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IgE: a Key Antibody in *Schistosoma* Infection

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Abstract

Although it is present at a low concentration in human serum, IgE antibody plays unparalleled roles in allergy and parasitic infection. It is a marker in Th2 response polarization during the infection of *Schistosoma.* Relatively abundant circulating IgE antibodies which are induced by cytokines, such as IL-4 and IL-13, bind the Fc-epsilon specific receptors on mast cells, basophils and eosinophils and trigger the degranulation of these cells, thereby increasing vascular permeability and killing the parasites. The protection provided by IgE has been verified in numerous independent and collaborative studies in several sites. The particular pattern of the increase in the production of IgE with age and association between worm specific IgE and resistance to reinfection shed light on the designs of control strategies and searches for novel vaccine candidates.

Key words: IgE, *Schistosoma*, Th2 response, mast cell, basophil, eosinophil, treatment.

1. Complex immune responses involved in schistosomiasis

The role of IgE in host immune protection against parasites was first found by work on the cell-mediated killing of schistosomes, as well as by epidemiological studies in the areas of endemic schistosomiasis [1]. The process involved in immune responses against *Schistosoma* is complex. This is not only due to the antigenic variation during the life cycle and the intensity of expression of antigenic component in the parasitic organism, but the mechanism by which *Schistosoma* evades host immune system. During the first 4-5 weeks following exposure to cercariae when host immune system is directed against worm antigens, the immune response is primarily Th1 in nature. During the normal infection when *Schistosoma* eggs are produced, the immune response becomes highly Th2-polarized. Coincident with the development of the Th2 response, there are notable increases in plasma IgE levels and the number of circulating eosinophils, which reflects the production of IL-4 and IL-5, the signature cytokines of Th2 cells helping class switching of B cells to IgE isotype and acting as a growth and survival factor for eosinophils, respectively [2]. It is possible that soluble egg antigen (SEA) inhibits DC TLR-initiated and MyD88-dependent activation pathways which induce IL-12 production and Th1-polarized response by binding C-type lectin DC-SIGN on dendritic cells [2, 3]. T helper cells and NK cells which are activated by DCs produce IL-4 which activates B cells to excrete IgE antibodies.

2. The effector cells IgE acts on in the infection of *Schistosoma*

A correlation between the intensity of infection and generation of anti-parasite IgE has been elucidated [4]. Th2 cells producing IL-4 and IL-5 seem to play critical roles in developing high level of anti-parasite IgE in schistosomiasis patients [5]. Antibodies of IgE isotype is involved in the protection against schistosomiasis by mediating macrophage toxicity. The protection has not only been observed in the natural development of the infection, but in the immunization with schistosomula-specific monoclonal IgE in which schistosome-specific IgE antibodies promoted macrophages to eliminate parasites [6].

The observed parallel increase in the production of eosinopils and IgE against *Schistosoma* promoted researchers to investigate the interaction between eosinophils and IgE antibodies. Although in most cases, IgE produced by B cells stimulates mast cells and basophils to release mediators which stimulate eosinophil differentiation and induce eosinophil cytotoxity, IgE can directly affect eosinophils by binding to FcεRI on eosinophils [7].FcεRI can mediate schistosomula-specific eosinophil-dependent cytotoxicity by signalling the release of eosinophil peroxidase (EPO). This provides the involvement of eosinophils in immunity against schistosomiasis with evidence (See Figure 1.). Experiments *in vivo* showed that eosinophils can kill *S.mansoni* in the presence of specific anti-schistosome IgE antibodies [8]. Furthermore, by using selective absorption of various isotypes or alternatively using competition with isotype-matched irrelevant myeloma proteins, IgE was shown to induce killing by mononuclear phagocytes, eosinophils, and platelets in both humans and rats. It should also be noted that in effector cell transfer experiment, cytophilic IgE was detected on macrophages, eosinophils and platelets from donor

rat and these armed cells provided naïve recipients with protection [9]. However, eosinophils seem not to be included in the immune response of limiting the viability of *Schistosoma* eggs in granulomatous formation [10]. Furthermore, inhibiting the generation of eosinophil precursors is incapable of altering IgE level [10].

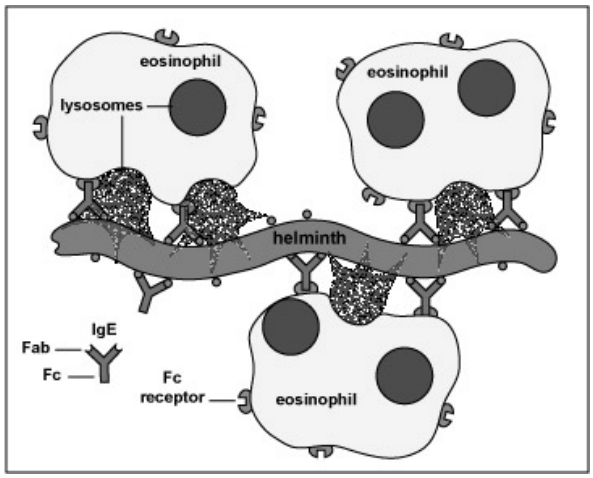

Figure 1. Opsonization of a helminth by IgE and Eosinophils. (From *Doc Kaiser's Microbiology* website) Cytokines and CD40 ligands expressed by Th2 cells function to stimulate B lymphocytes to express a class of antibodies called IgE. IgE acts as an opsonizing antibody to stick phagocytic eosinophils to helminths and allows the released major basic proteins and eosinophil cationic proteins to be focused on the targets for extracellular killing of the helminths. The Fab portion of IgE recognizes epitopes on the helminth, while the Fc portion binds to Fc receptors of activated eosinophils. The lysosomal proteases of eosinophils are able to destroy the tough integument of helminths. IgE also promotes inflammation to recruit phagocytes.

3. Seroepidemiology of schistosomiasis

The pivotal role IgE plays in protective immunity against schistosomes is not only evident in animal experiment observations, but also prominent in human seroepidemiological studies. In Brazil, adolescents with high resistance to infection by *S.mansoni* have specific IgE levels that are six- to eightfold higher than those with low resistance [11]. Infection history, sex, age, ethnicity and immune system may affect the development of immune response. Moreover, these factors can be active in a collaborative manner. Protective immunity against *Schistosoma* is developed gradually with the increase of age [12]. So the characteristic pattern of *Schistosoma* infection-age curve is related to the effector mechanism of protective IgE antibodies and class switch between IgE/IgG4. Children produce significant amounts of IgG4 which is thought to interfere with complement activation by IgG1 and block mast-cell degranulation by competing with specific anti-parasitic IgE for antigenic worm antigen [12]. Therefore, the slow achievement of epidemiologically significant immunity may reflect a delayed development of the protective IgE response and early production of IgG4 which blocks the activity of anti-parasitic IgE. Other antibodies, including IgM and IgG2, which are elicited against egg polysaccharide antigens and carbohydrate epitopes expressed at or released from the surface of the young schistosomulum, also appear to block the expression of protective antibodies [4]. Mutapi et al. [13] indicated that the production of anti-SEA IgE in the high infection area was significantly higher than in the low infection area, whereas the level of anti-worm IgE was lower in the high infection area than in the low infection area. Anti-SEA IgE is directed towards the egg antigens which reflect the late phase of schistosome infection. In high infection population, the transmission rate is high and acquired immune responses have been established against parasitic eggs which are the major immunogenic substances in the late phase. Therefore, the anti-egg IgE is more in the high infection area than in the low infection area. In contrast, in the low infection area where the immune responses are mainly directed towards adult worms the anti-WWH IgE is dominant. But the study in Masongaleni about *S.mansoni* infection showed a positive association between anti-worm IgE and intensity of infection. Heterogeneity of antigen epitopes of these two species may result in the discrepancy [14]. Further researches for finding out the mechanism of sex hormonal effects on antibody isotype production are needed before drawing the conclusion that the differences between male and female isotype levels are due to the hormonal difference [13]. Moreover, some factor (s) other than age, gender, infection intensity and number of previous treatments has been found to facilitate the presentation of antigens in different ways to generate distinct anti-SWAP IgE responses [5].

4. The effect of treatment on humoral immune responses

Praziquantel, the most effective chemotherapy so far has been believed to be synergetic with host immune response. It can destroy adult worms' tegument, induce paralysis of worms and expose internal antigens [15]. Host humoral and cellular immune responses can be active following the exposure of these antigens. Mutapi et al. [16] have assessed the humoral response developed in the treatment with infection. They found that production of IgA and IgG2 was significantly smaller after treatment than before treatment. This may be due to the fact that these antibodies are directed to the glycanic antigens on the surface of adult worms. After treatment these antigens disappeared, the amount of IgA and IgG2 fell down. Conversely, the levels of IgE, IgG1 and IgG4 against SEA are significantly higher in post-treatment cohorts than the pre-treatment cohorts. There is some evidence

that the localization of IgE stimulating antigens are beneath the worm tegument and the 22 kDa *S.mansoni* antigen beneath the tegument can stimulate the IgE response [17]. Furthermore, IgG4, the antibody regulates IgE-derived anaphylactic responses, also increased simultaneously with IgE. But the study in Kenya about changes of human isotype responses to *S.mansoni* antigens following treatment indicated that no significant differences were observed between pre-treatment and post-treatment isotype responses to egg antigens [18]. It also showed that IgG subclass responses to adult worm antigens were significantly lower after treatment, while IgE levels against adult worm antigens were significantly higher after treatment than before treatment. Similar phenomena were observed in another study in which anti-schistosomular tegument (STEG) IgG4 significantly decreased and anti-STEG and anti-soluble worm antigen preparation (SWAP) IgE increased after treatment in population which showed resistance to reinfection [19]. This resistant group was much older than the group susceptible to reinfection. Isotype switch had occurred in the resistant group and treatment promoted *in situ* protective isotypes to recognize epitopes and display their effector functions.

Some studies [20] also evaluated the IgE-induced basophils' histamine releasability following treatment. They found that concentration of IgE in post-treatment blood is irrelevant to histamine-releasability. Thus it would appear that post-treatment changes in the level of histamine-releasability *in vitro* were regulated either at the cellular level or by serum factors affecting the *in vivo* sensitisation, priming or neutralisation of the basophils or of other surface-bound factors, other than ELISA-detectable parasite-specific IgE.

5. Discussion

IgE as the major antibody in Th2 response is controlled by macrophages, dendritic cells and T cells. Its role in allergic inflammation and hypersensitivity is achieved through activating mast cells and basophils which release histamine, eicosanoid, TNF, IL-4, IL-13 and IL-5. IL-5 promotes the proliferation and differentiation of eosinophils. Both of allergen and *Schistosoma* can initiate the production of IgE Therefore, allergy and schistosomiasis are both largely Th2-polarized. IgE participates in the pathology of *Schistosoma* egg-induced granuloma formation. It also provides the protection against fatal damages caused by schistosome infection. Its production is dependent on age with infected adults excreting more IgE than infected children.

It should be noticed that not only resistance to infection is age-dependent, but reinfection is also related to age, with children being more susceptible than adults. This difference in immune status is thought to be dependent on the balance of anti-schistosome antibody isotypes which seems to vary with age. In particular, IgE is associated with resistence to reinfection, whereas IgG4 is implicated in susceptibility to reinfection. Anti-SEA and anti-worm IgG4 level was positively associated with reinfection intensity, whereas pre-treatment anti-Adult Worm Antigen IgE was negatively correlated with reinfection for *S.haematobium* and *S.mansoni* [4, 12, 17 and 21]. This also suggested that the effect of IgE preserved for a long time after treatment. There may be memory B cells produced. In the study in Kenyans, a significant association between post-treatment levels of anti-adult worm IgE and resistance to reinfection was also observed [18]. The susceptibility to infection may be involved in the idiotypic immunity in which the pro-inflammatory antibodies and cytokines are suppressed. The low IgE and dominant IgG4 are also seen as a pattern of immunoregulation of hypersensitivity. If not modulated, adult worm and egg antigens-derived uncontrolled Th2 responses tend to induce exaggerated inflammation which causes damage to host health. The antigen presenting cells (APC) or the regulatory T cells can attrite the extremely biased Th2 responses by excreting IL-10 and TGF-beta. In this situation, the immune response will become either the balanced Th1/Th2 response in which resistance to infection without much lethal diseases is shown or the modified Th2 response in which inversed magnitude of IgE/IgG4 production is evident. Regulatory T cells may produce IL-10 which counteracts the effect of IL-4 on the isotype switch of B cell to IgE, while inducing the production of IgG4 by B cells [22]. The regulatory events may be gradually achieved in the course of infection. In *S.mansoni* infection of mice, initial Th0/Th1-cell responses give way first to pro-inflammatory Th2 cell responses, followed by a decline in parasite-specific T-cell responses [22]. Therefore, the relationship between IgE and IgG4 is not invariable even in definitive individuals. The studies on the regulatory environment of the production of IgE and IgG4 will not only provide us with the insight into the resistance or susceptibility to helminth infection, but also with ideas of designing the strategies of intervening into the allergy.

Without the knowledge of activities of cytokines related to production and suppression of IgE, such as IL-4, IL-5 and IL-12, the clear understanding of the relationship between schistosomiasis and IgE is undermined. It is also necessary to be aware that besides IgE, soluble factors, mast cells mediators, or cytokines (IL-5, granulocyte-macrophage colony-stimulating factor, or TNF-alpha) can upregulate the IgE-dependent cytotoxicity mediated by eosinophils [11]. IgE response should be seen in the broader context of a Th2 –dependent regulatory circuit in which increased IL-5 is significantly associated with resistance to reinfection [23] and IgA antibodies are related to acquisition of immunity. Thus, it is of critical importance for us to further survey the

interaction of cytokines and IgE antibodies and, if possible, the synergy of antibodies and cytokines in initiating mast cells, basophils and eosinophils.

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