Global issues in allergy and immunology: Parasitic infections and allergy

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1. To learn T_H2 immune responses are the primary mediators in helminth infections.
2. To explore structural homology between allergens derived from parasites and aeroallergens.
3. To learn similar immune mechanisms exist between atopic conditions and helminth infections.
4. To discover the potential negative association between helminth infection and allergy.

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Allergic diseases are on the increase globally in parallel with a decrease in parasitic infection. The inverse association between parasitic infections and allergy at an ecological level suggests a causal association. Studies in human subjects have generated a large knowledge base on the complexity of the interrelationship between parasitic infection and allergy. There is evidence for causal links, but the data from animal models are the most compelling: despite the strong type 2 immune responses they induce, helminth infections can suppress allergy through regulatory pathways. Conversely, many helminths can cause allergic-type inflammation, including symptoms of "classical" allergic disease. From an evolutionary perspective, subjects with an effective immune response against helminths can be more susceptible to allergy. This narrative review aims to inform readers of the most relevant up-to-date evidence on the relationship between parasites and allergy. Experiments in animal models have demonstrated the potential benefits of helminth infection or administration of helminth-derived molecules on chronic inflammatory diseases, but thus far, clinical trials in human subjects have not demonstrated

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unequivocal clinical benefits. Nevertheless, there is sufficiently strong evidence to support continued investigation of the potential benefits of helminth-derived therapies for the prevention or treatment of allergic and other inflammatory diseases. (J Allergy Clin Immunol 2017;140:1217-28.)

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The frequency of allergic disease has been increasing in urban and urbanizing populations,[1] whereas an overall decrease in rates of infections has been observed. Studies of the inverse association between parasitic infections and allergy suggest the existence of a causal link.

Although human subjects can be infected with some 300 species of worms and more than 70 species of protozoa,[2] we will focus on soil-transmitted helminths (STHs), also called geohelminths. Worldwide, it is estimated that 1.5 billion human subjects are infected with one of these species.[3] We will also refer to *Schistosoma* species, which infect human subjects through contact of skin with water infested with larvae and are estimated to infect 230 million persons.[4]

For example, Fig 1 shows typical features of a rural household in a village of Conde, northeast Brazil, from 2005, in which the prevalence of helminth infections was 83.5%.[5] In the city of Salvador, 185 km away, the frequency of helminth infection among children was less than 20%.[6] An ecological study including all Brazilian municipalities reported that hospitalization rates for asthma were lower in those endemic for *Schistosoma mansoni* or STH parasites.[7] A typical urban underserved neighborhood of Salvador is presented in Fig 2.[6]

The purpose of this narrative review is to inform clinicians and researchers of the most current evidence on the interrelationship between parasitic infections and allergy from epidemiologic studies to mechanisms and molecules identified in helminths that are candidates for novel therapeutics.

GLOBAL TRENDS IN PARASITE INFECTIONS AND ALLERGY

Global trends

Allergic diseases are among the most common chronic diseases,[1] particularly in populations undergoing urbanization.[8] Individual allergy risk is considered to reflect a complex interaction between genetic predisposition and environmental exposures over the life course.[9] Geographic differences in the prevalence of allergy between and within populations is more likely to reflect exposures to common environmental factors that can either increase or decrease risk. The most consistent environmental exposures considered to reduce allergy risk are those associated with rural residence and include farming, animal exposure,[10] and infections with parasites.[11]

Protective immunity against STHs is mediated through type 2 immune mechanisms,[11] and parasites can survive to cause chronic infections by modulating these allergic inflammatory responses. The prevalence of STH infections is decreasing worldwide. This reflects a combination of factors leading to reductions in transmission of these infections, including reductions in extreme poverty and improvements in the living environment (potable water and disposal of feces) and the wide availability of anthelmintic drugs. Reductions in STH prevalence, although beneficial, might raise concerns in case of being causally associated with allergy.

Abbreviations used
AAMΦ: Alternatively activated macrophage
ES: Excretory-secretory
FOXP3: Forkhead box protein 3
GWAS: Genome-wide association study
ILC: Innate lymphoid cell
ILC2: Type 2 innate lymphoid cell
SNP: Single nucleotide polymorphism
SPT: Skin prick test
STH: Soil-transmitted helminth
tIgE: Total IgE
Treg: Regulatory T

Epidemiologic evidence for associations between parasites and allergy

There is evidence in support of protection against allergy by STH infections, but many studies in human populations present discordant effects.

Meta-analyses of observational studies have shown differences in effects on asthma symptoms for different parasites: although *Ascaris lumbricoides* was associated with an increased risk of asthma, hookworm infection was associated with a reduced risk.[12] In contrast, studies that have measured the presence of *Ascaris* species–specific IgE, which is recommended by some as a marker of infection in areas of low prevalence[13] but is perhaps more appropriately used as a marker of allergic sensitization to *Ascaris* species, have shown consistently positive associations with asthma symptoms and even disease severity.[14,15]

In the case of atopy, which is generally measured based on allergen skin prick test (SPT) reactivity, most cross-sectional studies have shown inverse associations with STH infections.[16] A meta-analysis of cross-sectional studies showed that current STH infections were protective against atopy, an effect that was consistent for all 3 of the most common STH infections and also schistosomiasis.[16] Although *Ascaris* species infections can be associated inversely with atopy, they are often associated directly with wheezing, as mentioned in the previous paragraph. STH infections are not alone in attenuating atopy. A cross-sectional study showed that several different childhood infections were associated independently and inversely with reactivity to SPTs, including the visceral worm *Toxoplasma gondii*, *Herpes simplex*, and EBV infections.[6] This observation raises the possibility that rather than mediating protection directly, STH infections might be markers of poor environmental conditions that mediate protection through alternative mechanisms. Interestingly, in the study mentioned above, *T gondii* was the only organism associated with a reduction in allergen-specific IgE levels in this population.[6]

Few prospective studies have explored the effects of geohelminths on allergy development. It has been suggested that the key effects of protective environmental exposures occur during early life, during which there might be a limited window of opportunity for such exposures to mediate their effects.[9] If this is

FIG 1. Typical features of a rural household in a village in the municipality of Conde, Brazil, in which the prevalence of helminth infections was 83.5% (picture taken in 2005).[5]

FIG 2. Typical urban underserved neighborhood of Salvador, Brazil, in which the prevalence of helminth infection among children was less than 20%.[6] Figure Attribution: original image by user sergio_65_ita (Sussuarana [Salvador] - DSC03080 [CC BY 2.0; http://creativecommons.org/licenses/by/2.0]), via Wikimedia Commons.

the case, prospective studies of the effects of STH infections on allergy should start in early childhood, ideally before birth, to measure any potential *in utero* effects of maternal STH infections. Four such prospective studies have been published to date: (1) a birth cohort in Ethiopia, where the prevalence of helminthiasis was considered too low to explore the effects on wheeze and eczema to 5 years[17]; (2) an observational analysis within a randomized controlled trial of anthelmintic treatment during pregnancy showed that maternal and childhood hookworm and childhood *Trichuris trichiura* were associated with a reduced risk of eczema at 5 years[18]; (3) a prospective study showed that *T trichiura* infections during the first 5 years of life were associated with a reduced risk of SPT reactivity in later childhood[19]; and (4) a birth cohort in a rural area did not show an effect of maternal STH infections on SPT reactivity, wheeze, or eczema during the first 3 years of life,[20] but follow-up of the cohort is in progress to determine whether childhood infections can affect the risk of allergy at school age.[21]

Another method used to test the causal link has been interventional studies, in which protective exposure (ie, the STH) is removed through anthelmintic treatment, thus intending to reverse any existing effects. If helminths are truly protective, one might expect to observe an increase in the prevalence of allergy in the group receiving treatment. Several intervention studies have inconsistent findings.[18,21-23] None of the studies were able to show an effect on the prevalence of asthma symptoms, one showed that a single dose of anthelmintic drugs given during the latter part of pregnancy was associated with an increased risk of eczema in infancy,[18] and 2 showed an increase in either the incidence[22] or frequency[23] of a positive SPT response after at least 1 year of treatment.

Overall, the evidence suggests that *A lumbricoides* infection and particularly *Ascaris* species–specific IgE are associated with an increased risk of asthma symptoms in endemic areas and that STH infections can reduce the prevalence of positive SPT responses but not specific IgE to aeroallergens. There is still very limited evidence that STH infections protect against allergic symptoms in human populations, and the effects of early-life exposures to STH infections on the development of allergy in childhood, either through maternal or childhood infections, are still insufficiently studied.

In case of schistosomiasis, all published studies have been cross-sectional, showing an inverse association between *Schistosoma mansoni* infection and SPT reactivity to common aeroallergens in most cases.[16] A recent study in Uganda was unable to demonstrate an association between *S mansoni* infection and wheeze, but an earlier study in Brazil showed that *S mansoni* infection was associated with a milder form of asthma.[24] See Fig 3 for a schematic representation summarizing the findings from epidemiologic studies of the relationships between helminth parasites, atopy, and asthma.

HOST IMMUNE RESPONSE AGAINST PARASITES

Helminths are the largest organisms to infect vertebrate hosts, leading to release of large quantities of parasite molecules that interact with the immune system. It might be expected that helminth infections would induce an overwhelming immune response, resulting in elimination of parasites while causing potentially damaging inflammation. However, coevolution of hosts and parasites over the millennia has allowed both host and parasite to survive through the development of mechanisms that dampen the host inflammatory response to the parasite or even allow the parasite to evade the host immune response, resulting in infections that are often asymptomatic.[11] For example, *Schistosoma* species adults, which live within the human vascular system, can survive for many years without inducing strong host inflammatory responses.[25]

Although the most widely studied host immune response against helminths is the acquired T_H2-type response, we will discuss both innate and adaptive host immune responses to helminth parasites. The T_H2-type response is characterized by production of high levels of the cytokines IL-4, IL-5, IL-9, IL-10, IL-13, IL-21, and IL-33. These cytokines orchestrate immediate hypersensitivity that involves B-cell class-switching to IgG_4 and IgE, eosinophilia, goblet cell hyperplasia and mastocytosis, alternative activation of macrophages, and influx of inflammatory cells, such as eosinophils, that contribute to parasite killing. Such a response can control parasite numbers by killing them in tissues or expelling them from the intestinal lumen. The host response to helminth infections is associated with allergic phenomena that are a consequence of killing or an attempt to kill or expel these parasites.[26] Examples are shown in Table I.

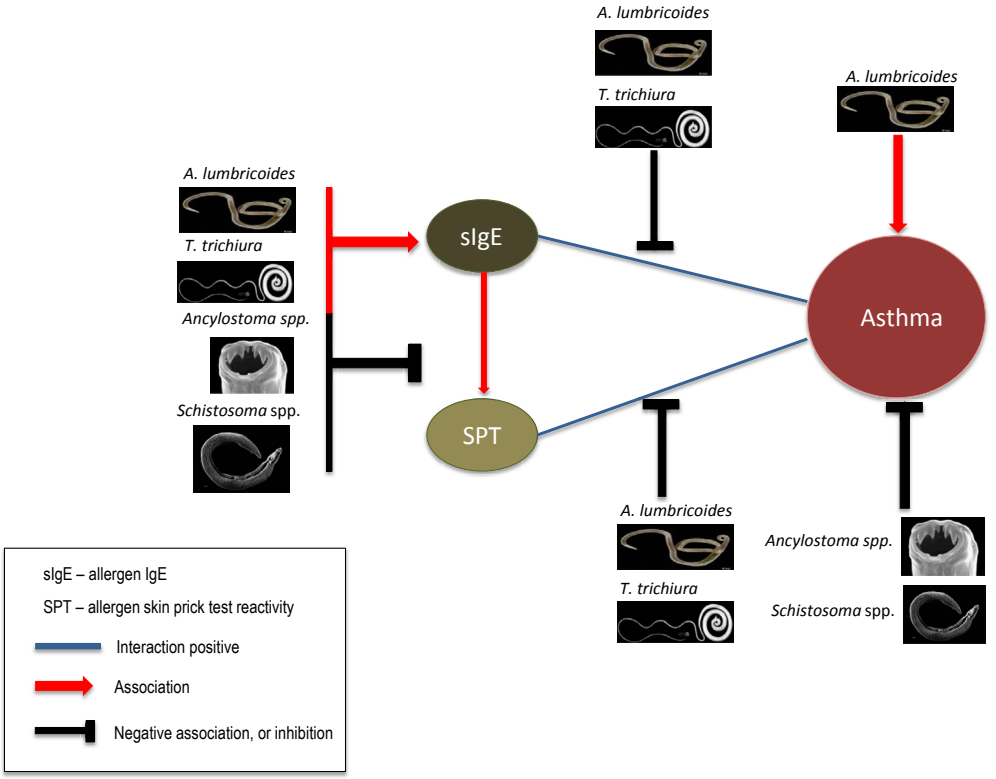

FIG 3. Schematic representation summarizing findings from epidemiologic studies on the relationships between helminth parasites, atopy, and asthma.

Although helminth parasites are universal in inducing all or most of these T_H2 effector pathways, in the host the specific effector pathway mediating protection varies between different parasites, lifecycle stages, and site of infestation. For example, the intestinal helminths *Heligmosomoides polygyrus* and *Trichinella spiralis*, are expelled from the intestinal lumen by several T_H2 effector pathways, such as IgE-mediated activation of mucosal mast cells. T_H1 responses can also have a role in protective immunity against some helminth parasites, such as *S mansoni*,[27] whereas the control of parasite burden in patients with strongyloidiasis is highly dependent on type 2 responses.[28]

One of the parasite's first contacts with the host's immune system is through conventional dendritic cells, which undergo alternative activation, such as in response to excretory-secretory (ES) molecules from the murine intestinal helminth parasites *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis*.[29] Helminth molecules bind to Toll-like receptors 2, 3, and 4 on the dendritic cell membrane, driving the acquired immune response from a naive T_H0 to a T_H2 profile.[30]

An important group of innate immunity cells, the innate lymphoid cells (ILCs), which lack B- or T-cell antigen-specific receptors and do not express myeloid or dendritic cell markers, has been shown to comprise 3 subsets: type 1 ILCs (related to the T1 profile), type 2 innate lymphoid cells (ILC2s; related to the T2 profile), and type 3 ILCs (related to the ThI7 profile).[31] ILC2s produce a large set of T2 cytokines (IL-4, IL-5, IL-9, IL-13, and IL-21) in response to stimulation with IL-25, IL-33, and thymic stromal lymphopoietin[31] and play an important role in protection against helminths. However, unlike T_H2 cells, ILC2s are stimulated by alternatively activated macrophages (AAMΦs), express MHC class II, and are able to endocytose and process antigen.[32] AAMΦs are phenotypically distinct from classically activated macrophages that are typical of T_H1-type responses. AAMΦs do not produce IFN-γ and, instead of inducible nitric oxide synthase, have upregulated expression of arginase-1, which has higher affinity for arginine, competing with inducible nitric oxide synthase present in classically activated macrophages. AAMΦs are induced during infections with several helminth parasites.[33] Interestingly, interaction between ILC2s and T_H2 cells for maintaining AAMΦs in the lungs of hookworm-infected mice has been reported.[34]

Other immune cells reported to play a role in immunity against helminth infection are the T_H17 cells, which are derived from $CD4^+$ T cells after antigen maturation. T_H17 cells are important for the clearance of several extracellular pathogens, such as bacteria and helminths.[35] In *Schistosoma japonicum*–infected mice, there was an increase in T_H17 cell numbers after granuloma development attributed to the presence of induced factors (eg, TGF-β, IL-23, and IL-21) in greater amounts than inhibitory factors (eg, regulatory T [Treg] and T2 cells and IL-4).[36]

Helminths have developed several mechanisms to suppress or avoid host antiparasite responses. For example, *S mansoni* has developed parasite stage-specific evasion strategies. Entry of cercariae through the skin is followed by the release of larval ES molecules of helminth products (eg, prostaglandin D_2) that cause host cells to release prostaglandin E_2.[37] Both host and parasite-derived prostaglandins induce the production of IL-10 in the skin, which inhibits the migration of epidermal Langerhans cells to the invasion site.[38]

The most remarkable evasion strategy used by helminths, particularly those dwelling within host tissues and in the blood and lymphatic systems, is downmodulation of the host immune

TABLE I. Examples of helminth infections and the allergic-type inflammatory responses with which they are associated

Helminth infection	Allergic-type reactions and syndromes
Intestinal helminths	
Ascaris lumbricoides	Asthma-like syndrome
Trichuris trichiura	Tropical dysentery syndrome
Hookworm	Ground itch/allergic enteritis
Strongyloides stercoralis	Larva currens/urticaria/asthma-like syndrome
Enterobius vermicularis	Itchy anus
Schistosomiasis	
Schistosoma mansoni	Cercarial dermatitis/acute schistosomiasis/ urticaria/asthma-like syndrome
Schistosoma haematobium	
Schistosoma japonicum	
Filariasis	
Wuchereria bancrofti	Tropical pulmonary eosinophilia/acute lymphangitis
Onchocerca volvulus	Sowda/acute popular onchodermatitis/ punctate keratitis
Loa loa	Calabar swellings
Others	
Toxocara species	Visceral larva migrans/asthma-like syndrome
Anisakis species	Gastroallergic/asthma-like syndrome/ urticaria/anaphylaxis
Paragonimus species	Asthma-like syndrome
Trichinella spiralis	Acute trichinosis
Echinococcus granulosus	Acute anaphylaxis associated with rupture of cyst
Ancylostoma braziliense	Cutaneous larva migrans

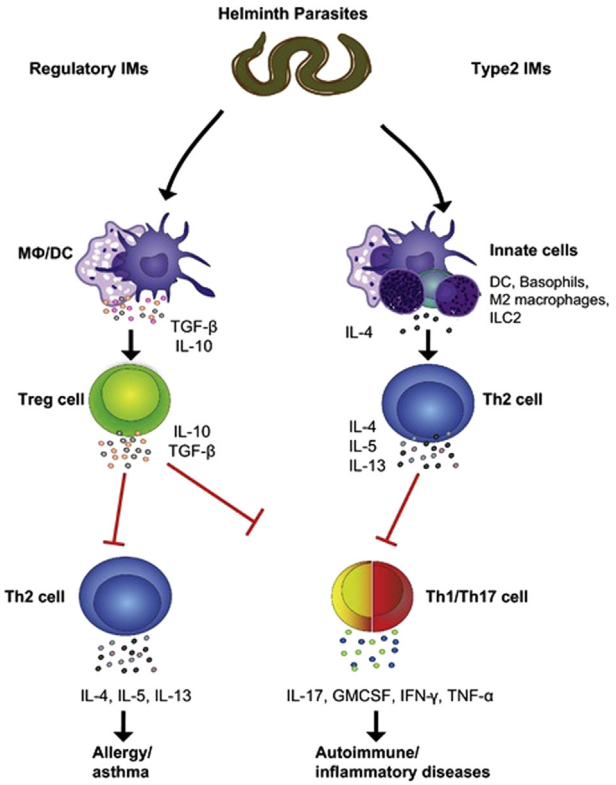

FIG 4. Helminths suppress autoimmunity and allergy through type 2 or regulatory immune response. Immunomodulatory molecules *(IMs)* of parasites activate innate immune cells that promote either T_H2 or Treg cell responses. IMs that induce TGF-β and IL-10 production by dendritic cells or macrophages *(Mø)* prime IL-10–or TGF-β–producing Treg cells to suppress T_H2, T_H1, or T_H17 responses. A separate set of helminth-derived IMs activate type 2 innate cells, including basophils, M2 macrophages, and ILC2s, and induce innate IL-4 production, which drives differentiation of T_H2 cells. T_H2 cells and type 2 innate immune cells can suppress T_H1 and T_H17 responses. Modified from Finlay et al.[47]

system, leading to a form of immunologic tolerance that might have effects on host responses to other infections and allergy. The cells mediating this effect are the Treg subset of the $CD4^+$ T lymphocytes that produce the immunomodulatory cytokines IL-10 and TGF-β. The presence of regulatory cells is associated with a reduction in T_H2 cell numbers and development of a modified type 2 immune response. Other cells involved are AAMΦs and regulatory B cells.[11]

COMMONALITIES BETWEEN THE IMMUNE RESPONSE TO PARASITES AND ALLERGY

The host immune response to helminth parasites has many features in common with allergy. Bronchial inflammation of atopic asthma is coordinated by cells of the adaptive immune system but also by ILC2s of the innate response, which together induce a type 2 response.[39] During helminth infections, type 2 immunity is initiated at the site of parasite invasion by epithelial cells, which release the alarmins IL-25 and IL-33 to prompt ILCs to produce IL-13 and other cytokines that are also involved in the pathoetiology of asthma. In the absence of either IL-25 or IL-33, resistance to helminth infection is severely impaired.[40] Treg cells have a dual role in helminth infections: they protect the host from excessive inflammatory responses during infection, but they also can decrease protective immunity and thereby permit parasite persistence.[41] In the case of asthma, several studies have shown allergic patients to have lower numbers of Treg cells in both bronchoalveolar lavage fluid and PBMCs.[42] Thus there are notable parallels between the immune responses associated with allergy and those observed in response to helminth infection.

Host type 2 immune responses to parasites and allergens are induced by a limited number of protein families that contain allergens, such as tropomyosins.[14] There is extensive structural homology between allergens from helminths and other environmental sources.[43] Furthermore, allergen homologues derived from parasites and aeroallergens not only exhibit IgE cross-reactivity but also can induce cross-sensitization in murine models.[44] Cross-reactivity between helminths and aerollergens has a number of important consequences, including false-positive reactions for specific IgE when used in the diagnosis of allergy and a potential increase in morbidity caused by inflammatory reactions directed against cross-reactive allergens. In the case of the latter, cross-reactivity could help drive the exaggerated responses associated with inflammatory syndromes that have been reported in human helminth infections, such as tropical pulmonary eosinophilia in the case of lymphatic filariasis[45] and Loeffler syndrome in patients with ascariasis.[46] Likewise, it has been suggested that immune modulation during

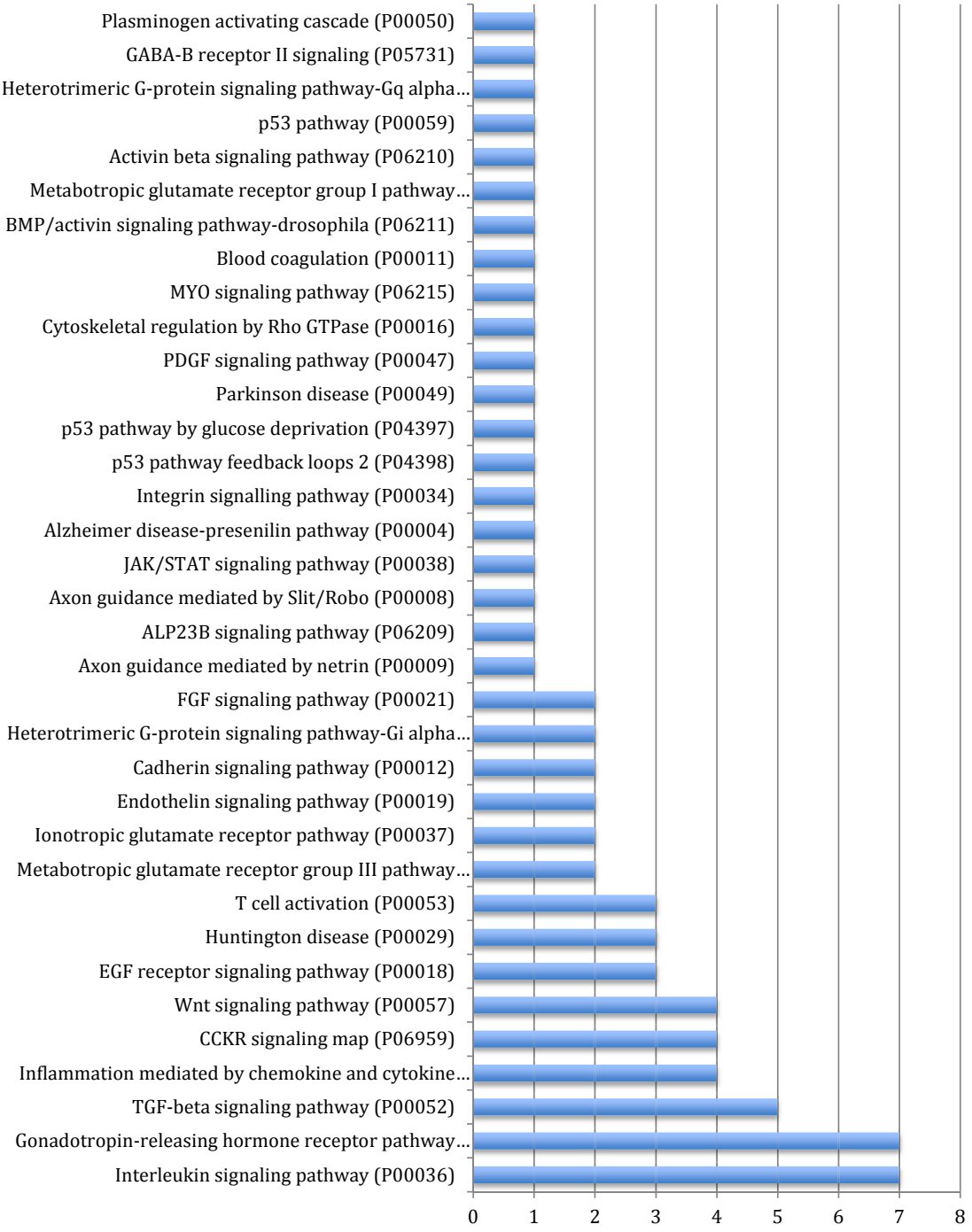

FIG 5. Pathway analysis using PANTHER, version 11,[49] for the top SNPs associated in GWASs for asthma to date. *EGF*, Epidermal growth factor; *FGF*, fibroblast growth factor; *JAK/STAT*, Janus kinase/signal transducer and activator of transcription; *PDGF*, platelet-derived growth factor.

chronic helminth infections, which subvert T_H2-mediated inflammation, permitting parasite survival, could affect atopic responses to common aeroallergens through either bystander effects or immunologic cross-reactivity.[44] See Fig 4 for information on how helminths suppress autoimmunity and allergy through type 2 or regulatory immune responses.[47]

GENETIC DETERMINANTS OF PROTECTION AGAINST HELMINTHS AND RISK OF ALLERGY

Characterization of parasite genomes and subsequent comparison of parasites to more complex species, such as mammalian hosts, have contributed to our understanding of the mechanisms of parasite evolution and have provided evidence for

the role of host-parasite interaction in genetic adaptation. An understanding of that genetic adaptation has elucidated candidate genes that might drive susceptibility to other diseases of the immune system, including atopy and asthma.[48] Thus genetic variants affecting any of the classical key inflammation-inducing factors, as well as proteins related to controlling inflammation through immunoregulatory mechanisms, such as Treg cells, might play a role on both helminth resistance and allergic conditions. Genetic studies have highlighted common variants (minor allele frequency [MAF] >10% to 30%) that affect allergy in many different ways. In Fig 5,[49] an analysis using the Protein Analysis Through Evolutionary Relationships, version 11,[50] is presented, showing different pathways related to the main genes described in genome-wide association studies (GWASs) to date, in which one can observe 3 of the top 4 pathways linked to asthma are related to interleukin signaling and inflammation.

The genetic variants that affect protection against helminths and risk of allergy can be organized in 2 main groups: those affecting T_H2 immune response and those affecting regulatory mechanisms.

Variants that affect the T_H2 immune response

Common genetic variants of type 2 immune signaling relating to allergy and asthma provide credence to the hypothesis that the origin of these allergy-promoting variants derives from evolutionary mechanisms and that their selection occurred in the presence of widespread endemic helminth infection.[51] A region on chromosome 5, 5q31-q33, for example, has been associated with resistance to *S mansoni* through the presence of genes such as granulocyte-macrophage factor *(CSF2)*, *IL3*, *IL4*, *IL5*, and *IL13*, which are important in protective immunity against *S mansoni*.[52] The same locus (5q31-q33) has been linked to asthma and atopy. Other relevant loci that are also linked to asthma are 7q and 21q.[53]

In terms of asthma susceptibility, several immune molecules have been associated with asthma/allergy. In both GWASs and candidate genes studies, some 200 genes have been associated with asthma or related phenotypes. Among these genes, there are those related to a possible modulation of plasma total IgE (tIgE) levels.[54] Association studies of genes encoding the epithelial cell–derived cytokines IL-33 and thymic stromal lymphopoietin and the *IL1RL1* gene encoding the IL-33 receptor ST2 highlight the central roles for innate immune response pathways that promote the activation and differentiation of T_H2 cells. These genes are the most consistent variants associated with asthma, allergy, and helminth infections across ethnically diverse populations.[55]

In this context GWASs for allergic diseases have pinpointed *IL33* and *IL1RL1* as key susceptibility genes for allergic asthma, underscoring the pivotal role of this pathway in the pathophysiology of this diseases.[56] Studies involving the genes codifying the *IL33/ST2* route have been widely replicated in different populations,[57] confirming their association with asthma[58] and blood eosinophilia.[59] The mechanism whereby the *IL33/ST2* axis induces T_H2-inflammation was demonstrated recently.[60] Local airway soluble ST2 levels, as well as circulating plasma soluble ST2 levels, contribute to neutralization of IL-33 in tissues.

The role of human genetic determinants of *IL33/ST2* in helminth infection is poorly understood. By using a generalized estimating equation model, 3 single nucleotide polymorphisms (SNPs) associated with higher *Schistosoma* species–soluble adult worm antigen-specific IgE/IgG_4 (a measure of resistance to *S mansoni*) were found.[61] The most significant SNP mapped to intron 1 and the allele, which has been shown to confer asthma risk in an African-American population, also conferred protection against schistosomiasis.

Major polymorphisms within the 5q31-q33 genomic region, which was previously associated with resistance to *S mansoni* infection, have been studied.[52,53] The region includes several genes related to immune function, including *IL4*, *IL5*, and *IL13* in the T_H2 cluster. Resistance to *Schistosoma haematobium* was associated with the *IL13*-1055T/T genotype,[62] which has also been implicated in asthma exacerbations.[63] Furthermore, a functional *IL13* polymorphism, rs1800925T, was shown to contribute to the risk of late-stage schistosomiasis caused by *S japonicum*.[64] In another study 2 quantitative traits, tIgE levels (representing T_H2 pathway activation) and *S mansoni* egg counts, which reflect host immunity to helminths, were investigated, providing a unique opportunity for genetic dissection of the T_H2 pathway in the context of schistosomiasis.[7] Significant associations were seen between 2 functional variants on the *IL13* gene and *S mansoni* egg counts, indicating *IL13* as protective but no associations of *IL13* gene variants with tIgE levels. Because the functional effect of both variants on the gene product IL-13 is to increase its amount or activity, this finding suggests IL-13 functions to increase antihelminth immunity, and functional variants might be an evolutionary vestige of selective forces that could now favor atopic phenotypes.[5]

Variants that affect immunoregulatory mechanisms

Alterations in regulatory cytokine levels are believed to play an important role in mediating immune suppression in helminth immune response. Genetic variants affecting *IL10* and *TGFB1* can be associated with both asthma/allergy and helminthiasis. We described a variant (rs3024496, G allele) in the *IL10* gene associated with suppression of IL-10 production in *A lumbricoides* antigen–stimulated cultures of peripheral blood leukocytes, and other variants within the same gene were positively associated with atopy and asthma and negatively associated with helminth coinfections.[65]

Several *IL10* promoter polymorphisms have been studied extensively. Some variants were significantly associated with high PBMC proliferative responses to *Onchocerca volvulus* antigen.[66] One of these promoter variants, G-1082A was also associated with immune-related diseases, including type 2 diabetes, multiple sclerosis, and asthma.[67] Moreover, the same variant was associated with pediatric asthma.[68] In an endemic area for *S mansoni*, alleles at the 3 promoter SNPs were associated with high tIgE levels in the same direction as in atopic subjects but not with egg counts. *IL10* promoter polymorphisms appear to influence nonspecific tIgE levels but not schistosomiasis-specific immunity.[7]

Genetic polymorphisms in *TGFB1* are associated with airway responsiveness and exacerbations in asthmatic children.[69] Common variants in the *TGFB1* gene affect both asthma/allergy and helminth infections. We demonstrated a negative association between rs1800470 (C allele), atopic wheezing, and allergy markers. In contrast, a positive association was observed between the haplotype ACCA and *T trichiura* and *A lumbricoides*

Box 1. Clinical notes I: Notes of relevance for clinical allergy practice on immunopathology of helminth infections

- Accuracy of allergy testing
  When dealing with patients from areas endemic for helminth infections, an allergy workup, including specific IgE measurement, might be more sensitive than an SPT, but in subjects with a very high tIgE levels, *in vitro* test results can be false positive.
- Interpretation of tIgE levels and blood eosinophilia
  Increased tIgE levels and peripheral blood eosinophilia might indicate helminth infection.
- Potential reduction in efficacy of vaccines for prevention of infectious diseases
  It is important that children and adults are free of worms for optimal vaccine efficacy.
- Risks of prolonged use of systemic corticosteroids and immunobiological suppressors of T2 inflammation mediators (anti-IgE, anti–IL-5, and anti–IL-4/IL-13)
  Treatment of severe asthma with continuous oral corticosteroids, anti-IgE, anti–IL-5, or anti–IL-4/IL-13 poses risk of helminth superinfection. It is advisable to observe the patient closely, investigate, and treat, if necessary, when living or coming from a region that is endemic for worms.

infection. This later haplotype was also associated with increased IL-10 production.[70]

The main cellular source of both IL-10 and TGF-β1 are Treg cells, which are critical for the maintenance of immune homeostasis. The activation of forkhead box protein 3 (FOXP3) transcriptional factor is pivotal for Treg cell function. The human *FOXP3* gene is located on the X-chromosome (Xp11.23), and because of sex differences among X-variants, insufficient efforts have been made to include X-variants in GWASs. Polymorphisms in the *FOXP3* gene have been evaluated in association studies for allergy,[71] but only a few studies on asthma have been reported. A study reported a significant interaction between SNPs in *FOXP3-IL2R* genes and specific IgE for worm eggs and asthma.[72] The SNPs rs2294019 and rs5906761 were associated with the risk of egg sensitization only in female subjects.[71] The heterozygote genotype for rs3761547 was a risk factor for allergic rhinitis, and this association was reproduced in gene-gene interaction analysis with rs3761548.[72]

Immune regulation of allergic disease results not only from protective environmental factors, including helminths, but also from genetic factors relating to *IL10* production or hyperactivation of type 2 immune responses. From an evolutionary perspective, the selective advantage acquired by human subjects able to mount an efficient protective immune response to helminth infections might make them more vulnerable to atopy and asthma.

IMMUNOREGULATION BY HELMINTHS AND CLINICAL PRACTICE

Treatment of allergic diseases with systemic corticosteroids at immunosuppressive doses increases the risk of opportunistic infections. The helminth reported to affect immunosuppressed hosts most frequently is *Strongyloides stercoralis*, occasionally resulting in uncontrolled dissemination of the parasite in the potentially fatal hyperinfection syndrome. *Strongyloides* species hyperinfection has been associated also with other immunosuppressive drugs, lymphomas, and infection with human T-cell lymphotropic virus 1.[73] Because of the presumed central role of IgE in protective immunity against helminth parasites, treatment of severe asthma with anti-IgE antibody raised concerns about the risk of severe or disseminated helminth infections. A multicenter randomized controlled trial of omalizumab for the treatment of asthma and rhinitis was safe in a population at risk for STH infections, although there was a modest increase in geohelminth infection.[74] The same safety concerns will be present in populations at risk of helminthiasis for other immunomodulatory compounds for the treatment of allergic diseases, particularly those targeting specific type 2 effector pathways, such as anti–IL-5 and anti–IL-13/IL-4.

Helminth infections induce cellular immune hyporesponsiveness.[11] Such hyporesponsiveness has been associated with suboptimal vaccine responses.[75,76] Among pregnant women, soluble parasite antigens cross the placenta and modify fetal immune responses in such a way as to possibly affect vaccine responses in childhood.[77] Modification of the host immune response to helminths affects how human subjects respond immunologically to other pathogens, such as those causing malaria[78] and tuberculosis[79]; however, effects on clinically measurable outcomes are less clear. See Box 1 for more information.

Reports have indicated possible benefits of helminth infections on autoimmune diseases, inflammatory bowel disease, and even in patients with metabolic syndrome.[80] For example, an inverse association between lymphatic filariasis and type 2 diabetes was reported,[81] and past infection with *S japonicum* was associated with a lower prevalence of metabolic syndrome.[82] Intestinal helminth infections were inversely associated with risk factors for cardiovascular diseases, such as body mass index and lipid levels.[83] See Box 2 for more information.

EXPLORING THE IMMUNOMODULATORY POTENTIAL OF HELMINTHS AND HELMINTH MOLECULES

Helminth infection and immunomodulation of diseases

An observational study of patients with multiple sclerosis who had acquired gastrointestinal helminth infections reported remission of multiple sclerosis for over 4 years. Patients infected with parasites had reduced inflammatory cytokine responses and enhanced production of both IL-10 and TGF-β. Six of these subjects were followed up, and remission continued into the sixth year, when 4 patients were offered anthelmintic treatment because of gastrointestinal problems. Subsequently, their multiple sclerosis activity resumed, whereas IL-10 and TGF-β expression decreased.[84]

Box 2. Clinical notes II: Note of relevance on protection against allergy and other chronic diseases

- Inverse association between helminth infection and allergy and other chronic diseases
  There is compelling evidence of a strong inverse association between infection by various helminths and biomarkers of chronic inflammatory diseases and allergy.
- Plausible causal association
  Direct causality is plausible, taking into consideration experimental studies in animal models and human subjects.
- No robust association between helminth infection and protection against diseases
  We found no robust evidence for causal associations between helminth infection and clinically relevant protection against disease.
- Exposure to helminths occurs in a diverse environment that might be itself protective
  In the real world exposure to helminths often occurs in a markedly different environmental, ethnical, and lifestyle context, including contrasts in ancestry, physical activity, diet, nutrition, stress, and exposure to air pollution and to microorganisms.
- Protective environment might overshadow the effects of helminth infection
  The potential influence of multiple factors in the health and disease balance might overshadow the effect of exposure to parasites.
- Inverse associations might not be directly causal
  The inverse associations between helminth infections and biomarkers of chronic inflammatory diseases and allergy might not be directly causal but linked to conditions related to parasite infections.

TABLE II. Helminth molecule candidates for the treatment of inflammatory diseases

Molecule	Study phase	Treatment	Results	References
Excretory/secretory-62	Animal models	Rheumatoid arthritis and systemic lupus erythematosus	Reduce disease severity and progression	Rodgers at al, 2015[93]
Neutrophil inhibitory factor (NiF)	Animal models and human subjects (phase I/II)	Acute stroke, allergen-induced lung inflammation, and diabetic retinopathy	No benefit in human stroke, favorable results in mouse models of lung inflammation, and retinopathy	Krams et al, 2003[94]; Schnyder-Candrian et al, 2012[95]; Veenstra et al, 2013[96]
Migration inhibitory factor (MiF)	Animal models	Colitis and allergic airway inflammation	Favorable	Cho et al, 2011[97]; Park et al, 2009[98]
Cystatins	Animal models	Colitis and allergic airway inflammation	Favorable	Whelan et al, 2014[99]
Helminth defense molecules	Animal models	LPS-induced inflammation	Favorable	Alvarado et al, 2017[100]
Anti-inflammatory protein 2 (AIP-2)	Animal models	Model of asthma	Favorable	Navarro et al, 2016[101]
TGF-β pathway manipulation	Studies *in vitro*	Molecular biology stage	Promising	Freitas et al, 2009[102]
Prostaglandin E_2 (PGE_2)	Studies *in vitro*	Molecular biology stage	Promising	Liu et al, 2013[103]
ShkT domains	Animal models and human subjects (phase I and II)	Human psoriasis	Unknown results	Beeton et al, 2006[104]
AcK1 and BmK1	Studies *in vitro*	Immunology stage	Promising	Steinfelder et al, 2016[92]

AcK1, Large family of ShK-related peptides; *BmK1*, large family of ShK-related peptides.

Experimental infections of human subjects with live parasites using either the pig whipworm *Trichuris suis* or the human hookworm *Necator americanus* have been reported.[85] The premise is that the immune system can be modulated with amelioration or remission of the inflammatory disease. In the case of treatment with *T suis*, parasite eggs are administered orally. Initial studies reported a beneficial effect on Crohn disease and ulcerative colitis.[86] *T suis* eggs have been used to treat other immune disorders. A randomized controlled trial tested the efficacy of *T suis* for the treatment of allergic rhinitis in Denmark but showed no efficacy. Although *T suis* infection generated a measurable antiparasite response, infection did not affect allergen-specific responses.[49] Patients with Crohn disease were infected with *N americanus*, with the majority showing improvements in symptom scores.[87] A trial of *N americanus* in patients with celiac disease was unable to demonstrate clinical benefit.[88] A small randomized controlled trial in patients with asthma showed no significant benefit of hookworm infection on clinical symptoms, bronchial responsiveness, or SPT reactivity.[89]

What might be the reasons for the disappointing findings of clinical trials to date? Experimental animal models have demonstrated helminth parasites reduce allergic reactivity, but

most studies have been designed to prevent the development of allergic reactivity rather than treat established disease. Only a handful of studies have reported the effects of these infections on already established allergic reactivity.[90] Most of the experimental data available suggest that once the allergic reaction is established, helminth infections can do little to revert the disease process, raising the question of whether there is any reasonable possibility of obtaining benefit through infections of patients with active disease. Nonetheless, there are sufficient doubts with respect to optimal timing of treatment, the dose, and systemic versus nonsystemic infections to justify future well-designed randomized controlled trials of helminth therapy for inflammatory conditions.

Tests with helminth molecules as immunomodulatory candidates

Recombinant proteins can reproduce the biological effects observed in infection with live worms. In experimental models of inflammatory disease, recombinant proteins derived from helminth molecules induce anti-inflammatory and inhibit proinflammatory cytokine production and promote regulatory cell recruitment and immune deviation.[91]

In mouse models helminth ES and helminth-derived synthetic molecules have shown usefulness in treating or preventing the development of inflammatory diseases, such as inflammatory bowel diseases, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and asthma. The synthetic production of ES-derived immune modulators avoids concerns raised by the use of live organisms.[92] Furthermore, molecule-based helminth treatment offers the advantage of delivery directly to the site of pathology.

We present in Table II[93-104] a summary of preclinical and clinical studies of helminth molecules for the treatment of chronic inflammatory conditions affecting human subjects.

DISCUSSION

There is conflicting evidence of an inverse association between exposure to helminth infections and human chronic inflammatory diseases, including allergic conditions. A possible causal relationship is supported largely by the findings from experimental animal models, whereas evidence from human studies has been equivocal. Evidence from clinical trials of live helminth parasites has been disappointing.

One explanation for the association between allergy and helminths in epidemiologic studies is the genetic evolutionary advantage of mounting strong type 2 responses protective against helminth infection, while increasing the risk of allergy.[65] However, large increases in the prevalence of allergy have occurred in a short time to be explained solely by genomic changes in human populations. This indicates the importance of environmental factors in aberrant immune reactivity. The sort of environmental and unhygienic living conditions in which parasite infections are likely to occur also expose populations to multiple other microorganisms that might contribute to modulation of inflammatory responses.[105,106] Studies have demonstrated that helminth infections, intestinal microbiota, and nutrition are interrelated.[107] Both the intestinal microbiota and nutrition can interact with the effects of helminth infections. Moreover, there is evidence that several other contextual factors not always controlled for in observational studies might contribute to the inverse association between helminths and allergy. Such factors include diet, nutrition, obesity, gut microbiome, physical activity, exposure to air pollution, stress, and use of vaccines and antibiotics, all of which are related to an urbanized lifestyle, which has clearly been an important risk factor for allergy.[108,109]

How do we interpret the negative results of clinical trials of live helminth infections when helminth infections or helminth-derived molecules have proved so effective in controlling animal models of inflammatory diseases? The effects of helminth infections in humans are related to parasite burden and duration of infection. No safety issues have been reported after administration of *T suis* ova thus far, even to immunosuppressed patients, but in general, there are safety and ethical concerns with treating human subjects with large infectious doses and maintaining infections for a period of years that might be required to induce clinically relevant immunomodulatory effects. In addition to this, some trials in patients with inflammatory bowel disease were unable to show an immunosuppressive effect of helminths because of a very high placebo response rate (unpublished). In some trials patients continued their immunosuppressive medications, making interpretation of data on the efficacy of helminth infections more difficult. Furthermore, trials in human subjects have attempted to modify preexisting disease, whereas most animal models have studied the ability of helminths to prevent disease.[110]

CONCLUSIONS

There is consolidated evidence from studies in human subjects of a negative association of helminth infection with allergy, although the effect seems to vary by helminth species, parasite burden, and age of infection. Helminth infections can also provoke symptoms of allergy, although such allergic inflammation tends to be modulated during chronic infections. Experiments in animal models of chronic inflammatory diseases have demonstrated the potential benefits of helminth infection or the use of helminth-derived molecules against allergic disease, but clinical trials in human subjects have been disappointing. We still have an inadequate understanding of the complex interplay between helminths and allergy, and there is a need for more studies in human subjects and experimental studies in animal models to understand these interactions more fully. Certainly, the exploitation of helminth-derived molecules for the treatment of inflammatory conditions offers promising new avenues for research and development.

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