

## Review Article

# Parasitic Helminths: New Weapons against Immunological Disorders

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The prevalence of allergic and autoimmune diseases is increasing in developed countries, possibly due to reduced exposure to microorganisms in childhood (hygiene hypothesis). Epidemiological and experimental evidence in support of this hypothesis is accumulating. In this context, parasitic helminths are now important candidates for antiallergic/anti-inflammatory agents. Here we summarize antiallergic/anti-inflammatory effects of helminths together along with our own study of the effects of *Schistosoma mansoni* on Th17-dependent experimental arthritis. We also discuss possible mechanisms of helminth-induced suppression according to the recent advances of immunology.

## 1. Introduction: Autoimmunity, Allergy, and Helminth Infection

In 1989, the “hygiene hypothesis” was proposed by D.P. Strachan in an article that claimed an inverse relationship between the occurrence of hay fever and numbers of siblings [1]. According to the hypothesis, atopic disorders are due to reduced exposure to microorganisms in childhood. Nowadays, the concept is becoming more accepted with accumulating evidence not only in atopic diseases but also in autoimmune inflammatory diseases. For instance, the incidence of multiple sclerosis (MS) is higher in high latitude countries (= westernized developed countries) than in equatorial areas [2]. Not only residents of western countries but also immigrants from developing countries are at high risk of developing inflammatory bowel diseases (IBDs) and asthma [3]. In the case of type 1 diabetes (T1D), a similar geographical distribution to the diseases above and an inverse correlation to hygiene conditions are observed [4]. A population-based ecologic study in Canada showed that IBD, including ulcerative colitis (UC) and Crohn’s disease (CD), correlated with a high socioeconomic status, low rate of enteric infection, and high rate of MS [5].

Many studies have demonstrated that helminth infections lower the risk of autoimmunity or allergy. For instance,

an inverse correlation between autoimmune liver diseases and *Strongyloides stercoralis* infection was demonstrated in Okinawa, Japan [6]. Cross-sectional studies on the relationship between skin prick tests and helminth infections suggested a general protective effect on the atopic reaction [7]. The authors summarized effects of geohelminths on the risk of asthma according to previous studies; that is, hookworm lowered but *Ascaris* increased the risk of asthma and *Trichuris* had no effect. Collectively, it is concluded that at least some helminths seem to have anti-allergic or anti-inflammatory effects in humans.

Experimental studies have also shown protective effects of helminth infections in animal models of autoimmunity (e.g., colitis, arthritis, and diabetes) and allergy (e.g., airway hypersensitivity) [3, 8–10]. In this review, we discuss possible mechanisms of anti-allergic/anti-inflammatory effects of helminths in animal models including autoimmune arthritis. Possible clinical applications and future prospects are also discussed.

## 2. Helper T Cell Subset Dependence of Experimental Immunological Disorders

Based on T cell skewing patterns and their relative importance in the pathogenesis, disorders with excessive immune

responses had been briefly classified as “Th1 diseases” and “Th2 diseases” according to the Th1/Th2 paradigm. However, the recent discovery of a novel pathogenic T cell subset (Th17) [11] led investigators to the concept of “Th17 disease.” While most atopic immune disorders (e.g., hay fever and bronchial asthma) can be classified as Th2 diseases, the classification of autoimmune diseases is relatively difficult. Experimental autoimmune encephalomyelitis (EAE) as a model of MS was long thought to be a Th1 disease; however, the recent studies using IL-12/23 subunit (p35, p19, or p40) deficient mice revealed the progression of the disease to be dependent on the IL-23/IL-17 axis (= Th17 response) rather than IL-12/IFN $\gamma$  axis (= Th1 response) [12]. The pathogenic role of IL-17 was shown directly by the finding that EAE development was significantly suppressed in IL-17-deficient mice [13]. The importance of the IL-23/IL-17 axis is supported also in human MS [12]. Regarding T1D, the diabetes observed in NOD mice (a model of T1D) has been classified as a Th1 disease despite the presence of some controversial study results [14–16]. Recent reports demonstrated that Th17 cells could also cause diabetes, but only after their conversion to Th1-type cells [17, 18]. This means that there is unknown plasticity of helper T subsets. Regarding IBD, the pathogenic roles of both Th1 and Th17 responses in TNBS-induced colitis (a model of IBD) are still controversial [19–23]. Collectively, some experimental autoimmune disorders cannot yet be distinctly classified as either Th1 or Th17 disease.

### 3. Protective Effects of Helminths against Immunological Disorders

The effects of schistosomes and other helminths on experimental autoimmunity/allergy are summarized in Table 1. Surprisingly, helminths have been shown to suppress all types (Th1, Th2, and Th17) of disease in the models described above [24–45]. Considering classical Th1/Th2 paradigm, it is reasonable to speculate that helminth-induced Th2-skewing with downregulation of Th1 immune responses results in an amelioration of Th1 diseases. As IL-4 is known to suppress Th17 development [46], Th17 response could also be suppressed as well as Th1 response in helminth-infected or helminth antigen-treated animals. In fact, STAT6-dependent IL-4/IL-13 signaling was shown to be essential in the suppression of TNBS-induced colitis [29] and EAE [25] by schistosome eggs, although the authors did not measure changes of IL-17. Given that the involvement of Th1 and Th17 in some forms of autoimmunity is still controversial, downregulation of both T helper responses may be beneficial for the amelioration of various kinds of autoimmunity. Along with other investigators, we recently found that schistosome-infected mice became resistant to experimental arthritis accompanying down-regulation of both Th1 and Th17 responses of splenocytes [47]. Likewise, Ruysers et al. reported suppression of TNBS-induced colitis by schistosome antigens, accompanying down-regulation of IL-17 gene expression in the colon and mesenteric lymph node (MLN) [28]. An intestinal nematode (*Heligmosomoides*

*polygyrus*) infection was also reported to suppress IL-17 production in MLN cells and lamina propria mononuclear cells [48]. The authors showed that the blocking of both IL-4 and IL-10 restored IL-17 production in vitro. Another study revealed that *Fasciola hepatica*-induced down-regulation of autoantigen-specific Th1 and Th17 responses (and protection from EAE) was dependent on TGF- $\beta$ , not IL-10 [49]. Although the mechanisms of Th17's down-regulation by helminths are not yet established, some of the mechanisms might be common to those of Th1's down-regulation (e.g., through induction of IL-4 and IL-10, down-regulation of IL-12p40) and others might be distinct.

In our study on experimental arthritis in mice [47], we found no increase of Treg-related gene expression (Foxp3, TGF- $\beta$  and IL-10) in the paws of *S. mansoni*-infected mice compared to the paws of uninfected control mice. As Treg cell population was known to expand in schistosome-infected or egg-treated mice [31, 32, 35, 50], the cells might participate in the regulation of the disease systemically rather than locally. To confirm the essential involvement of Treg cells in the antiarthritic effects of schistosome, further studies (e.g., persistent Treg depletion experiments) are necessary. In contrast to our result, in the case of diabetes in NOD mice, schistosome egg antigens induce infiltration of Treg cells at a local inflamed site (pancreas) [32]. Likewise, filarial nematode (*Litomosoides sigmodontis*) infection induced Treg cells and protected mice from the diabetes [39]. *H. polygyrus* also protected mice from the diabetes; however, the protection was not dependent on Treg cells [40]. In addition to schistosome and nematodes, tapeworm (*Taenia crassiceps*) infection also has anti-diabetic effects in multiple low-dose streptozotocin-induced diabetes (MLDS) in mice [45, in this issue]. In the study, alternatively activated macrophages (AAM $\phi$ ) increased whereas Treg population did not increase. Taken together, these studies suggest that there may be various mechanisms in anti-diabetic effects of helminths.

We also found that schistosome-induced down-regulation of Th1 and Th17 occurred in the same period after the infection, corresponding to the beginning of egg-laying (unpublished observation). This result suggests that egg deposition is the major stimulus to lower Th17 responses (as well as Th1 response) in murine experimental schistosomiasis. Further studies using schistosome eggs are currently in progress in our laboratory.

Some epidemiological studies support that helminth infections are protective against atopic reactions and/or symptoms [51–53]. The helminth-induced suppression of Th2 diseases (atopic disorders etc.) is difficult to explain in terms of the Th1/Th2 paradigm. In the paradigm, theoretically, helminth infections are expected to cause IgE overproduction and hypereosinophilia, followed by exacerbation of allergic reactions. Indeed, persistent bronchoalveolar eosinophilia, airway hyperresponsiveness [54], and exacerbation of allergic airway inflammation [55] were observed in *Toxocara*-infected mice. One interesting explanation of anti-allergic effects of helminths is introduced in a review by Fallon and Mangan [56], in which Th2 responses are subdivided to “allergic” and “modified”, with helminth-induced Th2 responses corresponding to the latter

TABLE 1: Suppression of experimental immunological disorders by helminthes.

Animal models	Th types	Helminths	Treatment	Proposed suppressive mechanisms	Refs
Collagen-induced arthritis (CIA)	Th17	<i>Schistosoma mansoni</i>	Infection	IL-17 ↓, TNF-α ↓, IL-6 ↓, RANKL ↓, Anti-collagen IgG ↑	[47]
		<i>Ascaris suum</i>	Worm Ag		[37]
Experimental autoimmune encephalomyelitis (EAE)	Th17	<i>Acanthocheilonema viteae</i>	Purified Ag (ES-62)	IFN-γ ↓, TNF-α ↓, IL-6 ↓, Anti-collagen IgG ↓	[78]
		<i>Schistosoma mansoni</i>	Infection	IL-12p40 ↓, IFN-γ ↓, TNF-α ↓, IL-4 ↑	[24]
			Egg	IFN-γ ↓, IL-4 ↓, TGF-β ↑, IL-10 ↑	[25]
		<i>Schistosoma japonicum</i>	Egg Ag	IFN-γ ↓, IL-4 ↑	[26]
		<i>Fasciola hepatica</i>	Infection	IFN-γ ↓, IL-17 ↓, Dependent on TGFβ	[49]
		<i>Trichinella spiralis</i>	Infection		[27]
Type 1 diabetes in NOD mice	Th1?	<i>Schistosoma mansoni</i>	Infection, Eggs	Inhibition of Ab class switch (Anti-insulin IgG ↓)	[81]
			Egg Ag	Treg	[32]
Streptozotocin-induced diabetes	Th1?	<i>Litomosoides sigmodontis</i>	Infection, Worm Ag	IL-4 ↑, IL-5 ↑, Treg	[39]
		<i>Heligmosomoides polygyrus</i>	Infection	Independent of IL-10 and Treg	[40]
TNBS/DNBS-induced colitis	Th1? / Th17?	<i>Taenia crassiceps</i>	Infection	AAMφ	[45]
		<i>Schistosoma mansoni</i>	Infection	IL-2 ↑, IL-4 ↑	[30]
Piroxicam-induced colitis	Th17?		Eggs	IFN-γ ↓, IL-4 ↓	[29]
		<i>Schistosoma japonicum</i>	Worm Ag	IFN-γ ↓, IL-17 ↓, TGF-β ↑, IL-10 ↑	[28]
		<i>Hymenolepis diminuta</i>	Egg Ag	IFN-γ ↓, IL-4 ↓, IL-10 ↑, Treg	[31]
		<i>Heligmosomoides polygyrus</i>	Infection	IL-10 ↑	[41, 44]
DSS-induced colitis	Th17? / Th2?	<i>Schistosoma mansoni</i>	Infection (male worm)	IL-17 ↓, Independent of IL-10	[48]
Systemic anaphylaxis	Th2	<i>Schistosoma mansoni</i>	Infection	Macrophage infiltration	[64]
		<i>Schistosoma mansoni</i>	Infection	IL-10-producing Bcell	[34]
Asthma/Airway hypersensitivity or inflammation	Th2	<i>Schistosoma mansoni</i>	Infection (male worm)	IL-5 ↓, IL-10 ↑	[33]
		<i>Schistosoma japonicum</i>	Egg Ag, Eggs	Treg	[35]
		<i>Heligmosomoides polygyrus</i>	Infection	Treg	[36]
		<i>Ascaris suum</i>	Purified Ag (PAS-1)	IL-4 ↓, IL-5 ↓, Eotaxin ↓, RANTES ↓, IL-10 ↑	[38]
		<i>Litomosoides sigmodontis</i>	Worm Ag	IL-4 ↓, IL-5 ↓, Eotaxin ↓, IgE ↓	[42]
			Infection	TGFβ ↑, Treg	[43]

↓:downregulation, ↑:upregulation

type characterized by predominant Treg and IL-10 responses and a relatively weak IL-5 response. (The authors, however, describe that such modifications are localized in the lungs and different from systemic responses.) Along with this hypothesis, administration of *Ascaris* extract was shown to inhibit not only IL-5 production but also eosinophilic inflammation in a murine asthma model [42]. Filarial infection also suppressed airway hyperreactivity and pulmonary eosinophilia in a murine asthma model [43]. The suppressive effect of the filarial worms on hyperreactivity was dependent on Treg cells and TGF- $\beta$ . As helminths seem to have both allergenic and immunomodulatory components [38] in their bodies, the balance of them may determine the outcomes (i.e., exacerbation or amelioration) of allergic disorders.

Helminthic infections often result in expansion and/or activation of Treg cells [31, 32, 35, 36, 50]. B cells are also suggested to be involved in disease suppression [34] through IL-10. However, the importance of IL-10 in helminth-induced suppression of atopic diseases is not fully established; that is, mesenteric lymph node cells from *Heligmosomoides*-infected IL-10-deficient mice could confer protection against allergic airway inflammation [36]. Likewise, in humans, anti-allergic effect of *Ascaris lumbricoides* is associated with Treg, but not with IL-10 [57]. In the case of mice, IL-35, a recently identified effector molecule of Treg cells [58], might be involved in the suppression. Other than the regulation of lymphocytes, helminth-derived products have potential anti-allergic effects on various kinds of cells. For instance, the filarial product ES-62 was shown to suppress the release of mediators from bone marrow-derived mast cells [59]. In addition, helminths generally induce AAM $\phi$  [60–63]. Such macrophages not only suppress the pathogenesis by the parasites themselves [61] but also may suppress pathological immune responses to autoantigens or allergens. The involvement of AAM $\phi$  in anti-diabetic effects was suggested in experimental tapeworm infection [45]. On the other hand, schistosome-modulated macrophages (but NOT AAM $\phi$ ) were involved in suppression of dextran sodium sulfate-(DSS-) induced colitis [64]. These studies suggest the presence of various suppressive mechanisms by helminths. Immune cells and mediators possibly involved in the helminth-induced immunomodulation are illustrated in Figure 1.

#### 4. Protective Effects of Helminths against Experimental Autoimmune Arthritis

Collagen-induced arthritis (CIA) is an autoimmune arthritis in mice and rats [65] widely used as a model of rheumatoid arthritis (RA). Although the role of the IL-12/IFN $\gamma$  axis in CIA has been controversial [66, 67], recent findings suggest that IFN $\gamma$  has ameliorating rather than exacerbating effects [68–71]. Instead, the IL-23/IL-17 axis was recently shown to be important in the pathogenesis of CIA [71–76] as well as RA in humans [77].

Regarding anti-arthritic effects of helminths, a filarial ES product ES-62 [78] and porcine roundworm *Ascaris suum* extract [37] were shown to suppress CIA in mice. As

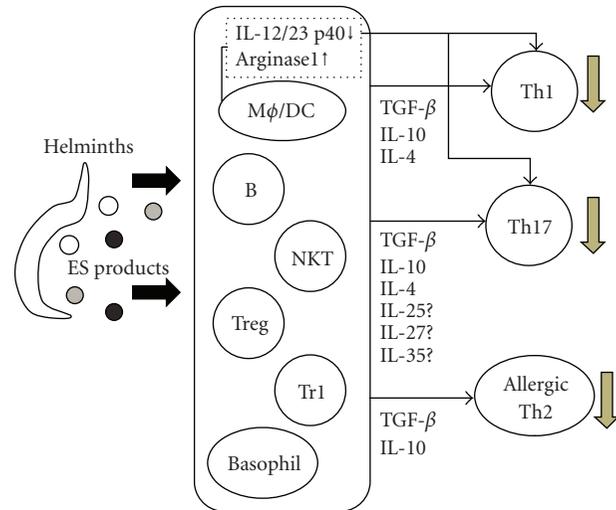


FIGURE 1: Possible involvement of immune cells and mediators in the helminth-induced immunomodulation on T helper subsets. Substances contained in the bodies of helminths or their excretory secretory (ES) products are recognized by innate immune cells via PAMPs receptors like TLRs. Thereafter, various changes occur in the immune cells, for example, down-modulation of IL-12/23p40 expression (DC), alternative activation (macrophages), proliferation and/or IL-10 production (Treg, Tr1, and B cells), and IL-4 production (basophils). We can observe suppression of immune disorders with down-regulation of pathogenic T helper subsets (Th1, Th17, and allergic Th2) as consequence of mixed effects of such immunological changes.

described, we examined effects of *S. mansoni* infection on CIA in mice. In humans, schistosomiasis has been reported as “arthritogenic” rather than anti-arthritic [79, 80]. In our experiments, however, *S. mansoni* infection lowered arthritis scores and numbers of arthritic paws [47]. Histopathological examination revealed that cell infiltration and bone/cartilage destruction were diminished in the infected mice.

In CIA and RA, the pathogenic roles of IL-1 and IL-6 are well established [82–84]. We observed that the marked augmentation of IL-1 $\beta$  and IL-6 gene expression in the paws was almost completely abrogated by *S. mansoni* infection [47]. It was especially noteworthy that receptor activator of NF $\kappa$ B ligand (RANKL) gene expression in the inflamed paws was also abrogated by *S. mansoni* infection. As RANKL expression is induced by proinflammatory cytokines including IL-17, TNF- $\alpha$ , and IL-1 $\beta$  [85] and essential to osteoclast development followed by bone destruction [86–88], this result suggests that schistosome infection has anti-arthritic effects preventing bone destruction. Interestingly, we also found that intraperitoneally administered schistosome worm antigens (SWAP) or egg antigens (SEA) did not affect the progress of CIA (unpublished observation). In the antigen-administered mice, levels of IL-10, TNF $\alpha$ , and IL-17 produced by splenocytes were comparable to those in antigen nonadministered control mice. Thus, regarding schistosome, there is a considerable difference in immunomodulating effects between infection and antigen administration.

## 5. Future Clinical Applications of Helminths and Their Products

As described above, our experiments with schistosome showed that anti-arthritis effects were observed only in the viable worm infected mice. Likewise, Hunter et al. showed that anticolic effects of *Hymenolepis diminuta* were dependent on a viable infection [41], and surprisingly, Melon et al. showed that therapeutic efficacy of the viable tapeworm was superior to dexamethazone treatment [44, in this issue]. Because of these observations in experimental models, attenuated or non/lowly-pathogenic helminths are worth testing directly for therapeutic effects. In fact, porcine whipworm (*Trichuris suis*) eggs and *Necator americanus* infective larvae have been clinically tested for the treatment of chronic inflammatory or allergic diseases. Reddy and Fried [89] summarized the recent progress in clinical trials using these two intestinal nematodes. Summers et al. reported that the administration of *T. suis* eggs effectively ameliorated both UC and CD [90, 91] without adverse effects. *N. americanus* is also under clinical trials for asthmatic patients [92]. This worm is considered superior to porcine whipworm in that repeated administration is not needed.

Although it is not permissible to directly apply highly pathogenic helminths (e.g., schistosome) to clinical use, purified or synthetic immunomodulatory products from such worms can be considered for clinical purposes. Various immunomodulatory molecules (carbohydrates, proteins, and lipids) have been identified; for example, Lacto-*N*-fucopentaose III (LNFP III) contained in schistosome eggs is an oligosaccharide as the molecule affecting B cells (especially B-1 cells) to induce IL-10 production [93]. LNFP III was also reported to alternatively activate macrophages [94]. A chemokine-binding protein (CBP) from schistosome eggs inhibited the recruitment of neutrophils [95] to inflammatory foci. Peroxiredoxin (Prx) is an antioxidant protein found in various species including helminths [96, 97]. The molecules from *S. mansoni* and *F. hepatica* alternatively activate macrophages and are involved in the induction of a Th2-type immune response [97]. The IL-4-inducing principle of *S. mansoni* eggs (IPSE) is the molecule that induces "primary" IL-4 production from basophils [98]. Regarding anti-arthritis effects, a glycoprotein from *Spirometra erinaceieuropaei* was shown to suppress RANKL-induced osteoclastogenesis, suggesting that there may be more anti-arthritis substances in various helminths [99].

## 6. Concluding Remarks

Helminth-based immunotherapy for immunological disorders is still in its infancy. It should be pointed out that helminths do not always suppress autoimmune/allergic disorders. There are epidemiological and experimental reports that helminths exacerbate such disorders [10]. Apart from Th2-biasing abilities of helminths, allergens contained in the worms may partially explain the mechanisms of exacerbation. *Ascaris* extract has cross-reactivity with domestic mite allergens [100]. Moreover, *Ascaris* was shown to have an allergenic component (APAS-3) [38]. Mice infected

with *Toxocara canis* showed exacerbation of allergic airway inflammation [55] whereas hookworm (*Nippostrongylus brasiliensis*) infection persistently reduced airway responsiveness in mice [101], suggesting that there are considerable differences of outcomes even among lung-migratory nematodes. Thus, careful selection of "therapeutic" helminths and their target diseases is essential. Further studies on the mechanisms of immunomodulation are necessary for future human applications. The roles of Th1/Th17/Treg-related regulatory cytokines (IL-25, IL-27, IL-35, etc.) in the helminth-induced suppression of allergy/autoimmunity have not been sufficiently studied. It is well known that the roles of cytokines in human Th17 differentiation are very different from those in mice [12, 102]. For clinical applications in the future, we should ascertain changes in Th17-related cytokine patterns not only in animal models but also in patients with helminthiasis. It was reported that concurrent filarial infection suppressed both Th1 and Th17 responses to *Mycobacterium tuberculosis* [103]. This implies that helminths have down-regulating activity of both Th1 and Th17 in humans as well as in mice.

In human RA, the relative importance of Th1 and Th17 is still unclear, and therefore, suppression of both T helper responses is recommended [102]. Thus, at present we can conclude that regulatory effects on both Th1 and Th17 are promising characteristics of helminths as anti-inflammatory agents. However, the interpretation of experimental results of helminth-induced immunomodulation may change depending on changes in basic immunological knowledge. Indeed, it was recently reported that T-bet expression was more important in the pathogenesis of EAE than the Th1/Th17 balance [104]. Therefore, further studies of helminth-induced amelioration of immune disorders should strictly follow the studies of the diseases' pathogenesis.

As noted, in experimental animal studies, viable helminth infections seem to be superior to the administration of worm antigens or killed worms in the therapeutic effects. This might be due to that viable helminths can regulate secretion of immunomodulatory molecules in the most appropriate conditions for their survival. Taken together with successful treatment of UC and CD with viable porcine whipworms [90, 91], the optimal attenuation of human parasites by gene manipulation may be useful for the clinical application of parasitic helminths in the future.

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## References

- [1] D. P. Strachan, "Hay fever, hygiene, and household size," *British Medical Journal*, vol. 299, no. 6710, pp. 1259–1260, 1989.

- [2] J. F. Kurtzke, "Multiple sclerosis in time and space—geographic clues to cause," *Journal of NeuroVirology*, vol. 6, supplement 2, pp. S134–S140, 2000.
- [3] D. E. Elliott, R. W. Summers, and J. V. Weinstock, "Helminths as governors of immune-mediated inflammation," *International Journal for Parasitology*, vol. 37, no. 5, pp. 457–464, 2007.
- [4] P. Zacccone, Z. Fehervari, J. M. Phillips, D. W. Dunne, and A. Cooke, "Parasitic worms and inflammatory diseases," *Parasite Immunology*, vol. 28, no. 10, pp. 515–523, 2006.
- [5] C. Green, L. Elliott, C. Beaudoin, and C. N. Bernstein, "A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues," *American Journal of Epidemiology*, vol. 164, no. 7, pp. 615–623, 2006.
- [6] H. Aoyama, T. Hirata, H. Sakugawa, et al., "An inverse relationship between autoimmune liver diseases and strongyloides stercoralis infection," *American Journal of Tropical Medicine and Hygiene*, vol. 76, no. 5, pp. 972–976, 2007.
- [7] C. Flohr, R. J. Quinnell, and J. Britton, "Do helminth parasites protect against atopy and allergic disease?" *Clinical & Experimental Allergy*, vol. 39, no. 1, pp. 20–32, 2009.
- [8] D. M. McKay, "The therapeutic helminth?" *Trends in Parasitology*, vol. 25, no. 3, pp. 109–114, 2009.
- [9] P. Zacccone, O. T. Burton, and A. Cooke, "Interplay of parasite-driven immune responses and autoimmunity," *Trends in Parasitology*, vol. 24, no. 1, pp. 35–42, 2008.
- [10] K. J. Erb, "Can helminths or helminth-derived products be used in humans to prevent or treat allergic diseases?" *Trends in Immunology*, vol. 30, no. 2, pp. 75–82, 2009.
- [11] H. Park, Z. Li, X. O. Yang, et al., "A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17," *Nature Immunology*, vol. 6, no. 11, pp. 1133–1141, 2005.
- [12] T. Aranami and T. Yamamura, "Th17 cells and autoimmune encephalomyelitis (EAE/MS)," *Allergology International*, vol. 57, no. 2, pp. 115–120, 2008.
- [13] Y. Komiyama, S. Nakae, T. Matsuki, et al., "IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis," *Journal of Immunology*, vol. 177, no. 1, pp. 566–573, 2006.
- [14] H. Toyoda and B. Formby, "Contribution of T cells to the development of autoimmune diabetes in the NOD mouse model," *BioEssays*, vol. 20, no. 9, pp. 750–757, 1998.
- [15] J. Cantor and K. Haskins, "Effector function of diabetogenic CD4 Th1 T cell clones: a central role for TNF- $\alpha$ ," *Journal of Immunology*, vol. 175, no. 11, pp. 7738–7745, 2005.
- [16] J.-T. Hung, J.-H. Liao, Y.-C. Lin, et al., "Immunopathogenic role of TH1 cells in autoimmune diabetes: evidence from a T1 and T2 doubly transgenic non-obese diabetic mouse model," *Journal of Autoimmunity*, vol. 25, no. 3, pp. 181–192, 2005.
- [17] D. Bending, H. De La Peña, M. Veldhoen, et al., "Highly purified Th17 cells from BDC2.5NOD mice convert into Th1-like cells in NOD/SCID recipient mice," *Journal of Clinical Investigation*, vol. 119, no. 3, pp. 565–572, 2009.
- [18] N. Martin-Orozco, Y. Chung, S. H. Chang, Y.-H. Wang, and C. Dong, "Th17 cells promote pancreatic inflammation but only induce diabetes efficiently in lymphopenic hosts after conversion into Th1 cells," *European Journal of Immunology*, vol. 39, no. 1, pp. 216–224, 2009.
- [19] L. Camoglio, A. A. te Velde, A. de Boer, F. J. ten Kate, M. Kopf, and S. J. van Deventer, "Hapten-induced colitis associated with maintained Th1 and inflammatory responses in IFN- $\gamma$  receptor-deficient mice," *European Journal of Immunology*, vol. 30, no. 5, pp. 1486–1495, 2000.
- [20] K. Tozawa, H. Hanai, K. Sugimoto, et al., "Evidence for the critical role of interleukin-12 but not interferon- $\gamma$  in the pathogenesis of experimental colitis in mice," *Journal of Gastroenterology and Hepatology*, vol. 18, no. 5, pp. 578–587, 2003.
- [21] T. Dohi, K. Fujihashi, H. Kiyono, C. O. Elson, and J. R. McGhee, "Mice deficient in Th1- and Th2-type cytokines develop distinct forms of hapten-induced colitis," *Gastroenterology*, vol. 119, no. 3, pp. 724–733, 2000.
- [22] Z. Zhang, M. Zheng, J. Bindas, P. Schwarzenberger, and J. K. Kolls, "Critical role of IL-17 receptor signaling in acute TNBS-induced colitis," *Inflammatory Bowel Diseases*, vol. 12, no. 5, pp. 382–388, 2006.
- [23] W. O'Connor Jr., M. Kamanaka, C. J. Booth, et al., "A protective function for interleukin 17A in T cell-mediated intestinal inflammation," *Nature Immunology*, vol. 10, no. 6, pp. 603–609, 2009.
- [24] A. C. La Flamme, K. Ruddenklau, and B. T. Bäckström, "Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis," *Infection and Immunity*, vol. 71, no. 9, pp. 4996–5004, 2003.
- [25] D. Sewell, Z. Qing, E. Reinke, et al., "Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization," *International Immunology*, vol. 15, no. 1, pp. 59–69, 2003.
- [26] X. Zheng, X. Hu, G. Zhou, et al., "Soluble egg antigen from *Schistosoma japonicum* modulates the progression of chronic progressive experimental autoimmune encephalomyelitis via Th2-shift response," *Journal of Neuroimmunology*, vol. 194, no. 1-2, pp. 107–114, 2008.
- [27] A. Gruden-Movsesijan, N. Ilic, M. Mostarica-Stojkovic, S. Stosic-Grujicic, M. Milic, and Lj. Sofronic-Milosavljevic, "*Trichinella spiralis*: modulation of experimental autoimmune encephalomyelitis in DA rats," *Experimental Parasitology*, vol. 118, no. 4, pp. 641–647, 2008.
- [28] N. E. Ruysers, B. Y. De Winter, J. G. De Man, et al., "Therapeutic potential of helminth soluble proteins in TNBS induced colitis in mice," *Inflammatory Bowel Diseases*, vol. 15, no. 4, pp. 491–500, 2009.
- [29] D. E. Elliott, J. Li, A. Blum, et al., "Exposure to schistosome eggs protects mice from TNBS-induced colitis," *American Journal of Physiology*, vol. 284, no. 3, pp. G385–G391, 2003.
- [30] T. G. Moreels, R. J. Nieuwendijk, J. G. De Man, et al., "Concurrent infection with *Schistosoma mansoni* attenuates inflammation induced changes in colonic morphology, cytokine levels, and smooth muscle contractility of trinitrobenzene sulphonic acid induced colitis in rats," *Gut*, vol. 53, no. 1, pp. 99–107, 2004.
- [31] H.-M. Mo, W.-Q. Liu, J.-H. Lei, Y.-L. Cheng, C.-Z. Wang, and Y.-L. Li, "*Schistosoma japonicum* eggs modulate the activity of CD4<sup>+</sup>CD25<sup>+</sup> Tregs and prevent development of colitis in mice," *Experimental Parasitology*, vol. 116, no. 4, pp. 385–389, 2007.
- [32] P. Zacccone, O. Burton, N. Miller, F. M. Jones, D. W. Dunne, and A. Cooke, "*Schistosoma mansoni* egg antigens induce Treg that participate in diabetes prevention in NOD mice," *European Journal of Immunology*, vol. 39, no. 4, pp. 1098–1107, 2009.
- [33] N. E. Mangan, N. van Rooijen, A. N. J. McKenzie, and P. G. Fallon, "Helminth-modified pulmonary immune response protects mice from allergen-induced airway hyperresponsiveness," *Journal of Immunology*, vol. 176, no. 1, pp. 138–147, 2006.

- [34] N. E. Mangan, R. E. Fallon, P. Smith, N. van Rooijen, A. N. McKenzie, and P. G. Fallon, "Helminth infection protects mice from anaphylaxis via IL-10-producing B cells," *Journal of Immunology*, vol. 173, no. 10, pp. 6346–6356, 2004.
- [35] J. Yang, J. Zhao, Y. Yang, et al., "Schistosoma japonicum egg antigens stimulate CD4<sup>+</sup>CD25<sup>+</sup> T cells and modulate airway inflammation in a murine model of asthma," *Immunology*, vol. 120, no. 1, pp. 8–18, 2006.
- [36] M. S. Wilson, M. D. Taylor, A. Balic, C. A. M. Finney, J. R. Lamb, and R. M. Maizels, "Suppression of allergic airway inflammation by helminth-induced regulatory T cells," *Journal of Experimental Medicine*, vol. 202, no. 9, pp. 1199–1212, 2005.
- [37] F. A. C. Rocha, A. K. R. M. Leite, M. M. L. Pompeu, et al., "Protective effect of an extract from *Ascaris suum* in experimental arthritis models," *Infection and Immunity*, vol. 76, no. 6, pp. 2736–2745, 2008.
- [38] D. M. Itami, T. M. Oshiro, C. A. Araujo, et al., "Modulation of murine experimental asthma by *Ascaris suum* components," *Clinical & Experimental Allergy*, vol. 35, no. 7, pp. 873–879, 2005.
- [39] M. P. Hübner, J. T. Stocker, and E. Mitre, "Inhibition of type 1 diabetes in filaria-infected non-obese diabetic mice is associated with a T helper type 2 shift and induction of FoxP3<sup>+</sup> regulatory T cells," *Immunology*, vol. 127, no. 4, pp. 512–522, 2009.
- [40] Q. Liu, K. Sundar, P. K. Mishra, et al., "Helminth infection can reduce insulinitis and type 1 diabetes through CD25- and IL-10-independent mechanisms," *Infection and Immunity*, vol. 77, no. 12, pp. 5347–5358, 2009.
- [41] M. M. Hunter, A. Wang, C. L. Hirota, and D. M. McKay, "Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis," *Journal of Immunology*, vol. 174, no. 11, pp. 7368–7375, 2005.
- [42] C. Lima, A. Perini, M. L. B. Garcia, M. A. Martins, M. M. Teixeira, and M. S. Macedo, "Eosinophilic inflammation and airway hyper-responsiveness are profoundly inhibited by a helminth (*Ascaris suum*) extract in a murine model of asthma," *Clinical & Experimental Allergy*, vol. 32, no. 11, pp. 1659–1666, 2002.
- [43] A. M. Dittrich, A. Erbacher, S. Specht, et al., "Helminth infection with *Litomosoides sigmodontis* induces regulatory T cells and inhibits allergic sensitization, airway inflammation, and hyperreactivity in a murine asthma model," *Journal of Immunology*, vol. 180, no. 3, pp. 1792–1799, 2008.
- [44] A. Melon, A. Wang, V. Phan, and D. M. McKay, "Infection with *Hymenolepis diminuta* is more effective than daily corticosteroids in blocking chemically-induced colitis in mice," *Journal of Biomedicine and Biotechnology*, vol. 2010, Article ID 384523, 7 pages, 2010.
- [45] A. Espinoza-Jiménez, I. Rivera-Montoya, R. Cardenas-Arreola, L. Morán, and L. I. Terrazas, "*Taenia crassiceps* Infection attenuates multiple low-dose streptozotocin-induced diabetes," *Journal of Biomedicine and Biotechnology*, vol. 2010, Article ID 850541, 11 pages, 2010.
- [46] S. Romagnani, "Regulation of the T cell response," *Clinical & Experimental Allergy*, vol. 36, no. 11, pp. 1357–1366, 2006.
- [47] Y. Osada, S. Shimizu, T. Kumagai, S. Yamada, and T. Kanazawa, "Schistosoma mansoni infection reduces severity of collagen-induced arthritis via down-regulation of pro-inflammatory mediators," *International Journal for Parasitology*, vol. 39, no. 4, pp. 457–464, 2009.
- [48] D. E. Elliott, A. Metwali, J. Leung, et al., "Colonization with *Heligmosomoides polygyrus* suppresses mucosal IL-17 production," *Journal of Immunology*, vol. 181, no. 4, pp. 2414–2419, 2008.
- [49] K. P. Walsh, M. T. Brady, C. M. Finlay, L. Boon, and K. H. Mills, "Infection with a helminth parasite attenuates autoimmunity through TGF- $\beta$ -mediated suppression of Th17 and Th1 responses," *Journal of Immunology*, vol. 183, no. 3, pp. 1577–1586, 2009.
- [50] A. S. McKee and E. J. Pearce, "CD25<sup>+</sup>CD4<sup>+</sup> cells contribute to Th2 polarization during helminth infection by suppressing Th1 response development," *Journal of Immunology*, vol. 173, no. 2, pp. 1224–1231, 2004.
- [51] A. H. J. van den Biggelaar, R. van Ree, L. C. Rodrigues, et al., "Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10," *The Lancet*, vol. 356, no. 9243, pp. 1723–1727, 2000.
- [52] M. Medeiros Jr., J. P. Figueiredo, M. C. Almeida, et al., "Schistosoma mansoni infection is associated with a reduced course of asthma," *Journal of Allergy and Clinical Immunology*, vol. 111, no. 5, pp. 947–951, 2003.
- [53] C. Flohr, L. N. Tuyen, R. J. Quinnell, et al., "Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam," *Clinical & Experimental Allergy*, vol. 40, no. 1, pp. 131–142, 2010.
- [54] E. Pinelli, C. Withagen, M. Fonville, et al., "Persistent airway hyper-responsiveness and inflammation in *Toxocara canis*-infected BALB/c mice," *Clinical & Experimental Allergy*, vol. 35, no. 6, pp. 826–832, 2005.
- [55] E. Pinelli, S. Brandes, J. Dormans, E. Gremmer, and H. van Loveren, "Infection with the roundworm *Toxocara canis* leads to exacerbation of experimental allergic airway inflammation," *Clinical & Experimental Allergy*, vol. 38, no. 4, pp. 649–658, 2008.
- [56] P. G. Fallon and N. E. Mangan, "Suppression of TH2-type allergic reactions by helminth infection," *Nature Reviews Immunology*, vol. 7, no. 3, pp. 220–230, 2007.
- [57] G. Matera, A. Giancotti, S. Scalise, et al., "*Ascaris lumbricoides*-induced suppression of total and specific IgE responses in atopic subjects is interleukin 10-independent and associated with an increase of CD25<sup>+</sup> cells," *Diagnostic Microbiology and Infectious Disease*, vol. 62, no. 3, pp. 280–286, 2008.
- [58] L. W. Collison, C. J. Workman, T. T. Kuo, et al., "The inhibitory cytokine IL-35 contributes to regulatory T-cell function," *Nature*, vol. 450, no. 7169, pp. 566–569, 2007.
- [59] A. J. Melendez, M. M. Harnett, P. N. Pushparaj, et al., "Inhibition of Fc $\epsilon$ RI-mediated mast cell responses by ES-62, a product of parasitic filarial nematodes," *Nature Medicine*, vol. 13, no. 11, pp. 1375–1381, 2007.
- [60] M. Rodríguez-Sosa, A. R. Satoskar, R. Calderón, et al., "Chronic helminth infection induces alternatively activated macrophages expressing high levels of CCR5 with low interleukin-12 production and Th2-biasing ability," *Infection and Immunity*, vol. 70, no. 7, pp. 3656–3664, 2002.
- [61] D. R. Herbert, C. Hölscher, M. Mohrs, et al., "Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology," *Immunity*, vol. 20, no. 5, pp. 623–635, 2004.
- [62] R. M. Anthony, J. F. Urban, F. Alem, et al., "Memory TH2 cells induce alternatively activated macrophages to mediate protection against nematode parasites," *Nature Medicine*, vol. 12, no. 8, pp. 955–960, 2006.

- [63] F. O. Martinez, L. Helming, and S. Gordon, "Alternative activation of macrophages: an immunologic functional perspective," *Annual Review of Immunology*, vol. 27, pp. 451–483, 2009.
- [64] P. Smith, N. E. Mangan, C. M. Walsh, et al., "Infection with a helminth parasite prevents experimental colitis via a macrophage-mediated mechanism," *Journal of Immunology*, vol. 178, no. 7, pp. 4557–4566, 2007.
- [65] J. M. Stuart, A. S. Townes, and A. H. Kang, "Nature and specificity of the immune response to collagen in type II collagen-induced arthritis in mice," *Journal of Clinical Investigation*, vol. 69, no. 3, pp. 673–683, 1982.
- [66] L. A. B. Joosten, E. Lubberts, M. M. A. Helsen, and W. B. van den Berg, "Dual role of IL-12 in early and late stages of murine collagen type II arthritis," *Journal of Immunology*, vol. 159, no. 8, pp. 4094–4102, 1997.
- [67] E. F. Rosloniec, K. Latham, and Y. B. Guedez, "Paradoxical roles of IFN- $\gamma$  in models in Th1-mediated autoimmunity," *Arthritis Research*, vol. 4, no. 6, pp. 333–336, 2002.
- [68] B. De Klerck, I. Carpentier, R. J. Lories, et al., "Enhanced osteoclast development in collagen-induced arthritis in interferon- $\gamma$  receptor knock-out mice as related to increased splenic CD11b<sup>+</sup> myelopoiesis," *Arthritis Research & Therapy*, vol. 6, no. 3, pp. R220–R231, 2004.
- [69] H. Kelchtermans, B. De Klerck, T. Mitera, et al., "Defective CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cell functioning in collagen-induced arthritis: an important factor in pathogenesis, counter-regulated by endogenous IFN- $\gamma$ ," *Arthritis Research & Therapy*, vol. 7, no. 2, pp. R402–R415, 2005.
- [70] I. M. Irmeler, M. Gajda, and R. Bräuer, "Exacerbation of antigen-induced arthritis in IFN- $\gamma$ -deficient mice as a result of unrestricted IL-17 response," *Journal of Immunology*, vol. 179, no. 9, pp. 6228–6236, 2007.
- [71] C.-Q. Chu, D. Swart, D. Alcorn, J. Tocker, and K. B. Elkon, "Interferon- $\gamma$  regulates susceptibility to collagen-induced arthritis through suppression of interleukin-17," *Arthritis & Rheumatism*, vol. 56, no. 4, pp. 1145–1151, 2007.
- [72] C. A. Murphy, C. L. Langrish, Y. Chen, et al., "Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation," *Journal of Experimental Medicine*, vol. 198, no. 12, pp. 1951–1957, 2003.
- [73] S. Nakae, A. Nambu, K. Sudo, and Y. Iwakura, "Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice," *Journal of Immunology*, vol. 171, no. 11, pp. 6173–6177, 2003.
- [74] E. Lubberts, L. van den Bersselaar, B. Oppers-Walgreen, et al., "IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF- $\kappa$ B ligand/osteoprotegerin balance<sup>1</sup>," *Journal of Immunology*, vol. 170, no. 5, pp. 2655–2662, 2003.
- [75] T. Yago, Y. Nanke, M. Kawamoto, et al., "IL-23 induces human osteoclastogenesis via IL-17 in vitro, and anti-IL-23 antibody attenuates collagen-induced arthritis in rats," *Arthritis Research and Therapy*, vol. 9, no. 5, article R96, 2007.
- [76] E. Lubberts, M. Koenders, and W. B. van den Berg, "The role of T cell interleukin-17 in conducting destructive arthritis: lessons from animal models," *Arthritis Research and Therapy*, vol. 7, no. 1, pp. 29–37, 2005.
- [77] S. Kotake, N. Udagawa, N. Takahashi, et al., "IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis," *Journal of Clinical Investigation*, vol. 103, no. 9, pp. 1345–1352, 1999.
- [78] I. B. McInnes, B. P. Leung, M. Harnett, J. A. Gracie, F. Y. Liew, and W. Harnett, "A novel therapeutic approach targeting articular inflammation using the filarial nematode-derived phosphorylcholine-containing glycoprotein ES-62," *Journal of Immunology*, vol. 171, no. 4, pp. 2127–2133, 2003.
- [79] S. L. Atkin, M. Kamel, A. M. A. El-Hady, S. A. El-Badawy, A. El-Ghobary, and W. C. Dick, "Schistosomiasis and inflammatory polyarthritis: a clinical, radiological and laboratory study of 96 patients infected by *S. mansoni* with particular reference to the diarthrodial joint," *Quarterly Journal of Medicine*, vol. 59, no. 229, pp. 479–487, 1986.
- [80] H. I. Ismail, F. A. Sallam, and H. A. Sheer, "The pathogenesis of arthropathy in experimental Schistosomiasis mansoni," *Journal of the Egyptian Society of Parasitology*, vol. 30, no. 3, pp. 943–949, 2000.
- [81] A. Cooke, P. Tonks, F. M. Jones, et al., "Infection with *Schistosoma mansoni* prevents insulin dependent diabetes mellitus in non-obese diabetic mice," *Parasite Immunology*, vol. 21, no. 4, pp. 169–176, 1999.
- [82] L. A. B. Joosten, M. M. A. Helsen, T. Saxne, F. A. J. van De Loo, D. Heinegård, and W. B. van den Berg, "IL-1 $\alpha$  $\beta$  blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF- $\alpha$  blockade only ameliorates joint inflammation," *Journal of Immunology*, vol. 163, no. 9, pp. 5049–5055, 1999.
- [83] N. Takagi, M. Mihara, Y. Moriya, et al., "Blockage of interleukin-6 receptor ameliorates joint disease in murine collagen-induced arthritis," *Arthritis & Rheumatism*, vol. 41, no. 12, pp. 2117–2121, 1998.
- [84] A. Kavanaugh, "Interleukin-6 inhibition and clinical efficacy in rheumatoid arthritis treatment—data from randomized clinical trials," *Bulletin of the NYU Hospital for Joint Diseases*, vol. 65, supplement 1, pp. S16–S20, 2007.
- [85] M. Tunyogi-Csapo, K. Kis-Toth, M. Radacs, et al., "Cytokine-controlled RANKL and osteoprotegerin expression by human and mouse synovial fibroblasts: fibroblast-mediated pathologic bone resorption," *Arthritis & Rheumatism*, vol. 58, no. 8, pp. 2397–2408, 2008.
- [86] E. Romas, M. T. Gillespie, and T. J. Martin, "Involvement of receptor activator of NF $\kappa$ B ligand and tumor necrosis factor- $\alpha$  in bone destruction in rheumatoid arthritis," *Bone*, vol. 30, no. 2, pp. 340–346, 2002.
- [87] E. Lubberts, B. Oppers-Walgreen, A. R. Pettit, et al., "Increase in expression of receptor activator of nuclear factor  $\kappa$ B at sites of bone erosion correlates with progression of inflammation in evolving collagen-induced arthritis," *Arthritis & Rheumatism*, vol. 46, no. 11, pp. 3055–3064, 2002.
- [88] E. Romas, O. Bakharevski, D. K. Hards, et al., "Expression of osteoclast differentiation factor at sites of bone erosion in collagen-induced arthritis," *Arthritis & Rheumatism*, vol. 43, no. 4, pp. 821–826, 2000.
- [89] A. Reddy and B. Fried, "An update on the use of helminths to treat Crohn's and other autoimmune diseases," *Parasitology Research*, vol. 104, no. 2, pp. 217–221, 2009.
- [90] R. W. Summers, D. E. Elliot, J. F. Urban Jr., R. Thompson, and J. V. Weinstock, "*Trichuris suis* therapy in Crohn's disease," *Gut*, vol. 54, no. 1, pp. 87–90, 2005.
- [91] R. W. Summers, D. E. Elliott, J. F. Urban Jr., R. A. Thompson, and J. V. Weinstock, "*Trichuris suis* therapy for active ulcerative colitis: a randomized controlled trial," *Gastroenterology*, vol. 128, no. 4, pp. 825–832, 2005.
- [92] K. Mortimer, A. Brown, J. Feary, et al., "Dose-ranging study for trials of therapeutic infection with *Necator americanus* in humans," *American Journal of Tropical Medicine and Hygiene*, vol. 75, no. 5, pp. 914–920, 2006.

- [93] P. Velupillai, W. E. Secor, A. M. Horauf, and D. A. Harn, "B-1 cell (CD5<sup>+</sup>B220<sup>+</sup>) outgrowth in murine schistosomiasis is genetically restricted and is largely due to activation by polylactosamine sugars," *Journal of Immunology*, vol. 158, no. 1, pp. 338–344, 1997.
- [94] O. Atochina, A. A. Da'dara, M. Walker, and D. A. Harn, "The immunomodulatory glycan LNFPIII initiates alternative activation of murine macrophages in vivo," *Immunology*, vol. 125, no. 1, pp. 111–121, 2008.
- [95] P. Smith, R. E. Fallon, N. E. Mangan, et al., "*Schistosoma mansoni* secretes a chemokine binding protein with antiinflammatory activity," *Journal of Experimental Medicine*, vol. 202, no. 10, pp. 1319–1325, 2005.
- [96] T. Kumagai, Y. Osada, N. Ohta, and T. Kanazawa, "Peroxiredoxin-1 from *Schistosoma japonicum* functions as a scavenger against hydrogen peroxide but not nitric oxide," *Molecular and Biochemical Parasitology*, vol. 164, no. 1, pp. 26–31, 2009.
- [97] S. Donnelly, C. M. Stack, S. M. O'Neill, A. A. Sayed, D. L. Williams, and J. P. Dalton, "Helminth 2-Cys peroxiredoxin drives Th2 responses through a mechanism involving alternatively activated macrophages," *FASEB Journal*, vol. 22, no. 11, pp. 4022–4032, 2008.
- [98] G. Schramm, F. H. Falcone, A. Gronow, et al., "Molecular characterization of an interleukin-4-inducing factor from *Schistosoma mansoni* eggs," *Journal of Biological Chemistry*, vol. 278, no. 20, pp. 18384–18392, 2003.
- [99] Y. Kina, S. Fukumoto, K. Miura, et al., "A glycoprotein from *Spirometra erinaceieuropaei* plerocercoids suppresses osteoclastogenesis and proinflammatory cytokine gene expression," *International Journal for Parasitology*, vol. 35, no. 13, pp. 1399–1406, 2005.
- [100] N. Acevedo, J. Sánchez, A. Erler, et al., "IgE cross-reactivity between *Ascaris* and domestic mite allergens: the role of tropomyosin and the nematode polyprotein ABA-1," *Allergy*, vol. 64, no. 11, pp. 1635–1643, 2009.
- [101] J. J. Reece, M. C. Siracusa, T. L. Southard, C. F. Brayton, J. F. Urban Jr., and A. L. Scott, "Hookworm-induced persistent changes to the immunological environment of the lung," *Infection and Immunity*, vol. 76, no. 8, pp. 3511–3524, 2008.
- [102] F. Annunziato, L. Cosmi, F. Liotta, E. Maggi, and S. Romagnani, "Type 17 T helper cells—origins, features and possible roles in rheumatic disease," *Nature Reviews Rheumatology*, vol. 5, no. 6, pp. 325–331, 2009.
- [103] S. Babu, S. Q. Bhat, N. P. Kumar, et al., "Human type 1 and 17 responses in latent tuberculosis are modulated by coincident filarial infection through cytotoxic T lymphocyte antigen-4 and programmed death-1," *Journal of Infectious Diseases*, vol. 200, no. 2, pp. 288–298, 2009.
- [104] Y. Yang, J. Weiner, Y. Liu, et al., "T-bet is essential for encephalitogenicity of both Th1 and Th17 cells," *Journal of Experimental Medicine*, vol. 206, no. 7, pp. 1549–1564, 2009.



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