

Immunologic responses to common antigens in helminthic infections and allergic disease

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Purpose of review

It is estimated that over 1 billion individuals are infected with helminth parasites worldwide. Epidemiologic studies have pointed to a protective role of helminthic infections in the development of allergy and asthma; however, evidence for this inverse association has not been consistently established. The focus of this review is to discuss the potential role of shared antigens between parasites and environmental allergens in modulating allergic immune responses, specifically tropomyosin.

Recent findings

Tropomyosin has been identified as a highly conserved molecule in invertebrates. In populations exposed concomitantly to mites, cockroach, *Ascaris*, and shrimp and other crustaceans and mollusks, IgE antibody responses to tropomyosin are found in over 50% of individuals. Evidence suggests that IgE cross-reactivity to tropomyosin has clinical relevance.

Summary

Mechanisms underlying the immunomodulatory effects of parasites in allergy and asthma remain poorly understood. Identification of molecules in intestinal parasites, particularly *Schistosoma mansoni* and *Ascaris lumbricoides*, associated with protection from or promotion of allergy and asthma, could provide the basis for novel forms of treatment or prevention of these diseases. Prospective studies will be necessary to clarify the role of tropomyosin and other parasite antigens shared with inhalant or food allergens in the development of allergic diseases.

Keywords

Ascaris lumbricoides, asthma, helminth infections, parasites, tropomyosin

Introduction

It has been estimated that 1.4 billion, 1.2 billion and 1 billion people worldwide are infected with *Ascaris lumbricoides*, hookworms (*Ancylostoma duodenale* and *Necator americanus*) and *Trichuris trichiura*, respectively. In communities where poverty and low sanitation are present, many individuals harbor more than one species of parasite, frequently for most of their lifetime. In these areas parasitic infections are acquired very early in life, causing malnutrition and impairment of growth and cognitive development, and should be the target of control programs. Several studies have suggested that helminthic infections may have a protective role in the development of allergy and asthma; however, the causal relationship between helminth infection and allergy has not been established with certainty. Alternatively, it has been hypothesized that allergic predisposition may protect against helminth infection. For example, it has been shown that a common asthma-associated genetic variant of the transduction and transactivating factor for Th2 immune signaling, STAT6, was associated with increased resistance to *Ascaris* infection in a large group of school-children from an area of endemic *Ascaris* infection in China [1•].

The relationship between helminthic infections, allergy and asthma

Communities in rural Africa typically have very low prevalence of asthma, and low rates of skin test reactivity to inhalant allergens. In addition, skin test positivity does not show significant association with asthma, as has been demonstrated in developed countries. Mechanisms associated with this inverse association are not completely understood. It has been proposed that high levels of IL-10 and transforming growth factor- β (TGF- β) produced during chronic infections with helminth parasites, as a result of generation of regulatory T cells, might downregulate allergic responses. Several lines of evidence point to the antiinflammatory properties of IL-10, particularly inhibiting skin test responses and mast cell degranulation. Another hypothesis is that high levels of IgG4 produced during parasitic infections could act as 'blocking antibodies' or be part of a modified Th2 response, since IgG4 is a Th2-dependent isotype not associated with clinical allergy [2].

Studies performed in Brazil [3•,4] and those carried out in rural communities in Ecuador [5,6] also point to a

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protective role of parasites in decreasing skin test reactivity and attenuating symptoms of asthma, particularly of infections with *Schistosoma*. In addition, intervention studies have provided support for a causal association between helminth infection and atopy [7^{••}]. Results of an open-label placebo-controlled randomized trial in Gabon revealed that children treated with antihelmintics (praziquantel and albendazole) every 3 months for a period of over 30 months presented an increase in the rate of developing skin test reactivity compared with children who received placebo; this effect was shown to be partially mediated by reductions in helminth infections [8^{••}].

By contrast, infections with *Ascaris lumbricoides* have not been associated with protection, but rather an increased risk of wheezing, asthma and allergic sensitization [9,10]. Our studies investigating the frequency of wheezing and IgE responses to inhalant allergens in a group of 150 children aged 3–6 years old who lived in an endemic area for *A. lumbricoides* in northern Brazil revealed that current infection with *A. lumbricoides* was strongly and independently associated with wheezing [10]. Evidence of *A. lumbricoides* infection in this group of children was found in 133/150 (88.6%) children: 106/150 children (70.6%) had *A. lumbricoides* detectable in stool samples, and 123/150 (82%) children presented IgE antibodies to *A. lumbricoides*. Egg counts ranged from 48 to 31 200 eggs/g of feces, indicating that in some children the burden of *Ascaris* larvae in the lungs may be quite significant. In addition, the presence of positive skin tests to inhalant allergens was significantly associated with wheezing in these children [10].

Cross-reactivity among invertebrates may be due to tropomyosin

Tropomyosins are proteins involved in contraction of muscle cells, together with actin and myosin. In non-muscle cells, tropomyosins participate in regulation of cell morphology and motility [11]. The structure of tropomyosin in muscle consists of two parallel α -helical molecules, wound around each other to form a coiled coil structure. In invertebrates, tropomyosins have been associated with IgE antibody responses. Tropomyosin has been identified as the major shrimp allergen: most shrimp-allergic patients react to tropomyosin and the protein binds to approximately 85% of shrimp-specific IgE antibodies from shrimp-allergic patients. Severe allergic reactions caused by ingestion of shrimp in sensitized individuals have been attributed to IgE-mediated responses to tropomyosin. In addition, it has been shown that tropomyosin is an important allergen in other crustaceans, in mollusks and in house dust mites [11]. Tropomyosin has also been identified as a major cockroach allergen from *Periplaneta americana* (Per a 7) among patients with asthma or rhinitis living in Brazil [12].

Subsequent studies confirmed the high degree of sequence identity of the cockroach allergen to tropomyosins from other invertebrates, particularly from mites (80% identity) and shrimp (82% identity) [12]. More recently, tropomyosin from *Blattella germanica* has been identified, and sequence analysis revealed that the protein presented 97% identity to *P. americana* tropomyosin [13].

Previous inhibition studies have identified IgE cross-reactivity between insects and parasites, and it has been suggested that this cross-reactivity may also be due to tropomyosin. Sequence of tropomyosin from *Anisakis simplex*, a fish parasite associated with induction of urticaria and other allergic symptoms in individuals who have ingested contaminated food, revealed that tropomyosins in nematodes are highly conserved. We have recently determined the complete sequence of the *A. lumbricoides* tropomyosin, and have demonstrated that it is an IgE-binding protein. Sequencing revealed a high degree of identity of *Ascaris* tropomyosin to tropomyosins from mites, cockroach, shrimp and other parasites such as *A. simplex* and *Onchocerca volvulus*.

Extensive studies on IgE-binding epitopes have provided strong molecular evidence for cross-reactivity among invertebrate tropomyosins [14]; at present, however, it is not clear whether allergenic cross-reactivity among mites, cockroach, foods and parasites is clinically relevant. Our results prompted us to speculate that cross-reactive allergens such as tropomyosin at the time of the initial *Ascaris* infections could facilitate subsequent development of cross-reactive IgE antibody responses upon exposure to mite or cockroach, which could lead to airway inflammation and asthma. Therefore, infection with *Ascaris* could have an adjuvant effect on the development of asthma, in the subset of *Ascaris*-infected individuals who develop IgE responses to tropomyosin. Alternatively, it has been proposed that exposure to cross-reactive parasite antigens *in utero* (by passage of parasite antigens through the placenta of infected mothers) or early in life could lead to tolerance, with suppression of allergic inflammation triggered by environmental antigens [7^{••}]. Interestingly, the reported frequency of IgE reactivity to mite or cockroach tropomyosins has been much lower among allergic patients living in Europe, the United States or Korea (6–16%) compared with those living in Africa or Brazil (50–55%) [12,13,15,16^{••},17^{••}]. Few studies have investigated the issue of clinical relevance of cross-reactivity to tropomyosin. Symptoms of food allergy after ingestion of shrimp and snails have been reported in European patients allergic to mites, and many of these patients received mite immunotherapy [18]. IgE antibody reactivity to shrimp among Orthodox Jews, who are prohibited from eating shellfish, has also been reported, and evidence indicates that this reactivity

appears to be due to cross-reacting tropomyosin [19]. Taken together, these observations suggest that exposure to other invertebrates containing tropomyosin as cross-reactive allergen, such as parasites, or concomitant exposure to tropomyosins from different sources could lead to increased sensitization, rather than tolerance.

Several issues including age of initial parasitic infection, parasite load, socio-economical conditions, lifestyle, and environmental allergen exposure may play a role in the complex relationship of parasite infections and development of allergic diseases. One possibility is that different parasites may cause distinct effects in modulation of the allergic immune response. Direct inflammatory responses in the lungs caused by parasite antigens can account for wheezing and other respiratory symptoms. The biological cycle of *A. lumbricoides* in man initiates with ingestion of infective eggs by the fecal–oral route. After infective eggs are swallowed, larvae hatched in the intestine invade the mucosa, migrate via the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return via swallowing to the small intestine, where they develop into adult worms. Other nematodes, including hookworms and *Strongyloides stercoralis*, also undergo pulmonary passage of larvae. Interestingly, comparison of *Ascaris* and *Schistosoma* tropomyosin sequences revealed a lower degree of identity, in the order of 57%, compared with tropomyosins from mites, cockroaches and other parasites (70–98%). Sequence identities of invertebrate tropomyosins to vertebrate tropomyosins, which are not allergenic, range from 50 to 60%, suggesting that *Ascaris* and *Schistosoma* tropomyosins may not share extensive IgE cross-reactivity. Moreover, *Schistosoma* molecules that can stimulate a suppressor immune response have been identified. In experimental infections, lacto-N-neotetraose, a carbohydrate molecule found in schistosomes, was shown to stimulate production of antiinflammatory cytokines by antigen-presenting cells. It has also been shown that the lipid compound lyso-phosphatidylserine may modify dendritic cell function, so that upon interaction with naïve T cells, regulatory T cells capable of producing IL-10 were induced [20**]. A major target antigen for human IgE responses, the 22.6 kDa antigen, has recently been identified in *Schistosoma haematobium* (Sh22.6), which is closely related to homologous molecules in other species, *S. mansoni* (Sm22.6) and *S. japonicum* (Sj22.6) [21*].

Conclusion

Atopy and asthma are related conditions, involving both environmental and genetic factors. Evidence suggests that events taking place between 2 and 3 years of age may be crucial determinants for the development of allergic diseases. The relationship of asthma and allergy, and helminthic infections remains controversial. Most likely, rather than a direct causative role, early exposure

to helminths may modulate immuno-inflammatory pathways involved in allergic inflammatory responses. It is important to acknowledge that several factors, such as exposure to endotoxin or pets early in life, bacterial and viral infections in childhood, use of antibiotics, housing conditions, lifestyle, physical activity and diet, may collectively play a role in the development of allergic diseases. Obviously, infections with intestinal parasites should be promptly treated, and studies should focus on identification of parasite components which may cause a protective effect or promote allergy. These molecules could provide the basis for novel forms of treatment or prevention of allergic diseases.

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