Review Article

Interrelationship among asthma, atopy, and helminth infections*

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Abstract

To describe the principal evidence in the literature regarding the interrelationship among helminth infections, atopy, and asthma, a nonsystematic review of the literature was conducted. Among the publications on the subject, we found a number in which there was controversy regarding the capacity of geohelminth infections to inhibit responsiveness to skin allergy tests and to minimize the symptoms of allergic diseases. However, although small in number, studies of patients infected with *Schistosoma* spp. suggest that these helminths can inhibit the responsiveness to skin allergy testing and minimize asthma symptoms. Evidence provided by *in vitro* studies suggests that helminthiases inhibit T helper 1- and T helper 2-type immune responses. This opens new therapeutic possibilities for the treatment of immune system diseases.

Keywords: Asthma; Helminths; Hypersensitivity; Epidemiology.

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Introduction

Despite the great scientific advances in the area of immunology and the new therapeutic options available, the prevalence of allergic diseases, such as asthma and rhinitis, has increased in developed countries.[1,2] However, the prevalence of asthma is low in developing countries.[3] It is important to find explanations for this fact, which is possibly related to the influence of the environment on the immune system.

In rich countries, the reduced exposure to infectious agents is among the environmental factors that can modify the immune system of human beings and contribute to the increase in the prevalence of allergic diseases. Helminth infections, for example, are rare in developed countries. In view of this, various studies have been conducted in recent years in attempts to ascertain whether the absence of exposure to helminth infections can contribute to the appearance of allergic diseases. In addition, there is the need to reveal the immunopathological mechanisms that could determine the inhibition of allergic responses in individuals infected with helminths.

A more in-depth investigation of the subject could identify alternatives for new treatments for immune system diseases. One of these alternatives is the use of helminth antigens in the development of vaccines for the treatment of allergic and autoimmune diseases. The objective of this article is to describe the principal evidence in the literature regarding the interrelationship among helminth infections and allergy.

Immune response in allergic diseases and helminth infections

One of the functions of the immune system is to protect the individual against infectious agents. However, dysfunction of this system can be the cause of diseases such as allergies and autoimmune diseases. The immune system acts through two patterns of acquired immune response: the T helper 1 (Th1) immune response; and the T helper 2 (Th2) immune response. The Th1 immune response occurs in autoimmune diseases, as well as in reaction to viral and bacterial infections. The Th2 immune response occurs in the reaction to helminth infections and in allergic diseases, such as asthma, rhinitis, and eczema.

In the Th2 immune response, allergens or helminth antigens stimulate T lymphocytes to produce Th2 cytokines, such as interleukin (IL)-4 and IL-5, IL-4 inducing B lymphocytes to produce immunoglobulin E (IgE), whereas IL-5 attracts and activates eosinophils. Eosinophilia and an increased serum level of IgE are, therefore, characteristics of the Th2 response. A portion of the IgE produced during the Th2 response is antigen-specific. When specific IgE binds to high-affinity receptors on the surface of mastocytes and basophils, it primes the immune system for allergic reactions to any exposure to the allergen. The Th2 immune response is reinforced whenever the antigen binds to specific IgE on the surface of mastocytes, which undergo degranulation, releasing mediators of the immediate allergic reaction (histamine, prostaglandins, and leukotrienes) as well as proinflammatory cytokines (IL-4, IL-13, and the regulated upon activation, normal T-cell expressed and secreted cytokine).[4,5]

Not all Th2 responses are equal. In the immune response to helminth infections, such as those caused by *Schistosoma mansoni*,[6,7] *S. haematobium*,[8] and *Onchocerca volvulus*,[9] in addition to the increased production of IL-4 and IL-5, there is also increased production of IL-10. Since IL-10 is a cytokine with immunosuppressive action, it seems to be important in the establishment of the immunological tolerance of the host to these helminths, which, in some cases, survive for up to 30 years.[10] However, in other helminth infections, as in the case of infection with *Ascaris lumbricoides*, the production of IL-10 is not increased.[11-13] In the Th2 response observed in allergic diseases, IL-10 production is decreased,[14,15] and the haplotype that determines the increased production of this cytokine is less common in patients with asthma than in patients without asthma.[16] It is considered plausible that production of IL-10 decreases in allergic diseases, since it is likely that the anti-inflammatory effect of this cytokine prevents the progression of the allergic inflammation.

Epidemiology of allergic diseases and the hygiene hypothesis

A study entitled The International Study of Asthma and Allergies in Childhood carried out a lengthy investigation of the prevalence of asthma worldwide. In that study, the prevalence of

wheezing in 13- and 14-year-old children in the last year varied considerably, ranging from 2.1% in Indonesia to 32.2% in England. In Brazil, the prevalence was 23.3%. In industrialized Western countries where English is the official language, as well as in some countries in Latin America, the prevalence of asthma is higher than in most developing countries.[3] Although genetic factors are known to play an important role in the variability of the prevalence of asthma worldwide, genetic factors cannot account for the recent sharp increase in the prevalence of asthma, allergic rhinitis, eczema, and allergy skin test reactivity seen in various countries.[1,2] This increase is probably related to the environmental changes that have occurred in recent decades.

Among the environmental factors that can influence the appearance of allergic diseases are childhood infections. In neonates, the immunological activity in the population of T lymphocytes in the umbilical core is predominantly Th2, similar to what happens in allergic individuals.[17] It is possible to suppose that there is a natural predisposition to the development of allergic diseases in childhood, and that the infectious diseases acquired at this age contribute the development of balanced immunological activity, thereby preventing the appearance of allergies. This is the hygiene hypothesis,[18] which has the support of publications that have demonstrated an inverse correlation between allergy and exposure to viral, bacterial, and helminth infections.[20-24] According to the hygiene hypothesis, the vaccination and sanitation policies implemented in recent decades in developed countries prevent infectious diseases in childhood, which hinders the immunological balance, thereby explaining the increased prevalence of allergic diseases.

Helminth infections and allergy

Studies evaluating the interrelationship among helminth infection, allergy skin test reactivity, and symptoms of allergic diseases have provided controversial results. In cross-sectional studies involving allergy skin tests, it has been shown that, among individuals infected with the helminths *S. mansoni* or *S. haematobium*, a small proportion test positive for aeroallergens.[8,23] In a retrospective study, one group of authors demonstrated that the frequency of symptoms indicative of asthma, a disease associated with atopy, is lower in patients infected with *S. mansoni*,[25] suggesting that this helminth can inhibit allergic airway inflammation. Population studies have demonstrated that infections with geohelminths (*A. lumbricoides*, *Trichuris trichiura*, and *Ancylostomidae*) also inhibit allergy skin test reactivity and the prevalence of wheezing, which is an indicator of asthma.[24-26] In a clinical trial, treatment with albendazole and praziquantel was shown to increase skin reactivity to aeroallergens in a population of individuals infected with geohelminths,[27] suggesting that it is the infection that inhibits the allergy, and not the allergy that protects against the infection.

Some studies, however, have demonstrated that patients infected with geohelminths present a higher frequency of allergy skin test reactivity.[28,29] In addition, a clinical trial with patients residing in slums demonstrated that treatment with albendazole reduces asthma symptoms,[30] suggesting that geohelminth infection could worsen the allergic airway inflammation in these patients. Furthermore, a cross-sectional study and a clinical trial,[31,32] both of which were published recently, suggest that geohelminth infections have no effect on asthma symptoms or on allergy skin test reactivity (Table 1).

Some explanations for these conflicting results have been proposed. Since many helminths have a pulmonary cycle in the acute phase of the infection, it is possible that, during this phase, there is a worsening of asthma symptoms, and that, during the chronic phase of infection, the symptoms improve. Another potential explanation is related to the parasite load of the population. It is possible that inhibition of allergic manifestations occurs only in infected individuals with a high parasite load. Some studies indicate that the allergy skin test reactivity is not inhibited, or is only slightly inhibited, in individuals with a low parasite load,[13,31] thereby supporting this hypothesis. However, other studies have demonstrated that inhibition of allergy skin test reactivity,[24] as well as amelioration of asthma symptoms,[33] occur with equal frequency in individuals with a high parasite load and in those with a low parasite load. Another possible explanation is that the lower capacity of geohelminths for stimulating the production of immunosuppressive cytokines, such as IL-10, results in a lower capacity for inhibiting the allergic inflammation.[11-13] The helminths *S. mansoni* and *S. haematobium* induce increased IL-10 production,[6-8] which could make them more capable of inhibiting allergic inflammation.

Table 1 - Studies evaluating the influence of geohelminth infections and infection with *Schistosoma* spp. on allergy skin test reactivity and on asthma symptoms.

Study design	Reference	Helminth	Effect
Clinical trial	Am J Respir Crit Care Med 156:50-4, 1997	Geohelminths	Induce
Prospective study	J Allergy Clin Immunol 102:414-20, 1998	Geohelminths	Induce
Cross-sectional study	Int Arch Allergy Immunol 123:145-8, 2000	*Schistosoma* spp.	Inhibit
Cross-sectional study	Lancet 356:1723-7, 2000	*Schistosoma* spp.	Inhibit
Cross-sectional study	Lancet 358:1493-9, 2001	Geohelminths	Induce
Cross-sectional study	Am J Respir Crit Care Med 165:1489-93, 2002	Geohelminths	Induce
Cross-sectional study	J Allergy Clin Immunol 111:995-1000, 2003	Geohelminths	Inhibit
Cross-sectional study	Am J Respir Crit Care Med 167:1369-73, 2003	Geohelminths	Inhibit
Prospective study	J Allergy Clin Immunol 111:947-51, 2003	*Schistosoma* spp.	Inhibit
Prospective study	J Infect Dis 190:1797-803, 2004	*Schistosoma* spp.	Inihibit
Clinical trial	J Infect Dis 189:892-900, 2004	Geohelminths	Inhibit
Cross-sectional study	Clin Exp Allergy 35:301-7, 2005	Geohelminths	No influence
Cross-sectional study	Ann Asthma Allergy Immunol 96:713-8, 2006	Geohelminths	No influence
Clinical trial	Lancet 13;367:1598-603, 2006	Geohelminths	No influence
Meta-analysis	Am J Respir Crit Care Med 174:514-23, 2006	Geohelminths	No influence
Cross-sectional study	Allergy 61:996-1001, 2006	Geohelminths	No influence
Cross-sectional study	Clin Exp Allergy 36:640-8, 2006	Geohelminths	Induce
Cross-sectional study	Int Arch Allergy Immunol 139:317-24, 2006	Geohelminths	Induce

Mechanisms by which by helminth infections inhibit allergies

Despite the current controversy regarding the subject, some hypotheses have been formulated to explain the potential mechanism by which allergy skin test reactivity is inhibited and symptoms are minimized in individuals infected with helminths. Initially, it was believed that the Th1 immune response had an antagonistic action to that of the T2 immune response, one inhibiting the other.[34] Therefore, it would be expected that viral and bacterial infections, which trigger a Th1 immune response, would inhibit the allergic inflammation (Th2), and that helminth infections (Th2) would stimulate the appearance of the allergic inflammation. However, this polarized form of classifying the immune response is too simplistic to be applied to human beings, in whom the Th1 cytokines participate in the inflammatory process of allergic diseases (Th2), (35,36) as well as in the inflammatory process of autoimmune diseases (Th1).[37,38] In addition, as described previously, some studies have suggested that helminth infections (Th2 response) inhibit the appearance of allergies (also Th2 response), which is incompatible with the polarized model of immune response (Table 2).

Table 2 - Characteristics of T helper 1 and T helper 2 immune responses.

	Th1 immune response	Th2 immune response
Cytokines involved	Interferon gamma	Interleukin-4 and interleukin-5
Participation of IgE	Absent	Present
Participation of IgG	Present	Absent
Participation of eosinophils	Absent	Present
Participation of mastocytes	Absent	Present
Participation of lymphocytes	Present	Present
Participation of neutrophils	Present	Absent
Pathologies	Autoimmune diseases and response to viral and bacterial infections	Allergic diseases and response to helminth infections

Th1: T helper 1 lymphocytes; Th2: T helper 2 lymphocytes; IgE: immunoglobulin E; IgG: immunoglobulin G.

Currently, one of the most widely accepted pathophysiological models to explain how helminth infections inhibit allergy involves the induction of regulatory mechanisms capable of limiting exacerbated Th1 and Th2 immune responses, which would prevent the appearance not only of allergic diseases, but also of autoimmune diseases. This would be achieved by regulatory cells,[39] as well as by immunosuppressive cytokines such as IL-10.[40,41]

The regulatory cells are lymphocytes and can be grouped into two main categories: $CD4/CD25^+$ regulatory cells and antigen-specific regulatory T-cells, both of which are important in the control of the allergic inflammation. The immunosuppressive effect of $CD4/CD25^+$ is exerted primarily through cell-cell contact, whereas that of antigen-specific regulatory cells occurs as a result of the secretion of IL-10 and of transforming growth factor beta.[42]

The role of regulatory cells in the inhibition of the Th2 immune response has been demonstrated *in vitro*: $CD4/CD25^+$ regulatory cells were shown to inhibit the proliferation of $CD4^+/CD25^-$ cells, as well as the production of IL-4 and IL-5, in atopic and nonatopic individuals.[43] *In vivo*, immunotherapy with grass pollen has been shown to induce the production of $CD4/CD25^+$ cells, which possibly contributes to the improvement of symptoms in allergic individuals who are submitted to this therapy.[41] In individuals infected with helminths, regulatory T-cells promote a state of immunosuppression,[44] leading to inhibition of the allergic inflammation.

Studies indicate that IL-10 also plays an important role in the inhibition of allergic inflammation in individuals with helminth infection. Individuals with allergic diseases have a decreased production of this cytokine,[14,15] whereas certain helminth infections, in turn, are highly likely to induce IL-10 production.[6-9] Some authors have demonstrated that, in individuals infected with *S. haematobium*, IL-10 inhibits the proliferation of peripheral blood mononuclear cells, which induces a state of anergy and contributes to controlling the allergic inflammation.[45] In other studies, it has been shown that, in individuals infected with *S. haematobium*, increased IL-10 production is associated with lower allergy skin test reactivity,[8] and that, in individuals infected with *S. mansoni*, IL-10 inhibits peripheral blood mononuclear cell production of Th2 cytokines.[7] In addition, the treatment of individuals infected with helminths promotes a decrease in IL-10 production,[7] as well as an increase in the skin response to aeroallergens,[27] thereby underscoring evidence that IL-10 plays an important role in the inhibition of allergic inflammation in individuals with helminth infection.

Another mechanism by which allergic responses are inhibited in patients with helminth infection is related to increased production of nonspecific IgE in infected patients. The nonspecific IgE saturates the IgE receptors on the surface of mastocytes, thereby preventing the specific IgE from binding with the allergens. Consequently, the allergens do not cause degranulation of mastocytes, and allergic inflammation is thus prevented. In one study, it was demonstrated that inhibition of the skin response to aeroallergens in individuals with helminth infection is associated with increased production of total IgE, thereby strengthening this hypothesis.[24] However, there are arguments against this model. Epidemiological studies have indicated that inhibition of the skin response to aeroallergens in individuals infected with geohelminths is not associated with high serum levels of total IgE.[8,33] In addition, there is evidence that the concentration of nonspecific IgE necessary to saturate the receptors on the surface of the mastocytes is very high, considerably higher than that found in most patients with helminth infection.[46] This occurs because the concentration of IgE receptors is regulated at the surface of the mastocytes, where higher serum levels of IgE induce an increase in the concentration of receptors, making it possible for the specific IgE to find receptors available for binding.[47]

Exposure to infections also protects against autoimmune diseases

Since the regulatory mechanisms induced by infectious agents also inhibit the exacerbated Th1 immune response,[48-50] it is expected that infections are capable of preventing the appearance of autoimmune diseases. Similar to what has occurred with allergic diseases, the prevalence of autoimmune diseases has increased in developed countries,[51-55] reflecting the influence of environmental factors. There is evidence that individuals who live in environments where there is a greater risk of infection are less likely to develop autoimmune diseases.[56,57] In addition, a clinical trial has demonstrated that exposure to helminths inhibits the clinical manifes-

tations of Crohn's disease and ulcerative rectocolitis, both of which are autoimmune diseases.[58]

Therapeutic potential of IL-10 and helminth antigens in the treatment of immune system diseases

Based on the knowledge obtained through the study of the influence of infections on allergic and autoimmune manifestations, new options for the treatment of immune system diseases have been proposed. Among future prospects is the use of IL-10 and helminth antigens as treatment modalities.

Clinical trials have already been conducted in order to evaluate the safety and efficacy of using IL-10 in the treatment of autoimmune diseases. In a study of 46 patients with Crohn's disease refractory to treatment with corticosteroids, intravenous administration of IL-10 was found to be safe and clinically efficacious when compared to that of the placebo.[59] In a study of 10 patients with psoriasis, IL-10 proved safe and appeared to be efficacious in the control of symptoms.[60] In another study, the administration of *Trichuris suis* eggs in patients with Crohn's disease and ulcerative rectocolitis led to remission in 86% of the cases.[58]

Conclusions

Despite the numerous publications on the subject, there is still controversy regarding the capacity of geohelminth infections to inhibit allergy skin test reactivity and minimize the symptoms of allergic diseases, such as asthma. Although there have been few studies of patients infected with helminths that induce IL-10 production (e.g., *Schistosoma* spp.), the results obtained to date suggest that these helminths can inhibit allergy skin test reactivity and minimize asthma symptoms. Evidence from in vitro studies suggests that helminthiases inhibit Th1 and Th2 immune responses by increasing IL-10 production. This opens new therapeutic possibilities for the treatment of immune system diseases. Studies evaluating the use of IL-10 and helminth antigens in the treatment of autoimmune diseases have already been carried out, with promising initial results.

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