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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/IFNγ 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, Ruyssers 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-β, 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-β 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 (AAMϕ) 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 schsitosome 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	*Schistosoma mansoni*	Infection	IL-17 ↓, TNF-α ↓, IL-6 ↓, RANKL ↓, Anti-collagen IgG ↓	[47]
		Ascaris suum	Worm Ag		[37]
		Acanthocheilonema viteae	Purified Ag (ES-62)	IFN-γ ↓, TNF-α ↓, IL-6↓, Anti-collagen IgG↓	[78]
Experimental autoimmune encephalomyelitis (EAE)	Th17	*Schistosoma mansoni*	Infection	IL-12p40↓, IFN-γ ↓, TNF- α ↓, IL-4↑	[24]
			Egg	IFN- γ ↓, IL-4↑, TGF-β ↑, IL-10↑	[25]
		Schistosoma japonicum	Egg Ag	IFN-γ ↓, IL-4↑	[26]
		Fasciola hepatica	Infection	IFN-γ ↓, IL-17↓, Dependent on TGFβ	[49]
		Trichinella spiralis	Infection		[27]
Type 1 diabetes in NOD mice	Th1?	*Schistosoma mansoni*	Infection, Eggs	Inhibition of Ab class switch (Anti-insulin IgG↓)	[81]
			Egg Ag	Treg	[32]
		Litomosoides sigmodontis	Infection, Worm Ag	IL-4↑, IL-5↑, Treg	[39]
		Heligmosomoides polygyrus	Infection	Independent of IL-10 and Treg	[40]
Streptozotocin-induced diabetes	Th1?	*Taenia crassiceps*	Infection	AAMϕ	[45]
TNBS/DNBS-induced colitis	Th1? / Th17?	*Schistosoma mansoni*	Infection	IL-2 ↑, IL-4 ↑	[30]
			Eggs	IFN-γ ↓, IL-4↑	[29]
			Worm Ag	IFN-γ ↓, IL-17↓, TGF-β ↑, IL-10↑	[28]
		Schistosoma japonicum	Egg Ag	IFN-γ ↓, IL-4↑, IL-10↑, Treg	[31]
		Hymenolepis diminuta	Infection	IL-10↑	[41, 44]
Piroxicam-induced colitis	Th17?	*Heligmosomoides polygyrus*	Infection	IL-17↓, Independent of IL-10	[48]
DSS-induced colitis	Th17? / Th2?	*Schistosoma mansoni*	Infection (male worm)	Macrophage infiltration	[64]
Systemic anaphylaxis	Th2	*Schistosoma mansoni*	Infection	IL-10-producing Bcell	[34]
Asthma/Airway hypersensitivity or inflammation	Th2	*Schistosoma mansoni*	Infection (male worm)	IL-5 ↓, IL-10 ↑	[33]
		Schistosoma japonicum	Egg Ag, Eggs	Treg	[35]
		Heligmosomoides polygyrus	Infection	Treg	[36]
		Ascaris suum	Purified Ag (PAS-1)	IL-4↓, IL-5↓, Eotaxin↓, RANTES ↓, IL-10↑	[38]
			Worm Ag	IL-4↓, IL-5↓, Eotaxin↓, IgE↓	[42]
		Litomosoides sigmodontis	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-β. 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 effecter 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 AAMϕ [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 AAMϕ in anti-diabetic effects was suggested in experimental tapeworm infection [45]. On the other hand, schistosome-modulated macrophages (but NOT AAMϕ) 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 .

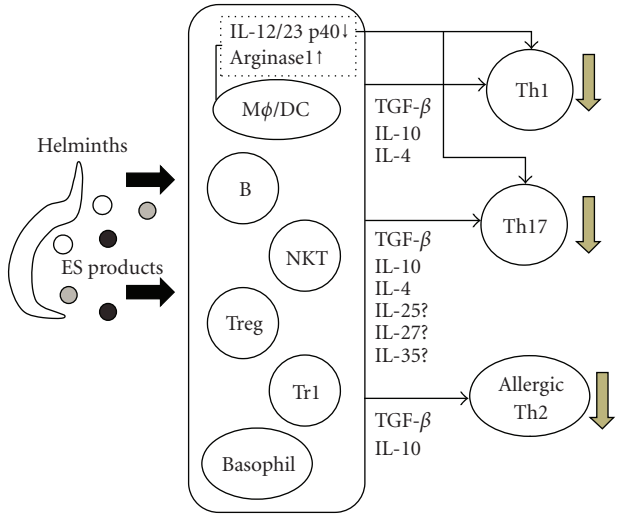

Figure 1: Possible involvement of immune cells and mediators in the helminth-induced immunomodulation on T helper subsets. Substances contained in the bodies of helminths or their excretory secretory (ES) products are recognized by innate immune cells via PAMPs receptors like TLRs. Thereafter, various 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.

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/IFNγ axis in CIA has been controversial [66, 67], recent findings suggest that IFNγ 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 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-1β 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 NFκB 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-α, and IL-1β [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, TNFα, 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-arthritic effects were observed only in the viable worm infected mice. Likewise, Hunter et al. showed that anticolitic 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 schsitosome eggs is an oligosaccalide 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 schsitosome 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-arthritic effects, a glycoprotein from *Spirometra erinaceieuropaei* was shown to suppress RANKL-induced osteoclastogenesis, suggesting that there may be more anti-arthritic substances in various helminths [99].

6. Concluding Remarks

Helminth-based immunotherapy for immnunological 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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