Published in final edited form as:

Crit Rev Immunol. 2016 ; 36(1): 1–11. doi:10.1615/CritRevImmunol.2016016545.

Role in Allergic Diseases of Immunological Cross-Reactivity between Allergens and Homologues of Parasite Proteins

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Abstract

Implied under the rubric of the hygiene hypothesis is that helminth infection can protect against allergic disease. It is well known that helminths induce processes associated with type 2 immune responses, but they also induce important regulatory responses that can modulate these type 2-associated responses—modulation that influences responses to bystander antigens including allergens. Indeed, most epidemiological studies demonstrate a beneficial effect of helminth infection on atopy, but there are also convincing data to demonstrate that helminth infection can precipitate or worsen allergic inflammation/disease. Reasons for these disparate findings are much debated, but there is a school of thought that suggests that helminth-triggered type 2-associated responses, including IgE to cross-reactive aeroallergens, can offset the regulatory effects imposed by the same organisms. The cross-reactivity among helminths and allergenic tropomyosins dominated the antigen/allergen cross-reactivity field, but recent data suggest that cross-reactivity is much more common than previously appreciated. It has been demonstrated that a high degree of molecular similarity exists between allergens and helminth proteins. Thus, an understanding of the mechanisms underlying the response induced by helminth infection and their impact on the induction of allergic disease in the host are critical for designing therapies using iatrogenic infections or parasite products to treat inflammatory diseases and for developing vaccines against helminth parasites.

Keywords

hygiene hypothesis; cross-reactivity; allergen; allergy; helminth

I. INTRODUCTION

Over the past 30 years, there appears to have been a significant increase in the worldwide prevalence of allergic diseases associated with Th2-type inflammation.¹ Interestingly, the prevalence of autoimmune diseases as well as systemic inflammatory syndromes—both felt

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to reflect Th1/Th17-mediated inflammation—have also increased during the same time. The increase in prevalence has been observed largely in high-income parts of the world,² although middle-income countries have seen similar trends.^{1,3} There has been a great effort to understand this apparent population-wide shift from an immunologically homeostatic/regulated state to a pro-inflammatory state, but no unifying explanation has emerged. Some data have shown links to pollution levels,^{4,5} dietary changes,⁶ or social dynamics,^{7,8} each of which (or their aggregate) can lead to a disruption to or an imbalance in immune and/or metabolic homeostasis.

One very popular explanation for the generalized increase in allergic and autoimmune disorders is the “hygiene hypothesis,” a concept suggesting that exposure to microbial products early in life modulates the immune system such that there is a diminished pro-inflammatory milieu in the host.^{9,10} Although there is an association between the decreased worldwide prevalence of infectious diseases, such as mumps, rubeola, tuberculosis, and hepatitis, and the increased prevalence of diabetes, allergies, and inflammatory bowel disease,² the hygiene hypothesis gained significant traction when it was found that helminth infections can modulate allergic effector responses.^{11–13}

Helminth infections (particularly from tissue-invasive helminths) or their products have indeed been shown to induce a profound immunoregulatory environment in their vertebrate hosts.^{14–18} In a multitude of animal studies, these multicellular worm infections have been shown to (1) prevent allograft rejection^{19,20}; (2) ameliorate inflammatory bowel disease^{21–23}; (3) prevent the development of Type 1 diabetes^{24,25}; (4) modulate the development of allergen-induced airways hyperreactivity^{26,27}; and (5) prevent weight gain and metabolic dysfunction in mice given a high-fat diet.²⁸ These observations highlight the importance of helminth infections to immune homeostasis, prompting the concept of co-evolutionary cross talk between worms and their vertebrate hosts.^{29,30}

Vertebrates are thought to have co-evolved with helminth infection for at least as far back (in evolutionary terms) as their move from an exclusively marine environment to a land environment.³⁰ It is logical to think that this co-evolution selected vertebrate hosts with a certain threshold for immune homeostasis that allowed the helminth-host relationship to be more symbiotic than parasitic.³⁰ Indeed, chronic helminth infection is almost never fatal and is rarely deleterious to its vertebrate hosts.

Historically, during the Agricultural Revolution (Neolithic period) humans transitioned from a nomadic life (based on hunting and gathering) to one based on agriculture and settlement, which fixed human populations geographically. The settlement of populations likely increased exposure to parasitic infections, which consequently increased infectious burdens, causing some individuals to be negatively influenced by massive parasitic colonization.

Today there is a huge effort to eliminate helminths from human populations in large part out of concern for public health and poverty prevention.³¹ Indeed, we have observed throughout the world increased standards of personal hygiene, better sanitation services in cities, and huge efforts to implement mass drug administration (MDA) to eliminate many neglected tropical diseases (NTDs). These efforts are promoting another big shift in the helminth-

human relationship that may, as a result, alter the incidence or severity of both autoimmune and allergic diseases. Epidemiologic studies on allergic diseases have not provided definitive answers—some show that infection with helminth parasites decreases allergic sensitization while others show the converse.³² Superimposed on these conflicting findings are more recent findings suggesting that there may be an explanation that relies on structural or molecular similarity between helminth antigens and aeroallergens.^{33–36}

II. THE HYGIENE HYPOTHESIS

The hygiene hypothesis, posited by David Strachan in 1989, emanated from a study examining the effects on allergy development in young children from infections carried from school to home by older siblings.³⁷ Prior to this study, the general concept was that infections, especially viruses, promote IgE-mediated allergic sensitization that in turn induces bronchial hyper-reactivity.³⁸ Strachan's data, in contrast, suggest that viral infections actually protect younger siblings from developing allergic diseases.³⁷ Epidemiological studies linking viral infections with protection against allergies have been much debated since.^{39–42}

The hygiene hypothesis gained fresh attention in 2000, when it was demonstrated that children infected with *Schistosoma hematobium* show less allergen-driven skin prick test reactivity than do noninfected controls.¹¹ These data were corroborated by a number of other studies (with other helminth infections) that demonstrated that *Ascaris lumbricoides*,^{13,43} hookworm,^{44,45} *Trichuris trichiura*,^{46,47} *Enterobius vermicularis*,⁴⁸ *Schistosoma mansoni*,⁴⁹ and again *S. hematobium*⁵⁰ infections are inversely correlated with the presence of atopy (largely defined by skin test reactivity).

The mechanisms underlying this inverse relationship between worm infection and atopy are not yet fully elucidated, though IL10 has been implicated as a major mediator. For example, it was shown that *S. mansoni* infection diminishes in vitro Th2 responses to *Dermatophagoides pteronyssinus* by decreasing allergen-specific IL5 production in an IL10-dependent fashion.⁵¹ More recently, it was shown that basophils of helminth-infected individuals are less reactive to IgE-specific stimulation than are those from noninfected donors.^{52–54} This is a modulation that also appears to be IL10-mediated.⁵⁵

It is intriguing that the majority of helminth parasites induce, at least acutely, a Th2-associated immune response in which T cells (and other cells) produce IL4, IL5, and IL13 at high levels. This pattern of cytokine production is qualitatively similar to that seen in allergic diseases. However, helminth infections, unlike allergic diseases, also induce high levels of IL10 the source of which is primarily antigen-stimulated regulatory T cells (Tregs)^{27,56} and regulatory B cells (Bregs).⁵⁷ This IL10-modulated Th2 response has been coined a “modified Th2” response.^{58,59}

It has also been shown that helminth-encoded molecules can act directly on antigen-presenting cells or on other cells capable of modulating inflammatory responses.^{60–62} These molecules include the filarial protein ES62,⁶³ fucopentaose from *S. mansoni*,⁶⁴ and cystatin from *Acanthocheilonema vitae*.^{16,65}

III. CAN HELMINTH INFECTION FACILITATE ALLERGIES?

Although the majority of the evidence suggests that helminths modulate allergic disease, a large number of data suggest that they either have little effect on allergic disease or even promote allergic sensitization and atopy. Despite the regulatory environment helminth infections can trigger in the host, it is not clear whether their influence on allergic disease is beneficial or deleterious. A systematic review and meta-analysis found that the presence of intestinal parasites overall has little to no impact on asthma.⁶⁶ However, there were found parasite-specific effects where a single infection (e.g., *A. lumbricoides*) was determined to be positively associated with asthma, whereas others (e.g., hookworm) showed some level of asthma protection.⁶⁶ Similar analyses were performed on the effects of helminths on atopy, and it was found that helminth infection could prevent overall skin test reactivity to allergens but not reactivity to house dust mite (HDM) or cockroach extracts. As with the asthma, there were some examples in which *Schistosoma* infection generally protected against SPT positivity but *Trichuris* was shown to be a risk factor for SPT positivity for cockroach extracts.⁶⁷

Not only did these meta-analyses provide no conclusive evidence for helminth infections having a beneficial effect on allergic disease; clinical trials using helminth infections to treat allergic rhinitis or asthma also failed to show a therapeutic benefit (these trials were recently reviewed).⁶⁸ Indeed, iatrogenic infection with hookworm was shown to have no effect on asthma symptoms⁶⁹ and *Trichuris suis* ova treatment was shown to have no effect on allergic rhinitis.⁷⁰ Furthermore, a well-conducted study showed that controlled infection with *T. suis* ova does not alter grass-pollen specific immune responses despite the induction of parasite-specific modified Th2 responses (e.g., IL4, IL5, IL13, IL10).⁷¹

Along with epidemiological studies associating helminth infections with decreased prevalence of allergies, a number of studies show the converse. For example, increased skin test reactivity to common allergens was found to be associated with *S. mansoni*,⁷² *Toxocara canis*,⁷³ *Clonorchis sinensis*,⁷⁴ *Anisakis simplex*,⁷⁵ and *A. lumbricoides*^{76–80} infections. In addition, helminths have been found to be associated with increased clinical manifestations of allergic rhinitis,^{74,77} chronic urticaria,⁷⁵ and asthma.^{72,73,77,78,80} Moncayo et al. observed that the presence of anti-*A. lumbricoides* IgE is associated with increased atopic and nonatopic wheezing.⁸¹

The debate about the beneficial versus detrimental effects of helminths on atopy or asthma is long-standing and so far without resolution.^{82–84} It seems, from many experimental and epidemiological studies, that the outcome on allergic disease is dictated by a fine balance between the pro-allergenic and pro-regulatory effects of helminth infection (Fig. 1), a balance that is hard to predict if the study population is not parasite-naïve.

IV. NEW INSIGHTS FROM A MOLECULAR SIMILARITY PERSPECTIVE

The observation that helminths can promote or facilitate IgE sensitization has been a challenge to understand at the interface of helminths and allergy. It has been speculated that the mechanisms by which helminths can increase allergic diseases are related to their ability

to (1) promote Th2 polarization⁸⁵; (2) potentiate IgE production to unrelated antigens through bystander mechanisms^{86,87}; or (3) induce cross-reactive IgE (based on the fact that common allergens share marked structural homology with helminth proteins).^{34,88,89}

It has been known that helminth proteins can induce IgE that cross-reacts to the common tropomyosin allergen.^{90–94} The level of conservation among tropomyosins from different species is very high, making antibody cross-reactivity unsurprising.⁹⁵ However, although much work has centered on tropomyosin, felt to be a major pan-allergen,^{88,95,96} the fact that it fits the definition of a minor aeroallergen^{97,98} has led to a more formal examination of allergens and their helminth homologues. Indeed, we have demonstrated that the glutathione-S transferase (GST) of the cockroach *Blattella germanica* (Bla g 5) and the GST of *Wuchereria bancrofti* display a significant level of IgE cross-reactivity even though there is a relatively low level (30%) of amino acid identity.³³ Moreover, our study demonstrated that the serum IgE of individuals infected with *W. bancrofti* can recognize one or two of the four major epitopes on Bla g 5.³³ Human IgE cross-reactivity among other GSTs has also been found for Der p 8, a GST of the HDM *Dermatophagoides pteronyssinus* (Der p) and Bla g 5,⁹⁹ as well as for the GST of *Ascaris* and the HDM GSTs from Der p and *Blomia tropicalis* (Blo t).⁹⁰ In addition, it has been shown that IgE levels against the GST of *A. lumbricoides* correlate with levels of Der p 8, Blo t 8, and Bla g (all GSTs) but not with those of Der p 2, a structurally unrelated allergen.¹⁰⁰ In contrast, it was recently demonstrated that IgE anti-Bla g 5 from helminth-naïve but cockroach-allergic individuals does not recognize parasite GST,¹⁰¹ which, according to this study, is coherent with surface structural studies of *Ascaris* and cockroach GST.¹⁰¹ Interestingly, sera from tropical-region individuals, who are putatively exposed to helminth and GST aeroallergens, are able to recognize *Ascaris*, cockroach, and HDM GSTs,¹⁰¹ perhaps because of selected epitopes' co-sensitization or cross-reactivity.

A high level of amino acid homology among allergens and helminth proteins has been suggested as one way to gain insight into the nature of allergenicity⁸⁹; this concept relies on shared structures that promote Th2-associated responses. Using in silico analyses to compare the sequence of 499 distinct allergens with entire proteomes of multiple organisms, we were able to show that ~40% of these had homologues in helminth and other parasite phyla and to speculate that cross-reactive IgE may be much more common than previously thought.¹⁰² While these analyses utilized linear amino acid sequences, a more recent analysis of 3D epitopes shared among allergens and helminth proteins suggested that cross-reactive conformational epitopes can also be identified, sometimes even in the absence of linear similarity, as is the case for the Bet v 1 (birch major allergen) and the expansin allergen families.³⁶ By expanding these analyses to include other microbes (protozoa, fungi, and bacteria) and the human genome, it was found that the higher the level of identity between an allergen and a protein found in helminth, protozoa, and fungi, the less likely it is to induce IgE in humans. This finding is believed to reflect its high level of homology to human proteins,¹⁰² which suggests that vertebrate hosts are more tolerant to antigens mimicking self-proteins than to antigens with little self-similarity.

V. PROTEIN SIMILARITY, ALLERGENICITY AND ALLERGIC SENSITIZATION

Molecular similarity between allergens and self proteins has also been explored as the basis of allergenicity.^{103,104} This association has been postulated to occur either because self-appearing allergens can intrude on immunological pathways, thereby modifying immune responses,¹⁰⁵ or because immune responses to “weak” antigens are dominated by Th2-associated responses.¹⁰⁴ The metagenomic data, however, point to IgE being driven by antigens quite distinct from self-proteins.¹⁰² Some of the apparently contradictory data may come from the definition of allergenicity itself, as some suggest that it relates to the ability to induce IgE^{106,107}; others suggest that it is the ability to induce Th2-associated CD4+ responses.^{105,108}

It should be noted, however, that the ability of a given antigen (or molecule) to induce Th2 polarization depends on its effect on components of the innate immune system and may therefore be associated with an adjuvant effect. During the ontogeny of the immune response, T cell subset differentiation into Th1, Th2, and Th17 requires certain instructions that often come from nonantigenic or weakly antigenic molecules such as lipids, carbohydrates, or nucleic acids, or from tissue-derived signals (e.g., alarmins) that can instruct innate cells. Antigenicity, in contrast, evaluated as the ability of a molecule to induce specific T or B lymphocyte response, is more often related to the similarity or dissimilarity between the antigen and self-proteins. Allergenicity requires both properties, as seen for Der p 1,¹⁰⁹ Der p 2,¹⁰³ and lipocalins.^{104,108} However, most often a single protein (or allergen) should not have the ability to be a good Th2 inducer (Th2 adjuvant) and a good T/B cell stimulator (antigen) concurrently.

In serologic surveys of filarial-infected travelers, it was found that they had increased IgE levels to *D. pteronyssinus* (HDM) and to *B. germanica* (German cockroach) but not to another aeroallergen (timothy grass) when compared with noninfected controls.¹¹⁰ Interestingly, HDM and cockroach extracts are rich in allergens with high levels of similarity to helminth proteins, including the major allergens from both extracts. In contrast, timothy grass has only two minor allergens with homologues in parasites, suggesting that serologically based allergy assays may be influenced by cross-reactive IgE.¹¹⁰ Thus, helminth infection may be able to induce IgE against certain environmental allergens that have an impact on the amount and function of allergen-specific IgE.^{33,110} Commonly, studies of helminth-infected indigenous populations find increased IgE prevalence to aeroallergens without increased positivity in allergen-induced skin tests.^{11,45,81,111} Such findings make the investigation of other cases of protein similarity very interesting because defined allergens such as chitins, lipocalins, major allergens of the cathepsin family (e.g., Der p 1), and others also have homologues in helminths.³⁴

The implications of the broad cross-reactivity seen between allergens and helminth proteins are still a matter of debate, but it is clear that despite inducing a strong anti-inflammatory response, helminth infections induce high levels of parasite-specific IgE that may bind allergen-specific epitopes. This cross-reactive IgE may offset the effects of immune bystander regulation by helminths and alter the parasite-allergy interaction (Fig. 1) to either promote or protect against allergy. These two outcomes are likely dictated by the balance

between regulatory features of helminth infection, such as induction of IL10, Tregs and Bregs, and the host genetics underlying allergic sensitization. Although the regulatory effects of helminth infections have drawn much more attention historically, their pro-allergenic properties cannot be disregarded, particularly given their important implications for helminth infections^{69–71,112} or helminth-derived products^{14,113–116} that are used in treatment of allergic diseases or as vaccine candidates. Indeed, the potential hookworm vaccine (rNa-ASP-2), which is structurally related to an important vespid allergen family protein,¹¹⁷ was shown to cause systemic urticarial reactions in patients previously infected with hookworm in a vaccine trial.¹¹⁴ This event teaches us that helminth products have the potential to be very allergenic and that their use requires caution.

VI. CONCLUSIONS

The interrelationship between helminth infection and allergy is still relatively unelucidated. The widespread molecular similarity among helminth proteins and environmental allergens has been studied and seems to be an important component of the balance between regulatory and pro-allergenic effects of helminth infections. Importantly, IgE induced against helminth proteins that can cross-react with aeroallergens can have an important impact on the use of helminths, or their products, in the treatment of allergic diseases, IgE serodiagnostics for allergies, and even the development of vaccines.

Acknowledgments

This work was supported, in part, by the Division of Intramural Research (DIR), National Institute of Allergy and Infectious Diseases (NIAID); Conselho Nacional de Pesquisa (CNPq); and Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG).

ABBREVIATIONS

Bla g	<i>Blattella germanica</i>
Der p	<i>Dermatophagoides pteronyssinus</i>
GST	Glutathione-S-transferase
HDM	house dust mite

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FIG. 1.

Balance between a potentiated or regulated helminth-specific response affects the outcome of allergic sensitization. Helminths can induce immune responses that regulate or promote allergic disease; they regulate atopy through IL10 and Tregs/Bregs and by the cross-reactive/blocking IgG seen in chronic infections (and potentially those in infancy); acute helminth infections are associated with the induction of Th2-associated responses, IgE potentiation, and the induction of cross-reactive IgE.