Coinfection with the Intestinal Nematode *Heligmosomoides polygyrus* Markedly Reduces Hepatic Egg-Induced Immunopathology and Proinflammatory Cytokines in Mouse Models of Severe Schistosomiasis

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Infection with the trematode helminth *Schistosoma mansoni* results in a parasite egg-induced, CD4 T-cell-mediated, hepatointestinal granulomatous and fibrosing inflammation that varies greatly in severity, with a higher frequency of milder forms typically occurring in regions where the disease is endemic. One possible explanation for this is that in these regions the degree of inflammation is lessened by widespread concurrent infection with gastrointestinal nematodes. We tested this hypothesis by establishing a murine coinfection model in which mice were infected with the intestinal nematode parasite *Heligmosomoides polygyrus* prior to infection with *S. mansoni*. In CBA mice that naturally display a severe form of schistosomiasis, preinfection with *H. polygyrus* resulted in a marked reduction in schistosome egg-induced hepatic immunopathology, which was associated with significant decreases in the levels of interleukin-17 (IL-17), gamma interferon, tumor necrosis factor alpha, IL-23, IL-6, and IL-1β and with increases in the levels of IL-4, IL-5, IL-10, and transforming growth factor β in mesenteric lymph node cells, purified CD4 T cells, and isolated liver granuloma cells. There were also increases in liver Ym1 and forkhead box P3 transcription factor expression. In another model of high-pathology schistosomiasis induced in C57BL/6 mice by immunization with schistosome egg antigens in complete Freund’s adjuvant, coinfection with the nematodes also resulted in a marked inhibition of hepatic immunopathology accompanied by similar shifts in cytokine production. These findings demonstrate that intestinal nematodes prevent Th1- and Th17-cell-mediated inflammation by promoting a strong Th2-polarized environment associated with increases in the levels of alternatively activated macrophages and T regulatory cells, which result in significant amelioration of schistosome-induced immunopathology.

Nearly one-half of the world’s human population is infected with one or more of a variety of parasitic helminths. A majority of the infections are with gastrointestinal helminths, and they occur mostly in tropical developing regions. It also has been observed that the highest density of helminth infections coincides with the lowest incidence of allergic and autoimmune diseases. This observation has prompted the formulation of the “hygiene hypothesis,” which states that living in an exceedingly clean environment predisposes humans to such conditions and that helminth infections can prevent and protect against the development of aberrant adaptive immune responses to normally nonimmunogenic foreign or self antigens (12, 19, 41, 74, 75). This idea has been greatly strengthened by supporting evidence obtained using experimental models of asthma (34), type 1 diabetes (17, 58, 76), experimental allergic encephalomyelitis (37, 59), Graves’ thyroiditis (51), and inflammatory bowel disease (22). Predictably, coinfections with helminths also lessen proinflammatory responses against other pathogens, usually resulting in reduced overall immunopathology, albeit sometimes at the risk of diminished protection (21, 50, 52, 62, 66, 68, 73). The ameliorating effect of helminths on disease susceptibility or magnitude has been attributed to the ability of these organisms to down-modulate the level of inflammation through induction of anti-inflammatory Th2-type cells and T-regulatory cells (Treg), as well as alternatively activated macrophages (AAM) (4).

Schistosomes are blood-dwelling trematode helminths that cause disease by eliciting a host granulomatous and fibrosing inflammatory reaction against tissue-trapped parasite eggs, which in the case of *Schistosoma mansoni* takes place in the liver and intestines. The immunopathology in schistosomiasis is mediated and orchestrated by CD4 T cells specific for schistosome egg antigens (SEA), and its severity varies greatly from person to person, as well as among inbred mouse strains. In human “hepatosplenic” schistosomiasis, severe liver pathology causes splenomegaly, portal hypertension, and death, whereas in the more prevalent “intestinal” schistosomiasis, there is significantly milder liver pathology and clinical disease (10). In mouse models of schistosomiasis, the CBA strain develops pronounced granulomatous inflammation compared with the smaller lesions in the C57BL/6 (BL/6) strain (13, 56). However, disease severity in the low-pathology BL/6 mice can be mark-

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edly exacerbated by concomitant immunization with soluble SEA in complete Freund’s adjuvant (CFA) (SEA/CFA) (55). Both the natural and induced forms of severe schistosomiasis correlate with high levels of the proinflammatory cytokines gamma interferon (IFN-γ) and interleukin-17 (IL-17) (55–57) indicative of the Th1 and Th17 subpopulations of CD4 T lymphocytes, respectively, although the IL-23-driven Th17 subset has recently been shown to be a more potent mediator and faithful indicator of severe disease (54, 57). On the other hand, an unopposed Th2 response signaled by the production of IL-4, IL-5, IL-10, and IL-13 results in a milder pathology (55), although there is a risk of increased hepatic fibrosis at a late stage of the disease, mainly through the action of IL-13 (15, 23).

The immunopathology in schistosomiasis is the product of a CD4 T-cell hypersensitivity reaction and as such shares mechanistic features with many T-cell-mediated autoimmune diseases. Moreover, the severity of schistosomiasis in individuals from areas where the disease is endemic is generally less than that in accidentally infected nonresidents (10, 18). We surmised that this could at least in part be due to the widespread coinfection with gastrointestinal helminths. To test this hypothesis, we established a murine coinfection model with S. mansoni and the intestinal hookworm nematode parasite *Heligmosomoides polygyrus* to examine the effect of concurrent nematode infection on the severity of schistosomiasis. *H. polygyrus* induces a strong host Th2-polarized response, which, in turn, is essential for subsequent worm expulsion (25, 65). We report here that administration of *H. polygyrus* prior to infection with schistosomes resulted in a marked reduction in hepatic egg-induced granulomatous inflammation in both the natural (CBA) and SEA/CFA-induced (BL/6) forms of high pathology. Disease amelioration correlated with significant decreases in the levels of proinflammatory cytokines in granuloma and mesenteric lymph node cells (MLNC).

**MATERIALS AND METHODS**

**Mice, parasites, infections, and immunizations.** Five- to six-week-old female CBA/J and BL/6 mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and maintained at the Animal Facility at Tufts University School of Medicine in accordance with the American Association for the Assessment and Accreditation of Laboratory Animal Care guidelines. CBA and BL/6 mice were infected by intraperitoneal injection of 85 cercariae of *S. mansoni* (Puerto Rico strain) obtained from infected Biomphalaria glabrata snails provided by Fred Lewis of the Biomedical Research Institute (Rockville, MD). Some mice were infected by gastric gavage with 40 third-stage larvae of *H. polygyrus* (U.S. National Helminthological Collection no. S1930) (69). Some BL/6 mice were also immunized by subcutaneous injection of 50 μg of SEA/CFA, as described previously (55). Treatment of BL/6 mice with SEA/CFA results in marked exacerbation of hepatic egg-induced immunopathology; either SEA or CFA by itself is ineffective at enhancing disease (55). SEA from *Biomphalaria glabrata* (Biotest, Arizona, AZ) was injected subcutaneously into groups of three to six mice.

**Experimental protocol.** CBA and BL/6 mice were infected with *S. mansoni* as described above. Some mice were also infected with *H. polygyrus* 4 weeks and again 2 days prior to infection with schistosomes. Some BL/6 mice were also immunized with SEA/CFA 1 day prior to and again 4 weeks after schistosome infection. All mice were sacrificed 7 weeks after schistosome infection and 11 weeks after the initial *H. polygyrus* infection.

**Cell preparations, cell cultures, and cytokine determinations.** Livers and mesenteric lymph nodes (MLN) were removed aseptically, and single-cell suspensions were prepared from MLN by teasing the tissues in complete RPMI 1640 medium supplemented with 10% fetal calf serum (Atlanta Biologicals), 4 mM L-glutamine, 80 U/ml penicillin, 80 μg/ml streptomycin, 1 mM sodium pyruvate, 10 mM HEPES, and 1X nonessential amino acids (all obtained from BioWhittaker), as well as 0.1% 2-mercaptoethanol. Erythrocytes were lysed by exposure to Tris ammonium chloride buffer (pH 7.2) (Sigma) for 15 min on ice. Cells were washed, and live cells that excluded trypan blue were counted and resuspended at the desired concentrations in complete RPMI 1640 medium. For purification of CD4 T cells, MLNC were negatively selected on CD4 MACS columns (Miltenyi Biotec) by following the manufacturer’s instructions. The resulting cell preparations contained >94% CD4+ cells as determined by flow cytometry. Granuloma cells (GC) were obtained by homogenization of the livers in a Waring blender, isolation of granulomas by sedimentation at 1 × g, extensive washing, and enzymatic digestion with 1 mg/ml of collagenase type H from Clostridium histolyticum (Sigma Chemical Co.). Bulk MLNC and GC suspensions (5 × 10⁶ cells/ml) or purified CD4 T cells from MLN (1 × 10⁶ cells/ml) plus normal irradiated syngeneic splenic antigen-presenting cells (APC) (4 × 10⁵ cells/ml) were incubated in the presence or absence of 15 μg/ml of SEA. After 48 h, the culture supernatants were removed, filtered, and stored at −36°C until they were analyzed by an enzyme-linked immunosorbent assay (ELISA). For IL-4, IL-5, IL-10, and transforming growth factor β (TGF-β), antibody, standard cytokines, and protocols were obtained from BD-PharMingen, and for IL-17, IFN-γ, and tumor necrosis factor alpha (TNF-α), antibody, standard cytokines, and protocols were obtained from R&D Systems, Inc.

**Hepatic immunopathology.** Sections of liver samples fixed in 10% buffered formalin and processed by routine histopathologic technique were stained with hematoxylin and eosin and examined by optic microscopy. The sizes of the granulomatous lesions were determined by computer-assisted morphometric analysis, as described previously (54). Ten to 20 granulomas were evaluated for each liver.

**Determination of worm and egg burdens.** The schistosome worm burden was assessed by perfusing the vasculature of infected mice with phosphate-buffered saline plus 25 mM sodium citrate. A small incision was made in the hepatic portal vein, and 20 ml of solution was injected into the aorta to flush out the worms. The worms were placed in medium and counted. The schistosome egg load was assessed by counting the number of eggs present in 1-mm³ fields of liver tissue in sections stained with hematoxylin and eosin.

**Real-time quantitative RT-PCR.** Total RNA was isolated from the livers of infected CBA mice using Trizol according to the manufacturer’s instructions (Invitrogen). RNA (1 μg) was subjected to DNase I treatment (Roche Molecular Biochemicals) and reverse transcribed using a high-capacity cDNA reverse transcription (RT) kit from Applied Biosystems. Real-time quantitative RT-PCR was performed with 10 ng of cDNA from each sample using either SYBR green analysis with a custom PCR array or Taqman analysis. All reactions were performed using an ABI 7300 instrument. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) levels were measured in a separate reaction and used to normalize the data. Reagents and protocols used for SYBR green and Taqman real-time quantitative RT-PCR were obtained from SuperArray Bioscience and Applied Biosystems, respectively. Using the average mean cycle threshold (Ct) value for GAPDH and the gene of interest for each sample, the following equation was used to obtain normalized values (14): 1.8&(Ct(GAPDH − Ct(gene of interest)) × 10⁻³².

**Statistical analysis.** Analysis of variance and Student’s *t* tests were used to determine the statistical significance of the differences among groups. A *P* value of <0.05 was considered significant. Each individual experiment was conducted with groups of three to six mice.

**RESULTS**

Coinfection with *H. polygyrus* and *S. mansoni* markedly reduces schistosome egg-induced immunopathology but does not affect the schistosome worm or egg burden in CBA mice. Naturally high-pathology CBA mice were infected with 40 *H. polygyrus* third-stage larvae 4 weeks and again 2 days prior to infection with schistosomes. This protocol was chosen in order to establish and maintain a Th2-dominant environment from the start of and throughout a subsequent 7-week schistosome infection (4, 25). Infection with *H. polygyrus* resulted in a marked reduction in the sizes of the hepatic granulomatous lesions induced by schistosome eggs (Fig. 1A). This inhibitory effect was strictly dependent on the sequence of the infections as it was completely abrogated when mice were infected simultan-
taneously with *H. polygyrus* and schistosomes or when *H. polygyrus* was inoculated after the schistosome infection (data not shown). *H. polygyrus* had no significant effect on the schistosome worm burden (Fig. 1B) or the number of eggs present per unit of area in the hepatic tissue (Fig. 1C), implying that the coinfection affected the host egg-induced immunopathology but not the schistosomes themselves.

**Coinfection with *H. polygyrus* causes a profound Th1/Th17-to-Th2 cytokine shift in schistosome-infected CBA mice.** *H. polygyrus* coinfection significantly reduced the intensity of the normally severe immunopathology displayed by schistosome-infected CBA mice. To assess the underlying changes in the immune response of these mice, we measured cytokine production in supernatants from SEA-stimulated bulk MLNC, CD4 T cells isolated from the MLNC, and GC after a 7-week schistosome infection. Compared with the mice infected only with schistosomes, there were significant decreases in SEA-induced cytokine production by bulk MLNC, CD4 T cells, and GC, which were generally restored or even increased in the presence of *H. polygyrus* coinfection with schistosomes or when *H. polygyrus* was inoculated after the schistosome infection (data not shown). *H. polygyrus* had no significant effect on the schistosome worm burden (Fig. 1B) or the number of eggs present per unit of area in the hepatic tissue (Fig. 1C), implying that the coinfection affected the host egg-induced immunopathology but not the schistosomes themselves.

**Coinfection with *H. polygyrus* causes upregulation of Ym1 and Foxp3 expression in schistosome-infected CBA mice.** The significant increases in the IL-4, IL-10, and TGF-β levels in the coinfected CBA mice prompted us to examine two likely mechanisms that may underlie the amelioration of egg-induced immunopathology. IL-4 has been shown to be critical for the development of AAM (26, 40, 44), and IL-10 and TGF-β have been associated with Treg development and function (3, 43, 71). Both AAM and Treg have previously been implicated in the control of excessive inflammation against the schistosome eggs (8, 30, 31, 46, 67). We examined the differential expression of the lectin Ym1, which is induced by IL-4 and signal transducer and activator of transcription 6 and serves as a marker of AAM (27, 40, 72), as well as the forkhead box P3 (Foxp3) transcription factor, which is a marker of Treg (24).

These findings suggest that early administration of *H. polygyrus* induces AAM and Treg, which are capable of inhibiting proinflammatory cytokines and thus preventing the development of severe egg-induced hepatic immunopathology.

**Coinfection with *H. polygyrus* and *S. mansoni* markedly reduces schistosome egg-induced immunopathology and promotes a Th2 shift in the cytokine response in SEA/CFA-immunized BL/6 mice.** Schistosome-infected BL/6 mice typically exhibit small hepatic egg granulomas; however, SEA/CFA immunization results in marked exacerbation of the lesions and sharp increases in the levels of IFN-γ and IL-17. This phenotype is similar to that seen in CBA mice, but because of the existence of suitable “knockout” mice with the H-2b background, the immunized BL/6 mice have been very useful for discerning the role of different genes in the induction of severe immunopathology (54, 55, 57). Using the same coinfection protocol, we investigated whether the presence of *H. polygyrus* affected the disease exacerbation resulting from immunization with SEA/CFA. Histologic analysis of the livers revealed that coinfection with *H. polygyrus* virtually abrogated the development of the severe immunopathology caused by SEA/CFA immunization, and the observed lesions were more comparable to those seen in the unimmunized BL/6 mice (Fig. 5). In addition, the marked increases in SEA-specific IL-17, IFN-γ, and TNF-α production by both MLNC and MLN-derived CD4 T-cell populations, as well as in GC populations (Fig. 2A). On the other hand, the levels of IL-4, IL-5, and IL-10 were considerably higher in the coinfected mice, and more pronounced increases were observed in the SEA-stimulated CD4 T-cell and GC cultures than in the bulk MLNC cultures; in turn, the increases in the level of TGF-β were greater in MLNC and GC than in CD4 T cells (Fig. 2B).

Significant decreases in the levels of IL-17, IFN-γ, and TNF-α induced by *H. polygyrus* in the schistosome-infected CBA mice were also observed at the mRNA level; importantly, the transcript levels of the innate immunity-associated proinflammatory cytokines IL-23, IL-6, and IL-1β, as well as the chemokines CXCL1 and CXCL2, were also markedly downregulated in the livers of the doubly infected mice (Fig. 3A). Conversely, in the coinfected mice there was marked upregulation of the IL-4 and IL-10 mRNA transcripts, as well as the mRNA transcripts of the chemokine CCL11 (Fig. 3B). These results indicate that the intestinal nematodes induced a strong Th2 shift in the Th1- and Th17-dominated response to schistosome infection in CBA mice.

**FIG. 1.** Hepatic immunopathology, worm burdens, and egg counts in CBA mice coinfected with *H. polygyrus* and *S. mansoni*. (A) Hepatic granulomatous inflammation, measured as described in Materials and Methods, was significantly decreased in CBA mice coinfected with *H. polygyrus* and *S. mansoni* compared with control CBA mice infected with *S. mansoni* alone. (B and C) There were no significant differences in the numbers of (B) *S. mansoni* worms or (C) *S. mansoni* eggs between CBA mice infected with schistosomes alone and CBA mice coinfected with *H. polygyrus*. Thirteen to 23 1-mm² fields were counted for each liver section, and 10 livers were counted for each mouse group. The immunopathology, worm, and egg data are representative of the results of two or three independent experiments. Sm, *S. mansoni*; Hp, *H. polygyrus*; ns, not significant.
FIG. 2. Cytokine production by SEA-stimulated bulk MLNC, CD4 T cells, and GC in CBA mice coinfected with *H. polygyrus* and *S. mansoni*. Cytokine levels in 48-h supernatants from SEA-stimulated bulk MLNC, CD4 T cells plus APC, and GC were measured by ELISA. (A) The levels of IL-17, IFN-γ, and TNF-α produced by bulk MLNC, CD4 T cells, and GC were significantly lower in CBA mice coinfected with *H. polygyrus* and *S. mansoni* than in CBA mice infected with *S. mansoni* alone. (B) The levels of IL-4 and TGF-β, but not the level of IL-5 or IL-10, produced by bulk MLNC were significantly higher in CBA mice coinfected with *H. polygyrus* and *S. mansoni* than in CBA mice infected with *S. mansoni* alone. IL-4, IL-5, and IL-10 production, but not TGF-β production, was significantly increased in CD4 T cells, and production of all four cytokines was significantly increased in GC. The bars indicate the means of triplicate determinations, and the error bars indicate the standard deviations; background cytokine levels from unstimulated cells were subtracted. The results shown are from one experiment that was representative of three experiments in which similar results were obtained. Sm, *S. mansoni*; Hp, *H. polygyrus*; ns, not significant.
lygyrus, although the differences were not always statistically significant (Fig. 6B).

**DISCUSSION**

Although widespread in mostly tropical regions, infection with a variety of parasitic helminths generally results in relatively low morbidity and even less mortality. In the case of infection with schistosomes, there is predictable severe disease in about 5 to 10% of the population, and residents of areas where the disease is endemic generally suffer from less symptomatic and milder clinical forms of the disease. The immunopathology in schistosomiasis is mediated by CD4 effector T cells, and the milder pathology settings have been widely at-

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FIG. 6. Cytokine production by SEA-stimulated bulk MLNC, CD4 T cells, and GC in SEA/CFA-immunized BL/6 mice coinfected with H. polygyrus and S. mansoni. Cytokine levels in 48-h supernatants from SEA-stimulated bulk MLNC, CD4 T cells plus APC, and GC were measured by ELISA. (A) The levels of IL-17, IFN-γ, and TNF-α produced by bulk MLNC, CD4 T cells, and GC were significantly lower in SEA/CFA-immunized BL/6 mice coinfected with H. polygyrus than in SEA/CFA-immunized BL/6 mice infected with S. mansoni alone. (B) The levels of IL-4, IL-5, and IL-10 produced by bulk MLNC were not significantly different in SEA/CFA-immunized mice coinfected with H. polygyrus and SEA/CFA-immunized mice infected with S. mansoni alone, but the level of TGF-β was higher in SEA/CFA-immunized mice coinfected with H. polygyrus than in SEA/CFA-immunized mice infected with S. mansoni alone. IL-4, IL-5, and IL-10 production, but not TGF-β production, by CD4 T cells was significantly greater in SEA/CFA-immunized BL/6 mice coinfected with H. polygyrus than in SEA/CFA-immunized BL/6 mice infected with S. mansoni alone, and the levels of all four cytokines were significantly greater in GC from SEA/CFA-immunized BL/6 mice coinfected with H. polygyrus than in GC from SEA/CFA-immunized BL/6 mice infected with S. mansoni alone. The bars indicate the means of triplicate determinations, and the error bars indicate standard deviations; background cytokine levels from unstimulated cells were subtracted. The results shown are from one experiment that was representative of three experiments in which similar results were obtained. Sm, S. mansoni; Hp, H. polygyrus; Imm, SEA/CFA immunization; ns, not significant.
tributed to the generation of host-protective immunoregulatory mechanisms linked to genetic predisposition (45, 78) or induced by transplacental passage of parasite antigen or anti-parasite antibody (7, 16, 48). In this study we tested the hypothesis that low pathology is at least in part determined by coinfection with intestinal nematodes. This hypothesis is based on the observations that nematode coinfection is prevalent in areas where schistosomiasis is endemic and that nematode infection creates a host immune environment associated with attenuated incidence of CD4 T-cell-dependent autoimmune diseases (19).

Using the murine model of schistosomiasis, we show here that coinfection with the trichostrongyle parasitic nematode _H. polygyrus_ resulted in significant inhibition of the natural (CBA) or SEA/CFA immunization-induced (BL/6) form of severe hepatic granulomatous inflammation caused by schistosome eggs. Coinfection with intestinal nematodes had no measurable effect on the viability or fecundity of the schistosomes. The reduction in disease intensity was accompanied by marked decreases in IL-17, IFN-γ, and TNF-α levels in bulk MLNC, GC, and purified CD4 T cells. These cytokines correlate with and variously drive the immunopathology in schistosomiasis (1, 49, 54, 55, 57). In particular, the proinflammatory function of IL-17, which induces chemokine-mediated leukocyte recruitment, has also been demonstrated in the context of other infectious and autoimmune diseases (32, 35, 61). IL-17 production is associated with a distinct subset of CD4 T cells, Th17 cells (28, 53), which are variously promoted by an array of innate immune cell-derived cytokines, including IL-6, TGF-β, IL-23, IL-21, and IL-1β (2, 9, 36, 34, 70). In the CBA mice coinfected with _H. polygyrus_, we indeed detected significant decreases in expression of IL-23p19, IL-6, and IL-1β, which explains the decreases in expression of IL-17 and of the neutrophil chemotactic CXCL1 (Gro-α) and CXCL2 (Gro-β) (54). On the other hand, there were marked increases in expression of IL-4, IL-5, IL-10, and TGF-β, as well as in expression of CCL11 (eotaxin), which collectively indicate that there was a Th1/Th17-to-Th2 shift in the cytokine environment.

The observed increases in IL-4, IL-10, and TGF-β production induced by coinfection with _H. polygyrus_ suggested a role for AAM and Treg, which characterize immunoregulatory mechanisms that have been linked to the down-modulation of schistosome egg-induced immunopathology (30, 31, 42, 46, 67). IL-4 is critical for the development of AAM (26, 40, 44), and IL-10 and TGF-β are anti-inflammatory cytokines widely associated with Treg activity (3, 43, 71). Indeed, the increase in expression of TGF-β together with the downregulation of IL-6 and IL-1β caused by _H. polygyrus_ is a setting conducive for Treg differentiation and development (9, 71). The levels of both the lectin Ym1 and the transcription factor Foxp3, which are markers of AAM and Treg, respectively, were significantly higher in coinfected mice than in mice infected with only schistosomes. These findings support the hypothesis that AAM and Treg have a role as effector mechanisms involved in the reduction of schistosome egg-induced immunopathology induced by _H. polygyrus_ coinfection; in fact, both mechanisms have also been implicated in helminth-induced amelioration of inflammation in a number of infectious diseases, as well as autoimmune diseases (4, 12, 22, 37, 77).

The ameliorating effect of nematode coinfection on the severity of schistosomiasis is similar to that exerted on a variety of autoimmune diseases (17, 22, 34, 37, 51, 58, 59, 76), thus offering a collective explanation for the lower incidence of these T-cell-mediated conditions in areas where helminths are endemic. Such an effect of nematodes with relatively little intrinsic pathogenicity appears to be beneficial for the host and is currently being explored as a therapeutic means to control inflammatory bowel disease in humans (63) and possibly other autoimmune diseases (37). On the other hand, the helminths may be detrimental under conditions in which a strong proinflammatory response is necessary to control other infectious agents (20, 29, 33, 39, 66).

In summary, preexposure to intestinal nematodes effectively protected mice from severe schistosomiasis using a regimen that provided optimal Th2 conditioning at the time of the schistosome infection and subsequent downregulation of pathogenic Th1- and Th17-cell-mediated responses. This successful time sequence closely mimics the sequence observed in areas where the disease is endemic, where individuals typically acquire intestinal nematode infections before they are exposed to bodies of freshwater contaminated with schistosomes. It should be noted, however, that while nematode coinfection averted severe Th1/Th17-mediated schistosome egg-induced hepatic immunopathology, schistosome infection by itself induces in the vast majority of individuals a Th2 response (6, 47, 60) that downregulates inflammation against other pathogens (21, 50, 52, 62, 66, 68, 73). In some instances, however, pathogens can induce a proinflammatory milieu that is conducive to exacerbated schistosome pathology (5). Regardless, a concept supported by our findings is that, as a whole, natural or therapeutically helminth infections can be important elements in the prevention and amelioration of aberrant or excessive CD4 T-cell-mediated disease.

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