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Identification of major human IgE-inducing parasite antigens: a path to therapeutic approaches?

David Dombrowicz, PhD

Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-EGID, F-59000 Lille, France

Corresponding author:

David Dombrowicz

Inserm U1011. Institut Pasteur de Lille.

1, rue du Professeur Calmette BP245.

59019 Lille Cedex, France.

Email: david.dombrowicz@pasteur-lille.fr

Phone number: +33 320 87 79 67

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Words: 1213 (without references, table & legend)

Type 2 immunity is a hallmark of allergic diseases, where it plays a detrimental role, and the major contributor to anti-helminth immunity^{1, 2}. It is characterized by the production of an expanding subset of alarmins (IL-25, IL-33, TSLP) and cytokines (IL-4, IL5, IL-9, IL-13, IL-31...) and by the involvement of a specific group of cell subsets associated with innate and adaptive responses (innate lymphoid cells -ILC-2, dendritic cells -DC-, alternatively activated macrophages, mast cells, basophils, eosinophils, Th2 and B lymphocytes) ultimately leading to IgE production by B cells. IgE binds to and acts through 2 specific receptors. FcεRI is a high affinity IgE receptor expressed by mast cells and basophils and, in humans, by antigen presenting cells (DC, epidermal Langerhans cells, monocytes/macrophages), eosinophils and platelets³. FcεRII/CD23 is a low affinity receptor mainly expressed by B cells and regulating IgE production. IgE-dependent FcεRI -mediated cellular cytotoxicity (ADCC) towards helminth larval stages carried out by eosinophils, macrophages and platelets is a key mechanism in anti-helminth immunity. Mast cells and basophils contribute to anti-helminth immunity mainly through cytokine and protease production, while a specific role for IgE-mediated enhanced antigen presentation has not been formally demonstrated in the context of helminth infections. In line with the (fairly long) timing of IgE isotype switching and affinity maturation and with larval stages being the main targets, (antigen-specific), IgE concentrations are positively correlated with immunity to reinfection, for instance in schistosomiasis⁴, rather than to protection against a primary infection. Thus, the identification of the major antigens promoting a strong IgE response is an important step both for establishing specific and sensitive diagnostic tools and testing new vaccine candidates.

In an interesting study, using filarial infections as a demonstrator, Hadadianpour *et al.*⁵ identified major filarial antigens recognized by human (h)IgE using a labor-intensive technique, previously applied for the identification of *Aspergillus* antigens⁶. This method is based on the generation of human monoclonal IgE antibodies from hIgE-expressing B cells, isolated from human PBMC. From 7 patients with lymphatic filariasis, tropical pulmonary eosinophilia, loiasis or onchocerciasis, 56 monoclonal hIgE antibodies were generated regardless of their antigenic specificity, then screened for their reactivity towards a *Brugia malayi* extract by ELISA, Western blot and specific "ImmunoCAP" assay. 26 hIgE antibodies were positive in at least one assay. Specificity against other extracts from these human pathogens was not assessed. However, 13 antibodies cross reacted with antigens from dog filaria *Dirofilaria immitis*. Importantly but surprisingly, these hIgE antibodies do not cross-react with 112 common allergens, which might share some common glycan epitopes with parasite antigens as reported in several studies⁷. This suggests that hIgE response during filarial infections is highly parasite specific. 16 hIgE were able to immunoprecipitate filarial antigens that were analyzed by mass spectrometry. 14 unique antigens were identified. All were excreted/secretory (E/S) proteins with a transthyretin-related (TTR) protein of unknown function being the dominant antigen for induction of hIgE response. Other proteins of interest were WbSXP-1, a nematode-specific secreted protein, whose homolog is a vaccine candidate against *Ascaris*, a filarial homologue of human migration inhibitory factor and an ubiquitously expressed 400 kDA polyprotein ladder-like protein (gp15/400). Production of recombinant antigens, in a bacterial expression system, hence lacking full native glycosylation, allowed further identification of 1 additional hIgE against *Wuchereria bancrofti*-specific antigens, that were not selected on the basis of reactivity against *B. malayi*. Screening for reactivity against 15 other recombinant TTR-family proteins identified multiple hIgE with restricted or broad TTR cross reactivity, confirming TTR proteins as major antigens inducing hIgE response against filariae. The functionality of hIgE-cognate filarial (dimeric) antigen recognition was assessed in an IgE-mediated passive systemic anaphylaxis test using hFcεRIα transgenic mice expressing a humanized FcεRI with a structure and cell distribution comparable to that found in humans⁸. Expectedly, cognate antigen injection induced hypothermia in hIgE-sensitized animals.

The advantages of the antigen-specific monoclonal hIgE approach chosen by Hadadianpour *et al.*⁵ over direct IgE purification from serum/plasma are obvious. First, contamination with other isotypes

might occur as hIgG concentrations in serum are much higher than hIgE ones and hIgG can display overlapping antigen specificity with hIgE. Second, monoclonal antibodies allow the precise identification of epitope recognized. Third, the unlimited availability of monoclonal hIgE antibodies not only allows a much more extensive biochemical characterization of the antibodies themselves but, importantly, of the identified antigens. Finally, together with the use of recombinant cognate antigens, monoclonal hIgE antibodies can be used in functional assays *in vitro* or *in vivo*. A promising, yet complex alternative approach is based on direct single cell RNA-sequencing (scRNA-seq) of hIgE-expressing B cells from plasma followed by cloning and expressing all the IgE-relevant sequences as recombinant antibodies and has allowed the identification of clonal high affinity hIgE from patients with peanut allergy⁹. A major advantage of this recent method is that scRNA-seq additionally provides extensive information about individual hIgE-expressing B cells (see Table 1 for comparison). However, it has not been used so far in the context of helminth infections.

Surprisingly, besides gp15/400, none of the few known filarial antigens recognized by hIgE, such as tropomyosin, paramyosin, glutathione S-transferase, aspartic protease inhibitor, Venom-Allergen-Like protein¹⁰, were identified by Hadadianpour *et al.*⁵ using monoclonal hIgE technology. A possible explanation for this barely overlapping helminth-specific antigen subsets identified by the 2 methods is that a monoclonal hIgE-based strategy for parasite antigen identification is able to select high affinity epitope(s) even when frequency of cognate IgE is very low. By contrast, procedures based on direct parasite antigen recognition by serum/plasma (polyclonal) IgE require higher frequency of cognate IgE but are probably less stringent regarding IgE affinity for a given epitope.

Finally, while the induction of hIgE-mediated passive anaphylaxis in hFcεRIα Tg mice unambiguously demonstrates that hIgE-helminth antigen interactions are driving a functional mast cell response *in vivo*, a conclusion drawn by authors from this experiment, namely that hIgE, through mast cell activation, acts as an early sensor of infection, driving further eosinophil and basophil infiltration, appears speculative in the absence of additional experiments. Indeed, IgE-mediated passive anaphylaxis is strictly dependent on mast cells and FcεRI. Thus, a role for any other FcεRI-expressing cell types, such as eosinophils or for CD23-expressing cells, cannot be established using this model. It is rather likely that, during an actual helminth infection, all FcεRI- and CD23 expressing cell types bearing receptor-bound antigen-specific hIgE, rather than mast cells only, are directly and concomitantly activated, upon encounter with the cognate antigen, and perform their respective function, including cytotoxicity, antigen presentation, cytokine or IgE production. Therefore, the passive transfer of helminth antigen-specific hIgE prior to the infection of hFcεRIα Tg mice with *B. malayi*, as proposed by the authors, remains the first key experiment to be performed for firmly establishing a protective role of antigen-specific monoclonal hIgE in *B. malayi* infection. Use of mice also humanized for IgE and CD23 would further increase the relevance of such a demonstration. This would pave the way, on one hand, for experiments aiming to determine which hFcεRI-expressing cell types contribute to this protective effect and, on the other hand, for testing the identified antigens in vaccinal strategies against deadly pathologies for which new therapeutic approaches are sorely needed. Should this experiment succeed, the monoclonal hIgE-based strategy described in the present work might be applied to identify new major antigens driving the IgE response in non-filarial helminth infections.

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Key step/Sequence order	I. Hadadianpour et al. ⁵	II. Croote et al. ⁹	Comment(s)
PBMC isolation	1		
In vitro B cell expansion	2		
hIgE ⁺ -B cell selection	3	1	I. ELISA. II. Flow cytometry
Hybridoma generation	4		
Single cell sorting	5	2.	
Clone amplification-hIgE purification	6		
scRNA-seq		3	II. Full transcriptome characterization
VDJ-C region sequencing & analysis	6'	(3)	II. Obtained from scRNA-seq
Recombinant hIgE expression		3'	
Antigen reactivity screening	7		I. ELISA, Western Blot, ImmunoCap
Antigen affinity purification	8		
Antigen identification	9		
Recombination antigen expression	10		
hIgE-cognate antigen recognition validation	11	4'	I. <i>In vitro</i> : ELISA, Western blot. <i>In vivo</i> : hIgE Anaphylaxis in hFcεR1α Tg mice. II. ELISA
Method illustration	Figure E1 ⁵	Figure 1 ⁹	

Table 1. Comparison of human monoclonal IgE-based methods.