflect a dominant regulatory environment (1, 176).

Antigen-Specific Hyporesponsiveness

A general finding is that chronic infections with filarial and schistosome parasites result in antigen-specific unresponsiveness among peripheral blood T cell populations, which fail to respond to *in vitro* challenge with specific parasite antigen (225, 313). A dynamic link between T cell anergy and the immunoregulatory environment in helminth infections is suggested by the strong correlation between IgG4 levels and unresponsiveness (29, 313). The fact that, as detailed below, hyporesponsiveness can be reversed by the chemotherapeutic removal of the parasite burden (101, 103, 242) argues that it reflects a direct effect of live parasites rather than an inherent incapacity of the host to respond to infection.

In filariasis, the hyporesponsive condition strongly correlates with the asymptomatic Mf carrier state (225, 313), while pathology cases are immunologically more reactive. Notably, unresponsiveness is associated with elevated levels of IL-10 and TGF-β production, and reactivity to parasite antigens can be restored, *in vitro*, with antibodies to these suppressive cytokines (144). During onchocerciasis, the filarial worm *Onchocerca volvulus* dwells in subcutaneous granulomata; T cells derived from these sites express IL-10 and TGF-β (68), with $CD4^+$ T cell clones from this tissue possessing a regulatory phenotype and suppressive functions (245). CTLA-4 may also be an important inhibitor of effector T cell signaling, as in lymphatic filarial patients, peripheral T cells challenged with parasite antigen in the presence of anti-CTLA-4 antibodies showed improved responsiveness (265).

Intriguingly, children born to filaria-infected mothers have higher CTLA-4 levels than children of uninfected mothers, implying a maternal-fetal imprinting of regulation (265). Long-term studies of filariasis-exposed communities have revealed that the maternal infection status is highly influential in determining the Mf^+ state of the offspring: children of microfilaremic mothers are more than twice as likely to become microfilaremic (154), while infants whose cord blood cells were hyporesponsive to parasite antigens and were born to Mf^+ mothers are nearly 12-fold more likely to themselves become infected than infants born to uninfected mothers (183). Conversely, humans exposed to filarial parasites later in life, either as migrants relocating to an area where filariasis is endemic (219) or as military personnel in the Pacific theater of the Second World War (47), show higher incidences of pathology and lower rates of the asymptomatic "tolerant" state. Thus, early-life exposure to filarial antigens promotes tolerance, possibly by prenatal exposure to antigen presented without inflammation or through the effects of soluble parasite immunomodulators on the fetus (183, 184).

A similar pattern of immune suppression is seen for schistosome infections of humans. In early infection, T cell proliferative responses are intact but become downmodulated during chronic infection (48). Cytokine responsiveness has also been reported to be suppressed in *Schistosoma haematobium*-infected individuals in regard to IL-4, IL-5, and IFN-γ production (102), while parasite-specific IL-10 positively correlates with egg positivity and infection intensity (209). In mouse models, IL-10 is pivotal in the suppression of potentially protective antischistosome responses (302). Evidence that helminth parasitic infection actively suppresses immune responses also comes from studies in which responses to parasite antigens increase after the drug-induced clearance of parasites. After drug treatment of filaria-infected (227) or schistosome-infected (48, 103) patients, immune responsiveness to the respective antigens is restored. Increased Th2 responsiveness after drug cure also positively correlates with resistance to reinfection (140).

These data illustrate the ability of helminth parasites to potently induce a regulatory environment, which is exquisitely tuned to maintain effector T cell populations in a repressed, unresponsive state. Importantly, if parasites are cleared or the immune response is potentiated, immune competence can be restored to the host (281). Thus, the suppression induced by parasitic infection is active, and many of the mechanisms may be initiated by the release of helminth-derived mediators (119).

The hypoproliferative state in tissue helminth infections could reflect interference with antigen-presenting cell (APC) populations. Filarial infection subverts monocyte and APC function: in Mf^+ patients, there is a preponderance of circulating $CD11c^{low}$ $CD123^{low}$ monocytic dendritic cells (DCs), which have downregulated CCR1 and may consequently be impaired in their migratory capacity (253), and lipopolysaccharide (LPS)-induced inflammatory cytokine release from Mf^+ donor monocytes is significantly depressed compared to that in uninfected or chronic-pathology patients (244), with responses being partly restored following anthelmintic treatment (252). Overall, APCs show a reduced ability to upregulate TLR (Toll-like receptor) (a family of innate pattern recognition receptors) expression following stimulation, a deficiency also observed for B cells from Mf^+ patients (15). Moreover, the T cell expression level of TLRs is also reduced in filarial infections (16), which is part of the general pattern of compromised TLR function during helminth infection (293). An interesting question, explored in Cellular Basis of Immunomodulation below, is whether certain APC populations are simply compromised in their function or converted into active regulatory and suppressive cell types.

Deficient Acquired Immunity

Human immunity to helminths is frequently ineffective in two key respects: the immune system is unable to clear chronic infections, and immune memory fails to protect against reinfection even after drug-mediated clearance. Indeed, classic immunity reminiscent of protection against viral and bacterial pathogens is rarely observed, with protection against helminth infection taking years to develop and seldom achieving sterile cure (5). However, effective immunity that significantly reduces the parasite burden is possible, as demonstrated by irradiated larval or cercarial vaccines in animal models of schistosomiasis, hookworm infection, and filariasis (178) as well as the more recent recombinant antigens (27). Hence, the generation of immunity is deficient in humans exposed to natural helminth infection.

Deficient immunity largely reflects inadequate Th2 responses, based on the more vigorous Th2 compartment in individuals exhibiting some degree of protection from reinfection. For example, the resistance of schistosome patients to reinfection following drug cure correlates strongly with the release of IL-4 and IL-5 (140), while in a separate study, those succumbing to reinfection showed lower-level IL-5 responses (102). Likewise, in human populations in areas where hookworm is endemic, IL-5 production correlates with resistance to reinfection after drug cure (228),

and in *Ascaris* infections, levels of IL-4, IL-9, IL-10, and IL-13 were most positively associated with protection (284). Moreover, clear genetic links between Th2-promoting gene loci (such as IL-13 and STAT6) and resistance to infection have been reported (150, 175, 201). Clearly, during chronic helminth infection, the Th2 capacity is downregulated, and protective immunity is compromised.

However, a recent study on schistosomiasis showed that protection from infection was associated with both Th1 (IFN-γ) and Th2 (IL-4 and IL-13) gene polymorphisms, raising the possibility of Th1-derived components contributing to immunity to schistosomes (96). Consistent with this, resistant individuals mount stronger IFN-γ responses (as well as stronger overall Th2 responses) to parasite antigens, indicating that both the Th1 and Th2 arms may be modulated in susceptible individuals (29, 232). Similar observations have been reported for human filariasis and hookworm infections and are mirrored in mouse studies of filariasis and schistosomiasis, as discussed below in Mouse Models of Infection.

Regulatory Cell Populations in Human Infection

The cellular basis of immunoregulation due to helminth infection involves the modulation of both the innate and adaptive immune responses through a suite of regulatory cell types (181). Tregs, the subset of T cells that maintain self-tolerance in humans and mice (139), are emerging as the most important regulatory phenotype in helminth infections. Several distinct Treg populations can be discerned, in particular "natural" Tregs, which express the transcription factor Foxp3 following their development in the thymus; "induced" Tregs, which switch to Foxp3 expression in the periphery; and Foxp3$^-$ type 1 regulatory (Tr1) cells. All these Treg populations can produce IL-10 and TGF-β in different settings (241). As well as restraining potentially damaging autoimmune responses, however, Tregs are also activated during many infections, dampening protective immunity and suppressing immune pathology (180). Moreover, the response to infection stimulates the parallel expansion of effector and regulatory subsets (276), and the outcome may depend on changing proportions of each type (280). A central question, therefore, is whether Tregs arise as a homeostatic response to inflammation or are driven in a selective manner by pathogens, including helminth parasites, in order to sustain infection.

The importance of suppressive cell subsets in human helminth disease was evident even before regulatory T cells were properly defined, in assays of T cells from hyporesponsive Mf$^+$ *B. malayi*-infected individuals (226) and in the demonstration that antibodies to IL-10 and TGF-β restored responsiveness to cultures of T cells from both filariasis (144) and schistosomiasis (145) patients. Asymptomatic Mf$^+$ individuals show elevated levels of IL-10 (173) and a suppression of Th1 inflammatory cytokines (such as IFN-γ) as well as key Th2 components such as IL-5 (243). Conversely, those individuals succumbing to lymphatic pathology have significant Th1 and Th17 components (14); the latter may be responsible for lymphatic inflammation. By flow cytometry, recent studies have established higher frequencies of CD4$^+$ CD25$^+$ CD127$^-$ Foxp3$^+$ Tregs in filariasis Mf$^+$ cases than in controls (17, 195) as well as higher overall expression levels of CTLA-4 among the CD4$^+$ peripheral T cell population of Mf$^+$ patients (265). It was suggested that CTLA-4 (and PD-1 [programmed cell death 1]) may be involved in blocking inflammatory bystander responses in infected patients (13). Recently, regulatory T cells from microfilaremic individuals, but not those from uninfected individuals, were shown to suppress both Th1 and Th2 peripheral blood mononuclear cell (PBMC) cytokine production, providing further evidence of a link between Tregs and the hyporesponsive state (297). In contrast, PBMCs from filaria-infected individuals with chronic pathology fail to upregulate Foxp3 in response to filarial antigen, potentially indicating that Tregs are deficient in these patients (14), although this is subject to the caveat that Foxp3 can also be activation induced in humans (298).

In the related infection onchocerciasis, IL-10-producing Tr1 cells are readily detected in hyporesponsive patients (245) and along with Foxp3$^+$ natural Tregs, induce IgG4 from B cells (246). Importantly, localized Treg induction around parasite nodules in tissues has been seen (148), and T cell clones from these granulomas or PBMCs included many that expressed IL-10 and/or TGF-β (68, 245). The role of DCs in inducing regulatory T cell responses is illustrated by the action of schistosome lysophosphatidylserine, which acts on human DCs to promote IL-10-producing Tr1 cells (290).

In human schistosome infections, CD4$^+$ CD25^{high} cell frequencies were significantly reduced after drug cure of *Schistosoma mansoni* infection (299), while in children, CD4$^+$ CD25^{high} CD127$^-$ Foxp3$^+$ proportions were positively correlated with the *S. haematobium* parasite burden (213). In the latter study, in adults resistant to reinfection with the parasite, Treg proportions were negatively correlated with infection intensities (213). This finding may imply that in the early stages of infection, Tregs expand, but later in life, once resistance has developed, Treg proportions are reduced upon infection due to the expansion of the T effector population.

In human gastrointestinal infections, evidence of Treg involvement is less extensive, and the analysis of peripheral blood T cells may not be an appropriate reflection of immune populations in the gut. Nevertheless, it was found that hookworm-infected individuals display higher proportions of circulating CD4$^+$ CD25$^+$ Foxp3$^+$ Tregs than uninfected controls (233). In addition, among patients with intestinal nematode infections, *in vitro* T cell responses to malaria and mycobacterial antigens were depressed but were rescued following Treg depletion (296).

IL-10-producing regulatory B cells (Bregs) are receiving particular interest in mouse models of helminth infection, as discussed below. Bregs have also been found in human patients infected with environmentally acquired helminths (56). IgG4-producing B cells associated with tolerance to filarial infections have been proposed to stem from IL-10-producing Bregs (131), producing an intriguing link between these two regulatory phenotypes. Thus, it seems likely that Bregs are also involved in the suppression of antihelminth immune responses.

DAMPENING BYSTANDER RESPONSES IN HUMANS

As evident from the data discussed in Immune Downregulation in Human Helminth Infection, many helminth infections can drive an antigen-specific anergic state, but suppression is not confined solely to parasite-specific responses. Indeed, there are broad effects of concurrent helminth parasite infections on vaccine, coinfection, and allergen or autoantigen responses in humans (Fig. 2), which (as discussed in Helminth Therapy in Humans) have led to human clinical trials using experimental helminth infections.

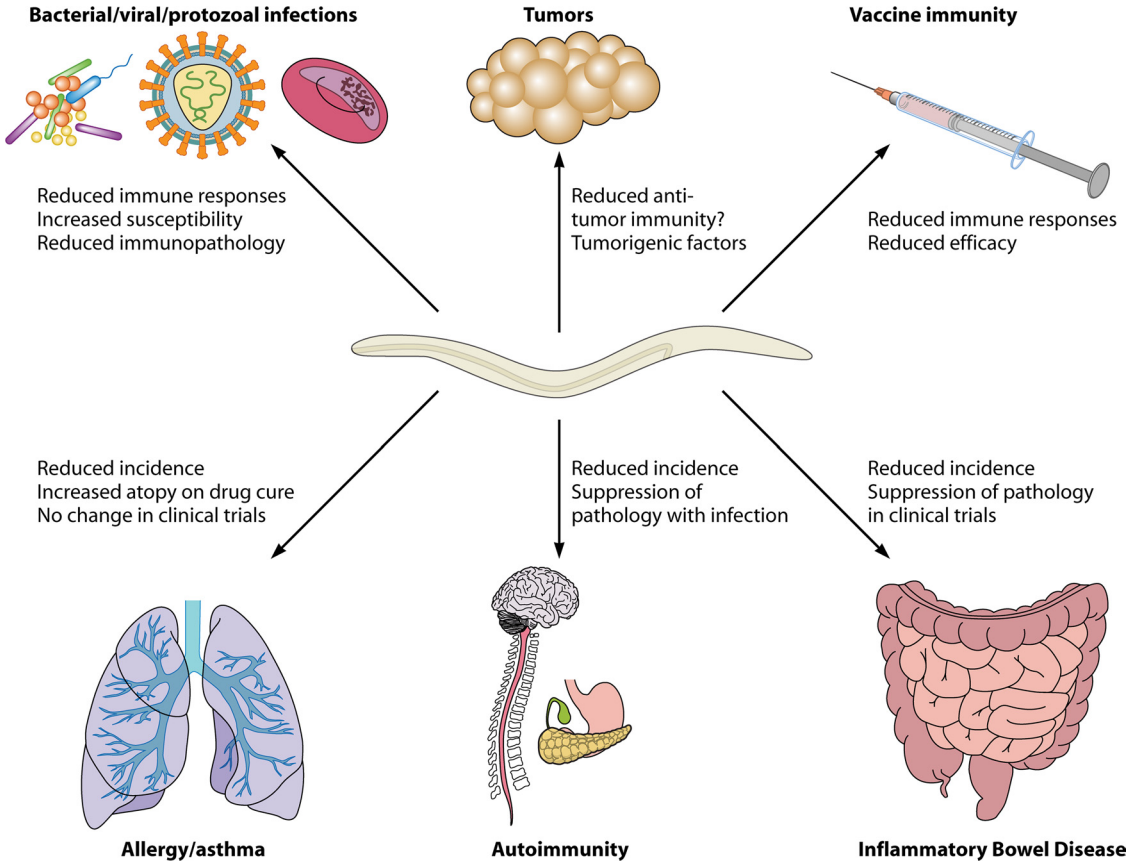

FIG 2 Immunoregulatory effects of helminths on bystander responses. Helminths can suppress a wide range of bystander immune responses, including those of both immunopathogenic and protective natures. Coinfection with helminths suppresses antibacterial, antiviral, and antiprotozoal immunity, leading to increased susceptibility and attenuated immunopathology or, in some cases, exacerbated pathology due to higher infection burdens. Antitumor immunity may be suppressed by helminth infections, which may also release directly carcinogenic factors, potentially leading to increased numbers of malignancies in infected individuals. Vaccine efficacy is compromised by helminth infections due to suppressed immune responses. Immunopathologies such as asthma, autoimmune diseases, and inflammatory bowel diseases are all reduced in prevalence in areas where helminth disease is endemic, and direct effects of helminth infections on the suppression of disease have been shown in clinical trials for inflammatory bowel diseases.

Compromising Vaccine Efficacy

A growing concern in developing countries is the extent to which helminth infections may interfere with childhood vaccination programs (31). Patients with schistosomiasis, for example, mounted weaker IFN-γ responses to tetanus immunization (239), as did onchocerciasis and lymphatic filariasis patients, who presented higher-level IL-10 responses instead (54, 214). Moreover, vaccine responses were significantly augmented in *Ascaris*-infected children given anthelmintic treatment prior to immunization, compared to the responses of placebo-treated controls (53), while a similar comparison of infected and treated recipients of *Mycobacterium bovis* BCG showed that helminth infections depressed antimycobacterial T cell responses, with concomitant increases in levels of TGF-β release (72). Investigations using mouse models have reiterated these effects (287). For example, *S. mansoni* infection interferes with the protective effect of BCG vaccination (71), and *Heligmosomoides polygyrus* infection reduces the efficacy of vaccination against *Plasmodium chabaudi* (268).

A related issue is whether maternal helminth infection during pregnancy may influence infants' vaccine responsiveness; however, a large-scale clinical trial recently showed that anthelmintic treatment of pregnant mothers had no positive effect on subsequent vaccine efficacy, as judged by cytokine or antibody responses (300). As the efficacy of the anthelmintic treatment and the analysis used has been called into question (312), more studies in this area are required to confirm these results.

Coinfection with Helminths

Helminths rarely infect the human host in isolation, particularly in the settings of tropical countries, and coinfections are therefore extremely common. Interest has focused in particular on the interactions between helminths and prominent infections with high mortality rates in the tropics, such as malaria, tuberculosis, and HIV.

There is currently controversy regarding whether helminths ameliorate (211) or exacerbate (69) malarial disease, as reviewed elsewhere previously (210). It is important that the different host-parasite combinations involved as well as the intensity and duration of infection may well show opposing influences on disease (147, 260). Immunoregulatory factors are very likely to mediate this interaction, and in children coinfected with intestinal helminths and/or schistosomes, the major change in immune responsiveness was increased IL-10 levels in response to *Plasmodium* antigen (110). Moreover, in an area where filariasis and

malaria are both endemic, PBMCs from filaria-infected subjects produced less IL-12p70, IL-17A, and IFN-γ but more IL-10 in response to malaria antigen (196, 197), consistent with diminished IL-12 responses from filariasis patients stimulated with malarial antigen (198).

Bacterial infections, such as tuberculosis, are highly prevalent in many areas where helminth infection is endemic (73). As mentioned previously, heightened CTLA-4 expression levels in filaria-coinfected patients may act with PD-1 (programmed cell death 1) to block protective Th1 and Th17 antimycobacterial responses (13). The suppression of these antimalarial/antituberculosis responses can lead to an insufficient control of the infection and increased pathology. In cholera patients, intestinal helminth infections also depress the antibacterial antibody response, particularly of the IgA isotype, which is important in protection (109). Thus, helminth coinfection can suppress immune responses to both systemic and intestinal bacterial infections.

In retroviral infections, anthelmintic treatment retards HIV disease progression (295); thus, helminths appear to encourage viral replication. This may be due to the suppression of the antiviral response or due to increased numbers of circulating antihelminth Th2 cells, in which HIV replicates preferentially (251). Indeed, in coinfection studies with rhesus monkeys, schistosome egg deposition (and the initiation of strong Th2 responses) coincided with an upsurge in circulating viral loads (12). Conversely, the suppressive effects of HIV extends to antihelminth immunity, with HIV infection inhibiting resistance to schistosome reinfection after drug cure (250) and correlating with lower levels of production of Th2 cytokines (33). HIV/AIDS predisposes individuals to other helminth parasitic infections, and pathologically intense opportunistic infections by *Strongyloides* species are common in areas of endemicity (33). Furthermore, human T cell lymphotropic virus type 1 (HTLV-1) infection predisposes individuals to *Strongyloides stercolaris* infections due to suppressed antiparasite immune responses (120), and coinfected patients show much higher Foxp3$^+$ Treg numbers and lower-level IL-5 responses than individuals infected with either pathogen alone (203).

The Hygiene Hypothesis

Epidemiological studies have pointed to the higher frequency of allergies (such as asthma, eczema, and allergic rhinitis) in economically developed countries than in developing countries (51, 134, 174). This has been attributed to increased standards of living in the developed world leading to lower rates of childhood infections and increased immune dysregulation, known collectively as the "hygiene hypothesis" (267, 303). Much attention has since been focused on the question of whether helminth infections are one of the major factors which counteract allergies in the developing world (52, 91). A number of studies have reported that helminth-infected cohorts do indeed show a lower allergic propensity (generally, skin test reactivity to allergens such as the house dust mite), in particular in children with *S. haematobium* (236, 288) and *S. mansoni* (8, 9, 194) infections. Evidence for a causal effect of parasites on reducing allergies stems from reports that anthelmintic clearance of infection increases skin test reactivity in children (92, 289).

An important question in both helminth infection and allergy is the importance of prenatal antigen exposure to the future reactivity of the newborn. In recent studies, anthelmintic treatment of pregnant mothers in a population living in an area where hookworm and schistosome diseases are endemic was shown to significantly reduce the incidence of atopic eczema in offspring (74, 207). These data also provide the first evidence for helminths modulating clinical allergy in humans, rather than skin test atopy (91).

Good correlations have been found between the inhibition of allergic reactivity and IL-10 production from T cells challenged with parasite antigen (288). Among important cellular mediators of allergic responsiveness are basophils; notably, in helminth-infected humans, the ability of basophils to respond to either IgE- or non-IgE-mediated activation is attenuated (156). This observation parallels the situation in mice, in which unresponsiveness was further demonstrated to be dependent upon IL-10 (157). In contrast, little evidence has been found to support the concept that helminth-induced IgE blocks allergic reactivity, in part because IgE receptor expression is highly upregulated during infection (79, 200).

Gastrointestinal nematode infections may also ameliorate allergy; a meta-analysis of all published data found that both *Trichuris* and *Ascaris* protect against the development of skin test atopy (83), although an earlier meta-analysis of clinical asthma found that only hookworm infection appeared to confer any protective effect, while *Ascaris* increased the risk (162). Thus, intestinal helminths may be more effective at suppressing atopic sensitization than controlling later-stage pathogenic mechanisms. It was also suggested that the suppression of allergies may require a parasite burden of a certain threshold level and/or a chronicity of infection (249, 260); if so, then meta-analyses which amalgamate data from areas with both low and high infection intensities would reduce the strength of the effects observed only in the latter.

Autoimmune diseases are considerably less prevalent than allergies, and few epidemiological investigations have been conducted on the effects of helminth infections on these disorders. A recent study reported that schistosome-infected individuals had lower levels of autoantibody than infection-free residents and that levels of autoantibodies increased in infected subjects treated with the antischistosome drug praziquantel (208). In terms of overt autoimmune pathology, there is a clear negative relationship between the incidence of multiple sclerosis (MS) in different countries and the prevalence of helminth infection, although the increased incidence of MS in economically developed countries also has many noninfectious contributory factors (90).

A stronger link between helminth infection and protection from MS emerged from Argentina, where patients serendipitously acquiring a range of gastrointestinal helminths (*Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *S. stercolaris*, and *Enterobius vermicularis*) subsequent to diagnosis remained in remission, with lower relapse rates than uninfected severity-matched patients (55). Furthermore, when a subset of the infected cohort was treated with anthelmintic drugs, these patients experienced a relapse of symptoms, in contrast to those who continued to be infected (57). Significantly, patients with a helminth-associated suppression of disease expressed elevated levels of IL-10 and TGF-β and expanded populations of both regulatory B and T cells compared to uninfected controls (55, 56).

Perhaps the most important unexplored territory is the interaction between helminths and the immune response to tumors. There is no epidemiological evidence that helminths compromise immune surveillance, although there are specific instances in

which individual parasite species are linked to particular cancers. The liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* are powerful causal factors in human cholangiocarcinoma, cancer of the bile duct (112, 263). There are also causal links between *S. haematobium* infection and bladder cancer, possibly due to the damage caused by the egress of eggs through the bladder wall (93). Most probably, these represent cases in which parasite-derived tumor promoters (262), acting in the context of immunomodulation, contribute to a carcinogenic outcome.

MOUSE MODELS OF INFECTION

Mouse model systems have been developed for each of the highly prevalent human helminth parasites. While some human-infective schistosome species are able to infect laboratory rodents, this is not the case for most human-infective nematode parasites, such as the filariae and gastrointestinal worms. However, in most cases, closely related rodent-infective species are available, as detailed below and in Table 1.

Schistosomiasis

S. mansoni is the most widely studied schistosome model in mice, with a growing body of literature also characterizing *Schistosoma japonicum* infections. Both of these intestinal schistosome species are well tolerated by most mouse strains, where cercariae penetrate the skin and migrate through the lungs before developing to paired adults residing in the hepatic portal vessel. There, they release eggs, which either emerge in the feces or are swept through the vasculature to become trapped in the liver, as occurs in human infection. While the urinary schistosome *S. haematobium* can maintain only limited infections in mice, the damage that this parasite causes to the bladder wall can be modeled by the direct microinjection of eggs (94).

In *S. mansoni*-infected mice, an initial Th1-dominated immune response switches to a Th2 profile upon the deposition of eggs (220); as in humans, eggs lodging in the liver provoke the predominant pathology of liver fibrosis. IL-13 is the chief mediator of fibrosis in schistosomiasis, as in IL-13 receptor α1 (IL-13Rα1)-deficient mice (which respond to IL-4 but not IL-13), fibrosis is greatly suppressed, and the rate of survival through the chronic phase of infection is consequently increased (229).

Schistosome egg antigen (SEA) is one of the strongest known Th2-driving stimuli, and both mouse and human SEA-pulsed DCs can prompt Th2 differentiation in cocultured T cells *in vitro* (80, 137). The central role of the DC is reflected in the Th2 induction *in vivo* by SEA-pulsed DCs (172) and the loss of Th2 responses in DC-depleted mice treated with either SEA or schistosomes (224). The chief DC-stimulating molecular motif within SEA was recently defined as the RNase glycoprotein ω-1 (80, 266). The depletion of ω-1 from SEA abrogates its Th2-inducing effects *in vitro*; however, ω-1-depleted SEA-pulsed DCs induce identical Th2 responses *in vivo*, and thus, it is not the only constituent of SEA with Th2-inducing properties (80, 266).

T cell hyporesponsiveness is also observed in *S. mansoni* infection of mice, as the $CD4^+$ T cell compartment becomes functionally anergic through the upregulation of the E3-ubiquitin ligase gene related to anergy (GRAIL). As this phenomenon could be replicated by the repeated stimulation of Th2 cells *in vitro*, it appears that this is a physiological response to chronic antigen stimulation rather than a specific effect elicited by the *S. mansoni* parasite (275). Thus, the host downregulates the response to schistosome infection, as it becomes more chronic, potentially damaging, and less likely to eradicate the infection. The further immunomodulatory effects of schistosomes are detailed below in Cellular Basis of Immunomodulation.

Filariasis

Laboratory models of human filarial parasites are constrained, as none can complete their life cycle in mice. For example, studies of the filarial parasite *B. malayi* are limited to the injection or implantation of the infective third-stage larvae (L3), adults, or microfilariae, which survive for weeks (larvae and microfilariae) to months (adults), depending on the mouse strain and sex. Nevertheless, two remarkable immunoregulatory effects on mice harboring infections with this species have been demonstrated. First, adult parasites surgically implanted into the peritoneal cavity of mice induced a novel macrophage phenotype now recognized as an alternatively activated macrophage (AAM) (2) (see "Alternatively Activated Macrophages" below); this cell type blocked the proliferation of activated T cells and hence acted in an immunosuppressive capacity. More recently, it was found that the same implantation stimulated the expansion of $Foxp3^+$ Tregs, even among bystander (ovalbumin [OVA]-specific) T cells. Moreover, Treg induction occurred in IL-$4R^{-/-}$ mice, which do not develop AAMs (192). Because both AAMs (14) and $Foxp3^+$ Tregs (14) are associated with human filariasis, these experiments suggest that the mouse model of *B. malayi* infection can be used to explore the generation of suppressive cell types by this human pathogen.

For many studies, it is preferable to study the full cycle of infection in mice, which is now possible with a natural filarial pathogen of cotton rats, *Litomosoides sigmodontis*. This parasite is transmitted by hematophagous mites and enters transcutaneously, migrating through the lymphatics to the pleural cavity, where mature adults produce circulating microfilariae (123). The *L. sigmodontis* model has shed light on mechanisms of immunity, specifically demonstrating that a mixed Th1/Th2 response is necessary to achieve protection. While IL-4- or IL-5-deficient mice are more susceptible to this infection (158, 264), the susceptibility of IFN-γ/IL-5 double-deficient mice is further increased (240), arguing that combinations of Th1 and Th2 elements are required for protection. As in filaria-infected humans, *L. sigmodontis*-infected mice develop an antigen-specific hypoproliferative defect alongside an expansion of regulatory T cells (277, 278, 280) and alternatively activated macrophages (279). Hyporesponsiveness can be reversed by manipulating GITR (glucocorticoid-induced tumor necrosis factor receptor-related gene) and CTLA-4 signaling (277, 278, 291), indicating the active and dynamic nature of suppression *in vivo*.

Gastrointestinal Nematodes

Ascaris, *Trichuris*, and hookworm species are the most prevalent human gastrointestinal helminths, the latter two of which can be appropriately studied in mouse models (Table 1). The closest model of hookworm disease in rodents is the rat parasite *Nippostrongylus brasiliensis*, which shares key life cycle characteristics (skin penetration and lung transit) with *Necator americanus* and *Ancylostoma duodenale* (40). In contrast to human hookworms, however, *N. brasiliensis* does not feed on host blood and therefore does not reproduce the chief pathological effect of anemia (125). Moreover, *N. brasiliensis* is ejected from the mouse or rat host within 2 weeks, while human hookworms can survive in the host for many years. To model chronic infection and immunoregula-

tion in humans, the preferred model is *Heligmosomoides polygyrus*, which completes its parasitic phase entirely within the digestive tract. Most mouse strains are unable to expel a primary infection of this parasite as a result of its profoundly immunoregulatory properties (177) but become resistant to secondary infections after drug cure of a primary infection, making *H. polygyrus* a useful model of acquired resistance to gastrointestinal helminth infection (6).

Both mouse models have supplied invaluable information about immune responsiveness and modulation in infection. The expulsion of primary *N. brasiliensis* and secondary *H. polygyrus* infections is highly Th2 dependent, requiring $CD4^+$ T cells and IL-4R signaling in both innate and adaptive cell populations (reviewed in references 3, 6, and 113). In addition, mast cells (113) and the goblet cell-derived defense protein resistin-like molecule β (RELM-β) are implicated in immunity to *H. polygyrus* (117).

The mouse model for human *Trichuris trichiura* infection is a closely related parasite, *Trichuris muris*, which can either maintain a chronic infection or be quickly ejected via a Th2-dominated $CD4^+$ T cell response, according to the host strain and parasite dose (45). In this model, immunity is effected through IL-9-dependent mast cells, smooth muscle hypercontractility (142, 234), and increased intestinal epithelial cell turnover (46). Normal laboratory infection with high doses of parasites quickly induces a protective Th2 response in resistant mice; however, the same strain of mouse can be rendered susceptible with low-dose exposure, in particular with "trickle" infections, which model more closely the rate of naturally acquired infection (22). This is reminiscent of parasitic infections of humans, where multiple exposures to parasites are required to build up resistance (see Immune Downregulation in Human Helminth Infection).

T. muris is a particularly valuable model of susceptibility and resistance to gastrointestinal helminths because of the sparsity of data on immune regulation in the human setting. However, two recent studies have analyzed mucosal immune modulation following helminth treatment of inflammatory bowel disease (IBD) (see Helminth Therapy in Humans). First, in an ulcerative colitis patient with *T. trichiura* infection, parasite colonization was shown to modify IL-17 levels while inducing Th2 cytokines and IL-22 in the colonic mucosa, with associated goblet cell hyperplasia (36). Second, a clinical trial of hookworm infection in patients with celiac disease showed an upregulation of hookworm antigen-specific Th2 cytokines and basal levels of IL-22, with suppression of IL-23, IFN-γ, and IL-17A production (97, 191). Thus, immune deviation in the gastrointestinal mucosa also occurs in human parasitic infections with respect to the suppression of inflammatory Th1/17 responses. Although relevant mouse models have provided us with a wealth of data on the regulation of the response to helminth parasites, further studies are required to link this information with susceptibility or resistance to human gastrointestinal helminths.

CELLULAR BASIS OF IMMUNOMODULATION

The immune response against helminth parasites involves an impressive range of innate and adaptive pathways for the induction and amplification of highly potent effector mechanisms. However, these potentially pathogenic responses also have to be regulated by the host immune system through counterbalancing immunoregulatory mechanisms. Moreover, it is now clear that in many instances, the same mechanisms have been coopted by parasitic organisms to diminish effective antiparasite immune responses. In this section, we explore the roles of dendritic cells (DCs), alternatively activated macrophages (AAMs), regulatory T cells (Tregs), and regulatory B cells (Bregs) in the control of immune responsiveness in experimental models of helminth infections.

Dendritic Cells

Both the stimulation and modulation of the host immune system by helminths is determined by DC populations; the depletion of DCs ablates the Th2 immune response to infection, while isolated DCs pulsed with helminth antigens readily induce Th2 responsiveness (42, 81). The role of DCs in inducing regulatory responses is illustrated by the action of schistosome lysophosphatidylserine, which acts on human DCs to promote IL-10-producing Tr1 cells (290), and the egg molecule ω-1, which drives murine DCs from mice to induce Foxp3 expression in T cells *in vitro* (316). In the *H. polygyrus* model, infection expands an unusual phenotype of $CD11c^{low}$ $CD103^-$ DCs, which preferentially drive Foxp3 induction in naive T cells (165, 258), while there is a loss of $CD8\alpha^{intermediate}$ DCs that normally traffic from the epithelium to the draining lymph node (21).

While the mechanistic pathways by which DCs induce Th1 and Th17 responsiveness via the production of IL-6, IL-12, and IL-23 and the upregulation of surface costimulatory molecules are well known, those involved in driving either Th2 or Treg outcomes are much less well understood (171). Tolerogenic DCs exhibit little evidence of maturation (upregulation of CD40, CD80, CD86, and major histocompatibility complex [MHC] class II), whereas microbial TLR ligands strongly induce these markers. However, a range of helminth molecules interfere with the ability of DCs to respond to TLR ligands and to produce IL-12 in response to stimulation (reviewed in references 81 and 119). DCs are also influenced by host "alarm" cytokines such as thymic stromal lymphopoietin (TSLP), and *T. muris* depends upon eliciting this product from the host to depress IL-12 responses (274), in contrast to other helminths, which are able to suppress DC IL-12 production directly without the requirement for TSLP (188).

No general pattern of receptors and signaling pathways through which helminths may inhibit DCs, or induce proregulatory DCs, has yet been established. Although some instances of TLR-mediated activation have been documented (290), it seems likely that helminth-specific pattern recognition receptors may extend well beyond the canonical TLR family, to include C-type lectin receptors (CLRs) (292), class A scavenger receptor (81), and, possibly, receptor types yet to be discovered. Furthermore, certain helminth products interfere with DC function at the intracellular level, by blocking antigen processing (187) or degrading mRNAs within the host (81). Defining the molecular interactions which result in the regulation of, and by, DCs is therefore of central importance to an understanding of host-helminth interactions.

Alternatively Activated Macrophages

Alongside the dominant Th2 response to helminth parasites, a powerful innate type 2 reaction emerges, including eosinophils, basophils, mast cells, and a distinct phenotype of macrophages, the alternatively activated macrophage (AAM) (151). AAMs are distinct from macrophages activated through IFN-γ in expressing high levels of arginine-metabolizing arginase 1, the chitinase-like molecule Chi3L3 (Ym1), and the resistin-like molecule RELM-α

(170) and in exerting profoundly antiproliferative effects *in vitro*. Mechanistically, it is likely that arginine inhibits cell proliferation by depleting the milieu of this amino acid, while a regulatory role for RELM-α is indicated by the exaggerated Th2 responses to schistosome infection in RELM-α-deficient mice (212). In contrast to their *in vitro* activity, AAMs *in vivo* are more closely associated with wound healing (169) and metabolic homeostasis (43); indeed, whether AAMs are regulatory or effector populations *in vivo* remains a controversial question.

The suppression of T cell proliferation by splenic adherent cells was originally noted for rodents infected with filarial parasites (155). Subsequently, a similar immunosuppressive effect was attributed to macrophages in mice peritoneally implanted with adult *B. malayi* filarial parasites (2). The *in vitro* suppressive nature of *B. malayi*-induced AAMs, together with the induction *in vivo* of Foxp3$^+$ Tregs by the same parasite (192), suggests that these macrophages fulfill an immunoregulatory role. In another murine filarial model, *L. sigmodontis* infection of the pleural cavity, AAMs are recruited to both the site of infection and the draining lymph nodes and suppress T cell responses at both sites in a TGF-β-dependent manner (279). Furthermore, in human filariasis, alternatively activated macrophage markers are upregulated in the blood of asymptomatic microfilaremics, the category displaying T cell hyporesponsiveness (18). Thus, in filarial infections at least, AAMs appear to suppress the immune response against the parasite, promoting anergy and/or tolerance.

AAMs are also induced in the gut in gastrointestinal nematode infections by pathogens such as *H. polygyrus* and *N. brasiliensis* (7, 318). Their presence can have detrimental effects on host immunity to concurrent pathogens. Coinfection with *Citrobacter rodentium* in *H. polygyrus*-infected mice results in increased *C. rodentium* bacterial loads and exacerbated *C. rodentium*-induced colitis. However, in coinfected STAT6-deficient mice, in which no AAMs are recruited to the gut, bacterial infection was not exacerbated (301). An interesting observation in these experiments was the increased levels of tumor necrosis factor (TNF) production by AAMs, a facet which may require further investigation.

The homeostatic role of AAMs also extends to protecting the host from potentially harmful inflammation. When schistosome eggs are deposited into the bloodstream and egress through the gut wall to be deposited into the feces, AAMs are required to maintain the integrity of the intestinal epithelium. In macrophage-specific IL-4Rα-deficient (LysM^{cre} IL-4Rα$^{-/flox}$) mice, commensal bacteria entered the tissues due to a lack of control of intestinal inflammation and deficient healing of the gut (116). In mice with a macrophage-specific arginase deficiency (LysM^{cre} Arg-1$^{-/flox}$), schistosome infection results in the formation of larger granulomas than those in control mice, and these granulomas do not shrink at chronic stages of infection, resulting in death due to increased fibrosis and Th2 cell-mediated inflammation (222). Importantly, macrophages from these mice can still undergo alternative activation, highlighting the role of arginase-1 in depleting arginine in the local milieu, directly suppressing T cell proliferation.

A broader question yet to be resolved is whether AAMs mediate primarily immunity rather than regulation. In both *H. polygyrus* and *N. brasiliensis* infections, the depletion of alternatively activated macrophages (using clodronate liposomes) increased susceptibility (7, 318). However, in LysM^{cre} IL-4Rα$^{-/flox}$ mice, resistance to *N. brasiliensis* was unaltered compared to that in wild-type controls (116). Disparities in the timing of these experiments argue that in AAM-depleted mice, immunity is likely delayed rather than ablated. Moreover, clodronate depletion, or arginase inhibition, has no effect on susceptibility or immune responses to *T. muris* (34). Hence, AAMs can be shown to be essential for the regulation of potentially pathogenic responses while acting in different contexts to either inhibit or promote functional immune mechanisms.

Regulatory T Cells

Evidence from human studies has long suggested that Tregs are important in helminth infections (see "Regulatory Cell Populations in Human Infection"), as strongly supported by data from animal models. Tregs are induced by *Brugia pahangi* (99) or *B. malayi* filarial infections (192), with the induction of Foxp3 expression within bystander OVA-specific T cell populations being demonstrated in the latter study. In *L. sigmodontis* infection, natural and inducible Tregs expand after infection and are required for long-term tolerance to the parasite (280). Treg induction is accompanied by a hyporesponsive phenotype of recruited Th2 cells, which are CD4$^+$ Foxp3$^-$ GITR$^+$ CTLA-4$^+$, and the induction of resistance to the parasite required both Treg depletion (using anti-CD25 antibody) and the simultaneous release of Th2 cells from suppression using either anti-GITR (277) or anti-CTLA-4 (278) antibody. Thus, Treg induction in *L. sigmodontis* infection results in the imprinting of a hyporesponsive phenotype onto parasite-specific Th2 cells, which finds a close parallel to the role of CTLA-4 in human filarial hyporesponsiveness (13, 265).

In mouse schistosome infections, Foxp3$^+$ Tregs are also recruited to the draining lymph nodes and the periphery of egg-induced granulomas in the liver (24, 159), and the forced retroviral expression of Foxp3 in schistosome-infected mice results in a reduction of granuloma size (257). In this infection, Tregs control granulomatous pathology at the intestinal site; a reduction in granuloma size correlates with increased numbers of CD4$^+$ CD25$^+$ CD103$^+$ Foxp3$^+$ cells, and the depletion of these cells results in larger granulomas in the colon (286). As noted above, in the case of ω-1, schistosome eggs release factors which enhance Treg induction in the presence of DCs, TGF-β, and retinoic acid (316), potentially modulating pathology.

In mice as in humans, the Th2 response in later stages of chronic schistosome infection is progressively downregulated, and granulomas reduce in size (32). Both regulatory cells and cytokines contribute to this downmodulation: Treg depletion with anti-CD25 antibody results in decreased egg production and increased granulomatous pathology (160). Among the cytokines, IL-10 is the most critical in dampening pathology and is produced by both Tregs and CD4$^+$ Foxp3$^-$ Th2 cells during infection (65, 118). Moreover, in IL-10/IL-12 double-deficient mice, which express exaggerated Th2 responses, excessive fibrosis results in a high mortality rate (122). However, Th1- or Th17-dominated inflammatory responses can also prove lethal in schistosomiasis, as in IL-10 (310) or IL-4 singly deficient mice, which succumb to severe liver damage and cachexia (38), or in the CBA mouse strain, which mounts an ultimately lethal Th17 response (237). Therefore, cytopathic effector responses, whether of the Th1/Th17 or Th2 type, must be regulated to ensure the survival of the host.

In mouse gastrointestinal parasitic infections, there is particularly strong evidence for the involvement of Tregs. A dramatic consequence of infection with *H. polygyrus* is the expansion and

activation of regulatory T cells in both the lamina propria (199) and draining lymph nodes (88, 230). A less-well-defined population of $CD8^+$ Tregs also expands in the lamina propria of *H. polygyrus*-infected mice (199). Excretory/secretory products of *H. polygyrus* (HES) can induce Treg differentiation *in vitro*, through the TGF-β pathway (100), and the inhibition of TGF-β receptor (TGF-βR) signaling *in vivo* leads to the expulsion of worms and a heightened Th2 response in chronically infected mice. The depletion of $Foxp3^+$ Tregs during *H. polygyrus* infection in DEREG mice (which express the diphtheria toxin receptor under the control of the Foxp3 promoter) increases Th2 responses without increasing resistance to the parasite, at least when assessed at the early time point of day 14 postinfection (231).

An expansion of $CD4^+$ $Foxp3^+$ Tregs is also seen in other gastrointestinal parasite infections of mice, including *Strongyloides ratti* in the intestine (28), and around the muscle-stage larvae of *Trichinella spiralis* (25) or in the spleen of rats similarly infected (104). The depletion of Tregs in DEREG mice immediately after infection with *S. ratti* resulted in the expression of protective immunity (28), but the depletion of Tregs using anti-CD25 antibody during *T. spiralis* infection results only in increased Th2 responses without affecting parasite burden. However, the ablation or blockade of both IL-10 and TGF-β (presumably from a non-Treg source) does increase resistance to the parasite (25).

In *T. muris* infections, Tregs accumulate in the lamina propria. Depletion using anti-CD25 antibody does not enhance worm expulsion but provokes increased gut pathology, indicating that conventional Tregs in this infection control pathological but not effective antiparasite immune responses (60). *T. muris* infection was also recently shown to induce the expansion of suppressive IL-35-producing $CD4^+$ $Foxp3^-$ "Tr35" cells in the intestine (49). Whether these are a common feature of parasitic infections or unique to *T. muris* remains to be established.

Regulatory B Cells

As well as their prototypic role in producing antibodies, B cells also produce inflammatory and immunoregulatory cytokines, as in the example of IL-10-producing B cells (sometimes known as B10 cells or Bregs), which can control autoimmune disorders such as experimental autoimmune encephalomyelitis (EAE) in mice (87). Suppressive B cells are activated during murine infections with *S. mansoni* (260) and *H. polygyrus* (305); in the latter case, Bregs from infected IL-10-deficient mice suppressed allergy and autoimmunity in uninfected recipients. However, in *S. mansoni* infections, IL-10 was found to be essential for suppression (260). Furthermore, the transfer of *S. mansoni*-induced Bregs induced the recruitment of $Foxp3^+$ Tregs to the inflammatory airways in an IL-10-dependent manner (4). IL-10 in *S. mansoni* infection was further shown to be important both for the expansion of IgG1-producing plasma cells in the liver and for the suppression of granulomatous responses during chronic infection. These results could be replicated in mice lacking the ability to class switch antibody (82). Thus, both immunoregulatory cytokine production and antibody production by B cells are important for immunomodulation in chronic schistosome infections.

Although definitive Breg surface markers or transcription factors in mice or humans have yet to be identified, recent work indicated that TIM-1 may be restricted in expression to Bregs (66). Future studies of Bregs using this or other markers may be able to define their mode of activity, and their dialogue with other regulatory cell populations, much more closely.

THE HYGIENE HYPOTHESIS IN MICE

The inverse relationship of allergy, autoimmunity, and inflammatory bowel diseases with parasitic infections in humans has attracted much attention as the hygiene hypothesis has evolved (see "the Hygiene Hypothesis"). Mouse models of parasitic infection and immune pathology are ideal for testing the mechanistic relationship between infection, pathology, and immune status, as reflected in studies investigating this relationship (Tables 2 and 3 and Fig. 3).

Allergy

A wide range of helminth species have been demonstrated to modulate allergic responses (78, 303), most notably the intestinal nematode *H. polygyrus*, which suppresses IgE and anaphylaxis in a model of dietary peanut allergy (23) as well as airway hyperresponsiveness, lung histopathology, eosinophil recruitment, and Th2 cytokines in alum-sensitized models of airway allergy (111, 304). The suppression of allergy was dependent on $CD25^+$ Tregs but was unaffected by anti-IL-10R treatment and could be transferred from infected, allergen-naive mice to uninfected, allergen-sensitized mice with $CD4^+$ cells, $CD4^+$ $CD25^+$ Tregs (304), or B cells (305). However, a subsequent study found that the suppression of airway allergy in *H. polygyrus* infection was lost in IL-10-deficient mice, indicating that IL-10 may play an important role in some settings (146). Interestingly, the same parasite is unable to modulate skin allergy, although this was tested some 10 weeks following infection of mice (111). As mentioned above, *H. polygyrus* excretory/secretory products (HES) can induce Tregs *in vitro* through the TGF-βR pathway. The transfer of Tregs induced *in vitro* by HES, or by mammalian TGF-β, also abrogated airway allergic inflammation, confirming the ability of helminth-induced Tregs to suppress allergic pathology (100). When administered with an allergen *in vivo*, HES can also abolish the subsequent allergic response to airway challenge (193).

Filarial parasites similarly suppress pathology in allergy models. The implantation of *L. sigmodontis* adults into the peritoneal cavity of mice reduces airway allergy upon subsequent sensitization and challenge (67). Both TGF-β and $CD25^+$ Tregs are enhanced in this system, although the depletion of these factors *in vivo* affected only physiological hyperreactivity and not tissue inflammation. Recombinantly expressed filarial cystatin (Av17, from the related species *Acanthocheilonema viteae*) can also inhibit allergic pathology when coadministered at the time of allergen sensitization or, subsequently, prior to challenge in a macrophage-, IL-10-, and partially Treg-dependent manner (248).

Infection with the gastrointestinal helminth *N. brasiliensis* prior to (but not after) allergen sensitization also blocked eosinophil recruitment to the lungs in an IL-10-dependent manner (307). However, in this model, *N. brasiliensis* stimulates an allergic response against its own components. As previous work established that hookworm-secreted proteases degrade eotaxin (59), it would be interesting to know if the related pathogen *N. brasiliensis* used a similar mechanism to suppress eosinophil accumulation. The excretory/secretory products of *N. brasiliensis* (NES), moreover, can potently suppress eosinophil infiltration, Th2 cytokines, anti-OVA IgE, and pathology (by histological scoring or plethysmography) when administered with a sensitizing allergen in a TLR2-

TABLE 2 Regulation of immunopathology by helminth infections in mice[a]

Parasite and model	Mechanism type	Reference(s)
Fasciola hepatica		
EAE	TGF–β dependent, IL–10 independent	294
Heligmosomoides polygyrus		
Peanut-specific food allergy	IL-10 dependent	23
House dust mite-specific airway allergy	Treg dependent, IL-10 independent	304
	Breg dependent, IL-10 independent	305
OVA-specific airway allergy	Treg dependent, IL-10 independent?[g]	111, 146, 304
NOD diabetes	Treg and IL-10 independent	167
NOD diabetes		247
EAE	Breg dependent (IL-10 independent)	305
TNBS colitis		273
	IL-10 dependent	254
IL-10-deficient T cell transfer colitis	IL-10 independent	107
IL-10-deficient piroxicam-induced colitis	$CD8^+$ cell dependent, IL-10 independent	76, 199
OVA-specific colitis		163
Hymenolepis diminuta		
Col II-specific arthritis	IL-4Rα, CD4, and IL-10 dependent	256
DNBS colitis	Macrophage and IL-10 dependent	129, 130
Litomosoides sigmodontis		
OVA-specific airway allergy[b]	TGF-β and $CD25^+$ Treg independent	67
NOD diabetes	TGF-β dependent; Th2, IL-10, and $CD25^+$ Treg independent	126, 127
Nippostrongylus brasiliensis		
OVA-specific airway allergy[c]	IL-10 dependent	307
Schistosoma japonicum		
Col II-specific arthritis[d]		114
TNBS colitis		319
Schistosoma mansoni		
Penicillin-specific anaphylaxis[d]	IL-10-producing Breg dependent; Treg, macrophage, and TGF-β independent	185
OVA-specific airway allergy[d,e,f]	$CD1d^{hi}$ B cell-dependent, IL-10-dependent expansion of Tregs[e]	186
	T or B cells transferred protection, IL-10 dependent[d]	4[e]
	$CD25^+$ Treg dependent (IL-10 independent)[f]	260[d]
		217[d,f]
NOD diabetes[d,f]		50[d]
	NKT cell dependent[f]	317[f]
Col II-specific arthritis[d]		215
DSS colitis[e]	Macrophage and IL-10 dependent (but not alternatively activated macrophages)	259
TNBS colitis[e]		204
Symphacia obvelata		
CFA-induced arthritis		221
Trichinella spiralis		
NOD diabetes		247
DNBS colitis		141
EAE	Dose dependent, transferred with splenocytes	104, 105

[a] EAE, experimental autoimmune encephalomyelitis; OVA, chicken egg ovalbumin; NOD, nonobese diabetic; TNBS, trinitrobenzene sulfonic acid; DNBS, dinitrobenzene sulfonic acid; TGF-β, transforming growth factor β; Treg, regulatory T cell; Breg, regulatory B cell; NKT, natural killer T; Col II, collagen II.
[b] *L. sigmodontis* adults implanted into peritoneal cavity prior to OVA-alum injection.
[c] Dependent on infection time: suppresses only when infection is prior to but not after sensitization.
[d] Mixed-sex infection.
[e] Male-only infection.
[f] Egg injection.
[g] IL-10-independent suppression in reference 304, and IL-10-dependent suppression in reference 146.

and TLR4-independent manner (283). A number of other helminth products can similarly interfere with allergen priming, including whole-body extracts of the human roundworm *Ascaris suum* (166) and a purified product (PAS-1) that suppresses allergic responses induced by another component of the same parasite (135).

Schistosomes are also potent inhibitors of allergies in mice, and animals infected with *S. mansoni* show attenuated cellular and

TABLE 3 Regulation of immunopathology by helminth products in mice[a]

Parasite and preparation	Model	Mechanism(s)	Reference(s)
Acanthocheilonema viteae			
Recombinant Av17 cystatin	OVA–specific airway allergy	Macrophage and IL–10 dependent, partially Treg dependent	248
Recombinant Av17 cystatin	DSS colitis		248
ES-62	Collagen-induced arthritis, airway allergy	Multiple interactions with B cells, dendritic cells, mast cells, and T cells	108, 190
Ancylostoma caninum			
ES	TNBS colitis		238
Ancylostoma ceylanicum			
ES or adult worm antigen	DSS colitis		41
Anisakis simplex			
Macrophage migration-inhibitory factor homolog	OVA-specific airway allergy	Increased IL-10, TGF-β, and Tregs	218
Ascaris suum			
Adult worm antigen	OVA-specific airway allergy		166
Ascaris suum PAS-1	*A. suum* APAS-3-specific allergy		135
Clonorchis sinensis			
Type 1 cystatin	DSS colitis		136
Heligmosomoides polygyrus			
ES	OVA-specific airway allergy	Induces Tregs *in vitro*, which suppress upon transfer	100
Hymenolepis diminuta			
Adult worm antigen	DNBS colitis	IL-10 independent	138
Litomosoides sigmodontis			
Adult worm antigen	NOD diabetes		127
Nippostrongylus brasiliensis			
ES	OVA-specific airway allergy	Dependent on protein fold; independent of TLR2/4 signaling and IL-10	283
Schistosoma japonicum			
SEA	OVA-specific airway allergy		311
Schistosoma mansoni			
SEA or SWAP	NOD diabetes	Increased NKT cells, galectin-1/3, TGF-β, and Tregs	314, 315, 317
SEA	EAE	Switch of EAE response from Th1 to Th2	320
SWAP	TNBS colitis		238
Toxascaris leonina			
Galectin-9 homolog	DSS colitis		143
Trichinella spiralis			
Homogenized muscle stage larvae	DNBS colitis		206
Recombinant TsP53	TNBS colitis		70

[a] ES, excretory/secretory products; SEA, soluble egg antigen; SWAP, soluble worm adult preparation; OVA, chicken egg ovalbumin; DSS, dextran sulfate sodium; DNBS, dinitrobenzene sulfonic acid; EAE, experimental autoimmune encephalomyelitis; TNBS, trinitrobenzene sulfonic acid; APAS-3, allergenic protein of *A.suum*; Treg, regulatory T cell; NKT, natural killer T; TGF-β, transforming growth factor β.

cytokine responses to allergen challenge (217, 260). Similarly, the administration of *S. japonicum* egg antigens to mice leads to the suppression of airway Th2 cytokines and responsiveness and histological inflammation, which was abrogated by the depletion of $CD25^+$ Tregs (311). However, the strength of protection depends on multiple factors, including the parasite load, the stage of infection, and the gender of the parasite (186, 260), as allergy is intensified in some settings. For example, productive (egg-laying) infections with *S. mansoni* exacerbated pathology, while male-only (and egg-free) infections suppressed allergen-specific lung re-

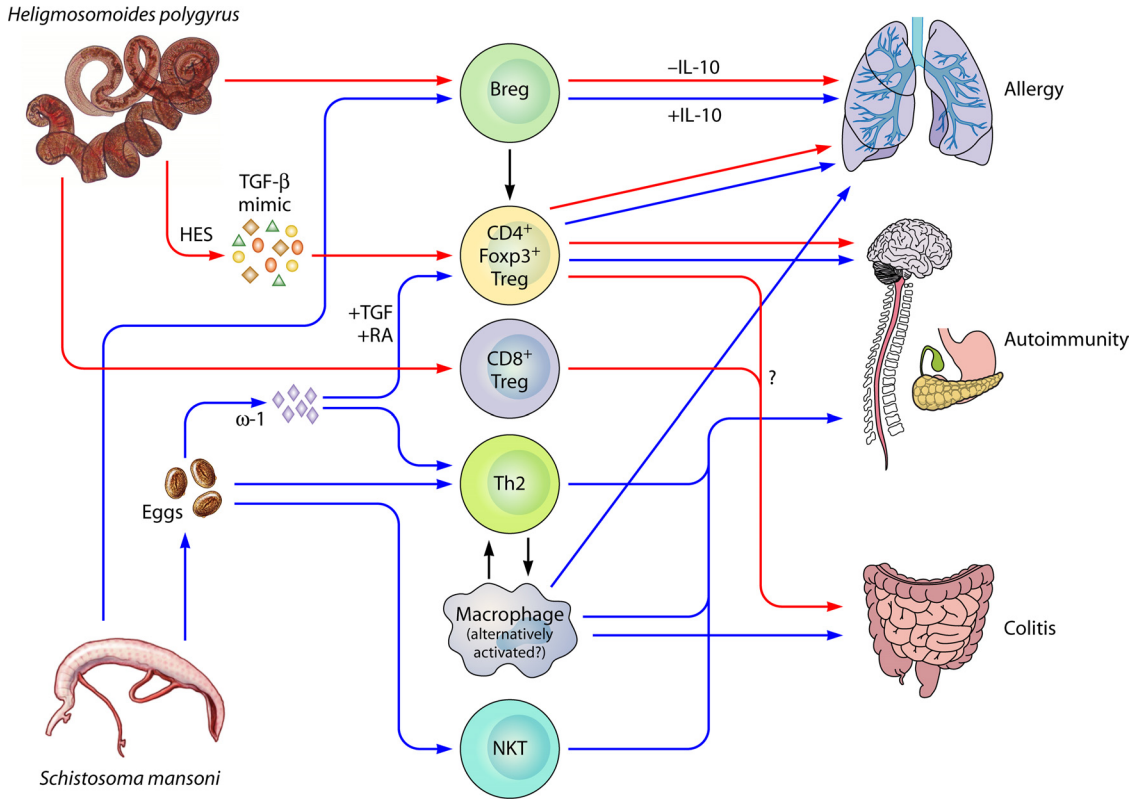

FIG 3 Suppressive mechanisms of *Heligmosomoides polygyrus* and *Schistosoma mansoni* on immunopathologies. Of all the helminths that infect mice, the effects of *H. polygyrus* (red arrows) and *S. mansoni* (blue arrows) on immunopathology models have been best characterized. Both parasites effectively suppress immune responses and pathology in models of allergy, autoimmunity, and colitis. $CD4^+$ $Foxp3^+$ (Forkhead box p3) Tregs (regulatory T cells) are induced by both *H. polygyrus* and *S. mansoni* through secretory molecules affecting the TGF-β (transforming growth factor β) and/or retinoic acid pathways, and these Tregs can suppress all immunopathologies. Suppressive Bregs (regulatory B cells) are also induced by both parasites, and functional suppression has been shown in allergy and autoimmunity through B cell IL-10 production (*S. mansoni*) or an IL-10-independent mechanism (*H. polygyrus*). *H. polygyrus* has also been shown to induce a regulatory population of $CD8^+$ T cells in the gut, which may, along with $CD4^+$ $Foxp3^+$ Tregs, be involved in the suppression of colitis in an IL-10-independent, TGF-βR-dependent manner. *S. mansoni* eggs and their products (especially the RNase ω-1) are powerful Th2 (T helper type 2) inducers, and skewing toward a Th2 response is protective in some models of autoimmunity. Th2 cytokines also induce the alternative activation of macrophages, which are functionally suppressive. Macrophages induced by *S. mansoni* infections (whether alternatively activated or not) are suppressive in all models of immunopathology studied. Finally, *S. mansoni* eggs induce the expansion of NKT (natural killer T) cells, which are deficient in the diabetic NOD mouse, and protect against disease.

sponses in a CD4-independent and IL-10- and B cell-dependent manner (186). Protection from allergy correlated quantitatively with the worm burden, and only the most highly infected animals were significantly suppressed (261), a finding which resonates with a recent study of *S. haematobium*-infected humans showing that the suppression of atopy correlated with infection intensity (236).

These subtle but crucial factors may explain why mechanistic insights into the *S. mansoni*-associated suppression of allergy differ between studies. Thus, Pacifico et al. showed that protection by *S. mansoni* was unchanged with anti-IL-10R administration, while Treg depletion using anti-CD25 antibody abrogated the suppression of eosinophil recruitment to the lungs (217). However, other authors reported that protection against allergy by *S. mansoni* is IL-10 dependent and could be transferred with B cells (4, 185) and, in one study, by $CD4^+$ T cells (260).

Autoimmunity

Multiple models of autoimmunity in rodents have revealed the suppressive capability of helminths in Th1/Th17-mediated immunopathologies (78, 189). An early example of this interaction was reported for rats infected with the nematode parasite *Symphacia obvelata*, in which complete Freund's adjuvant (CFA)-induced arthritis was reduced (221). In type II collagen-induced arthritis (CIA), infection with *S. mansoni* reduced collagen II-specific antibodies and inflammatory cytokine production, while pathology negatively correlated with parasite burden (215). Similarly, *S. japonicum* was also shown to suppress CIA; however, in a stage-specific manner, early-stage infection (2 weeks postinfection) significantly suppressed arthritis, collagen II-specific antibody titers, and inflammatory cytokine production, while productive egg-laying infection (7 weeks postinfection) had no effect (114). Thus, the schistosome suppression of arthritis pathology may depend on a lack of egg-induced inflammation, as seen in asthma models of *S. mansoni* infection (186). The rat tapeworm, *Hymenolepis diminuta*, also downregulates CFA-induced arthritis in mice in an IL-4Rα-, CD4-, and IL-10-dependent manner, consistent with suppression being due to Th2 induction in these mice (256). Collagen-induced arthritis can also be alleviated by the filarial nematode molecule ES-62 (190). This modulator has direct effects on T cells, B cells, and innate cells, acting by altering intracellular signaling (108).

Nonobese diabetic (NOD) mice develop spontaneous diabetes over the first 6 months of life. Infection with *H. polygyrus* (167, 247), *T. spiralis* (247), *L. sigmodontis* (126, 127), or *S. mansoni*, either by live infection (50) or by nonliving schistosome (314, 315, 317) or filarial (127) antigen administration, delays onset or ameliorates disease in these mice. Proposed mechanisms of protection by live infection include a skewing of the inflammatory response toward Th2 cells (50, 247) or a TGF-β-dependent mechanism independent of Th2 cells, Tregs, or IL-10 (126). *S. mansoni* egg antigens may confer protection by the expansion of invariant natural killer T (iNKT) cells (which are deficient in NOD mice) (317) or by the expansion of Tregs, cell-bound TGF-β, or alternatively activated macrophages (314, 315).

The development of pathology in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis can be ablated by many parasites, as first shown with *S. mansoni* (153, 255). During *H. polygyrus* infection, B cells transfer protection against EAE in an IL-10-independent manner, similar to the B cell-mediated suppression shown in asthma (305). In rats, EAE pathology is controlled by *T. spiralis* infection in a dose-dependent manner by a mediator that could be transferred with nylon wool-depleted, T cell-enriched splenocytes (105). *S. mansoni* SEA administration is beneficial, as it skews the antimyelin response from Th1/Th17 to Th2 (320). Infection with the liver fluke *Fasciola hepatica* also results in a delayed onset and an ameliorated pathology of EAE through an IL-10-independent, TGF-β-dependent mechanism, while the control of the antiparasite response is IL-10 dependent (294). Thus, multiple mechanisms may control parasite-specific and bystander immunosuppression. Not all parasitic infections control EAE, however, as infection of rats with *Strongyloides venezuelensis* did not alter EAE progression by any of the parameters measured (44).

As helminth parasites can be thought of as long-term xenotransplants, the possibility that they would prolong allogeneic transplants in animals has been investigated. Notably, kidney allograft survival in rats was prolonged 3-fold by infection with *N. brasiliensis*, which caused a marked reduction in numbers of graft-infiltrating $CD8^+$ T cells and an overall increase in IL-4 levels (161). A similar shift was achieved by administering whole-worm extract prior to grafting, suggesting that the induction of a potent Th2 response was able to inhibit the $CD8^+$ T cell-mediated transplant rejection. That same group subsequently demonstrated that cardiac transplant survival in mice was similarly promoted by *N. brasiliensis* and provided evidence that infection shifted the $CD8^+$ T cell population into a type 2 ("Tc2") state (168).

Inflammatory Bowel Disease

Human inflammatory bowel diseases represent important and often severe pathologies, including ulcerative colitis and Crohn's disease (128). Several mouse models for IBD-like colitis differ in their speed of onset, severity, chronicity, location of inflammation, and mechanism of action, depending on the relative contributions of the adaptive immune system, the innate immune system, and/or commensals in the gut (77, 78, 306). In largely innate cell-mediated dextran sulfate sodium (DSS) colitis, male-only *S. mansoni* infections (similarly to protection in airway allergy [186]) could suppress pathology through a macrophage- and IL-10-dependent mechanism (259). In T cell-dependent trinitrobenzene sulfonic acid (TNBS)-induced colitis, schistosome infections (204), eggs (75, 319), or whole-adult-worm extract (238) suppressed pathology and Th1/Th17 cytokines and induced the Th2 cytokines IL-10 and TGF-β.

H. polygyrus can similarly counteract pathology in bacterially induced colitis (301), TNBS-induced colitis (273), T cell transfer colitis (107), and spontaneous colitis in IL-10-deficient (76) but not TGF-βR-compromised (133) mice. Thus, the suppressive effects of *H. polygyrus* appear to depend on TGF-βR, but not IL-10R, signaling.

The administration of *Ancylostoma* hookworm excretory/secretory products can also suppress DSS-induced (41) and TNBS-induced (238) colitis, and products of the tapeworm *Hymenolepis diminuta* are able to dampen pathology in T cell-mediated dinitrobenzene sulfonic acid (DNBS)-induced colitis (138). The downregulatory effects of *H. diminuta* were found to be dependent on alternatively activated macrophage induction, and in fact, the administration of alternatively activated macrophages could protect against colitis in naive mice (130). Intriguingly, remission in human Crohn's disease was also found to be associated with the accumulation of alternatively activated macrophages in the gut, further highlighting their wound-healing role (130). Filarial recombinant Av17 cystatin could also suppress DSS-induced colitis, and although the mechanism of protection against colitis was not dissected, protection against airway allergy using this protein was macrophage and IL-10 dependent and partially Treg dependent (248).

T. spiralis infection, or administration of *T. spiralis* antigens into the rectal submucosa, suppresses pathology in DNBS-induced colitis (141, 206). Recently, this effect was replicated in the TNBS-induced colitis model with the subcutaneous administration of rTsP53, a 53-kDa protein of *T. spiralis* (70).

Although the suppressive effects of administering helminth infection or helminth products have focused largely on immunoregulatory mechanisms, an important mechanism of protection may be goblet cell hyperplasia and increased mucous production seen in antiparasite responses, which could also ameliorate the barrier defect seen in inflammatory bowel diseases (308).

HELMINTH THERAPY IN HUMANS

The epidemiological and immunological evidence for the suppression of immune dysregulatory diseases such as allergy, autoimmunity, and inflammatory bowel disease has led to several clinical trials of treatment with live helminth parasites (Table 4). These trials can be seen as the ultimate test for the hygiene hypothesis: if parasitic infection prevents immune dysregulation, then infection of affected individuals with parasites should cure disease. However, a number of caveats should be borne in mind when assessing these trials.

First, individuals who live in areas where helminth disease is endemic are exposed to parasitic infections from an early age (and potentially in the womb), prior to the development of immune dysregulatory disease. Therefore, parasitic infection may be required at an early age to encourage the appropriate development of the immune system. Due to ethical and practical considerations, most clinical trials have been carried out on individuals already affected by immune dysregulatory disease, and it may be much more difficult to suppress an ongoing reaction than prevent its development.

Second, due to ethical considerations, many trials using parasitic infection must use an asymptomatic dose (for example, in *N. americanus* infections), which may be much lower than that re-

TABLE 4 Regulation of immunopathology in human trials[a]

Disease	Parasite treatment (regimen)	No. of subjects	Effect(s)	Reference(s)
Allergic rhinitis	*Trichuris suis* (2,500 ova every 3 wk for 24 wk)	96 (49 infected, 47 placebo)	No change in clinical disease	19
Allergic rhinoconjuctivitis	*Necator americanus* (10 larvae)	30 (15 infected, 15 placebo)	No clinical benefit; no suppressive immune response or reduction of allergic immune response	30, 84
Celiac disease	*Necator americanus* (15 larvae total)	20 (10 infected, 10 placebo)	No clinical benefit; suppression of intestinal inflammatory cytokines	61, 191
Crohn's disease	*Necator americanus*	9 (all infected)	Trend toward reduced disease; CDAI at baseline, 165; CDAI at wk 20 postinfection, 64 ($P = 0.132$)	58
Crohn's disease	*Trichuris suis* (2,500 ova every 3 wk for 24 wk)	29 (all infected)	Significant suppression of pathology; 79.3% response, 72.4% remission	270
Crohn's disease and ulcerative colitis	*Trichuris suis* (2,500 ova initially, boosts of 2,500 ova every 3 wk)	CD, 4 infected, 2 given boost; UC, 3 infected, 2 given boost	CD, 3/4 patients entered remission; UC, 3/3 improved (mean, 43% improvement)	269
Ulcerative colitis	*Trichuris suis* (2,500 ova every 2 wk for 12 wk)	52 (29 infected, 23 placebo)	Significant suppression of pathology; UCDAI, 8.75–7.5 for placebo ($P = 0.1167$), 8.77–6.1 for infected ($P = 0.0004$); simple index, no change for placebo ($P > 0.05$), decrease for infected ($P < 0.0001$)	271
Ulcerative colitis	*Trichuris trichiura* (500, 1,000, and 200 eggs)	1 (infected)	Disease remission after infection; downregulation of mucosal inflammatory cytokines; switch to IL-22	36
Multiple sclerosis	Various (3 *Hymenolepis nana*, 3 *Trichuris trichiura*, 3 *Ascaris lumbricoides*, 2 *Strongyloides stercolaris*, 1 *Enterobius vermicularis*)	24 (12 infected, 12 matched controls)	Significantly fewer exacerbations when infected; drug cure of 4 patients[b] led to increase of symptoms to uninfected control levels; MARR, 0 for infected, 1.09 for uninfected ($P < 0.0001$); increase after drug cure, $P = 0.007$; decreased inflammatory cytokine levels, increased IL-10, TGF-β, and Treg levels with parasitic infection	55-57
Multiple sclerosis	*Trichuris suis* ova (2,500 ova every 2 wk for 24 wk)	5 (all infected)	Trend toward reduced disease; no change in peripheral Tregs or alternatively activated macrophages	26, 89

[a] CDAI, Crohn's disease activity index; CD, Crohn's disease; UC, ulcerative colitis; UCDAI, ulcerative colitis disease activity index; MARR, median annual relapse rate.
[b] Two patients were infected with *A. lumbricoides*, 1 was infected with *T. trichiura*, and 1 was infected with *S. stercolaris*.

ceived during natural infections (205) and may not be efficacious in suppressing pathology. Finally, good quality controls are often unavailable, if they are used at all. Where blinded matched controls are used, participants may realize that they are infected due to mild symptoms associated with infection, such as skin rash, cough, and gastrointestinal symptoms (20, 205). A placebo effect is therefore difficult to discount in many trials. Nevertheless, trials have been ongoing for the last 10 years, beginning with the administration of *Trichuris suis* ova (TSO) in inflammatory bowel disease by Summers et al. (269). Since this success, many other trials have been carried out, using *T. suis* ova or *T. trichiura* or *N. americanus* infections.

The first published clinical trial tested TSO in Crohn's disease and ulcerative colitis patients (269). *T. suis* is the pig whipworm, which, although closely related to the human whipworm, *T. trichiura*, cannot maintain a chronic infection in humans and is ejected within a few weeks. Thus, TSO treatment regimens consist of repeated administration every 2 to 3 weeks. In the first trial, TSO treatment showed a trend toward the suppression of both Crohn's disease and colitis (269), which led to further larger-scale trials for Crohn's disease (270) and a placebo-controlled trial for ulcerative colitis (271), both of which showed a significant suppression of disease.

More recently, TSO therapy has been used in allergic rhinitis,

with no change in clinical symptoms (19). Some researchers have argued that this may be due to the timing of the treatment, as it was initiated only just prior to the pollen season and, hence, allergen exposure (272), or to the low dose of parasites at a site distant from pathology (115). In addition, a trial for multiple sclerosis showed a trend toward reduced numbers of new lesions by magnetic resonance imaging (89). However, no changes in inflammatory or regulatory cytokines or cells were seen, and the mechanism of action of TSO treatment remains unknown. *T. suis* ova are now produced under good manufacturing practice (GMP) guidelines and are available commercially (Ovamed GmbH). Clinical trials are also now planned (http://clinicaltrials.gov/) for the use of TSO for allergies to peanuts and tree nuts (clinical trial identifier NCT01070498) and irritability in autism (clinical trial identifier NCT01040221).

T. suis is a swine parasite that is not adapted to humans and causes significant side effects, including gastrointestinal upset and diarrhea (20). These symptoms appear to abate after several weeks of treatment, implying a suppression of the inflammatory response in the gut during chronic stimulation. Some researchers have turned to human pathogens for an alternative to TSO, and several studies using human hookworm have been carried out. Hookworms have been linked most strongly of all parasites studied to the suppression of asthma in populations living in an area of endemicity (162), and at low levels experimental infections can be tolerated without significant pathology (205). As hookworm is a human-adapted parasite, it also maintains chronic infections for months to years, with the life span of the adult worm alone being between 1 and 18 years (37).

The first clinical trial of hookworms as a therapeutic agent was for Crohn's disease, where infection resulted in a trend toward decreased pathology in an unblinded open-label trial (58). Subsequently, trials for celiac disease (61) and allergic rhinoconjunctivitis (85) have been carried out. Although neither of these small-scale trials showed a significant suppression of pathology, the celiac disease trial did show some suppression of inflammatory cytokines in the gut (191), associated with a switch to a gluten-specific Th2 response (191). Thus, it remains to be seen whether human hookworm infection will be a viable option for the treatment of human immunopathologies.

Although clinical trials using helminth infection have yielded interesting prospects for the treatment of immune dysregulatory disease, the ultimate goal of this work is to identify the molecular mechanism by which parasites achieve this and to replicate this using a commercially produced drug. An intermediate step in this process is the use of parasite-derived products to replicate the protective effect of the infection and, thus, identify individual molecular motifs responsible for suppression. Although positive results have come from administering parasite products in mouse models of immune dysregulatory disease (Table 3), no parasite products have yet been administered as treatments for human disease.

CONCLUSIONS

Immunoregulation by helminths is now understood to be a major survival mechanism that has evolved through the close host-parasite relationship over eons of time (3). Moreover, many exciting immunological insights and therapeutic possibilities are developing from the study of helminth parasites. Epidemiological indications of a protective effect against some of the maladies of the industrialized world have been supported by in-depth field studies as well as extensive laboratory experimentation. This information now suggests future strategies which can exploit both the general principles elucidated and the specific modulatory mediators discovered for the control of both infectious and immunopathological diseases.

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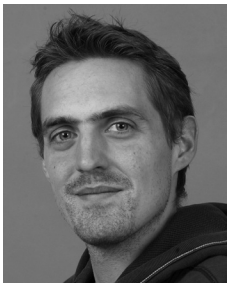

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Rick M. Maizels is in the University of Edinburgh's Institute of Immunology and Infection Research. He is an immunologist interested in fundamental questions of how and why parasites manipulate the sophisticated mammalian immune system and how that system has evolved in the face of parasite immunomodulatory strategies. His laboratory (http://maizelsgroup.biology.ed.ac.uk/) focuses on the most complex parasites to invade the body, multicellular helminths, which cause widespread tropical diseases while displaying a profound immunoregulatory capability. The central questions which his group addresses are (i) how do parasites manipulate the host immune system, (ii) what is the impact of this modulation on immunological diseases, and (iii) what parasite molecules are responsible for immunomodulation? Before taking the Chair of Zoology at Edinburgh in 1995, Dr. Maizels was Professor of Parasite Immunology at Imperial College London, where he moved in 1983. Prior to this, he held positions at the National Institute for Medical Research in London (1973 to 1976 and 1979 to 1983) as well as the University of California, Los Angeles (1977 to 1979), and the California Institute of Technology (1976 to 1977).