



Medicine in focus

Geohelminth infections: Impact on allergic diseases

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Abstract

Geohelminth infections are highly prevalent infections with a worldwide distribution. Epidemiological studies have shown an inverse relationship between geohelminth infection and allergy leading to the suggestion that geohelminths protect against allergy. A causal association is supported by the findings of intervention studies in humans and experimental animal models. Geohelminths cause chronic infections during which an intimate host–parasite interaction develops permitting the parasite to survive but protecting the host from damaging inflammation. Geohelminth parasites modulate allergic inflammation directed against parasite antigens and the same mechanisms may affect responses to inhalant aeroallergens. The mechanisms proposed to explain the allergy-modulatory effect of geohelminths include the induction of regulatory T cells and the creation of an immunosuppressive environment in relevant tissues. New treatments being considered for the treatment of asthma include live infections with hookworms. Insights provided by how geohelminths modulate inflammatory responses may allow the development of new treatments that mimic these effects.

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1. Introduction

1.1. Geohelminth infections and allergy

Geohelminth (or intestinal helminth) infections are important enteric pathogens that affect poor populations with limited access to clean water and sanitation. The most prevalent geohelminth parasites are *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm, and *Strongyloides stercoralis* that between them are estimated to infect over two billion humans (Savioli & Albonico, 2004). Geohelminths tend to cause chronic infections in populations that live in endemic regions and these infections cause significant morbidity through effects on nutrition, growth, and physical fitness.

In contrast to geohelminth infections, allergic diseases (including asthma, rhinoconjunctivitis, eczema, and food allergy) are relatively rare in less-developed areas of the world but are recognized as the most common chronic diseases in industrialized countries where they may affect up to 40% of the population. There is strong evidence that the prevalence of allergic disease has increased dramatically over the past 30 years in industrialized countries and allergic disease also appears to be becoming an important cause of morbidity in urban populations living in non-industrialized countries. The inverse relationship between the prevalence of allergic disease and geohelminths has led to suggestions of a causal association in which geohelminth infections have been hypothesized to provide protection against the development of allergic disease.

Epidemiological studies that have examined the relationship between geohelminths and allergy are inconclusive and have provided stronger evidence for an inverse association between geohelminths and asthma or atopy

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than for other types of allergy (Cooper, 2004). The strongest evidence for a causal association between geohelminth infections and allergy has been provided by small intervention studies that have shown increases in the prevalence or risk of atopy after treatment of infected children (Lynch et al., 1993; van den Bigelaar et al., 2004).

Allergic diseases have multifactorial aetiologies and develop from complex interactions between genes and environment. The role of individual environmental factors in determining the development of allergy is likely to be limited and geohelminth infections may be one of several chronic infectious exposures that can interact with host genotype and other environmental factors to influence allergy development.

The human immune system has evolved in the presence of intense exposure to geohelminth and other helminth infections, and the allergic response may have evolved as a host protective mechanism against these parasites. For example, there is evidence that an important asthma-associated gene, a variant of STAT6, is associated with resistance to ascariasis (Peisong et al., 2004).

Successful parasitism has required an adjustment between host and parasite, permitting the parasite to survive but protecting the host from immune pathology. The relative absence of helminths and other chronic infectious exposures capable of inducing strong immunoregulatory signals in modern industrialized societies may have contributed to the development of dysregulated immunity to exogenous antigens such as aeroallergens that can cause inflammatory disease.

2. Pathogenesis

2.1. Modulation of immune response by geohelminth infections

A key feature of geohelminth infections is the ability to cause chronic infections. This is essential for geohelminth survival because the parasites, with few exceptions, are unable to replicate within the human host, and must contaminate extensively and continuously the host's environment to ensure survival to the next generation of fertile adult worms in the human intestine.

The requirement for causing long-lasting infections may have led to the ability of the parasite to induce immunoregulatory mechanisms in the host that prevent or limit parasite killing and expulsion. These mechanisms cause a 'tolerization' of the host to parasite antigens such that continuing infections do not elicit a strong host effector response against the parasite.

Geohelminth infections are potent inducers of type-2 immune responses and the drive to Th2 polarization is so potent in many helminth infections that bystander proteins become targets for Th2 cell responses including the induction of a Th2-cell phenotype in naïve T cells that express receptors for unrelated antigens (Liu et al., 2002).

Because helminths are such potent adjuvants for type-2 immunity, then why don't these infections exacerbate rather than ameliorate allergic responsiveness? In fact they can, and a classic example is Loeffler's syndrome, which is an asthma-like illness associated with acute exposures to ascariasis. However, with repeated infections, the host may down-regulate allergic inflammatory responses and a chronic infection phenotype develops (Fig. 1). There are tight controls on immune pathology during chronic infections, even in an environment that is strongly Th2-polarized, and the immune regulatory mechanisms induced may suppress allergic inflammation to non-parasite allergens such as aeroallergens.

2.2. Mechanisms of helminth-induced suppression of allergy

There are two distinct phases in the allergic response that could be modulated by concurrent geohelminth infection: sensitization and effector stages. The sensitization phase is characterized by the induction of Th2 responses (i.e., production of specific IgE) while the effector stage includes reactions that follow the early expansion of type-2 responses such as degranulation of IgE-primed mast cells (M), the release of pro-inflammatory mediators, and the local recruitment of effector cells of the innate and adaptive immune response. The effector phase is responsible for the expression of allergic inflammation and allergic disease.

Studies of experimental animal models of asthma using ovalbumin (OVA) or house dust mite as the allergen stimulus, have provided evidence for a suppressive effect of geohelminth infections against allergic inflammation in the lungs (Wohlleben et al., 2004). For example, infecting mice with *S. stercoralis* before OVA sensitization results in a suppression of chemokine mediator levels in bronchoalveolar lavage fluid, and chronic *Heligmosoides polygyrus* infections reduce airway allergic responses to OVA and house dust mite (Maizels et al., 2004). In these models, both the sensitization (IgE production) and effector phases appear to be affected by concurrent helminth infection.

In the case of humans, there is little evidence to suggest that sensitization is suppressed by geohelminth

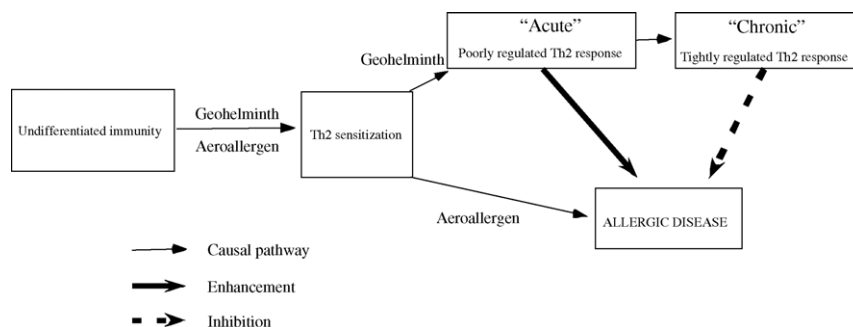


Fig. 1. Schematic illustration for the relationship between geohelminth infection and allergy. An early undifferentiated immune response to geohelminths and inhalant aeroallergens may be primed to become Th2-polarized in susceptible individuals. Early acute infections with geohelminths are poorly regulated and are associated with strong allergic inflammatory reactions to the parasite. Strong type-2 immunity during acute geohelminth infections may promote enhanced type-2 immunity to aeroallergens at mucosal surfaces and exacerbate allergic disease. Repeated and long-term infections with geohelminths induce a chronic immune phenotype associated with strong immune regulatory mechanisms that control allergic inflammatory responses to the parasite and may inhibit allergic inflammation associated with aeroallergens.

infection. In fact, sensitization to aeroallergens appears to be enhanced in infected individuals and a high proportion have significant levels of allergen-specific IgE in the absence of skin prick reactivity and clinically apparent allergic inflammation. The lack of allergic inflammation points to a shutting down of effector pathways.

Several mechanisms have been proposed to explain how concurrent geohelminth infection may modulate host immunity to aeroallergens. Direct effects might occur through cross-reactivity between epitopes of aeroallergens and helminth allergens, and there is strong evidence for extensive immunological cross-reactivity between helminth allergens and those of arthropods such as house dust mite. Antigen-specific modulation of parasite antigens could also, therefore, suppress the inflammatory response to cross-reactive antigens from aeroallergens.

Alternatively, modulation of allergic inflammation could occur through bystander effects. Several geohelminths have a pulmonary phase of larval migration and the induction of anti-inflammatory responses in the lung caused by passage of larvae could affect simultaneously the immune response induced in the respiratory mucosa to aeroallergens. Such effects might include the generation of populations of immune suppressive macrophages such as alternatively activated macrophages (AAM), populations of pulmonary dendritic cells that preferentially provide tolerogenic or suppressive signals to T cells (e.g., through production of IL-10) with which they interact in the same immune compartment, and populations of regulatory T cells that are capable of suppressing immune responses in a non-antigen-specific manner.

2.3. Regulatory T cells

Studies of the regulation of allergy in humans indicate that regulatory CD4⁺ T cells have an important role and several populations have been described: (1) CD25⁺ T cells, and a subset of cells that are CD25 high that appear to mediate suppressive functions in humans (Baecher-Allan, Brown, Freeman, & Hafler, 2001), whose effects are mediated largely through contact-dependent mechanisms such as via inhibition of IL-2R α in target cells; (2) Tr1 cells that are induced from naïve cells in the presence of IL-10 and are associated with suppression of immunity through cytokine-dependent mechanisms (IL-10 and TGF- β); and (3) Th3 cells that are induced following mucosal inoculation of antigen and mediate oral tolerance. Although distinct subtypes of regulatory T cells have been described, there may be considerable overlap in both their phenotypic characteristics and mechanisms of immune regulation (cytokine-mediated versus contact-dependent). Both Tr1 cells and CD4⁺ CD25⁺ T cells can suppress type-2 cytokine production *ex vivo* (Akdis et al., 2004; Ling et al., 2004) and following successful allergen immunotherapy, there appears to be an expansion in both these cell populations (Jutel et al., 2003).

Regulatory T cells may have a central role in geohelminth-mediated suppression of allergy (Fig. 2). Studies of populations infected with schistosomiasis have provided evidence for a role of increased production of IL-10 in mediating protection against atopy (van den Biggelaar et al., 2000) and asthma (Araujo et al., 2004). The source of the IL-10 is not clear and may derive from adherent cells (macrophages), or regulatory T cells. Regulatory populations of B cells may be

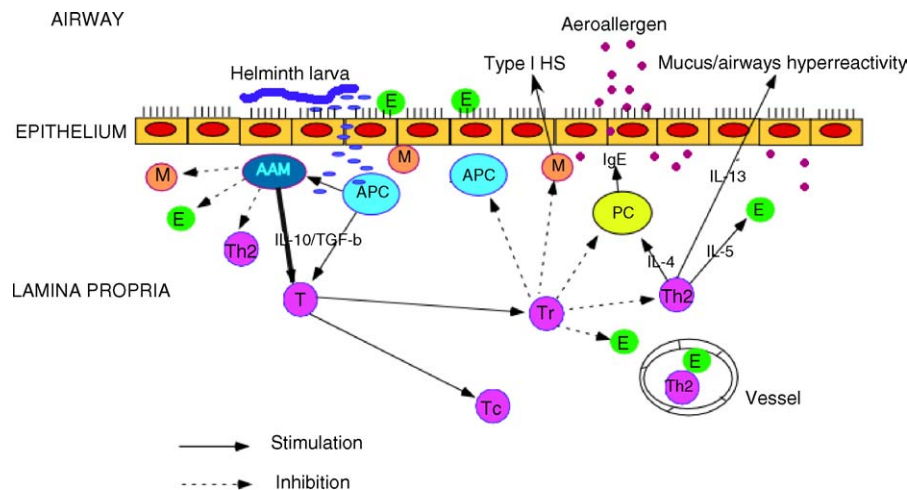


Fig. 2. Potential mechanisms of geohelminth-associated immune regulation of host immunity to aeroallergens in the lungs. Many helminths have a pulmonary phase of larval migration. Helminths employ multiple mechanisms to suppress the host antiparasite immune response including induction of alternatively activated macrophages and induction of T regulatory cells (Tr). Tr can exert their effects through the release of cytokines (i.e., IL-10 and TGF- β) or through contact-dependent mechanisms. Antigen presenting cell (APC), eosinophil (E), mast cell (MC), T helper cell producing type-2 cytokines (Th2), plasma cell (PC), anergic conditioned Th2 cell (Tc), hypersensitivity (HS).

important also and a murine model of schistosomiasis has provided evidence that IL-10 produced by B cells can protect against systemic anaphylaxis (Mangan et al., 2004). Tr1 cells are important in regulating antiparasite responses (Satoguina et al., 2002) and may have bystander effects on non-parasite immunity through IL-10-dependent mechanisms. Whatever the source, IL-10 is a potent immunoregulatory cytokine that has potent anti-allergic effects including the suppression of dendritic cell and macrophage function, eosinophil (E) activation and mast cell degranulation, and extravasation of immune cells to the tissues (Fig. 2).

2.4. Secreted helminth molecules

Helminth parasites secrete considerable quantities of proteins and glycoproteins into the host environment, many of which are capable of modulating antiparasite immunity (Falcone, Loukas, Quinnell, & Pritchard, 2004; Maizels et al., 2004). Such molecules interfere with crucial stages in the immune response such as extravasation (blocked by parasite lectins and glycans through binding to endothelial selectins), chemokine attraction (hookworms release proteases capable of degrading eotaxin), release of host proteases (inhibited by helminth serpins), attack by reactive nitrogen and oxygen intermediates by eosinophils and other effector cells (inhibited by helminth antioxidants such as glutathione-S-transferase).

Helminth parasites also may secrete cytokine homologues such as TGF- β that may be important in regu-

lating the antiparasite response, and produce protease inhibitors that are capable of blocking peptide antigen presentation and of eliciting an IL-10 response from macrophages. Lipid-like molecules of schistosomes such as lyso-PS can interact with dendritic cells to induce T regulatory phenotypes in naïve T cells (van der Kleij et al., 2002), and homologous molecules have been identified in *Ascaris*.

3. Therapy

There are a number of therapies under study based on the observation that helminths modulate inflammatory disease. The most advanced in clinical use is the treatment of inflammatory bowel diseases with live porcine whipworm, *Trichuris suis*, and observations from a randomized controlled trial have provided some evidence for clinical efficacy (Summers, Elliott, Urban, Thompson, & Weinstock, 2005). There are also studies investigating the therapeutic benefit of experimental infections with hookworm in patients with respiratory allergy (Falcone & Pritchard, 2005). The use of live geohelminth infections in the treatment of inflammatory diseases is unlikely to become widespread because of problems in cultivating and preserving adequate quantities of viable larvae and eggs if not for aesthetic reservations. More important advances may develop from an understanding of how geohelminth infections modulate allergic inflammation and could lead to the development of synthetic analogues that target specific effector pathways in the allergic response. For example, analogues

of helminth molecules that induce innate cells in the lung to produce anti-inflammatory cytokines (such as IL-10) could be delivered by aerosol to dampen pulmonary inflammation in asthma.

4. Conclusion

Geohelminth parasites are associated inversely with allergy risk. Evidence for a causal association is from the findings of human intervention studies and murine allergy models. Studies of humans infected with schistosomes have shown an association between an increase in IL-10 and reduced risk of atopy and asthma, and similar effects may occur during geohelminth infections. Geohelminths may modulate allergy by induction of regulatory immune cells or by inducing an environment in the tissues that inhibits allergic inflammation. Geohelminths secrete many molecules capable of modulating different arms of the allergic effector response. The most promising area for future research is likely to be the investigation of the mechanisms by which geohelminth infections modulate allergic inflammation that could lead to the development of new treatments that imitate the anti-allergic effects of these parasites.

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