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REVIEW

Current Understanding of Immunity Against Schistosomiasis: Impact on Vaccine and Drug Development

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Abstract: Schistosomiasis is a neglected tropical disease inflicting significant morbidity in humans worldwide. The disease is caused by infections with a parasitic trematode belonging to the genus *Schistosoma*. Over 250 million people are currently infected globally, with an estimated disability-adjusted life-years of 1.9 million attributed to the disease. Current understanding, based on several immunological studies using experimental and human models of schistosomiasis, reveals that complex immune mechanisms play off each other in the acquisition of immune resistance to infection/reinfection. Nevertheless, the precise characteristics of these responses, the specific antigens against which they are elicited, and how these responses are intricately regulated are still being investigated. What is apparent is that immunity to schistosome infections develops slowly and over a prolonged period of time, augmented by the death of adult worms occurring naturally or by praziquantel therapy. In this review, aspects of immunity to schistosomiasis, host–parasite interactions and their impact on schistosomiasis vaccine development are discussed.

Keywords: schistosomiasis, immunity, schistosomiasis vaccine development, resistance to reinfection

Introduction

Schistosomiasis is an ancient disease that has plagued humans since around 1500 BC.[1] It is a neglected tropical disease caused by infection with one of six geographically distinct parasitic blood flukes belonging to the genus *Schistosoma*.[2,3] The three most clinically important species are *Schistosoma mansoni* and *S. japonicum*, causing hepatointestinal schistosomiasis, and *S. haematobium*, causing urinary schistosomiasis. Geographically, transmission of *S. mansoni* is localized to Latin American countries, parts of Africa and the Arabian Peninsula, while *S. japonicum* is endemic in the People's Republic of China, the Philippines and Indonesia, and *S. haematobium* infections occur mainly in Africa and in certain loci in the Arabian Peninsula.[4–6] Although schistosomiasis is primarily endemic in tropical and subtropical regions of the world, active transmission has now been reported in locales previously known to be free of schistosomiasis.[7,8]

Globally, schistosomiasis currently impacts over one billion people, with over a quarter of those currently infected in 78 countries and more than 780 million people at risk of infection.[9,10] Despite the relatively low mortality rate associated with schistosomiasis, totaling 290,000 deaths annually, the disease causes

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significant morbidity in humans, particularly in sub-Saharan Africa, where most of the infections occur.[3] Clinically, the symptoms of schistosomiasis are chronic and stealthy, manifesting as fevers, anemia, hepatosplenomegaly, genital lesions and irreversible fibrotic tissue damage. The burden of schistosomiasis is estimated at 1.9 million disability-adjusted life-years (DALYs),[11] although the reported DALYs associated with the disease vary tremendously depending on the sources cited.[12]

The control of schistosomiasis has been nothing short of challenging to both policy makers and the research community. Despite the benefits of having achieved some success in morbidity reduction in certain regions through the implementation of concerted approaches that combine mass drug administration (MDA), intermediate snail host molluscicide, health education, and water sanitation and hygiene (WASH) programs, these approaches have not been hugely successful[13,14] owing to pertinent logistical challenges, including poor MDA coverage, unabated reinfection rates in hyperendemic areas, shortfall in drug delivery and adherence, and lack of appropriate infrastructure. While experts in the field agree that vaccination in conjunction with current control measures represents our best hope of achieving elimination, the blatant reality is that no such vaccine is currently available for human use.[2] A review covering key features of schistosome biology and the development of schistosomiasis vaccine was published in 2020.[2] This present review discusses what is currently known regarding immunity to schistosome infection and reinfection, and the implications for vaccine and drug development.

Immunology and Host–Parasite Interactions in Schistosome Infection

Because of the complexity of the schistosome developmental cycle, the immune systems of infected hosts have to contend with multiple life-cycle stages of the parasite, including invading cercariae, migrating schistosomula, adult worms and eggs deposited by adult female worms. Cumulatively, all these stages in the infected host express thousands of highly antigenic molecules capable of eliciting strong humoral and cellular immune responses.[15,16] While an increase in some of these antigen-specific responses is observable during the chronic phase of infection, others appear to be heavily downregulated.[15,17] With respect to the immunology of human schistosomiasis, three main areas have been the subject of research: immunodiagnostics, immunopathogenesis and resistance to schistosome infection. While the immunodiagnostic aspect focuses on characterizing which types of elicited immune responses are diagnostic of schistosome infection,[18] immunopathogenesis is focused primarily on host immune responses to antigens released by eggs trapped within the tissues of hosts.[3,5,19] One very important consideration in these areas of research is the continuous exposure to schistosome antigens over a prolonged period of time owing to the chronic nature and endemicity of schistosomiasis, resulting in fluidic maturation of the immune response to different levels of antigen exposure.

What We Have Learnt from Experimental Animal Studies

The establishment and the use of the experimental animal models of schistosomiasis have undoubtedly provided invaluable knowledge on the biology of schistosomes as well as insights into host–parasite interactions as they relate to immunity and the strategies employed to manipulate these responses.[15,20] In particular, the murine models of schistosome infection and disease have provided a significant framework for the design of human immunological studies.[20,21] Evidence from mouse studies has shown that both specific humoral and cell-mediated immune responses are essential for resistance against schistosome infection.[20,22] Specifically, efficacy studies using radiation-attenuated (RA) cercariae revealed that the protection observed in mice exposed to attenuated cercariae was primarily associated with interferon-γ (IFN-γ) production and antibody production after multiple rounds of vaccination.[20,22–25] In other studies, co-administration of interleukin-12 (IL-12) with RA vaccine resulted in almost sterile immunity linked to a high induction of IFN-γ,[26–28] while the induction of IL-10 seemed to diminish resistance to reinfection.[29] Furthermore, mice deficient in IL-10, IL12p40 and IL-13R α2 had progressive and accelerated lethal liver fibrosis following *S. mansoni* infection.[30] Studies using experimental semi-/non-permissive hosts, such as rats and rhesus macaques, have also shown that resistance to schistosome infections is almost entirely antibody dependent.[31,32]

Based on the success of RA cercariae vaccination, several candidate antigens were identified based on reactivity of cells and sera from immunized mice. The results from testing these candidate antigens were less promising

but provided the premise for two vaccine candidates: recombinant 28-kDa glutathione S-transferase of *Schistosoma haematobium* (rSh28GST)[33–35] and 14-kDa fatty acid-binding protein from *Schistosoma mansoni* (Sm14),[36–40] which have successfully completed phase III and phase IIa trials, respectively. The development of other candidate antigens has focused primarily on identifying key molecules that play crucial roles in parasite survival, such as membrane biogenesis/renewal, nutrient uptake and immune evasion strategies. Some of the vaccines from these categories have been shown to also have some therapeutic properties,[41] possibly by interfering with the adult worm evasion mechanisms and thereby making them susceptible to the host effector systems.[15]

During the chronic phase of schistosomiasis, granulomatous reactions form around the host trap eggs and their secreted egg antigens (SEAs), constituting the host defense against tissue attack/damage. The immunopathophysiology of schistosomiasis has been reviewed elsewhere.[5,42] Since the granulomas themselves could be detrimental because of progression to liver fibrosis, studies have shown that infected mice develop effective anti-SEA immune responses (granuloma formation).[42,43] Studies using gene knockout mice have also provided invaluable insights into the role of the host immune response to worm development and granuloma formation.[44–46] The acute stage of infection in mice is mostly associated with a Th1-type immune response which is dramatically shifted to a Th2-dependent response at the onset of oviposition. This immunological shift is thought to be caused by the interaction of certain carbohydrate epitopes from the egg antigens with the host dendritic cells.[47,48] Although the upregulation of a Th2 cytokine IL-13 seemed to promote and exacerbate liver fibrosis,[49] the complete abrogation of Th2 responses results in rapid fatality caused by uncontrolled severe tissue damage in IL-4-deficient mice infected with *S. mansoni*.[50–52] In another study, the interruption of IL-4Ra-mediated signaling led to severe disease and fatality.[53] While a Th1-type response is beneficial during the acute stages of schistosomiasis, an uncontrolled polarization toward the Th1 response, as shown in IL-10-/IL-4-deficient mice, is lethally harmful to the host.[54] In chronically infected patients, low levels of IL-5 and elevated levels of Th1-dependent cytokines are associated with severity of hepatosplenic schistosomiasis.[55] Studies in mice have also demonstrated that the Th17-type immune response, particularly IL-17 production, promotes liver damage.[56] IL-12p40$^{-/-}$ mice, deficient in IL-12 or IL-23 production, showed significantly lower pathology associated with considerably low secretion of IFN-γ and IL-17 by lymphoid cells stimulated with schistosome SEAs. In contrast, IL-12p35$^{-/-}$ mice producing IL-23 and not IL-12 developed severe granulomas linked to high levels of IL-17.[56] Follicular helper T cells and Th9 cells have also been implicated in promoting egg-induced hepatic granulomas and fibrosis.[57,58] Thus, Th2 immunity functions like a two-edged sword, on one hand protecting the host against excessive granulomatous inflammation, and on the other, causing host immune-dependent liver damage. A balance between Th1 and Th2 responses may therefore be necessary to prevent severe pathology.[59] A schematic summarizing some of the key components of the host immune response during schistosome infection is shown in Figure 1.

The murine models of schistosomiasis have definitely contributed immensely to our understanding of the immunology and immunopathology of schistosomiasis; however, these models are not without their limitations and flaws. One of the major limitations of the mouse model is the low level of recovered adult worms following experimental challenge with penetrating cercariae.[28] In addition, since infected mice do not live long enough after primary schistosome infection, they cannot be used in studies on immune correlates of reinfection resistance.

What We Have Learnt from Human Studies

Human epidemiological studies have provided useful information on host–schistosome interactions that complement the data from experimental animal studies. When studying the immunology of human schistosomiasis, it is pertinent to bear in mind that there are a number of unique facets to the host–parasite relationships involving the different life stages exposed to the host immune system. What is very clear is that there are overriding differences between the host immune response profiles against antigens derived from worms and those derived from eggs, regardless of the endemic population sampled.[60] While most studies report robust immune responses to egg antigens early on, which then taper off as infections proceed into the chronic stage, induced responses to soluble worm antigen preparations are sustained throughout the chronic stage of the disease.[61–63]

Because of the heterogeneity of human populations, the status of the individuals being studied is also crucial. For

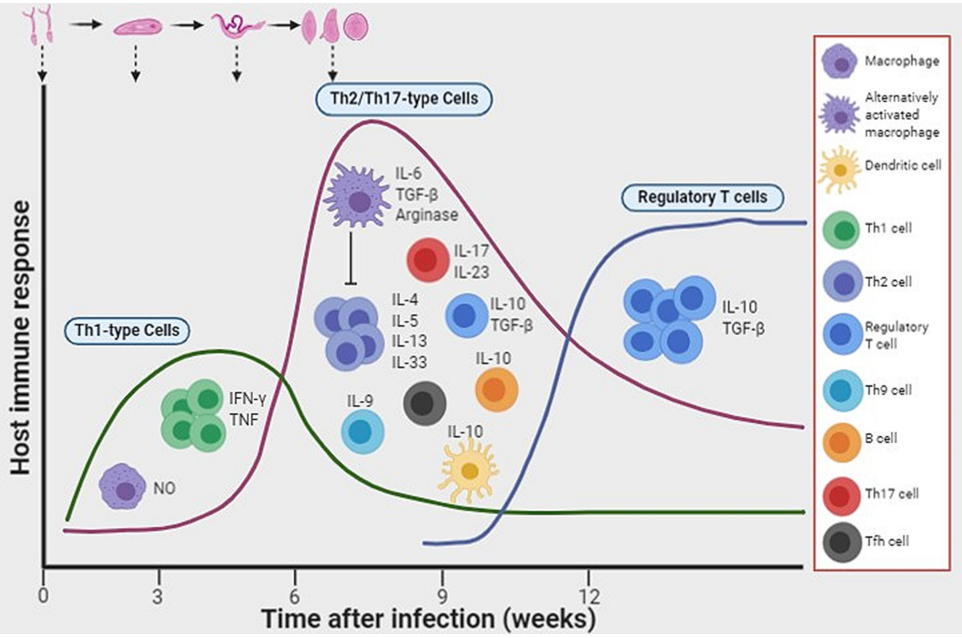

Figure 1 Induction of host immune responses after infection with schistosomes. Following infection with schistosomes, the early immune response that develops is a T helper 1 (Th1)-dependent cellular response. As the worms mature into adults and the females start to lay eggs, there is an increased production of interleukin-10 (IL-10) by dendritic cells, and a Th2 response ensues. In addition, B cells produce IL-10 in response to antigens derived from eggs and adult worms. Populations of regulatory T cells and alternatively activated macrophages also develop. Image created with BioRender (app.biorender.com)
Abbreviations: NO, nitric oxide; IFN-γ, interferon-γ; TNF, tumor necrosis factor; TGF-β, transforming growth factor-β; Tfh, follicular helper T cells.

instance, it is important to know whether the individuals are currently uninfected or infected, and for how long,[64,65] whether their mothers were infected during pregnancy[66] and whether they have been treated with praziquantel (PZQ).[67,68] All of the aforementioned factors, including many other scenarios, will determine a person's immune status at the time of study. Therefore, when interpreting these human population studies, one should always remember that the study of human immune responses to schistosomiasis is almost exclusively based on serum antibodies, cytokines and/or the responsiveness of peripheral blood mononuclear cells. It is possible that these sources may not be a true representation of what is happening within the immune microenvironment of a granuloma or around migrating schistosomula. Nonetheless, these are the specimens that are readily available, except in very rare circumstances when tissue becomes available through biopsy or autopsy. Regardless of these limitations, several aspects of the immunology of human schistosomiasis have been successfully characterized.

Immunity to Reinfection in Humans

The possibility of humans acquiring immune resistance to schistosome reinfection has long been a subject of discussion.[69] Clear evidence now indicates that protective immunity does develop in people living in endemic areas, however very slowly.[17,19,70] The hypothesis that the acquired schistosomiasis resistance observed in humans is linked to the stimulation of host protective immune responses to antigens released as a result of worm death is supported by many studies.[71–74] Regardless of the geographic setting, epidemiological and immune correlate data obtained from schistosome-endemic regions indicate an age-dependent acquisition of resistance to reinfection. Children under the age of eleven are generally more susceptible to infection and reinfection in endemic areas than their adult counterparts, partly as a result of their history of exposure and infection intensity.[3,75–77] Identifying immune "signatures" that correlate with protection is a key process in understanding resistance to schistosome infection and/or reinfection.

As already discussed, resistance to schistosomiasis in mice is associated primarily with Th1-type immune responses (see "What We Have Learnt from Experimental Animal Studies"). In contrast, in humans, Th2-type responses (although not exclusively) have been repeatedly associated with protection against reinfection. Multiple lines of evidence indicate that the production of parasite-specific IgE, eosinophils and cytokines such as IL-5 and IL-4 is required for resistance to reinfection,[78–84] and that soluble IgE receptors and/or those expressed on eosinophils and B cells are also associated with

resistance to reinfection.[85] IL-33, a member of the IL-1 family of cytokines, has been associated with Th2-dependent protective immune response against helminth infections.[86] A 2018 study showed an inverse correlation between plasma IL-33 levels and schistosome pathology in children living in an endemic area.[87] In contrast to the protective effects of higher schistosome-specific IgE production, induction of IgG_4 is linked to susceptibility to infection, potentially negating the protective effects of other antibody types, including IgE.[82,88] Following PZQ therapy, the level of parasite-specific IgG_4 in infected adults decreases while IgE maintains pretreatment levels or sometimes increases, whereas the ratio of IgE/IgG_4 levels in children following treatment seems to be lowered.[15] The production of IgG_4 in humans by IL-10-producing regulatory B cells[88] is consistent with the finding that IL-10 production in mice negates the development of resistance to reinfection.[29]

The general hypothesis is that the death of adult worms, either occurring naturally or following PZQ treatment, results in the release of parasite immunogens which cross-react with antigens from migrating larvae and consequently stimulate protective IgE responses. The implication is that the greater the exposure, the more rigorous the protective immune response generated.[17] This hypothesis provides a plausible explanation as to why children are more susceptible to infection and reinfection while adults who have had many cycles of exposure and worm death develop resistance, albeit over a long period of time.[5] Although IgE production appears to be critical to the development of resistance to schistosome reinfection in humans, developing and/or deploying a vaccine based on IgE is highly unlikely owing to documented health and safety issues relating to hypersensitivity reactions.[12,89,90] Therefore, care should be taken with regard to how we mine and utilize the immune correlate findings from chronically infected individuals, particularly those with acquired resistance following PZQ treatment. Although ongoing schistosomiasis control programs do not feature vaccines, it is of great importance that research in this area intensifies as genuine progress toward schistosomiasis elimination and possible eradication can only be achieved through vaccination.[2]

Human Challenge Model: A New Paradigm

A team of researchers led by Dr. Meta Roestenberg, from Leiden University Medical Center in the Netherlands, pioneered the first human challenge model of schistosomiasis. These scientists performed the first controlled human *S. mansoni* infection using male cercariae in order to assess infectivity and possible adverse events.[91] The results showed that all naïve volunteers recruited for the study showed IgM and IgG_1 seroconversion, as well as specific $CD4^+$ T cell-dependent cytokines.[91] Another clinical trial focusing on single-sex female controlled human *S. mansoni* infection is currently underway (https://clinicaltrials.gov/ct2/show/NCT04269915). In another study using human skin explants, Winkel et al showed that penetrating *S. mansoni* cercariae induce regulatory immune responses characterized by the production of IL-10 and pro-inflammatory IL-6.[92] There has also been a growing interest in the use of controlled human infection (CHI) models.[93–96] Implementation of the CHI schistosome model (CHI-S) in the context of testing vaccine candidates would undoubtedly provide valuable information on early protective efficacy as well as data on vaccine-mediated immune correlates of protection.

Schistosomiasis Vaccines: Target Profiles, Recent Advances and Challenges

Historically, vaccination has been the most effective approach for preventing diseases caused by infectious pathogens.[12,97] Of the hundreds of candidate antigens that have been identified and tested in various animal models of schistosomiasis, only three have made it into clinical trials to date. Phase II and III clinical trials in Africa have already been concluded for *S. haematobium* 28-kDa glutathione S-transferase (rSh28GST),[34,98] while *S. mansoni* 14-kDa fatty acid-binding protein (Sm14) is currently in phase IIb clinical trials,[36,99] and a phase Ib trial is underway for *S. mansoni* tetraspanin, a 9-kDa surface antigen (Sm-TSP-2).[100,101] Details on the immunogenicity, tolerability and/or efficacy of these candidates have been reviewed elsewhere.[2] Another candidate antigen, the large subunit of *S. mansoni* calpain (Sm-p80), has been approved for human clinical trials which are scheduled to begin in 2021.[102,103]

Despite the considerable research efforts that have been devoted to the development of a schistosomiasis vaccine, progress toward identifying more promising candidates or actualizing the deployment of a licensed vaccine has been very slow. Reasons for this slow progress include the complexity of the parasite life cycle, parasite immune evasion strategies and limited knowledge on immune correlates of protection, to mention but a few. In order to continue an upward trajectory with respect to schistosomiasis vaccine development, there are

still important questions that need to be addressed. For instance, what is (or should be) the ideal target profile of an effective schistosomiasis vaccine? In two separate meetings organized by the Bill and Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases, experts in the field came up with the ideal target profile (preferred product characteristics [PPC]) for a schistosomiasis vaccine. The general consensus from these meetings was that an ideal vaccine should reduce adult schistosome numbers and egg excretion by at least 75%.[12,104,105] The advent of technologies to measure schistosome circulating anodic antigens (CAAs)[106] and/or circulating cathodic antigens (CCAs)[107] in serum or urine samples from infected individuals has made it possible to quantify worm burden in humans instead of just relying on fecal egg output, thereby providing valuable data on vaccine efficacy. In addition, other questions regarding how the vaccine should be tested, dosage, choice of adjuvant and frequency of administration need to be tackled. Even at the point when a candidate antigen is ready for clinical trials, the design and execution of the trials pose their own challenges. The regulatory requirements and the substantial cost required to conduct clinical trials are also worth mentioning. In spite of these seemingly unsurmountable challenges facing schistosomiasis vaccine development, the long-term potential public health benefits of deploying an effective vaccine make the continued development efforts worthwhile.

Concluding Remarks

There is still a lot to understand about the complexity of the host–schistosome relationship. As far as this host–schistosome interplay is concerned, it is imperative to always bear in mind that there are multiple and complex responses at play whether resistance to infection and/or reinfection or the immunopathology of schistosomiasis is being discussed. Despite the advances in technologies and their associated benefits, it is also useful to recognize that more tools and new approaches are still needed if we are to expand our horizon and fully understand this complex interplay. The advent of the CHI-S model[91] and tools to manipulate parasites in controlled studies are now providing platforms for us to start generating more proof to complement correlation studies.

Finally, several key questions still need to be considered. What mechanism(s) are involved in schistosomula killing? What specific factors are employed by schistosomes to survive in their immunological hostile environment? Are the immune responses induced in a newborn from an infected mother protective or regulatory? In-depth correlative studies of various immune responses in addition to documented cases of chronically infected individuals and the development of resistance to reinfection in treated individuals will undoubtedly provide some useful answers.

Disclosure

The author reports no conflicts of interest for this work.

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