

Helminths and Asthma

Risk and Protection



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KEYWORDS

- Helminths • Asthma • Type 2 response • Regulatory molecules • Symptoms
- Anthelmintic treatment

KEY POINTS

- Type 2 response is the main response involved in both asthma and helminth infections. Some helminths may induce protection or worsen symptoms of asthma.
- The duration of infection, parasite load, and helminth species are factors that may influence the modulation of the immune response in asthma.
- Antigens derived from helminths with immunomodulatory properties may be new therapeutic candidates for asthma treatment or prevention.

INTRODUCTION

It is estimated that more than 1.5 billion people are infected by at least 1 species of geohelminths,¹ and more than 230 million people are infected by *Schistosoma* spp.² The prevalence of these infections is widely distributed, especially in less affluent communities.^{1,3} In general, the symptoms are similar between species, including gastrointestinal manifestations, malnutrition, general malaise, and weakness. However, some species (*Necator americanus*, *Ancylostoma duodenale*, *Strongyloides stercoralis* and *Ascaris lumbricoides*) that bear a lung cycle can induce respiratory symptoms, such as cough, shortness of breath and wheezing.

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Asthma affects more than 350 million people worldwide.⁴ It is heterogeneous and complex, with a variety of clinical phenotypes. Although asthma has been associated with increased urbanization, the mechanisms of this relationship are unclear.⁵ The hygiene hypothesis proposed by Strachan in 1989⁶ attempted to explain why asthma and other allergic diseases were increasing in industrialized countries. A possible explanation for this trend was a low early exposure to viral and bacterial antigens, which induce a T helper 1 (T_H1)-type response and result in lack of regulation of the immune system, predisposing to the type 2 immune response in newborns, which is associated with allergic diseases.^{6,7} Several studies also have shown that helminth infection, by stimulating regulatory T cells (Tregs) and inducing the production of interleukin (IL)-10 regulatory cytokines, can prevent allergy in humans^{8–10} and in animal models of asthma.^{11–13} The aim of this review is to discuss how helminth exposure may influence asthma and the potential application of helminth molecules in the prevention or treatment of asthma.

IMMUNOPATHOLOGY OF ASTHMA AND HELMINTH INFECTIONS

Although helminths and asthma induce similar immune responses, they have different characteristics (Fig. 1). The type 2 immune response is the major pathway involved in the immunopathogenesis of most cases of asthma and immunity against helminths. This response is initiated after exposure to helminths and allergens by epithelial cells, which release IL-25, IL-33, and thymic stromal lymphopoietin

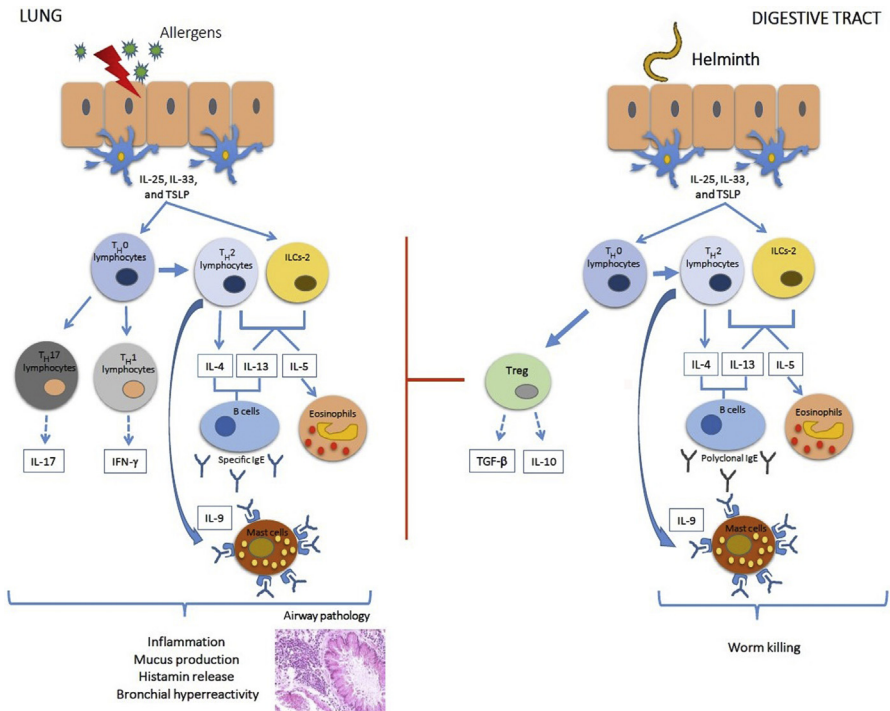


Fig. 1. Overview of the immune response in asthma (left panel) and helminth infections (right panel). Note that Tregs from helminth infections have the potential to suppress the asthmatic response in the lung.

(TSLP), inducing the cells of the innate and adaptive system to produce IL-4, IL-5, and IL-13. Different cell types, such as the innate lymphoid cells (ILCs2), basophils, eosinophils, mast cells, neutrophils, macrophages, and T lymphocytes and B lymphocytes are important in the immunopathogenesis of asthma and helminth infections. Thus, the interaction of these cells with cytokines stimulate IgE synthesis, and the release of inflammatory mediators, mucus production, and tissue remodeling. This interaction results in immunopathologic processes observed both in asthma and during a helminth infection.

It is known that the type 2 response is critical for the control of helminth infections and is the hallmark of allergic diseases.¹⁴ In addition, T_H1 cell and T_H17 cell immune responses have been associated with asthma severity (reviewed by Lambrecht and Hammad¹⁵) and diseases caused by helminthic infections (reviewed by Cortes and colleagues¹⁶ and Allen and colleagues¹⁷). In asthma, Kobayashi and colleagues¹⁸ have shown that the administration of interferon (IFN)- γ increases airway hyperresponsiveness in an animal model and other studies have associated high levels of IL-17 with resistance to corticosteroid treatment in both an asthma animal model¹⁹ and in humans.²⁰ As for helminth infections, the cytokines IFN- γ ²¹ and IL-17²² have been associated with exacerbated granulomatous inflammation in *Schistosoma mansoni*-infected patients. On the other hand, these cytokines also amplify the type 2 response to a more pathologic state in both asthma and helminthic infections, especially with *S. mansoni*. Randolph and colleagues²³ have observed that the transfer of T_H1 cells and T_H2 cells together caused more robust eosinophilic inflammation in comparison to a transfer of T_H2 cells alone in an animal model. Moreover, Irvin and colleagues²⁴ identified cells with IL-4⁺CD4⁺ T_H17 phenotype in humans, and the amount of IL-17 released by these cells in the bronchoalveolar lavage (BAL) was associated with bronchial hyperreactivity and airway obstruction. Finally, in an experimental model of schistosomiasis, the T_H17 response associated with severe hepatic granulomatous pathology was dependent on the expression of CD209a by dendritic cells,²⁵ with IL-4 or IL-13^{26,27} responsible for positively regulating expression in these cells.

A type 2 response is the main pathway of the immunopathogenesis of both asthma and helminth infections (reviewed by Cruz and colleagues²⁸); T_H1 and T_H17 responses are associated with severity, but the regulatory immune response is the great difference between them. In asthma, a reduction in Tregs has been reported in peripheral blood mononuclear cells (PBMCs) and BAL of patients with moderate to severe asthma.^{29–31} In helminth infections, Tregs seem to protect the host from an excessive inflammatory response but also may limit the protective immunity and allow persistence of the parasite.³² Because of this regulation induced by helminth infections, especially by *S. mansoni*, several studies have shown that these infections can control or prevent inflammation observed in autoimmune and allergic diseases, such as asthma^{8,10,12,13,33}

HELMINTH AND MODULATION OF THE IMMUNE RESPONSE IN ASTHMA

The life cycles of helminths are complex and, depending on the species, may include several intermediate hosts, different gateways, and migration within the host. In some species, such as *S. mansoni*, *Strongyloides stercoralis*, *A. lumbricoides*, and the hookworms, this migration can take them to the lungs. Consequently, helminths can influence lung immunopathology by direct damage to the lung tissue by the spread and deposition of eggs or release of immunomodulators.³⁴

There are 4 factors that determine the modulatory effect of helminth infections on allergic diseases: (i) duration of infection, (ii) parasite load, (iii) host genetics and (iv) helminth species.³⁵

Long-term infections seem more likely to induce immunomodulatory effects that suppresses allergic inflammation caused by parasitic and nonparasitic antigens. Layland and colleagues³⁶ observed that animals sensitized with ovalbumin (OVA) 5 weeks after infection by *S. mansoni* showed a reduction in allergic inflammation of the airways, but this did not happen when the animals were sensitized 1 week after infection. In addition, heavy infections may induce immunomodulation, whereas mild infections induce the opposite effect. Studies in an experimental model of airway hyperresponsiveness have shown that administration of larvae of *Strongyloides venezuelensis*³⁷ or larvae of *Heligmosomoides polygyrus*³⁸ induced a protective effect. In humans, hookworm-infected asthmatic individuals with a high parasite load of 48 to 1458 eggs per gram of feces presented with less wheezing.³⁹ Host genetics may influence the ability to induce immunoregulatory mechanisms in the host. The authors' group described the variant (rs3024496, G allele) and other variants within the *IL10* gene that were associated with decreased IL-10 production in peripheral blood leukocyte cultures stimulated with *A. lumbricoides* antigens and a concomitant positive association with atopy and asthma.⁴⁰ Finally, different helminth species may exert different effects on the risk of developing allergic diseases, including asthma.⁴¹ Cooper and colleagues⁴² conducted a longitudinal study in an endemic region for geohelminths and showed that although children of mothers infected with geohelminths had more wheezing, children infected during the first 3 years of life had reduced risk of wheezing.

IMPACT OF HELMINTH INFECTIONS IN ASTHMA

There are several studies associating helminth infections with asthma symptoms, especially wheezing. These associations vary when comparing studies in animal models, populations of endemic areas, and clinical trials. Some species worsen or trigger asthma symptoms and others tend to prevent them. A systematic review⁴¹ on the association of infections by intestinal parasites with asthma showed that infection with *A. lumbricoides* associated with an increased prevalence of asthma. Studies conducted in urban areas in Brazil also have shown a positive association between infection by this parasite and bronchial hyperresponsiveness in children⁴³ and associated a high parasitic load of *A. lumbricoides* with symptoms of asthma.⁴⁴ Nevertheless, another study did not observe an association of *A. lumbricoides* infection with wheezing and asthma symptoms.⁴⁵ A possible explanation for the effects of *A. lumbricoides* infection is its pulmonary cycle, because symptoms of asthma may be due to inflammation of the airways caused by migration of the larva or by an increased T_H2 inflammatory response. Other species, such as *Toxocara* spp.^{46,47} and *Strongyloides* spp, also are associated with asthma symptoms. The seroprevalence of *Toxocara* spp has been positively associated with high levels of total IgE and specific IgE to allergens, positive skin tests to allergens, and asthma prevalence and morbidity.⁴⁸ Other studies, meanwhile, have observed seropositivity to *Toxocara* spp associated with atopy but not with wheezing/asthma in children.^{49,50} Regarding infection by *Strongyloides* spp, several studies have shown that *Strongyloides stercoralis* infection seems to mimic exacerbations of asthma, which may be refractory to the usual treatment of asthma.^{51,52} Notwithstanding, a meta-analysis did not report any significant effect of *Strongyloides stercoralis* infection on the risk of asthma.⁴¹ Other species of helminths, such as *Trichuris trichiura*^{41,45} and *Enterobius vermicularis*,^{41,53} do not seem to be risk factors for asthma.

What has motivated scientific interest are the species that can modulate the immune response in asthma and, consequently, prevent its symptoms. The most encouraging results were observed with *S mansoni* infection. Several observations in animal models have demonstrated that infection by this helminth seems to prevent against the development of allergies, including asthma.^{12,54,55} In relation to studies of *S mansoni*-infected individuals, Medeiros and colleagues⁵⁶ have shown that asthmatic individuals living in an endemic area for *S mansoni* had a milder course of asthma at 1 year of follow-up compared with asthmatics not living in an endemic area of *S mansoni*. Additionally, it was shown that PBMCs from asthmatic individuals living in an endemic area and infected with *S mansoni* produced lower levels of IL-4 and IL-5 and higher levels of the regulatory cytokine IL-10.⁹

Hookworm infections also seem to protect against wheezing, asthma, and allergic diseases.⁴¹ In a double-blind, placebo-controlled study, however, Feary and colleagues⁵⁷ showed that skin administration of 10 larvae of *N americanus* to asthmatic subjects did not result in improved bronchial hyperresponsiveness or other measures of asthma control. The infection was well tolerated, indicating that other studies that mimic natural infection are feasible and could be performed.

The impact of helminthic coinfections also has been studied. Alcântara-Neves and colleagues³³ found no association between the number of different current helminth infections with asthma, regardless of atopic status, in children in Latin America.

There are few studies reporting the capacity of helminthic infections to induce regulation when allergy is established. Wilson and colleagues³⁸ and Negrão-Corrêa and colleagues³⁷ observed that administration of *H polygyrus* and *Strongyloides venezuelensis*, respectively, after establishment of airway inflammation by OVA, were able to suppress allergic airways inflammation in the animal model. The first study noted that infection by *H polygyrus*, intestinal helminth of rodents, elicited Tregs that modulated allergen-induced pathology in vivo, with a reduction in numbers of eosinophils in the BAL. The second study observed that infection reduced airway hyperresponsiveness 48 hours after OVA challenge.

Overall, although the results of studies are highly variable, helminth infections appear to reduce asthma morbidity. Ponte and colleagues⁵⁸ performed a country-wide ecological study in Brazil and observed that populations exposed to infections by *S mansoni* and intestinal helminths had lower hospitalization rates due to asthma.

EFFECT OF ANTIHELMINTH TREATMENT ON ASTHMATICS

One way to investigate the impact of helminth infections on asthma is to treat the infections and observe any variation on asthma control. The reports vary depending on the species of helminth targeted by the treatment. A study conducted in asthmatics in Venezuela, where *A lumbricoides* and *T trichiura* infection were predominant, found that after treatment with albendazole subjects improved in symptoms of asthma.⁵⁹ Studies performed in children in an area endemic to geohelminths in Ecuador⁶⁰ and in a semiurban area in Uganda⁶¹ found no association between anthelmintic treatment with asthma symptoms.

On the other hand, the authors' group conducted a double-blind, placebo-controlled study to assess the influence of anthelmintic treatments on asthma severity in individuals living in an area endemic for schistosomiasis and geohelminths. A clinical worsening of the disease was observed after 6 months and 12 months of treatment with anthelmintics.⁶²

Overall, *S. mansoni* is the parasite that consistently induces protection against development of allergies. Furthermore, several antigens of this parasite have been reported to prevent immune-mediated diseases of both T_H1 and T_H2 profiles.

IMMUNOMODULATORY MOLECULES OF HELMINTHS

Because helminth infections can modulate the exacerbated inflammatory response in asthma and consequently reduce its severity, researchers have investigated the potential for molecules derived from these parasites in exerting a regulatory function. A murine model of OVA-induced asthma showed that administration of excretory/secretory products of the helminth *Fasciola hepatica* reduced the accumulation of mucus, eosinophils, and lymphocytes in the airways of allergen challenged mice.⁶³ Recombinant proteins of *S. mansoni*, Sm22.6, Sm29, and PIII¹³ or the antigen derived from schistosomula tegument (Smteg)⁶⁴ also were able to regulate the production of IL-5 and IL-13 and subsequent BAL eosinophilia in an experimental model of asthma. In addition, both studies observed that parasitic antigens are able to reduce lung inflammation and serum levels of OVA-specific IgE. The reduction observed in these inflammatory parameters was associated with increased levels of IL-10 and/or frequency of Tregs.⁶⁴ A study evaluating the effect of *Nippostrongylus brasiliensis* excretory-secretory products on the development of asthma in a murine model showed that reduction in IL-4 and IL-5 levels in the airways was independent of the presence of Toll-like receptors 2 and 4, IFN- γ , and, most importantly, IL-10.⁶⁵ In addition, Pitrez and colleagues⁶⁶ noted that different extracts of helminths inhibited lung allergic inflammation in mice and that IL-10 does not seem to play a central role in some helminth-host interactions. The investigators also point out that early exposure to helminth extracts could be a potential strategy to explore primary prevention in asthma.

Recently, the authors' group evaluated the in vitro effect of the *S. mansoni* Sm29 antigen on activation/regulation markers and T_H2 cytokine production by T lymphocytes from subjects with severe asthma. In addition to increased production of IL-10 by PBMCs from these individuals, the authors noticed that the antigen induced an increase in the frequency of Treg lymphocytes (ie, $CD4^+CD25^{high}$ T cells) and a decrease in the frequency of activated T lymphocytes (ie, $CD4^+CD25^{low}$ and $CD4^+CD69^+$ T cells).¹⁰ Moreover, the addition of the Sm29 antigen reduced the frequency of $CD4^+IL-5^+$ and $CD4^+IL-13^+$ T lymphocytes in the group of individuals with severe asthma, whereas the levels of IL-10 in PBMCs stimulated with the allergen *Der p1* were increased.¹⁰

There are several mechanisms by which helminth-derived products can modulate the inflammatory response in asthma. Some of the main reports are summarized in **Table 1**. The induction of IL-10 seems to be the main helminth antigen-mediated mechanism of protection by modulating the exacerbated inflammatory response in asthma.⁶⁵ There are other regulatory mechanisms, however, induced by helminth-derived products, involving the induction of regulatory lymphocytes, dendritic cells, macrophages, and cytokines, such as transforming growth factor β and IL-35 (reviewed by Logan and colleagues⁶⁷).

Clinical trials have shown helminth products can benefit individuals with inflammatory diseases.⁶⁸ In asthma, most studies have been conducted in vitro or in an experimental model. Thus, clinical trials with these helminths derived molecules are needed. The identification of a molecule with immunomodulatory properties against asthma may open a new phase in the therapy and control of this disease.

Table 1
Helminth antigens involved in the modulation of the inflammatory response in asthma

Helminth Antigen	Model of Asthma	Mechanisms of Protection	Reference
<i>Fasciola hepatica</i> excretory-secretory products	Murine model of OVA-induced asthma	↓ mucus, eosinophils, and lymphocytes in the airways	Finlay et al, ⁶³ 2017
Recombinant proteins of <i>S. mansoni</i> (Sm22.6, Sm29, and PIII) Antigen derived from Smteg	Murine model of OVA-induced asthma	↓ IL-5, IL-13 and eosinophils in BAL ↓ inflammatory cells in the lungs ↓ OVA-specific IgE ↑ IL-10 and Tregs	Cardoso et al, ¹³ 2010; Marinho et al, ⁶⁴ 2016
<i>Nippostrongylus brasiliensis</i> excretory-secretory products	Murine model of OVA-induced asthma	↓ IL-5 in the airways independent of IL-10 production	Trujillo-Vargas et al, ⁶⁵ 2007
Different extracts of helminths (<i>Angiostrongylus costaricensis</i> , <i>Angiostrongylus cantonensis</i> , and <i>A. lumbricoides</i>)	Murine model of OVA-induced asthma	↓ lung allergic inflammation independent of IL-10 production	Pitrez et al, ⁶⁶ 2015
Recombinant <i>S. mansoni</i> Sm29 antigen	PBMC of asthmatic individuals	↑ IL-10 levels in supernatants ↑ CD4 ⁺ CD25 ^{high} ↓ CD4 ⁺ CD25 ^{low} and CD4 ⁺ CD69 ⁺ -activated cells ↓ CD4 ⁺ IL-5 ⁺ and CD4 ⁺ IL-13 ⁺	de Almeida et al, ¹⁰ 2017

FUTURE CONSIDERATIONS AND SUMMARY

A protective role of helminthic infections on the development of allergic diseases, such as asthma, has been reported. Although infections by *S. mansoni* have been consistently associated with protection, species of geohelminths have been related to increased symptoms of asthma. Helminth species and several other factors, such as host genetics, parasite load, coinfections, environment, poverty, timing, and duration of infection, may influence the modulation of the immune response and disease outcomes. The potential benefits of helminth infection in preventing asthma have been observed in animal models and in some observations of endemic area populations. Regarding the therapeutic potential of parasites for asthma, there are some positive observations in animal models and, to date, no significant results in clinical trials. Nonetheless, several experimental studies have demonstrated the regulatory potential of helminth antigens for asthma and, as such, deserve further investigation with the potential goal of primary prevention and/or novel treatment of asthma and allergies.

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