

Parasitic Nematode Modulation of Allergic Disease

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Incidence of allergic diseases such as asthma has increased at an alarming rate in Western countries in the past few decades. However, in parts of the world in which parasitic nematode infections are highly prevalent, allergy remains uncommon. Hence, it has been postulated that nematodes offer humans protection against this type of disease. This article reviews the evidence to support this idea, considering data from human studies and results from investigations into the protective effects of nematodes in animal models of allergic disease. The evidence strongly favors a protective role for nematodes; thus, the search is on to find the molecules involved, with a view toward using them for therapeutic purposes. The article also describes the nature and mode of action of recently characterized nematode-derived molecules with antiallergic properties and highlights their therapeutic efficacy in allergy models.

Introduction

Nematodes constitute a highly successful phylum, representing one of the most abundant groups of animals on earth. Although most species are free-living, the phylum also contains parasites of virtually every known multicellular organism [1]. This and the fact that parasitism has severe and even fatal consequences for the host in many cases dictates that nematodes are of substantial medical, veterinary, and economic importance.

Nematodes generally are small organisms, but the existence of larger parasitic species (eg, *Ascaris lumbricoides*, which may grow to more than 40 cm) has been documented for thousands of years [1]. Typically, nematodes are slender, bilaterally symmetrical organisms that are enclosed in a noncellular cuticle. This cuticle is shed four times during the course of a nematode's life,

with the five stages of existence often referred to as L1 through L5 (the last being the adult stage) [1].

Adult parasitic nematodes inhabit two locations within humans: the gastrointestinal (GI) tract and the tissues. The most common GI nematodes of humans are *A. lumbricoides*, *Trichuris trichiura*, *Necator americanus*, and *Ancylostoma duodenale* (the latter two species being the hookworms). An infected individual may harbor more than one type of these parasites, and collectively, the four species of worm have been estimated to infect more than one third of the world's population. The major tissue-dwelling nematodes of humans are the filarial nematodes, which infect hundreds of millions of people. The adult worms may live in the lymphatic system (eg, *Wuchereria bancrofti*, *Brugia malayi*) or the subcutaneous tissues (eg, *Onchocerca volvulus*) [1]. Infection with GI nematodes may arise through ingestion of eggs (*A. lumbricoides*, *T. trichiura*) or penetration of the skin by L3 larvae (hookworms) [1]. Infection with filarial nematodes takes place when L3 larvae are transferred to humans by blood-feeding insects, such as mosquitoes and blackflies that act as vectors [1]. Most people infected with nematodes are asymptomatic, but some species can cause very severe medical conditions, such as elephantiasis (*W. bancrofti*, *B. malayi*) and blindness (*O. volvulus*) [1].

Evidence that Parasitic Nematodes Can Protect Humans From Allergy

There are many reports of nematodes surviving in humans for more than a decade [2], a somewhat remarkable feat given the effectiveness of the human immune system. Therefore, it is assumed that long-term infection must depend on nematodes somehow suppressing this system. This idea has been particularly well studied with respect to the lymphatics-dwelling filarial nematodes. Analysis of the immune response during human infection with these worms generally indicates that individuals having patent infection (ie, having larval stages [microfilariae] in their bloodstreams) show reduced lymphocyte proliferative responses and decreased production of the cytokine interferon- γ but increased production of the cytokines interleukin-4 (IL-4) and IL-10 and the antibody type IgG4 [3]. As IL-4 is

Table 1. Studies suggesting nematode infection protects humans from allergic diseases

Nematode species	Observation	Reference
Various gastrointestinal nematodes	Reduced skin reactivity to house dust mite allergen with infection	Hagel et al. [42]
Various gastrointestinal nematodes	Increased skin reactivity to house dust mite allergen and increased serum IgE against environmental antigens after anthelmintic treatment; decreased reactivity with increased worm infection	Lynch et al. [30]
<i>Ascaris lumbricoides</i> and <i>Necator americanus</i>	Inverse correlation between incidence of asthma and infection	Selassie et al. [43]
<i>A. lumbricoides</i> and hookworms	Inverse association between skin-test reactivity to various allergens and infection	Nyan et al. [44]
Hookworm	Inverse association between recent wheeze and infection	Scrivener et al. [45]
<i>A. lumbricoides</i> and hookworms	Reduced skin-test reactivity to various allergens with increasing worm burden	Cooper et al. [46]
<i>A. lumbricoides</i>	Inverse association between recent wheeze and infection	Dagoye et al. [47]
<i>A. lumbricoides</i> and <i>Trichuris trichiura</i>	Increased skin reactivity to house dust mites after anthelmintic treatment	van den Biggelaar et al. [48]
<i>A. lumbricoides</i> and hookworms	Inverse correlation between skin sensitization to house dust mites and infection	Flohr et al. [49]

classically a cytokine associated with T-helper type 2 (Th2) cells [4], and IL-10 is classified as an anti-inflammatory cytokine [5], such an immune response can be defined as being of a Th2, anti-inflammatory phenotype. Humans probably have a considerable advantage in the production of such an immunologic phenotype because, as alluded to previously, although filarial nematode infection can result in severe pathology, such as elephantiasis, most infected people exhibit little evidence of an inflammatory response or overt tissue destruction/disruption [6].

Similar conclusions recently have been drawn with respect to GI nematodes [7], and it is now accepted that a Th2-like, somewhat anti-inflammatory immunologic phenotype is a general feature of nematode infection. An interesting characteristic of this phenotype is that in some cases, it has been reported to extend to subsequent responses to non-nematode antigens (eg, to antigens in vaccines targeting bacterial infections that rely on Th1 responses for efficacy) [8]. Thus, one immediate question is whether such a change in immune responsiveness could lead to alterations in susceptibility to diseases associated with aberrant Th1-associated inflammatory responses, such as the autoimmune diseases. In relation to this question, great interest currently exists in the idea that the recent alarming increase in autoimmune diseases in the industrialized world (but not the Third World) reflects decreased infection with pathogens such as parasitic worms (the "hygiene hypothesis") [9]. Consistent with this idea, it has been suspected for many years that autoimmune diseases may be less prevalent in areas of nematode transmission [10]. However, considerable evidence also indicates that nematode infection is associated

with decreased allergy, a perhaps surprising fact given the Th2-associated status of this disease type [11].

This section examines results from human and animal studies. Most, although not all, human studies tend to support the idea that nematode infection can protect against allergy. This has been measured by factors such as skin reactivity to allergens or wheezing and also and more consistently by comparing symptoms before and after anthelmintic treatment of patients. This subject is reviewed elsewhere [8,10,12,13,14], and Table 1 lists the major findings from the original papers. Many recent studies also have shown that nematode infection can protect against allergic disease, in particular lung-associated inflammation, in murine models (Table 2). Thus, GI- and tissue-dwelling filarial nematodes have been shown to modulate many components of the response to inhaled allergens (eg, ovalbumin). The effects observed include airway hyperresponsiveness inhibition, airway inflammation reduction as measured by factors such as eosinophilia, and lowering of levels of allergy-associated molecules in the lungs (eg, IgE and eotaxin).

Mechanism of Action

Role of Th2 polarization and T regulatory cells

As mentioned previously, nematode infections are chronic and have been classically characterized by the induction of a Th2 immune response [15]. However, more recently, they also have been associated with T regulatory cell (Treg) responses [16]. It is convenient to simply view these two types of immune response in terms of their associated cytokines (eg, IL-4, IL-5, and IL-13 for Th2 responses;

Table 2. Studies indicating nematode infection can protect mice from allergic diseases

Nematode species	Observation	Reference
<i>Strongyloides stercoralis</i>	Suppression of allergic response to ovalbumin in the lungs	Wang et al. [32]
<i>Heligmosomoides polygyrus</i>	Inhibition of allergic responses to peanut extract	Bashir et al. [33]
<i>Nippostrongylus brasiliensis</i>	Inhibition of ovalbumin-induced airway eosinophilia and eotaxin and specific IgE levels in the lungs	Wohlleben et al. [25]
<i>H. polygyrus</i>	Inhibition of airway inflammation to ovalbumin and Der p 1	Wilson et al. [24••]
<i>H. polygyrus</i>	Suppression of ovalbumin-induced airway eosinophilia and bronchial hyperreactivity	Kitagaki et al. [26]
<i>H. polygyrus</i>	Suppression of ovalbumin-induced airway eosinophilia	Rzepecka et al. [50]
<i>Litomosoides sigmodontis</i>	Inhibition of IgE production, lung eosinophilia, and airway hyperresponsiveness to ovalbumin	Dittrich et al. [28•]

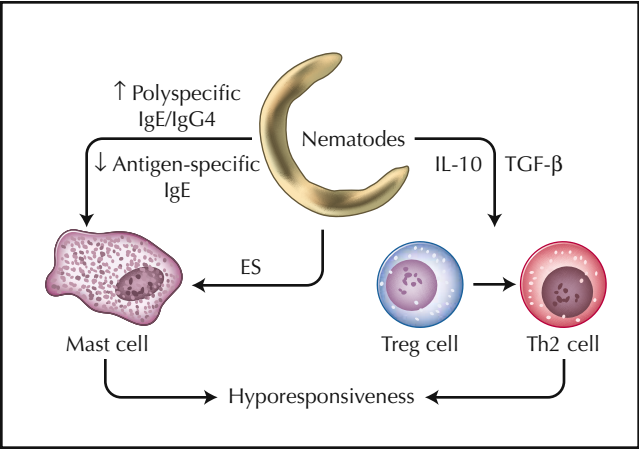


Figure 1. Potential mechanisms of nematode-induced suppression of allergic disease. Infection with nematodes can result in the induction of T regulatory cells (Tregs) that are refractory to antigen and can suppress T-helper type 2 (Th2) effector responses. Alternatively, it has been proposed that nematodes can antagonize Th2-driven inflammation by producing polyspecific IgE/IgG4 or reducing antigen-specific IgE to block allergen-induced mast cell degranulation. Moreover, certain excretory–secretory products (ES) have been shown to directly inhibit mast cell responsiveness by subverting FcεRI signaling. IL-10—interleukin-10; TGF-β—transforming growth factor-β.

IL-10 and transforming growth factor-β [TGF-β] for certain regulatory responses) (Fig. 1). Nematodes can polarize immune responses toward Th2 via their effects on dendritic cells (DCs), the sentinels of the immune system that sample and process foreign molecules for presentation to T cells. Presentation of peptides derived from antigens is accompanied by signals generated by DC surface costimulatory molecules and secreted cytokines interacting with receptors on T cells. This combination impacts on T-cell polarization [17]. Thus, nematode antigens must contain information that facilitates DC-driven Th2 polarization. Relative to antigens that induce Th1 responses, nematode-derived molecules generally have been shown to have little or only partial effect on DC activation as measured by upregulation of markers such as costimulatory molecules [18,19]. The induction of Th2 responses therefore may reflect particular char-

acteristics of nematode molecules [20]. However, the advantage of this to the worms is uncertain, as evidence from rodent models of GI nematode infection suggests that Th2 immune responses are protective [21]. This is also supported by some human epidemiologic studies [7]. Moreover, Th2 responses are associated with inflammatory pathology during GI nematode infection [22].

Regulatory responses appear to be generated in response to any chronic inflammatory insult in an attempt to prevent it from getting out of hand, but recent evidence suggests that nematodes may contribute via inhibition of protective immunity to worm persistence during infection [23]. What is particularly relevant to this article is that regulatory responses do not just inhibit inflammatory responses to nematodes but also to heterologous antigens. This means that responses to other infections or even vaccines [8] may be compromised and susceptibility to diseases associated with aberrant inflammatory responses altered. The Th2 dominance associated with nematode infection provides an attractive argument to explain the helminths' ability to inhibit Th1-associated autoimmune diseases, but it obviously cannot hold up with respect to allergic diseases, which themselves are Th2-dependent [11]. However, Th1 and Th2 responses may be dampened by anti-inflammatory regulatory responses [16]. Hence, the ability of nematodes to protect against allergic diseases may be explained in this way. Consistent with the latter, the ability of *Heligmosomoides polygyrus* to inhibit allergic airway inflammation in the mouse has been shown—using adoptive transfer experiments—to be dependent on CD4⁺CD25⁺ Tregs [24••]. In terms of cytokines, C57BL/6 mice showed increased IL-10 production in response to infection, whereas BALB/c mice demonstrated augmented TGF-β. The latter result may explain why using BALB/c knockout mice did not identify a role for the anti-inflammatory IL-10 in generating the anti-inflammatory response [24••], in contrast to that observed with C57BL/6 animals [25,26]. These results are also consistent with the ability of T-cell lines expressing IL-10 or TGF-β to protect against allergy in the ovalbumin sensitization model [27]. A more recent study

on the ability of *Litomosoides sigmodontis* to inhibit the airway response to ovalbumin in BALB/c mice also found a role for Tregs and TGF- β , but only in response to airway hyperreactivity and not lung inflammation [28•]. This raises the possibility of GI and tissue nematodes impacting on certain components of the allergic response by using different mechanisms.

Role of nonspecific IgE production

The idea of regulatory responses preventing the development of allergic disease during infection by certain nematodes is clearly supported by experimental evidence, but other possible explanations have been tested. Nematodes tend to induce considerable nonspecific IgE secretion during infection (which may prevent specific mast cell-mediated or basophil-mediated attack), and it has been hypothesized that by saturating Fc ϵ RI sites, these antibodies may block mast cell degranulation [29]. Certainly, an association between high-circulating, nonspecific IgE levels and protection against allergy has been reported in many studies [29]. Moreover, increased cutaneous allergic responses after anthelmintic treatment are associated with a corresponding decrease in nonspecific IgE [30]. Nevertheless, it has been found that *Nippostrongylus brasiliensis* infection does not reduce mast cell degranulation in response to ovalbumin in the skin of sensitized mice, even though the infection generates a massive increase in nonspecific IgE levels [25]. Also, it has been reported, again using *N. brasiliensis*, that a small amount of IgE specific for the parasite antigen Nb-Ag1 can still facilitate mast cell degranulation in the presence of much greater levels of nonspecific IgE [29]. Finally, studies on humans infected with a variety of filarial nematodes indicate that the relative levels of polyclonal IgE to filaria-specific IgE do not tend to reach that which is required for inhibition of filaria-induced mast cell or basophil degranulation [31•]. The same outcome was observed when investigating dust mite-specific IgE. Thus, overall, it appears that saturation of Fc ϵ RI by polyspecific IgE antibodies during nematode infection cannot alone explain protection from allergy (Fig. 1).

Although nematode infection increases polyspecific IgE production but, as mentioned previously, does not appear to block the IgE response to allergens, there have been reports in which the opposite seems to be the case. For example, Wang et al. [32] reported that infection of mice with *Strongyloides stercoralis* resulted in reduced antiovalbumin IgE levels in the lungs. Similarly, *H. polygyrus* infection resulted in decreased circulating IgE levels in mice in response to peanut allergen [33]. However, *H. polygyrus* infection also has been shown to increase ovalbumin-specific IgE and total IgE in a murine model of atopic asthma [26].

Nematode infections also can be associated with the production of high levels of IgG4, an antibody that com-

petes with IgE for allergen binding but does not promote mast cell or basophil degranulation (Fig. 1). However, studies investigating whether high levels of IgG4 can protect against allergic results in humans frustratingly have produced conflicting results [27].

Identity of Molecules Involved in Immunomodulation in Animal Models and Their Mechanism of Action

Excretory-secretory products of *Nippostrongylus brasiliensis*

Excretory-secretory products containing as-yet-undefined components of adult stage *N. brasiliensis* have been found to prevent the development of asthma (ovalbumin hypersensitivity model) in the lungs of mice in a similar manner to infection with the parasite itself [34]. Administration of the excretory-secretory products during the sensitization period entirely blocked eosinophilia and mucus production in the lungs and significantly inhibited airway hyperreactivity. Ovalbumin-specific IgG1 and IgE levels in the bloodstream and the amount of IL-4 and IL-5 in the lungs were all reduced by exposure to the excretory-secretory products (Fig. 1). No role was found for Toll-like receptor 2, Toll-like receptor 4, interferon- γ , or IL-10. Moreover, Th2 responses to the excretory-secretory products developed as normal. The active agent within the excretory-secretory products appears unlikely to be a protein, as it is resistant to heat and proteinase K. Similarly, intratracheal installation of excretory-secretory products derived from the *N. brasiliensis* L3 stage reduced neutrophil influx in response to lipopolysaccharide in the lungs of Wistar rats [35].

Ascaris suum PAS-1

In 2002, an *A. suum* extract was reported to inhibit lung inflammation and hyperresponsiveness and to suppress IL-4, IL-5, and eotaxin in response to hen's egg white [36]. More recently, it was discovered that *A. suum* contains a protein—APAS-3—that upon immunization and challenge can induce Th2-dependent, eosinophilic airway hyperreactivity in BALB/c mice and that another *A. suum* product—PAS-1—inhibits this response [37]. Inhibition is associated with reduced levels of Th2 cytokines (IL-4, IL-5) and chemokines (eotaxin, RANTES [regulated on activation, normal T expressed and secreted]) and considerably elevated IL-10 levels in bronchoalveolar lavage fluid. Production of IgG1 and IgE also was shown to be blocked as determined by measurement of levels in the blood. PAS-1 is most active when administered prophylactically at immunization and then at challenge stages; administration at immunization only reveals a partial effect, but PAS-1 is completely ineffective when given only at challenge. PAS-1 also induces IL-10 and TGF- β production in macrophages. This is associated with loss of proinflammatory cytokine production [38].

Dirofilaria immitis–derived antigen

Imai and Fujita [39] have studied the properties of a purified, 15-kD protein from the canine filarial nematode *Dirofilaria immitis*: DiAg (*D. immitis*–derived antigen). This molecule induces polyclonal proliferation of B cells and nonspecific IgE production. DiAg prevents passive cutaneous anaphylaxis reactions in rats [39]. This was not due to an effect on the number or viability of mast cells or to differences in the amount of histamine released, but given the relative dismissal of this mode of action in the human situation, it surprisingly appears to be due to non-specific saturation of FcεRI.

ES-62

ES-62 is a phosphorylcholine-containing glycoprotein secreted by filarial nematodes that possesses a wide range of immunomodulatory properties that are largely anti-inflammatory [20]. As a consequence of this, the molecule has been tested in murine models of autoimmune and allergic disease and has been found to be active against collagen-induced arthritis [40] and type I hypersensitivity in the skin and lungs [41••].

With respect to allergy, ES-62 was found to be active in two murine models: ovalbumin-induced airway hypersensitivity and immediate-type hypersensitivity to oxazolone in the skin [41••]. In the former, ES-62 reduced peribronchial inflammation and mucosal hyperplasia, inhibited eosinophilia, and prevented release of the signature cytokine required for airway inflammation development, IL-4. In the latter model, ES-62 targeted inflammation as shown by reduced ear swelling. This was correlated with effects on mast cells. Subsequent in vitro analysis revealed that ES-62 directly prevented mast cell degranulation and release of mediators of allergy induced via ligation of FcεRI. The mechanism of action involved inhibition of key signal transduction events involved in mast cell activation, including phospholipase D–coupled, sphingosine kinase–mediated calcium mobilization and nuclear factor-κB activation. ES-62 was found to mediate these effects by forming a complex with Toll-like receptor 4 that results in the sequestration and perinuclear degradation of protein kinase C-α, a molecule found to be critical for mast cell activation [41••] by a caveolae/lipid raft, proteasomal-independent mechanism. Work is currently under way to develop small, phosphorylcholine-containing derivatives of ES-62 for use as drugs to treat allergic diseases.

Conclusions

The weight of evidence in support of parasitic nematodes preventing allergy is impressive, as it is derived from human epidemiologic studies and work in the laboratory using murine models. The latter type of research has facilitated investigation of mechanism of action and in some cases identification of the actual molecules involved in the antiallergic process. Not surprisingly, all of this has led

scientists to consider the therapeutic potential of parasitic nematodes. Therefore, within the past few years, certain species of these worms have been used in clinical trials aimed at ameliorating inflammatory diseases. Although the trials are mainly targeted against Crohn's disease, one trial determining the hookworm's effect on asthma also has recently started [13•]. It will be of great interest to see whether this trial has a positive outcome and whether the next step could be the use of defined nematode molecules in the treatment of human allergic disease.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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