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Review Article

Human Helminths and Allergic Disease: The Hygiene Hypothesis and Beyond

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Abstract. There is much debate about the interaction between helminths and allergic disease. The "Hygiene Hypothesis," a very popular concept among scientists and the lay public, states that infections, especially during childhood, can protect against allergic diseases. Indeed, helminth infections are known to induce regulatory responses in the host that can help the control of inflammation (including allergic inflammation). However, these infections also induce type-2-associated immune responses including helminth-specific IgE that can cross-react against environmental allergens and mediate IgE-driven effector responses. Thus, it is the delicate balance between the parasites' anti- and pro-allergenic effects that define the helminth/allergy interface.

The immune system has evolved, in large part, through its interaction with microbes and parasites, an interaction that drives specific or specialized immune responses to deal with the widely varying groups of microorganisms. For example, parasite-derived induction of interleukin (IL)-4, IL-5, and IL-13 coordinate the prototypical responses to metazoan helminth pathogens,[1] whereas viral- and bacterial-specific induction of Type 1 and Type 2 interferons are required for control of these types of infections.[1] Interestingly, these responses (broadly inflammatory in nature) themselves, if uncontrolled, can harm the host by causing allergic diseases (Th2-associated inflammation) or autoimmune/inflammatory disorders (typically Th1- and/or Th17-associated). Typically, on the heels of such inflammation come anti-inflammatory networks that are required to prevent long-standing tissue damage.[2]

These regulatory (or anti-inflammatory) processes triggered during infection underlies the "Hygiene Hypothesis"[3] that states that infections, especially during childhood when immune responses are being "educated" and the T- and B-cell memory pool is being created, protect against inflammation-associated disorders[4] because they modulate or limit immune-mediated effector responses. Indeed, the presence of helminth infections has been associated (to a small degree) with modulation of the severity of inflammatory bowel disease,[5] diabetes,[6] and arthritis[7–9] to cite just a few examples.

There is little consensus among the many studies that have examined the interaction between helminth infection and atopy (Table 1). This lack of consensus is most likely related to the differences in outcome measures/definitions used in the many studies that have used a variety of outcomes including: 1) the severity or frequency of asthma, rhinitis, or eczema; 2) the frequency of allergen sensitization by skin prick tests (SPTs); or 3) the levels of allergen-specific IgE (asIgE) levels in the blood. Other causes for the disparate results relate to variation among the species of infecting helminths and differences in the age of the populations being studied. To attempt to reconcile these differences, meta-analyses have been performed; these, too, have not been conclusive. For example, while *Ascaris lumbricoides* was found to be a risk factor for the development of asthma, hookworm infection was associated with a protective effect.[60] Infection with other parasites such as *Trichuris trichiura*, *Enterobius vermicularis*, and *Strongyloides stercoralis* had no effect on the outcome of asthma.[60] Conversely, the presence of *A. lumbricoides* was found to lower the frequency of atopy (measured by SPT) to at least one environmental allergen in most studies[61] (Table 1), but not to the perennial allergens, cockroach or house dust mite (HDM).[61] Hookworm infection has also been associated with protection from atopy to some allergens, but not to HDM or to cockroach extract.[61] Interestingly, the majority of the published studies demonstrate that while helminth infection decreases the frequency of SPT positivity, these infections are associated with increased allergen-specific IgE (asIgE) (Figure 1).

The concept that helminth infection modulates allergic diseases emerged in the 1970s[62–64] and has been debated ever since.[40,65–70] As depicted in Table 1, it has often been observed that helminth infections commonly reduce the frequency of SPT reactivity and increase the levels of asIgE (Table 1 and Figure 1). This apparent dichotomy was felt to reflect the expansion of polyclonal IgE-secreting B cells, an expansion that would lead to high levels of IgE with multiple specificities leading to an inability to trigger a mast cell or basophil response. It was thought that allergens, in such conditions, could not physically cross-link the asIgE bound to the high-affinity Fc epsilon (FcεRI) because of the multiple differing IgE antibody specificities on proximal FcεRIs. Although theoretically possible, this concept has largely been discarded based on studies that suggest that the ratio of polyclonal to antigen-specific IgE needed to prevent basophil or mast cell degranulation rarely is achieved in vivo since it requires only cross-linking a few hundred FcεRIs on cell membranes to trigger activation.[71,72] More recent data allow us to propose other mechanisms at work in helminth infection that drive asIgE in helminth-infected populations (e.g., cross-reactive IgE) or modulate SPT positivity (e.g., IL-10) as discussed below.

Because chronic helminth infections often induce both IgE and IgG isotypes, especially IgG4 antibodies, it has been proposed that IgG can also contribute to the modulation of type I hypersensitivity responses. IgGs are usually induced in

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TABLE 1

Detailed list of human studies examining the influence of helminth infection on atopy

			Helminth	Allergen(s)	Clinical evaluation		SPT‡	
First author, year	Country	*N*	Parasites*	Assessed†	Outcome	Effect	Prevalence	asIgE§
Authors concluded that helminths offer protection against allergies								
Hagel, 1993[10]	Venezuela	89	*Al*	Not informed	ND		↓	↓
van den Biggelaar, 2000[11]	Gabon	520	*Sh*	HDM	ND		↓	ND
Araujo, 2000[12]	Brazil	175	*Sm*	HDM, mold	ND		↓	Trend ↓
van den Biggelaar, 2001[13]	Gabon	520	*Sh*	HDM	ND		↓	↑
Nyan, 2001[14]	Gambia	429	*Al*	Various	Wheeze	No change	↓	ND
Scrivener, 2001[15]	Ethiopia	604	Hkw, *Al*	HDM	Wheeze	↓	No change	No change
Huang, 2002[16]	Taiwan	3,107	*Ev*	Not informed	Asthma, rhinitis	↓	ND	ND
Cooper, 2003a[17]	Ecuador	4,433	*Al*, *Tt*	Various	Wheeze, rhinitis, rash	No change	↓	ND
Cooper, 2003b[18]	Ecuador	2,865	Various	Various	ND		↓	
Dagoye, 2003[19]	Ethiopia	563	*Al*	HDM, CR	Wheeze	↓	No change	
Wahyuni, 2005[20]	Indonesia	466	*Bm*	HDM	ND		Trend ↓	↑
Flohr, 2006[21]	Vietnam	1,601	Hkw, *Al*	HDM, CR	ND		↓	ND
Rodrigues, 2008[22]	Brazil	1,055	*Al*, *Tt*	Various	ND		↓	
Endara, 2010[23]	Ecuador	3,901	*Al*, *Tt*	Not informed	Eczema	↓	↓	ND
Supali, 2010[24]	Indonesia	441	*Bm*	CR	ND		↓	
Rujeni, 2012[25]	Zimbabwe	672	*Sh*	HDM	ND		↓	↓
Kanobana, 2012[26]	Cuba	958	*Tc*, *Al*, Hkw	Not informed	Asthma	↑ (Tc) ↓ (Hkw)	ND	ND
Alcantara-Neves, 2012[27]	Brazil	1,445	Various	Various	Asthma/wheeze	No change	↓	No change
Mendonça, 2012[28]	Brazil	1,148	*Tc*	HDM, CR	ND		↓	↑
Manuel, 2012[29]	Malaysia	170	*Tc*	Not informed	Rhinitis	↓		
Oliveira, 2014[30]	Brazil	91	*Sm*	HDM, CR, mold	ND		↓	ND
Authors found mixed or no association or took no conclusions								
Davey, 2005[31]	Ethiopia	7,649	Various	HDM, CR	Wheeze	No change	↓	
Ponte, 2006[32]	Brazil	113	*Al*	HDM	Asthma	No change	No change	No change
Calvert, 2010[33]	South Africa	3,322	*Al*	HDM	EIB	↑	↓	No change
Vereecken, 2012[34]	Cuba	1,285	*Al*, *Tc*, Hkw	HDM, CR	Asthma	No change	↓	↑
Souza, 2014[35]	Brazil	20	*Al*	HDM	ND		ND	No change
Alcantara-Neves, 2014[36]	Brazil	1,271	*Al*, *Tt*, *Tc*	Various	ND		↓	No change
Hamid, 2015[37]	Indonesia	623	*Al*, *Tc*	HDM, CR	Wheeze, eczema	No change	↓	↑ (*Tc*)
Wordemann, 2008[38]	Cuba	1,320	*Ev*, Hkw, *Al*	Various	Asthma, rhinitis, AD	↑ (*Ev*, *Hkw*) ↓ (*Al*)	No change	ND
Obeng, 2014[39]	Ghana	1,385	*Sh*, *Al*, *Tt*	Various	Asthma/wheeze	No change	↓ (*Sh*) ↑ (*Tt*)	NE
Authors concluded that helminths are a risk factor for allergies								
Kayhan, 1978[40]	Turkey	100	*Al*	Not informed	Asthma	↑	ND	ND
Joubert, 1980[41]	South Africa	259	*Al*	Various	ND	↑	↑	↑
Alshishtawy, 1991[42]	Egypt	105	*Sm*	HDM, pollen	Asthma	↑	ND	↑
Buijs, 1997[43]	Netherlands	1,379	*Tc*	HDM, cat, dog	Asthma	↑		↑
Lynch, 1997[44]	Venezuela	89	*Al*	HDM	Asthma	↑	↑	↑
Dold, 1998[45]	Germany	~2,300	*Al*	Various	Asthma, rhinitis	↑	↑	↑
Palmer, 2002[46]	China	2,164	*Al*	Various	Asthma	↑	↑	ND
Benicio, 2004[47]	Brazil	1,132	*Al*, *Tt*	Not informed	Wheeze	↑	ND	ND
Daschner, 2005[48]	Spain	135	*As*	*As*E	Chronic urticaria	↑	ND	ND
Obihara, 2006[49]	South Africa	359	*Al*(IgE)	HDM	Asthma	↑	↑	↑
Bahceciler, 2007[50]	Istanbul	1,018	*Ev*	Various	Wheeze, rhinitis	↑	No change	ND
Pereira, 2007[51]	Brazil	1,011	*Al*	Various	Wheeze/asthma	↑	↓	

(continued)

TABLE 1
Continued

First author, year	Country	*N*	Helminth	Allergen(s)	Clinical evaluation		SPT‡	asIgE§
			Parasites*	Assessed†	Outcome	Effect	Prevalence	
Hagel, 2007[52]	Venezuela	470	*Al*	*AE*, HDM	Asthma	↑	↑ (*Al*-IgE)	ND
Hunninghake, 2007[53]	Costa Rica	439	*Al*	HDM, CR	Asthma	↑	↑	↑
Alcantara-Neves, 2010[54]	Brazil	682	(IgE)*Tt*, *Al*	Various	Wheeze	↑	ND	↑
Walsh, 2011[55]	United States	12,174	*Tc*	NE	Asthma	↑	ND	ND
Choi, 2011[56]	Korea	1,116	*Cs*	Various	Asthma, rhinitis	No change	↑	↑
Moncayo, 2012[57]	Ecuador	376	*Al*	*AE*, HDM, CR	Wheeze	↑	No change	↑
Buendia, 2015[58]	Colombia	313	*Al*	HDM	Asthma	↑	↑	↑
Webb, 2016[59]	Uganda	2,316	Various	Various	Wheeze	↑	↑	↑

* *Al* = *Ascaris lumbricoides*; *As* = *Anisakis simplex*; *Bm* = *Brugia malayi*; *Cs* = *Clonorchis sinensis*; *Ev* = *Enterobius vermicularis*; Hkw = hookworm; *Sh* = *Schistosoma haematobium*; *Sm* = *Schistosoma mansoni*; *Tc* = *Toxocara canis*; *Tt* = *Trichuris trichiura*.
† *AE* = *Ascaris lumbricoides* extract; *AsE* = *Anisakis simplex* extract; CR = cockroach; HDM = house dust mite.
‡ SPT = skin prick test.
§ asIgE = aeroallergen-specific IgE; AD = allergic dermatitis; EIB = exercise-induced bronchorreactivity; ND = not determined.

FIGURE 1. Aggregated overview of multiple studies on the helminth/allergy interface. The areas shaded black indicate increased prevalence of allergic reactivity in the presence of helminth infection, the areas shaded white indicate decreased prevalence, and those in gray indicate no change in prevalence on clinical outcome (left circle), skin prick test (SPT; middle circle), and aeroallergen-specific IgE (asIgE; right circle).

quantities 1,000- to 10,000-fold greater than those of IgE, and as such, the IgG antibodies bind antigen prior to the antigen being available to trigger an IgE-mediated effector response. This so-called "blocking phenomenon" has been explored, and two mechanisms have been identified: physical[73,74] and inhibition of target cells by FcγRIIb activation by IgG complexed to antigens.[74–76] Although other IgG isotypes have been implicated in physical IgE blocking, IgG4 seems to play a major role.[77] It has been demonstrated that IgG can intercept allergen before it binds to IgE present on membranes of mast cells and basophils,[74] and that allergen-IgG complexes can deactivate target cell by activation of the inhibitory Fc receptor (FcγRIIb), that in turn activates phosphatases in the molecular cross-linking regions of IgE shutting down FcεRI signaling.[78,79]

A more unifying explanation suggests that IL-10, a primarily T-cell–derived cytokine commonly induced in chronic helminth infection,[80–82] may underlie the protection from SPT positivity.[11,83] Indeed, it is believed that the IL-10 modified Th2 response may be responsible for the parasite-antigen-specific tolerance imprinted on the host by helminth infection.[80,84,85] Parasite-induced IL-10 or other regulatory mechanisms—that can involve cell populations such as Tregs[81,86] and Bregs[87–89]—can increase the IgE-induced activation threshold of basophils,[90] regulate T-cell[91,92] and B-cell activation,[92] promote IgG class switch,[93] and IgG4-producing B-cell differentiation and proliferation.[94] Moreover, IL-10 has been shown to drive down the production of IgE while at the same time induce isotype switching to IgG4.[95,96]

Despite the regulatory responses that helminth infections can induce in the host, these may not be sufficient to counteract the Th2-associated processes that mediate many allergic diseases. This puts into a framework the concept that a very delicate balance between pro- and anti-allergenic effector responses is required to maintain homeostasis. It is widely known that helminth parasites are associated with antigen-driven expansion of Th2 cells[97–99] along with polyclonal T-cell activation.[97–99] Interestingly, allergen extracts and helminths excretory/secretory products often share similar properties that can lead to Type 2-associated responses. For example, both are rich in proteases[100] that can promote Th2 differentiation through protease-activated receptor 2[101–103] directly on T cells[102] or indirectly by inducing IL-33 or thymic stromal lymphopoietin production by tissue cells[104,105] or IL-13 production by macrophages.[106] In addition, both allergens and helminths are known to increase numbers and activity of type

2 innate lymphoid cells[107–110] that license dendritic cells to promote Th2 priming in lymph nodes.[111]

Along with this strong, specific, and polyclonal Th2 activation induced by helminth infection, these infections also induce both polyclonal- and antigen-specific IgE production.[112] Whether a result of this Th2-associated response or of some other type of response (e.g., Treg, IL-10, transforming growth factor-β), it has been observed that helminth infection causes decreases in IgG responses to parenterally-administered vaccines[113] and increases in IgE responses to bystander antigens.[114–117] This IgE bystander effect has been suggested to be one of the reasons that helminth parasites can promote allergic reactivity through mechanisms that include: B-cell IgE polyclonal activation; IgE potentiation in which infection creates an environment that will favor IgE production to other nonparasite antigens; and IgE cross-reactivity among parasite antigens and environmental allergens.

There has been increased interest in IgE cross-reactivity involving helminth parasites and allergens as well.[116–128] We have demonstrated that helminth infection can be associated with increased IgE responses to many different allergens, especially those structurally related to parasite antigens.[116] Individuals infected with filarial parasites were shown to have higher levels of IgE against HDM and cockroach extracts (that have several major allergens with homologues in filarial parasites) but not against timothy grass extract, an allergen extract with just a few minor allergen homologues in helminths.[116]

In more detailed studies, cross-reactivity among allergens and parasite molecules has been well described for tropomyosin,[120,122,129] considered a pan-allergen.[130] Tropomyosins are highly conserved across many species and cross-reactivity is not surprising from the structural point-of-view. This allergen has dominated discussions about helminth-allergen cross-reactivity, and many reviews have already discussed its implications in detail.[131,132] However, studies on allergen and parasite protein sequences have found that huge numbers of allergens have both linear[133] and conformational[134] epitopes with significant similarity to homologous helminth proteins. The structural basis for this "allergenicity" has been inferred from bioinformatic analyses, in which it has been shown that the level of identity conservation between allergens and parasite proteins were negatively correlated with IgE prevalence to that allergen.[133] Furthermore, most of the major allergens with homologues in helminth parasites show medium to low levels of conservation with helminth proteins (amino acid identities ranging from 20% to 40%),[133] levels of identity deemed unlikely to be subject of antibody cross-reactivity. Nevertheless, evidences of cross-reactivity among less-conserved pairs of antigens have been demonstrated recently,[116,117,120,123,133] suggesting that this may be a broader phenomenon than previously appreciated. It was noticed that extracts of the cockroach *Blatella germanica* (Bla g) can inhibit the binding of IgE to several *Anisakis simplex* allergens.[118] Similarly, IgE binding to several *Ascaris* allergens can also be inhibited by *Dermatophagoides pteronyssinus* (Der p) or *Blomia tropicalis* (Blo t) extracts, including glutathione-S-transferase (GST).[120]

GSTs are major allergens of HDM,[119] cockroach,[135] mold,[136,137] and parasites.[138,139] Among the 13 classes of canonical GSTs, there are many that show very little amino acid conservation.[140] Even with the small degree of sequence conservation, cross-reactivity among parasite and allergenic GST has been demonstrated formally.[123] There was found to be a significant positive correlation of antiallergenic (Bla g 5, Der p 8, and Blo t 8) and antiparasite (*Ascaris* and filarial) GST-specific IgE levels in humans.[123,138] In addition, experimental models have corroborated these findings. For example, *Heligmosomoides polygyrus* infection induced IgE anti-cockroach GST,[123] and immunization studies with *Ascaris* antigens induced IgE and Th2 cells against HDM extract.[117] Despite helminth protein and allergen cross-reactions leading to cross-sensitization in humans are possible,[58,141–144] formal proof has not, to date, been demonstrated, especially for poorly conserved allergen-helminth proteins pairs.

Thus, the interface between helminth infection and allergic disorders reflects the delicate balance between the regulatory responses and the pro-allergenic effects of the parasites. Despite the relatively consistent finding that the presence of an active helminth infection results in lower prevalence of SPT to common environmental allergens, the fact that these same helminth infections markedly increase levels of antigen-specific IgE suggest that the complex interplay among this antigen- and allergen-specific IgE, the high affinity FcεRI on effector cells, the regulatory and effector cytokines, and the cells at barrier sites must be studied in concert to truly understand this very complex interaction.

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