

Immunoglobulin E and Effector Cells in Schistosomiasis

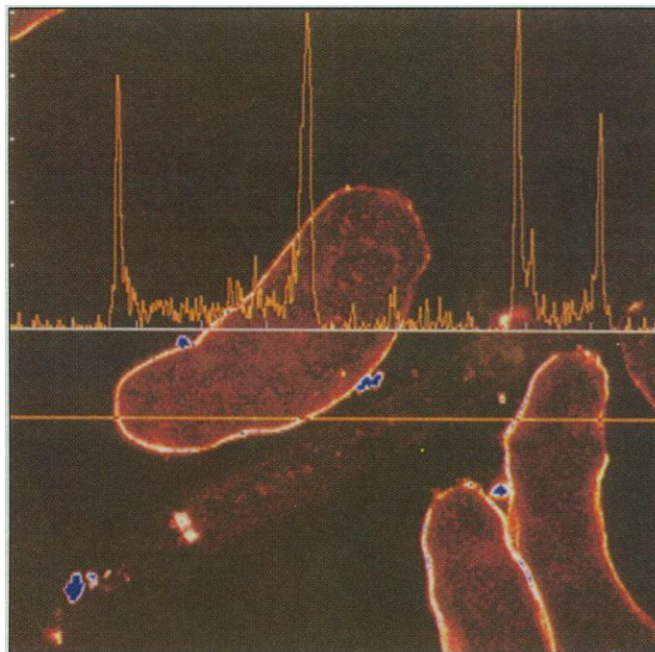
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Schistosomiasis is a chronic and debilitating disease, affecting 200 million people throughout the world. Infection by *Schistosoma mansoni* is characterized by the presence of adult worms in the portal and mesenteric veins of humans and other mammals, whereas *S. haematobium* worms live mostly in the urogenital venous system. A complex migratory cycle is initiated when infective larvae, shed by infected freshwater snails, penetrate the skin. The infective larvae transform into schistosomula in the host's skin and, over several weeks, develop into sexually mature, egg-laying worms. The pathology in this disease occurs as a result of the parasite's eggs in the host tissues.

Acquired resistance to schistosome infection requires antibody-dependent mechanisms. In all animal models and in humans, elevated immunoglobulin E (IgE) concentrations, including IgE specific for schistosomes, and blood and tissue eosinophilia are hallmarks of schistosomiasis. In mice, there is a functional dichotomy in the CD4⁺ T cell response to *S. mansoni* (1)—both T_H1 and T_H2 responses are seen. Now it is thought that schistosome worms stimulate protective T_H1 cell responses that are down-regulated by egg-induced T_H2 cell responses. Like eosinophil and IgE levels, interleukin 4 (IL-4) and IL-5 production by T_H2 cells increase at about the time that the worms mature and egg production begins, suggesting a causal link between eggs and T_H2 cell responses (2, 3). These results indicate that both expression of protective immunity and the pathological reactions are regulated by a complex network of coordinated responses, a T_H cross-regulatory circuit (4). In rat, primate, and human schistosomiasis, antibody-dependent, cell-mediated cytotoxicity

(ADCC) is the main mechanism of killing parasite larvae; whereas in mice, cytotoxicity in schistosomiasis requires activated macrophages.

In vitro cytotoxicity assays and in vivo passive transfer experiments show that ADCC systems consist of inflammatory cells (macrophages, eosinophils, platelets) as cellular partners and IgE and subclasses of IgG or IgA as humoral components. This key role of IgE antibodies in defense against schistosomes has led to a reevaluation of the general biological function of IgE. The



Surface antigens on the schistosomula of *Schistosoma mansoni*. The parasites were incubated with mouse monoclonal antibodies and fluorescein-labeled antibody to mouse IgG. The staining was visualized and analyzed by confocal laser microscopy.

first in vivo evidence that IgE antibodies could be an essential component of protective immunity was provided by passive transfer of monoclonal IgE molecules directed against schistosomes (5, 6). The induction of resistance to infection by adoptive transfer of eosinophils or platelets bearing cytophilic IgE clearly indicated that the IgE on these effector cells was crucial (5). These experimental observations are relevant to human immunity, as established by several seroepidemiological studies. In an area in Gambia endemic for *S. haematobium*, a link was established be-

tween the production of IgE against schistosomes and the acquisition of immunity during reinfection (7). 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; other Ig isotypes are either similar in both groups or higher in the least resistant subjects (8). More recently, the combination of low IgE antibodies to *S. mansoni* with high IgG4 was associated with 100 times more susceptibility to reinfection than usual (8). Similar observations have also been made in Kenya in a community infected by *S. mansoni*, again supporting a role for IgE in preventing human infection by schistosomes (9). These studies in humans confirm the experimental evidence and open a new dimension in the study of the cellular networks involved in IgE interactions.

Immunoglobulin E activates skin mast cells and blood basophils by way of a unique, high-affinity receptor for IgE (FcεRI). Mast cells and basophils are known to participate in immediate hypersensitivity reactions, but a direct effector function in anti-schistosome immunity has never been demonstrated for these cells. However, rat mast cell mediators can increase the cytotoxicity of other effector cells (5). The demonstration that both polyclonal and monoclonal IgE antibodies induce anti-schistosome cytotoxicity and the release of pharmacologically active mediators by inflammatory cells raised the possibility that hitherto unsuspected receptors for IgE might exist on mononuclear phagocytes, eosinophils, and platelets. Indeed, IgE binds to these cells with low affinity. The inhibitory effects of various antibodies to receptors, combined with structural studies, led to the description of a second class of IgE receptor, FcεRII, on mononuclear phagocytes, eosinophils, and platelets (10). The similarity between the B cell differentiation antigen CD23 and FcεRII, the cloning of FcεRII-CD23, and the availability of antibodies to CD23 allowed the demonstration of CD23, or CD23-related molecules, on human eosinophils and platelets (11). Various antibodies to CD23, which bind to a subpopulation of eosinophils and platelets, strongly inhibited cytotoxicity against schistosomula targets (11). In contrast to FcεRI, which is constitutively expressed by mast cells and basophils, FcεRII is detected mainly on activated cells, the number of which increases in pathological and experimental conditions associated with elevated

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IgE; the expression of the receptor could indeed be induced by IgE (11).

There are two forms of FcεRII-CD23: FcεRIIa, which is developmentally regulated and expressed only on B cells; and FcεRIIb, inducible in the other cell populations, including an eosinophilic cell line. These findings are consistent with the possibility that inducible FcεRII-CD23 participates in the binding of IgE to eosinophils. However, the low mRNA levels and membrane expression of FcεRII-CD23, together with the finding that a non-mast cell population, the Langerhans cell, can coexpress FcεRII and FcεRI (12), raised the possibility that eosinophils and platelets also express FcεRI. Indeed, with monoclonal antibodies, the α chain of FcεRI can be shown to be expressed by a subpopulation of human eosinophils and to be involved in IgE binding (13), and the mRNAs for FcεRI α, β, and γ chains can be detected in eosinophil RNA extracts. Moreover, there is evidence that FcεRI, able to induce a selective release of eosinophil granule proteins, can mediate eosinophil-dependent cytotoxicity against schistosomula (13), and similar findings have recently been obtained in blood platelets. Thus, in addition to its role in mediating allergic responses, FcεRI, expressed on eosinophils and platelets, may participate in a physiological protective immune response against schistosomes.

Besides IgE, soluble factors, mast cell mediators, or cytokines (IL-5, granulocyte-macrophage colony-stimulating factor, or tumor necrosis factor α) can upregulate the expression of IgE receptors, as well as IgE-dependent cytotoxicity mediated by eosinophils. In addition, adhesion molecules, including integrins (CR3 on eosinophils or IIbIIIa on platelets, S-type lectins (Mac2/e binding protein) or selectins have been implicated as accessory molecules, reinforcing the cytotoxic capacity of eosinophils or platelets and confirming the variety of interactions between effector cells and their parasite targets.

Although the respective functions of the various IgE receptors remain to be elucidated, their striking diversity is consistent

with the effector role of IgE antibodies suggested by experimental observations and immunoepidemiological studies in human populations. In a broader context, IgE response in schistosomiasis and its role in protective immunity have to be regarded as part of a T_H2-dependent regulatory circuit. In human populations, increased IL-5 is significantly associated with resistance to reinfection whereas, at least in this study, there was no correlation with interferon γ (IFN-γ) production (14). In addition to the IgE response, there is an unsuspected association of specific IgA antibodies with acquisition of immunity (15). There is therefore increasing evidence that protective immunity in human schistosomiasis is associated with T_H2 rather than T_H1 responses.

Whether a T_H1 or T_H2 response occurs is influenced by, among other factors, the number of exposures to antigen. In the mouse, cell-mediated mechanisms associated with T_H1 cell responses predominate in mice vaccinated once, whereas further immunizations stimulate T_H2 cell responses, such as enhanced IgG1 production, that also contribute to protective immunity (16). Thus, depending on the context, T_H1 or T_H2 responses can protect against infection with schistosomes, a result compatible with the protective role of IgG1 antibodies in mice (17) and the age-dependent acquisition of immunity after multiple exposures to parasite infection in humans (9). Finally, it is now clear that multiple cytokines can be secreted by cells other than T_H1 or T_H2 cells. Besides mast cells, eosinophils, a pivotal cell population in the immune response to schistosomes, express the IL-5 gene and secrete IL-5 in response to various stimuli, among which are immune complexes with IgE and IgA (18). Thus, there are regulatory networks independent of the T_H1 and T_H2 cells' cross-reactive circuits and, attractive as it may be, a simple dichotomy cannot account for the multiple facets of immunoregulation in schistosomiasis. The reasons why schistosomes, and other helminths like nematodes, preferably induce T_H2 responses for protective immunity are not yet clearly de-

fined. Interestingly, schistosomes release enzymes such as serine proteases that are able to potentiate IgE responses and secrete molecules such as adrenocorticotrophic hormone or α-melanocyte stimulating hormone, known to down-regulate IFN-γ production (19, 20).

These observations go to the heart of vaccine strategies against schistosomiasis. Among several promising molecules, the *S. mansoni* glutathione-S-transferase (Sm28 GST) induces both IgE and IgA antibodies. These antibodies are associated with protection in experimental models, as measured by worm burden reduction and decrease in parasite fecundity (21). The more we improve our understanding of the immune response in human schistosomiasis, the more opportunities we create for the development of anti-schistosome and, maybe more generally, anti-helminthic vaccines.

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