

COMMENTARY:

Helminths, allergic disorders and IgE-mediated immune responses: Where do we stand?

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Th2 responses induced by allergens or helminths share many common features. However, allergen-specific IgE can almost always be detected in atopic patients, whereas helminth-specific IgE is often not detectable and anaphylaxis often occurs in atopy but not helminth infections. This may be due to T regulatory responses induced by the helminths or the lack of helminth-specific IgE. Alternatively non-specific IgE induced by the helminths may protect from mast cell or basophil degranulation by saturating IgE binding sites. Both of these mechanisms have been implicated to be involved in helminth-induced protection from allergic responses. An article in the current issue of the *European Journal of Immunology* describes the generation of an anti-*Nippostrongylus brasiliensis*-specific IgE antibody which was used to identify a novel *N. brasiliensis* antigen (Nb-Ag1). The authors demonstrated that Nb-Ag1 specific IgE could only be detected for a short period of time during infection, and that these levels were sufficient to prime mast cells thereby leading to active cutaneous anaphylaxis after the application of Nb-Ag1. This is the first report clearly showing that a low level of helminth-specific IgE, transiently produced, is able to induce mast cell degranulation in the presence of large amounts of polyclonal IgE.

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Introduction

A prominent feature of infections with helminths is that they selectively induce strong Th2 type immune responses characterized by increased numbers of

CD4⁺ T cells secreting cytokines such as IL-4, IL-5, IL-9 and IL-13. Furthermore, the numbers of eosinophils, mast cells and basophils increase in the blood and at the site of infection (e.g. gut, liver, lung, skin). However, the greatest hallmark of a helminth infection is the large amounts of IgE detected in the serum of infected animals and humans.

It is well accepted that Th2 responses have evolved in order to efficiently combat infections with helminths and numerous studies in mice suggest that, depending on the parasite, Th2 cells, eosinophils or mast cells are critical for protective immunity, if not for the initial infection, then at least for a secondary infection [1]. Interestingly, with the exception of *Trichinella spiralis*

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Abbreviations: Nb-Ag1: *Nippostrongylus brasiliensis* antigen 1 ·

NES: *Nippostrongylus brasiliensis* excretory- secretory products ·

Treg: T regulatory cells

and *Schistosoma mansoni* (*S. mansoni*) [2–4], there is little evidence suggesting that IgE plays a significant role in host defence against helminths. One of the reasons for this may be that helminths often induce large amounts of polyclonal non-parasite-specific, and very little parasite-specific IgE. Thereby protecting the helminth from IgE mediated mast cell or basophil degranulation during the helminth's migration through the skin or other organs.

Although Th2 responses usually predominate during helminth infections, helminths also induce strong regulatory responses. These include the induction of Foxp3⁺ CD4⁺ regulatory T cells (Treg) [5], alternatively activated macrophages [6] and also CD4⁺ Tr1 IL-10-producing T cells [7]. Infections with *S. mansoni* also have a strong Th1 component induced by the adult worm where as, in contrast, the eggs selectively induce Th2 type responses. Protection, at least in mice, has been shown to be dependent upon Th1 responses [8].

The balance between pro- and anti-inflammatory responses determines the fate of the parasite and the immune-pathology induced in the host. Currently it is unclear whether the regulatory responses have a greater benefit for the host, e.g. protecting from immune pathology or the parasite, e.g. enabling completion of the life cycle, and in some instances, life long persistence. In any case, it appears that the co-evolution of the host immune response and the pathogenic helminths has led to a mutual benefit: survival of both the pathogen and the host.

Helminth infections and the development of allergic disorders

Recent epidemiological studies indicate that helminth infections, in particular, schistosomes or hookworms [9, 10], protect from the development of atopy. These findings are supported by publications showing that infection of mice with *Strongyloides stercoralis*, *Nippostrongylus brasiliensis* (*N. brasiliensis*), *Heligmosomoides polygyrus* (*H. polygyrus*) and male *S. mansoni* show reduced allergic responses [5, 7, 11–14]; however, currently it is unclear by which mechanism helminths can suppress allergic responses in humans. Van den Biggelaar *et al.* [15] found that the inverse association between the degree of infection with schistosomes and a positive skin-prick test was associated with the amount of IL-10 present in the serum of the patients. This result has led to the suggestion that IL-10 and/or transforming growth factor- β secreted by antigen presenting cells (APC) or Treg cells in response to a chronic helminth infection directly interferes with allergic effector mechanisms by inhibiting mast cell degranulation or inhibiting Th2 cell proliferation [16]. Supporting this

view are studies showing that the suppression of allergic responses in mice infected with *N. brasiliensis* or *H. polygyrus* were dependent upon IL-10 or CD4⁺Foxp3⁺ Treg cells [5, 7, 12, 14].

Helminths, allergy and the IgE blocking hypothesis

Before the induction of regulatory and immunosuppressive responses became the favourite explanation of how helminths can suppress allergic disorders, the IgE blocking hypothesis was often used to explain this phenomenon. It was suggested that non-specific IgE induced by the helminth infection protected from mast cell or basophil degranulation by saturating the IgE binding sites on these cells thereby inhibiting the binding of allergen specific IgE. Currently this explanation is no longer in vogue not because it has been experimentally extensively investigated and disproved but, in my opinion, simply because explaining the decreased allergic responses often observed in animals and humans infected with different helminths by the induction of Treg cells is more “trendy” because numerous researchers are investigating this very interesting and without a doubt important mechanism in great detail.

Nevertheless, there is anecdotal evidence supporting the IgE blocking hypothesis. Protective effects of helminth infections on allergic reactivity are associated with high levels of IgE in the serum [17–20]. In addition, it has also been shown that allergic sensitization of human lung fragments could be inhibited by saturating IgE binding sites [21] and that the increase in allergen-induced cutaneous skin reactivity after the treatment of anti-helminthic drugs strongly correlates with a decrease in total IgE levels [22]. The induction of polyclonal IgE by the helminth may also protect the parasite from the host defence by a similar mechanism: inhibiting the binding of helminth-specific IgE to the mast cells or basophils. This would also explain why the helminths induce the production of large amounts of nonspecific IgE in the first place and why humans infected with helminths very rarely develop anaphylactic reactions in comparison with atopics. Interestingly, comparing allergic IgE responses with IgE responses induced by helminth infections, both in humans and in animals, it is clear that in the first case much of the IgE is specific for the allergen, whereas in the latter most of the IgE is not helminth antigen specific. Why and how helminths induce the production of these large amounts of polyclonal IgE is not known. Furthermore, the production of polyclonal IgE may also be a defence mechanism of the host, protecting from anaphylactic shock or other allergic symptoms; however, it is also

possible that inducing polyclonal IgE simply is a prerequisite for suppressing the induction of helminth specific IgE, thereby explaining the lack of anaphylaxis and also lack of protection against some type of helminths, since one of the most important defence mechanisms, mast cell and basophil degranulation, cannot be utilized by the host.

Many unanswered questions remain. Firstly, is the hypothesis correct that the large amounts of polyclonal IgE induced by the helminths can inhibit allergen and helminth antigen induced degranulation of mast cells *in vivo*? Secondly, is the induction of polyclonal IgE associated with the inhibition of helminth specific IgE generation? Currently it is not clear which, if any, of the two hypotheses is correct. It has been reported, that mice infected with *N. brasiliensis* and immunized with OVA (a combination which induces up to 50-fold increased amounts of IgE in the serum as compared to the levels found in OVA only immunized mice) showed no decrease in OVA-induced mast cell degranulation in the skin in comparison with uninfected mice immunized with OVA [7]. This finding strongly argues against the IgE blocking hypotheses. This view is supported by a very elegant study of Pochanke *et al.* published in this issue of the *European Journal of Immunology* [23]. The authors successfully generated an IgE-producing B cell hybridoma cell line and by using a cDNA phage display library were able to clone and identify a novel *N. brasiliensis* antigen (Nb-Ag1) which binds to *N. brasiliensis*-specific IgE. The levels of Nb-Ag1-specific IgE were measured in the serum of *N. brasiliensis*-infected mice and were only detected for a short period of time and only after a challenge *N. brasiliensis*-infection. Most importantly the authors could show that applying recombinant Nb-Ag1 subcutaneously led to IgE-mediated active cutaneous anaphylaxis during primary, secondary and tertiary *N. brasiliensis* infections. To my knowledge, this is the first report clearly showing that low levels of helminth-specific IgE responses are generated in parallel to large amounts of polyclonal IgE and can lead to mast cell degranulation. Furthermore, this report [23] raises very interesting and important questions, that based on the results presented in it, and the novel tools generated, may now be addressed. For example, will the application of recombinant Nb-Ag1 by itself (with or without alum) induce Th2 responses as was reported for *N. brasiliensis* excreted/secreted products (NES) [24, 25]? If so, will this type of immunisation protect from an infection with *N. brasiliensis*? Using a similar approach to that described in studies by Pochanke *et al.*, [23], novel antigens binding helminth-specific IgE may also be identified for other pathogenic helminths infecting humans or livestock. Identifying these antigens may aid in IgE/mast cell-dependent vaccine development. It

may also be possible to directly generate antigen-specific IgE for prophylactic or therapeutic use; however, it remains to be investigated whether other helminths also induce specific IgE responses which are able to induce mast cell degranulation. The study of Pochanke *et al.*, [23] clearly indicates that these responses may be present but difficult to detect.

Taken together, at least for the model helminth *N. brasiliensis*, the IgE blocking hypothesis can be discarded. *N. brasiliensis*-infected mice show both allergen and helminth-specific active cutaneous anaphylaxis in the presence of large amounts of polyclonal IgE. It remains to be seen whether the helminth-specific IgE response against Nb-Ag1 plays a role in host defence against the helminth. This appears likely since NES applied alone or together with alum can induce very strong Th2 responses and the production of NES-specific IgE [24, 25]. Furthermore, Trujillo-Vargas *et al.*, showed [25] that mice immunized with NES and OVA generated NES- but not OVA-specific IgE clearly indicating that *N. brasiliensis* produce substances which drive a helminth-specific IgE response under conditions where an allergen-specific IgE response cannot be generated.

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