



2007 Research Grant Program Winning Abstract

B Cell Alternative Receptors

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Human schistosomiasis, caused by three main species of tissue invasive parasitic trematodes, currently affects over 207 million individuals and remains a significant cause of morbidity in developing countries. Vaccine development for this disease has been hampered by a poor understanding of the mechanisms involved in protective immunity in humans. A relatively consistent finding in field-based studies is a correlation between high serum concentrations of parasite-specific IgE and resistance to reinfection following curative chemotherapy. However, the role(s) of putatively protective IgE remains elusive. Furthermore, although B cells are the producers of IgE, remarkably little is known about human B cell function and the mechanisms involved in the maintenance of elevated serum IgE in schistosomiasis.

The focus of this proposal will be to define the interplay between human B cells and parasite antigens. We have found that resting, naïve human B cells do not respond to schistosomal antigens, suggesting that endogenous B cell receptors do not recognize schistosomes. Thus, we hypothesized that B cells might utilize unconventional mechanisms, such as alternative receptors, to sense parasite infection. Because the intrinsic ability to secrete higher levels of IL-4 is also associated with resistance to schistosomiasis, we hypothesized that IL-4 might alter the ability of the B cell to recognize antigens. In collaboration with the Centers for Disease Control and Prevention and the Kenyan Medical Research Institute, the correlates of immunity to schistosomiasis in an occupationally hyper-exposed group of Kenyan laborers are being investigated. Our preliminary data suggests that increased expression of the IL-4-induced IgE receptor found on B cells, CD23 (Fc ϵ 1541;RII), is strongly associated with a history of resistance against *S. mansoni* in the occupationally-exposed population. CD23-bound IgE must be cross-linked by antigen to induce cellular activation, suggesting that preexisting schistosome-specific IgE may play a role in antigen capture by B cells in immune individuals. However, the biology of this interaction is complex in schistosomiasis because schistosomes synthesize a glycoprotein, IPSE/alpha-1, which binds IgE in the Fc region (non-antigen specific region). Using our novel in vitro model system, we generated data that suggests B cell differentiation is inhibited by non-antigen specific cross-linking of CD23-bound IgE. Thus, IPSE/alpha-1 may be an immune evasion tactic utilized by the parasite to inhibit protective IgE production. We aim to dissect the role of CD23/IgE complexes in eliciting protective immunity to schistosomes and the potential roles of IPSE/alpha-1 in immune evasion by correlating field-based clinical studies with our in vitro model system which recapitulates B cell differentiation. This portion of the study includes an additional collaborator, Dr. Helmut Hass, who has generously provided recombinant IPSE/alpha-1.

Although CD23 likely has an important role in maintaining immune responses to parasite antigens in immune individuals, receptors which play a role in naïve B cell recognition of schistosomes during a primary infection remain undefined. Our preliminary data suggest that IL-4 treatment of naïve B cells from uninfected/unexposed donors allows for



recognition of crude schistosomal antigens. Interestingly, we found that IL-4 stimulates human B cells to upregulate innate immune receptors not previously identified on these cells, namely Toll-like receptor 4 and NOD2, suggesting a potential novel mechanism by which IL-4 augments protective immunity. We aim to detail the specific antigens and receptors involved in IL-4 mediated human B cell recognition of parasitic antigens using our in vitro experimental model system.

Efforts to mitigate the impact of schistosomiasis in endemic regions have focused on chemotherapy of active infections with Praziquantel (PZQ), control of intermediate snail hosts and improved sanitation. Continued morbidity and transmission despite these interventions and the specter of schistosome resistance to PZQ underscore the importance of vaccine development for this parasite. We hope defining the mechanisms by which human B cells recognize and process schistosomal antigens will lead to better strategies for vaccination against these large, metazoan parasites.

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