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TOPICS EXPLORING LOA-LOA, ONCHOCERCIASIS, HOOKWORM, ASCARIS, TRICHURIS (A SANCHEZ AND R FUJIWARA, SECTION EDITORS)

Human Ascariasis Increases the Allergic Response and Allergic Symptoms

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Abstract Ascariasis is still very prevalent; one billion people are infected all around the world. In rural areas, severe ascariasis impairs the immune responses to natural infections and vaccination programs. However, in urbanized areas, improved hygiene conditions and periodic anthelmintic treatments have led to light forms of ascariasis, where parasite-induced immunosuppressive effects are surpassed by the immunostimulating effects of the infection. During the last years, the clinical impact of this type of ascariasis on allergic diseases, especially asthma, has been well documented, and it is currently accepted that this relationship should be considered when analyzing allergy prevalence in tropical and temperate countries. This review focuses on the emerging evidence that supports the stimulatory effects of ascariasis on the allergic responses and its clinical importance. Advances on the role of type 2 innate lymphoid cells (ILC2) in helminth immunity and allergy pathogenesis as well as new genetic findings supporting the links between helminthiases and allergy are discussed. We show that ascariasis, beyond its known effects on human health, is able to modify the natural history of asthma, increasing Th2 responses and IgE synthesis to cross-reactive and species-specific mite allergens, being a risk factor for asthma and asthma severity.

Keywords Ascariasis · IgE · Allergy · House dust mites · Helminths · Asthma · Genetics · ILC2

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Introduction

The most common human helminthiases are caused by soil-transmitted nematodes (*Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenalis*, *Necator americanus*, *Strongyloides stercoralis*), filarial nematodes (*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*), and platyhelminth flukes (*Schistosoma haematobium, Schistosoma mansoni*, *Schistosoma japonicum*). The immune response elicited by these infections differs depending on the type of parasite, lifecycle, host age, burden of co-infections (polyparasitism), and parasite loads. However, all share as hallmarks an increase in circulating IgE levels, peripheral and intestinal eosinophilia, and the activation of genes and cytokine networks related to type 2 immunity and immunomodulation [1, 2].

A. lumbricoides induces a Th2-biased immune response, similar to that observed in the allergic response but associated with parasite-induced immunomodulation, a condition that could be evolutionary related with the helminths ability of parasitic life. Therefore, ascariasis can influence allergic diseases by either stimulating or suppressing the allergic response, probably depending on the severity of the infection, which in turn is determined by host genetic susceptibility and the degree of exposure. A number of epidemiologic surveys suggest that nowadays, severe, chronic infections, with heavy worm loads and polyparasitism are present in rural areas of the

tropics, while intermittent and low-intensity infections occur mainly in urbanized areas, being *A. lumbricoides* and *T. trichiura* the most common parasites. As a consequence, risk or protector factors for allergy in the tropics include helminthiases. During the last few years, it has become clear that ascariasis may influence several aspects of allergy, such as prevalence, diagnosis, severity, and prevention. Studying the relationships between ascariasis and allergy could help to understand fundamental questions about type 2 immunity, allergy mechanisms, and clinical phenotypes. Since an inverse prevalence rates between helminthiases and allergy has been found, future research could provide insights on the origin of the high prevalence of allergy in urbanized zones of the tropics. In this review, we analyze the evidence supporting that, in the current relationship between ascariasis and allergy, the most important effect of ascariasis is increasing allergic symptoms.

The Increasing Trends of Allergy

Allergic diseases (allergy) result from the interaction between genetic predisposition and environmental factors. Among genetic predisposing factors, atopy (the tendency to react with IgE antibodies against innocuous antigens, a condition also known as "IgE sensitization" or merely "sensitization") is one of the most studied. However, other heritable components are required to conform to the clinically evident phenotype. The best known environmental factors are the allergens, including molds, pollens, house dust mites (HDM), foods, pets, etc. People in the tropics are permanently exposed to HDM allergens, which are the main cause of asthma in this zone. However, other factors and conditions, such as pollution, diet, biodiversity, microbiome composition, and infections (viral and parasitic) can modify the natural history of allergy. During the few last years, the epigenetic modifications induced by some of these environmental signals have been revealed. Asthma, rhinitis, and atopic dermatitis are the prototypes of allergic diseases. In addition, there are a number of allergic reactions including those to foods, stinging insects, and drugs that could induce anaphylaxis, a severe, life-threatening condition. The prevalence of allergic diseases is increasing worldwide including underdeveloped countries of the tropics [3]. Among the numerous possible factors underlying this trend [4], the progressive lack of the immunomodulatory effect of helminthiases is salient. These infections have already been controlled in most industrialized countries and are under control in urbanized zones of the tropics (Fig. 1). Then, the relationships between helminthiases and allergy extend beyond the basic and clinical sciences to cover important worldwide epidemiological trends. These interesting links are partially explained by the common aspects of helminth immunity mechanisms and the allergic response. A number of

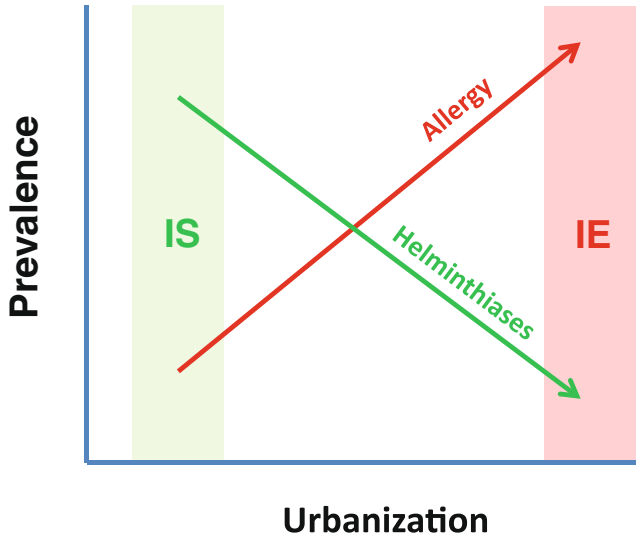

Fig. 1 Hypothetical presentation of the effect of helminthiases control on the prevalence of allergic diseases. Immunosuppression (IS) reaches its maximum when helminthiases are prevalent and the burden of infections is very high; inducing severe disease. In this setting, the prevalence of allergic symptoms is low. Immunostimulation (IE) is higher when the prevalence of helminthiases is lower, allowing intermittent and mild infections that increase allergic symptoms. The hypothesis assumes that the changes operate on a population genetically predisposed to allergy

recent reports on basic immunoparasitology have provided a better understanding of the immune responses to helminth infections (reviewed in [2]). Here, we present just a brief discussion of the role of innate lymphoid cells 2 (ILC2) on helminth immunity and allergy.

The Immune Responses to Helminths and Allergens: Emerging Roles for Innate Lymphoid Cells 2

Immunity to *Ascaris* involves antibodies and cellular mechanisms of the innate and adaptive responses. However, sterile immunity is not common and reinfection occurs frequently. After ingesting an embryonated infective egg, *Ascaris* lifecycle in the human host comprises larval penetration through the gut epithelia, migration through tissues, and adult settlement in the gut. The migration process causes tissue damage and antigen exposure to the immune system. *Ascaris* infection induces increased expression of the cytokines IL-4, IL-5, IL-9, IL-10, and IL-13; synthesis of specific antibodies to its antigens/allergens (including IgE); high titers of polyclonal IgE; eosinophilia; and activation of mast cells and basophils. This immune reaction is collectively known as Th2-type immunity and is similar to that observed in allergic inflammation. In the early stages of infection, ILC2 play an important role, whereas M2 macrophages and lymphocytes participate in later stages. However, together with this Th2-skewed immune profile, *Ascaris* induces immunosuppressive responses including the expansion of regulatory T and B cells

and production of suppressive cytokines (IL-10/TGF-β). After repeated exposure to the parasite, several effector mechanisms confer adaptive immunity and contribute to destroy the larvae during early stages of their migration (the so called "hepatic barrier"), or to expel the adult worms from the intestine. *Ascaris* induced high total IgE levels but most of these antibodies are not specific [5], resulting from a polyclonal stimulation of B cells [6]. This irrelevant IgE binds to its receptors on mast cells and eosinophils precluding their degranulation, and reducing the effector response against larvae [7].

The discovery of the cells currently known as ILC2 emerged from experimental nematode infections [8–10]. After their first descriptions in 2010, other reports have supported the role of ILC2 in immunity to helminths. Yasuda et al. showed that during infection by *Schistosoma venezuelensis*, lung epithelial cells produce IL-33 and induce proliferation of a type of ILC2. Their effects were independent of adaptive immunity but dependent on the IL-33 produced by the lung epithelium [11]. Indeed, the number of ILC2 was greater in the resistant mice strain BALB/c infected with *Heligmosomoides polygyrus* when compared with the susceptible C57BL/6 strain, thus supporting their role in anti-helminth immunity [12]. ILC2 cells also have the capacity to proliferate in response to helminth carbohydrate chitin [13]. Moreover, IL-33$^{-/-}$ mice did not develop eosinophilia and goblet cell hyperplasia after intranasal administration of chitin [11]. Interestingly, some helminth infections suppress immune response by blocking the production of IL-25 and IL-33. Zaiss et al. found that *H. polygyrus bakeri* induces the production of IL-1β by epithelial cells in vivo and in vitro, blocking the production of IL-25, IL-33, and the proliferation of ILC2, allowing infection chronicity [14].

ILC2 control eosinophil homeostasis in helminth infection and macrophage differentiation to M2 phenotype [9, 10], possibly because the IL-5 and IL-13 produced by these cells induce epithelial eotaxins and adhesins that promote eosinophil trafficking into the lung and other tissues [15, 16]. ILC2, through MHCII, collaborate with T lymphocytes that produce IL-2 that induces ILC2 proliferation and increased immunity [17]. Recently, these properties have also been observed in a mice model of asthma where ILC2 significantly increased the lung Th2 inflammatory responses to chronically administered ovalbumin [18].

ILC2 are involved in granuloma formation by *Schistosoma* eggs in the liver [19, 20]. In contrast, they produce amphiregulin that can repair tissue damage induced by influenza virus infection [21]. This cytokine seem important for controlling helminth infection because amphiregulin-deficient mice have more parasite burden at day 14 post infection with *Trichuris muris* when compared with the control wild type [22]. Another important ILC2-related cytokine is IL-9. Turner et al. showed that IL-9 receptor-deficient mice infected with *Nippostrongylus brasiliensis* have less ILC2 (Lin$^-$Th1 1.2$^+$), IL-13, IL-5, and amphiregulin and more egg count and tissue damage during parasite migration [23].

In humans, Boyd et al. found increased IL-13 producing ILC2 in peripheral blood of adult patients with filarial infection. In this study, these cells expressed *GATA3*, similar to had been previously shown in mice [24]. In contrast, Nausch et al. found diminished ILC2 in peripheral blood of *S. haematobium* infected children [25•]. Since the immune responses to helminths and the allergic response have some similarities, the findings about ILC2 on type 2 immunity and helminth infection resistance have led to the study of their role in the allergic reaction [26]. A number of publications have shown that, as happens during helminth infection, these cells react early producing IL-13 and IL-5 during sensitization with various allergen extracts [27•] and recombinants allergens [28, 29] with the same dependence on IL-25 and IL-33 epithelial cytokines [28]. ILC2 are involved in the severity of allergy in an independent way or associated to T lymphocytes activation [18, 27•]. Moreover, it has been shown that asthmatic individuals have more ILC2 (Lin$^-$CD127$^+$CRTH2$^+$) in peripheral blood than patients with rhinitis and healthy individuals. In vitro, these cells produced higher quantities of IL-5 and IL-13 when cultured with IL-25 and IL-33 plus IL-2 [30]. It can be speculated that in the tropics, allergic individuals with an ILC2-hyperactive phenotype and concomitant helminth infection might have a boosted allergic response and more severe symptoms.

Immunogenetics of the IgE Responses to *Ascaris* and Allergens

Since the immune response to helminthiases shares several mechanisms with the allergic reaction, it is expected that they also have common genetic basis. In fact, several variants have been found associated with both helminth infections and allergy. Moreover, most of researchers in the field think that allergy is a collateral consequence of a protective response evolutionary modeled by helminth infections. However, most of the genes and polymorphisms associated with the IgE response to allergens and allergic diseases have not been related to helminth resistance. This suggests that IgE responses to allergens probably have their own evolutionary roots. This topic has become more complicated as it is realized that the number of the so-called immune response genes is greater than previously suspected. In this section, we discuss the genetic factors influencing the antibody response to helminths with emphasis on *Ascaris* and the scenarios in which they could contribute to the IgE sensitization to non-parasitic allergens.

Several facts suggest that there is an important genetic influence defining the susceptibility to helminth infections. It is

typical that worm loads are over-dispersed in the infected communities with 20 % of the individuals harboring 80 % of the parasites [31]. Individual predisposition to get infected by heavy or light worm loads is maintained in treatment-reinfection studies [32], and aggregates in families [33, 34]. Epidemiological studies revealed than in addition to exposure and household determinants, genetic factors account for an important proportion of the variation in worm loads [35–38].

Genetic factors have been also found to influence the levels of protective antibodies against helminths, as shown for the IgG levels to larval and adult worm antigens in humans infected by *W. bancrofti* [36]. The heritability of circulating antibody levels against helminths (particularly IgG_1 and IgG_2) ranges between 70 and 80 % depending upon time and isotype [39], and gene expression analyses have found that many genes differentially expressed between resistant and susceptible animals are indeed implicated in antibody synthesis [40]. *A. lumbricoides* is very allergenic and, as explained earlier, induces in the host a type-2 skewed immune profile with several features that resemble the allergic response to non-parasitic allergens including the synthesis of specific IgE [41]. The role of this isotype in the resistance to *Ascaris* is controversial, but some studies have shown that worm loads and the proportion of re-infected children after treatment is significantly lower in individuals with the highest levels of anti-*Ascaris* IgE antibodies [42]. In endemic populations, most of the infected individuals produce specific IgE to *Ascaris* without developing allergic symptoms, suggesting that the regulation of the antibody response to helminths is polygenic, and genetic loci influencing the strength and specificity of the IgE response to helminths do not necessarily confer susceptibility to allergic asthma or IgE sensitization.

Nevertheless and considering the overlap in biological pathways implicated in the immune responses to helminths and allergens, it has been hypothesized that some genetic variants influencing the IgE response to helminths may also predispose to develop IgE sensitization with non-parasitic allergens [43] or even predispose to allergic diseases [44, 45]. Although the empirical evidence is limited, it can be noted that (i) the major histocompatibility complex (MHC) participate in determining susceptibility to helminthic infections [46]; (ii) some genetic variants are associated to both, susceptibility to helminthic infections and allergic sensitization, as shown for the genes encoding for interleukin 13 (*IL13*), the signal transducer and activator of transcription 6 (*STAT6*), and chitotriosidase; and (iii) other genetic loci regulate the antibody response to helminths without predisposing to allergy.

Studies in humans and other mammals support the role of genetic factors in the predisposition to *Ascaris* [37, 47] but few genes have been identified so far [43, 48–51, 52•]. A summary of genes and genomic regions associated with the susceptibility to human ascariasis is presented in Table 1.

Common Genes for Ascaris Response and Allergic Phenotypes

The enhanced resistance to parasitic worms through genetic variation has been observed in Th2 immune signaling genes and some also contribute to allergic susceptibility. Peisong et al. found an association between a common genetic variant of the 3′-UTR regulatory elements of *STAT6* and *Ascaris* egg counts in China [49]. In addition, a cross-population comparison between haplotypes in China and United Kingdom revealed a negative correlation between worm burden and expected risk of asthma [43]. The 5q31 locus is another example of a common locus for the susceptibility to helminthic infection and allergic diseases. It contains genetic variants in the *IL13* gene associated with the worm burden of *Ascaris* in a Chinese population.

Table 1 A summary of genes and genomic regions associated with the susceptibility to human ascariasis

Gene	Locus	Genetic variant	Effect	Population	Ref.
IL10	1q31-q32	rs3024492	Allele C of rs3024498 was negatively associated with helminth infection	Brazil	[52]
IL13	5q31	−1055 C > T	In combination with a common variant in the 3′region of *STAT6* contribute to diminish *Ascaris* burden	China	[49]
STAT6	12q13	Microsatellite in exon 15′UTR/3′UTR haplotypes	Carriers of the short allele in the microsatellite in combination with SNPs haplotypes have lower levels of *Ascaris* infection	China	[49]
		3′UTR SNP 4219 G/A	Homozygotes GG have the lowest egg counts and protected to carry more than 960 eggs per gram of feces	China	[49]
–	13q33-34	D13S1265 D13S285	linkage with egg counts of *A. lumbricoides* in stool and total IgE levels. Quantitative trait locus for *Ascaris* burden	Nepal	[48, 50]
TNFSF13B	13q33	G3980 > C	GG homozygotes have higher levels of IgG to Ascaris. In asthmatics; carriers of the G allele have higher levels of IgE against the resistance marker ABA-1	Colombia	[51]

Genes encoding for human chitinases have been also identified as a potential link between ancestral responses to invertebrates and the susceptibility to allergic phenotypes. In humans, chitinases promote Th2 responses. The acidic mammalian chitinase (AMCase) is induced in epithelial cells and macrophages by an IL-13-mediated pathway and is expressed at high quantities in human asthma [53]. Genetic polymorphisms in chitinase genes have been associated with asthma [54], and asthmatic children exhibited increased chitinase activity and increased YKL-40 levels in BALF [55]. Genetic variants in the gene encoding chitotriosidase (*CHIT1*) have not only been associated with the response to filarial infection but also with asthma [56, 57].

Experiments using different strains of mice and rats demonstrated the MHC-restriction in the recognition of excretory-secretory products of *Ascaris* and the genetic control of the antibody response to its antigens [58–62]; however, the relationship between human MHC alleles and the specificity of the antibody response to *A. lumbricoides* is unknown.

The Ascaris Susceptibility Locus in Chromosome 13q33

Linkage studies identified a quantitative trait locus (QTL) accounting for the variability in *Ascaris* egg counts and total IgE levels in chromosome 13q33-34 [48]. A second linkage-based genome scan including 1258 members of a single pedigree identified three potential QTLs influencing susceptibility to *A. lumbricoides* with genome-wide significance, localized on chromosomes 8, 11, and 13 [50]. Of these regions, the 13q33 locus is of great interest because it contains the gene *TNFSF13B* encoding for the cytokine B cell activating factor (BAFF). We studied the role of common variants in the 13q33 locus on the IgE and IgG levels against *Ascaris* and the putative resistance marker ABA-1, and identified a region of 125 kb harboring two polymorphisms significantly associated with antibody levels against *Ascaris* [51]. The effect of this variant was observed in both, non-asthmatic and asthmatics suggesting that participates in pathways implicated in antibody synthesis under physiological conditions and is not directly associated with allergic sensitization and/or asthma. At this point, it is unclear if the association in *LIG4* is functionally related with this gene or resulted of the linkage disequilibrium with other variants. Furthermore, the polymorphism rs10508198 (3980G>C) in the *TNFSF13B* gene was associated to the specific IgG levels to *Ascaris*. The carriers of the wild-type genotype GG have the highest levels of specific IgG to *Ascaris* in both non-asthmatics and asthmatics, suggesting that *TNFSF13B* may regulate the strength of the antibody levels against *Ascaris*. There was no association between markers in the 13q33 locus and the IgE levels to HDM s or the presence of asthma [51].

The Complex Relationship Between Ascariasis and Allergy

The first observations about ascariasis and allergy were around the presence or increase of allergy symptoms (mainly asthma and urticaria) associated with *Ascaris* infection [63, 64]. The next link was the finding that both, helminthiases and allergy, were associated with high levels of total IgE, which was further extended to other features of the immune responses to both processes [65–68]. This has been followed by epidemiological reports that, using several approaches, have shown that ascariasis is a risk factor for asthma [69–77]. However, although there is abundant scientific literature supporting the boosting effect of ascariasis on allergic responses [5, 63–67, 69–76, 78–92, 93•, 94•, 95, 96•, 97, 98] (Table 2), a number of questions remain regarding the mechanisms for inducing an increased allergic response and asthma symptoms in a condition naturally accompanied by immunosuppression (reviewed in [99, 100]). The answers could be related to several factors such as the permanent co-exposure to both HDM and *A. lumbricoides* that induces an enhanced Th2 response, cross reactivity between *Ascaris* and HDM allergens, nonspecific boosting of the allergic responses by *Ascaris* components, and intermittent *Ascaris* infections and deworming campaigns. Our recent work has focused on some of these aspects, as follows.

Exposure to HDM Allergens and Ascaris Infections Is Permanent in the Tropics

One of the particularities influencing allergy in the tropics is the permanent exposure to HDM and helminth infections. The mean annual temperature and humidity of 28 °C and 85 %, respectively, favor mites' growth and the lifecycle of *Ascaris*. Children born and raised in underdeveloped tropical countries are sensitized to both mite and *Ascaris* allergens at an early age [92]. For some sources such as *Blomia tropicalis*, the adult level of sensitization is reached at the age of 3 years [92, 101]. Therefore, an interesting characteristic of allergy in the tropics is the high rate of sensitization to HDM allergens and the high strength of that specific IgE response. This phenotype has been described in Asian as well as Latin American tropical countries and could be the result of a selective effect of perennial exposure on the population genetically susceptible to atopy and hyperreactivity to *Ascaris* infection. This population will be sensitized by very small amounts of allergens, an often forgotten feature of atopy, but the strength of the IgE response could increase with perennial exposure, as occurs in the tropics.

Table 2 List of experimental and epidemiological data supporting that ascariasis enhances IgE responses to environmental allergens and allergic symptoms

Finding	References
Natural infection is associated with a polarized Th2 cytokine response and high levels of total and anti-*Ascaris* IgE	[5, 65, 73, 78–85]
In some individuals, natural infection induces IgE-mediated allergic respiratory and cutaneous symptoms	[63, 86, 87]
In experimental human and animal models, bronchial challenges with *Ascaris* extract induce asthma symptoms	[64, 66, 67]
Experimental ascariasis in animals enhances IgE response to bystander antigens	[88–91]
Human ascariasis enhances IgE response to mite species-specific allergens	[92, 93•, 94•]
Several epidemiological surveys have found that ascariasis is a risk factor for asthma and atopy	[69–75, 93•, 94•, 95, 96•]
IgE responses to *Ascaris* allergens is more frequent and stronger in mite-sensitized asthmatic patients	[76, 81, 97, 98]

Cross Reactivity Between Mites and Ascaris Components Has Clinical Significance

Since ascariasis and HDM exposure are very common in the tropics, it is possible that IgE responses to both sources can be increased by cross-reacting epitopes. We first described that there is high cross reactivity between HDM and *Ascaris*, mostly determined by tropomyosins. In this work, we also confirmed that ABA-1 (Asc s 1), a polyprotein of *Ascaris* spp., does not have cross reactivity with mite allergens. In other words, that ABA-1 is useful for diagnosing ascariasis in HDM-sensitized subjects [99, 102]. These investigations were followed by the isolation and immunological characterization of *Ascaris* tropomyosin (Asc l 3) as the main cross-reactive allergen of this nematode [103] and the finding that *Ascaris* glutathione transferase (GST) apparently has less allergenic activity than tropomyosin [104, 105]. Having isolated and produced them as recombinant proteins, we were able to evaluate the role of these and other allergens as risk factors for asthma and asthma severity. In a nationwide study that included 356 asthmatics and 435 controls, we found that sensitization to *Ascaris* and mite tropomyosins were risk factors for asthma in the Colombian population [93•]. This work confirmed that sensitization to both *Ascaris* and *Dermatophagoides pteronyssinus* extracts were important risk factors for asthma and, in addition, for the first time showed that a molecular component of *Ascaris* is strongly associated with asthma. Since there is strong cross reactivity among mites and *Ascaris* tropomyosins, it is possible that primary sensitization (being from mites or *Ascaris* components) had been boosted by perennial exposure to the other cross-reacting source. In other asthma cohort from the tropics, we also found that not only sensitization to *Ascaris* extract but also to mite and *Ascaris* components were associated with symptoms of asthma severity, mainly severe dyspnea and more than four visits to the emergency room during last year [94•]. These studies support the role of *Ascaris* sensitization to species-specific and cross-reactive allergens in asthma pathogenesis, and, together with other recent reports [95, 96•], show that ascariasis is an important factor modifying the IgE responses and the natural history of asthma in the tropics.

Ascariasis Induces Nonspecific Boosting of IgE Responses to Mite Allergens

As has been observed in experimental models, ascariasis can boost the IgE/Th2 responses to bystander antigens [88–90]. Since it might help to explain the increasing allergy effects of *Ascaris*, we have explored this aspect in human ascariasis. Evaluating the evolution of the immune responses in children of the FRAAT birth cohort [106], we found that *Ascaris*-sensitized children had stronger IgE to the mite *B. tropicalis*. To rule out the confounding effect of cross reactivity, we used species-specific components and found that those reacting with IgE to ABA-1 (a marker of nematode infection) had increased IgE responses to Blo t 5 and Blo t 12, two species-specific allergens of *B. tropicalis* [92]. This *Ascaris*-induced nonspecific boosting of the IgE responses to HDM components was also detected in a large nationwide population co-exposed to *A. lumbricoides* and HDM, where IgE levels and frequencies of sensitization to mite allergen extracts were greater in subjects sensitized to Asc s 1. In fact, these individuals had at least twice the odds of being sensitized to HDM [93•]. Furthermore, in a cohort of asthmatic patients living in the tropics, *Ascaris*-sensitized patients had significantly higher IgE levels to the HDM allergens Der p 2 and Blo t 5 [94•]. All these findings support the idea that the Th2/IgE hyperresponsiveness induced by *Ascaris* infection (as detected by IgE antibodies to *Ascaris* extract or ABA-1) includes the responses not only to *Ascaris* antigens but also to HDM allergens. It is well known that ascariasis induces a polyclonal nonspecific stimulation of B cells; therefore, it can be hypothesized that the involved components also stimulate mite allergens-memory B cells that in the tropics are in permanent allergen-specific stimulation. It has been extensively shown that specific IgE to HDM is the most important risk factor for asthma in the tropics and some temperate countries. Therefore, any condition that increases this allergic response

could also increase symptoms and severity of this disease. *Ascaris* components and host genetic background influencing this boosting effect are only beginning to be unraveled, and deserve further investigations.

Conclusions

Human ascariasis, in addition to its direct harmful effects, has other health impacts, among them boosting the Th2 allergic responses and increasing allergy symptoms. Since it is known that ascariasis induces some degree of immunomodulation, it seems that in the real life, especially in urban settings where this infection coexists with perennial mite exposure, the Th2 enhancement effects surpass the immunosuppressive influence of this helminthiasis. There is evidence suggesting that the increased allergic responses induced by ascariasis could be determined by any or a combination of the following: early age exposure and sensitization to allergens from both sources and cross reactivity between *Ascaris* and HDM *Ascaris*-induced nonspecific boosting of the IgE reactivity to mite-specific allergens

Compliance with Ethics Guidelines

Conflict of Interest Luis Caraballo, Nathalie Acevedo, and Emiro Buendia declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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