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IMMUNOBIOLOGY OF SCHISTOSOMIASIS

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ABSTRACT

Schistosomes are parasitic worms that are a prime example of a complex multicellular pathogen that flourishes in the human host despite the development of a pronounced immune response. Presently, the number of infected individuals with schistosomes is estimated to be 250 million, and even though only small proportions of them become sick and die, schistosomiasis remains a medical problem ofgreat significance. The high incidence of infection of man with *Schistosoma mansoni*, *Schistosoma japonicum* or *Schistosoma haematobium*, as well as the chronic debilitating diseases produced, places these organisms among the world's most important infectious agents. Understanding how the immune system deals with such pathogens is a daunting challenge. The past decade has seen the use of a wide range of new approaches to determine the nature and function of the immune response to schistosomes. Our search in the PubMed and Google Scholar databases led to the identification of 105 reviews of schistosomiasis published between 2007 and 2018, of which 32 were identified as reviews of immunobiology of schistosomiasis, leaving aside reviews that solely focused on schistosomiasis (n = 73). Qualitative content analysis was used to extract and synthesise descriptions of search, selection, quality appraisal, analysis, and synthesis methods. We further assessed quantitatively how often certain methods (e.g. search strategies, data analysis procedures) were used by the reviews.

KEYWORDS: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma haematobium.*

INTRODUCTION

Schistosomiasis, a systemic helminthes infection, is one of the most important socio-economic and poverty-related health problems that affect human development in developing countries. It is also the second most prevalent tropical disease after malaria.[1] Epidemiological studies continue to expose the damage caused by schistosomiasis throughout the developing world. The World Health Organization (WHO) estimates that, over 260 million individuals required treatment for schistosomiasis, and that an additional 800 million were at risk of infection, with over 90% of these individuals living in Africa where both *S. mansoni* and *S. haematobium* are endemic.[2] The estimated mortality owing to *Schistosoma haematobium* and *Schistosoma mansoni* in sub-Saharan Africa is 280,000 per year.[3] The immune response is intimately involved in the development of many of the pathological changes that accompany infection; infected individuals can have resistance to super infection; and schistosomes survive for years in the host despite a strong immune response. More recently, interest in these parasites has increased owing to demonstrations that schistosome maturation and fecundity are, in some way, dependent on the host immune response. Schistosomes, like other parasitic helminths, induce marked T HELPER 2 (TH2) responses, providing a model system for studying the development and function of this type of immune response.[3]

Biology of Schistosomes

Schistosomes are digenetic trematodes which undergo alternation of generations. Sexual reproduction takes place in the definitive host (man and other mammals) and an asexual reproduction in the intermediate host (snails). Eggs are passed from the body of the definitive

host in the excreta (urine or feces depending on the species of schistosome). These eggs hatch in fresh water, producing free-living ciliated embryos called miracidia. The miracidia must seek, find, and penetrate a specific species of snail within a few hours in order to survive. After one month, the miracidia develop into mother sporocysts, then multiple daughter sporocysts and finally cercariae. If the snail survives the infection, the cercariae are released gradually over duration of several months. The cercariae, free-swimming larvae, can penetrate the unbroken skin of the definitive host within minutes. During penetration, the cercariae lose their external layer and are then called schistosomula. Schistosomula migrate through the tissue into the lymph, blood vessels, and the lungs where they remain for several days. They then migrate to the liver where they mature into adult male and female schistosomes. The adult worms mate and, depending on the species, pass into the mesenteric or the vesical venules. The fertilized female worm produces 300-3,000 eggs per day. Half of these are excreted from the body, while those remaining may be trapped in the tissue.[4]

Schistosomes Evasion of the Host Immune Response

It is a necessary characteristic of all successful parasitic infections that they can evade the full effects of their host's immune responses; parasites have developed many different ways of doing this. Some even exploit cells and molecules of the immune system to their own advantage:

1. Molecular mimicry: sharing of antigens between parasite and host, the pathogen's surface antigens closely resemble host antigens and are therefore not recognized as being foreign.
2. Antigen Masquerade/Disguise: Schistosomes, acquire a surface layer of host molecules, so that the host does not distinguish them from 'self'. Schistosomules cultured in medium containing human serum and red blood cells can acquire surface molecules containing A, B and H blood-group determinants. They can also acquire MHC molecules.
3. Immunosuppression: This is a universal feature of parasite infection and has been demonstrated for both antibody- and cell-mediated responses. Schistosomes
   1. Release several proteases that cleave antibody molecules
   2. Release products that prevent macrophage activation
   3. Release inhibitory factors (Such as Phosphorylcholine (PC) containing molecules) that suppress T-cell activity
4. Resistance membrane: the tegument of schistosomes thickens during maturation to protect them from toxic onslaught. schistosomes have surface-associated glutathione S-transferases which makes them to resist the oxidative burst.
5. Other mechanisms include: Antigen masquerade, antigen shedding/modulation, epitope inaccessibility, effector cell blockade, Schistosome derived anti-inflammatory molecules and immunological misinformation.[4]

Development of the Immune Response in Infection

In the course of an infection, the immune response progresses through at least three phases. In the first 3–5 weeks, during which the host is exposed to migrating immature parasites, the dominant response is T helper 1 (TH1)-like. As the parasites mature, mate and begin to produce eggs at weeks 5–6, the response alters markedly; the TH1 component decreases and this is associated with the emergence of a strong TH2 response. This response is induced primarily by egg antigens. During the chronic phase of infection (infections are long lived and worms continue to produce eggs — ~300 per day in the case of each *Schistosoma mansoni* female), the TH2 response is modulated and granulomas that form around newly deposited eggs are smaller than at earlier times during infection. From work in the mouse, there now seems to be a correlation between the inability to form granulomas, or the development and persistence of a highly pro-inflammatory TH1-like response beyond the acute phase, and the development of hepatotoxic liver disease.[5] By contrast, TH2-cell-mediated granulomas seem to protect hepatocytes, but allow the development of fibrosis.[6] Although it is clear that severe fibrosis occurs in human schistosomiasis, there is debate over the existence of the hepatotoxic form of disease. TH2 responses are also strongly implicated in naturally acquired resistance to re-infection with schistosomes.[6]

Immune-related pathologies during Schistosomiasis

Schistosomiasis causes a range of morbidities, the development of which seems to be influenced to a large extent by the nature of the induced immune response and its effects on granuloma formation and associated pathologies in target organs.[7] Two main clinical conditions are recognized in Schistosomes-infected individuals — acute schistosomiasis and chronic schistosomiasis.

Acute schistosomiasis: Acute schistosomiasis in humans is a debilitating febrile illness (Katayama fever) that can occur before the appearance of eggs in the stool and which is thought generally to peak between 6 and 8 weeks after infection. During acute illness, which is less well studied than chronic disease, there is a measurable level of tumour-necrosis factor (TNF) in the plasma, and peripheral-blood mononuclear cells (PBMCs) produce large quantities of TNF, interleukin-1 (IL-1) and IL-6.[8] Notably, cytokine production by PBMCs after stimulation with parasite antigen reflects a dominant T HELPER 1 (TH1), rather than TH2, response5. Presumably, in the natural progression of the disease, the developing egg-antigen induced TH2 response down regulates the production and effector functions of these pro-inflammatory mediators; the production of IL-10 during this period might have a crucial role in this process.[9]

An examination of disease in mice has shown that an inability to develop a TH2 response to regulate the initial pro-inflammatory response that is associated with acute

schistosomiasis is lethal. This first became apparent when C57BL/6 Il4−/−mice were infected with *S. mansoni*. Coincident with the onset of parasite egg production in these animals, a condition that was similar to severe acute schistosomiasis in humans developed, which was characterized by cachexia and significant mortality.[10] These mice developed relatively normal hepatic granulomas (although they lacked an eosinophil component), but pathological changes in the intestine were more evident in the absence of IL-4. Analyses of the immune responses of infected Il4–/– mice showed that there was a correlation between elevated levels of nitric oxide (NO) and disease severity.[11] Treatment with uric acid, which is a peroxyradical scavenger, had marked ameliorative effects[12] which indicates that a combination of reactive oxygen and nitrogen intermediates might have a role in acute disease.

Chronic schistosomiasis: Chronic disease is graded according to severity. The most serious form is a life-threatening hepatosplenic disease, which is usually accompanied by severe hepatic and periportal fibrosis, portal hypertension and portosystemic shunting of venous blood.[7] Fibrosis itself is ranked on the basis of ultrasound patterns that provide a quantitative tool for assessing the severity of disease.[10] Although TH2 responses seem to have a crucial role in modulating potentially life-threatening disease during the initial stages of schistosomiasis, prolonged TH2 responses contribute to the development of hepatic fibrosis and chronic morbidity.[6] The main TH2 cytokine that is responsible for fibrosis is IL-13. So, schistosome infected mice in which IL-13 is either absent (Il13−/−), ineffective (IL-4 receptor α-chain-knockouts; Il4rα−/−) or neutralized by treatment with soluble IL-13Rα–Fc fail to develop the severe hepatic fibrosis that normally occurs during infection, which leads to prolonged survival of these mice.[10] The mechanism by which IL-13 is able to promote fibrogenesis has been elucidated in a series of recent studies.[13,14,15] These findings might have implications beyond schistosomiasis for the possible use of IL-13-blocking therapies in other fibrotic diseases.

It is not clear yet whether IL-13 is important for hepatic fibrosis in human schistosomiasis. Most humans who are infected with schistosomes develop TH2 responses.[16] but, as expected in an out bred population, the intensity of the response differs between individuals. On the basis of the amount of IFN-γ or IL-5 (or other TH2 cytokines) that is produced by PBMCs in response to antigen, some individuals do seem to have a more TH1-like response. In one of the few studies that have attempted systematically to correlate the immune response with disease severity, patients with hepatosplenomegaly owing to *S. mansoni* infection were found to have a TH1-like response and high plasma levels of TNF receptor I (TNFRI) and TNFRII, whereas individuals who had less severe disease but similarly intense infections (as assessed by counting the number of eggs in faecal samples) had TH2 responses and low plasma levels of soluble TNFR.[17]

How do schistosomes induce TH2 responses?

It has been recognized for some time that it is the egg stage of the schistosome that is responsible for inducing the TH2 response during infection. By contrast, the worms themselves seem to be poor inducers of a TH2 response. As for certain other helminth products, schistosome eggs or soluble antigens that are derived from the eggs induce an intense TH2 response without the need for additional adjuvant.[18] Recent work has shown that carbohydrates on egg antigens are integral to this process and, specifically, that a polylactosamine sugar (lacto-N-fucopentaose III) acts as a TH2 adjuvant. The emerging role of carbohydrates as factors that are important for the induction of the immune response during schistosomiasis opens up the possibility that innate pattern-recognition receptors that identify carbohydrates might have a crucial role in the induction of a TH2 response. The recent identification of a wide range of C-type lectin receptors that are expressed on the surface of dendritic cells (DCs) indicates various candidates that could be involved in the innate recognition of antigens from pathogens that initiate a TH2 response.[19]

Schistosomiasis: Effects on Concurrent Disease

Most people who live in areas that are endemic for schistosomiasis are also exposed to many other infectious diseases. Given the counter-regulatory effects that are exerted by TH1 and TH2 cells on each other's development, there is growing interest in whether existing infection with schistosomes (or any other chronic infection that is associated with a strongly polarized TH response) influences an individual's immune response against, and therefore their susceptibility to, disparate pathogens. In addition, the realization that morbidity during schistosomiasis is dependent on the TH2–TH1 balance of the immune response raises interesting questions about the potential for co-infection to affect the outcome of pathological changes that are associated with schistosome infection.[2,19]

In clinical settings, co-infection of hepatitis B or C virus (HBV or HCV) with schistosomes is common The confluence of these viral and helminth infections in the liver, together with the opposite requirements for TH1-like anti-viral immunity and the observed dominant TH2 response during schistosomiasis, offers a possible explanation for the increased occurrence of chronic hepatitis-virus infection in schistosomiasis patients. Indeed, there is evidence that schistosomiasis prevents the development of TH1 responses to HCV.[20] and some evidence that HBV and HCV infections are a factor in the development of hepatosplenic schistosomiasis. However, schistosome infection of HBV transgenic mice actually suppressed viral replication in an IFN-γ-

dependent manner soon after the onset of egg production.[21]

In experimental settings, mice that have schistosomiasis are less able to mount specific anti-viral CD8+ and TH1 immune responses (and, consequently, are less able to clear virus) have greater susceptibility to malaria and are extremely susceptible to infection with *Toxoplasma gondii*, a parasite that induces marked TH1 responses and that is lethal in mice that have defects in IFN-γ production.[22]

Whether schistosomiasis affects susceptibility to HIV-1 or whether these infections interact in any way is an area of much interest at present. In vitro, TH2 cells have, in some cases, been found to support HIV replication more strongly than TH1 cells,[23] which led to the hypothesis that helminth infections contribute to the high prevalence of AIDS and HIV infection in Africa.[24] Consistent with the in vitro findings, recent studies have shown that, compared with T cells in the peripheral blood of *S. mansoni*-infected individuals, those in schistosome and HIV co-infected individuals responded to egg antigen by making less IL-4 and IL-10, but similar (low) amounts of IFN-γ, which indicates that there is a swing in the overall balance of the response from TH2 to TH1.[24]

In direct contrast to the situations that are discussed above, ongoing TH2 responses in chronic schistosomiasis might be beneficial during co-infection with other pathogens (for example, the intestinal nematode *Trichuris muris* against which TH2 responses are host protective, and in preventing the onset of TH1-mediated autoimmunity (for example, diabetes mellitus in genetically predisposed non-obese diabetic mice) and mitigating against allergy.[25]

Susceptibility Factors for Infection

In areas where schistosomiasis is endemic, there is an obvious pattern of age-dependent intensity of infection; individuals who are below the age of puberty carry the most parasites, and those in older age brackets are generally less heavily infected. Drug treatment of affected populations followed by careful assessment of re-infection status has shown that children usually become heavily re-infected, whereas older individuals might become re-infected, but remain less heavily infected than they were before treatment. So, in endemic areas, older individuals are resistant to re-infection. A comparison of immune responses between those individuals who are susceptible and those who are resistant to re-infection has shown that there is a correlation between immunoglobulin-E responses to worm (not egg) antigens and immunity, which implicates IgE in the protective effector mechanism.[26]

Mice that are infected with *S. mansoni* are unable to clear the primary infection, but nevertheless are partially resistant to super infection. However, the use of mice for studies of resistance to re-infection has been questioned on two points. First, resistance in mice might, in large part, be due to the development of portosystemic vascular shunts. In these animals, immature parasites of a secondary infection might find it difficult to localize to the portal vasculature and, instead, will be carried by the blood flow, through varies, to non-permissive areas of the vasculature. This resistance is, therefore, more anatomical than immunological, and it is related to pathological changes that are more prevalent in infected mice than in infected humans. Second, the cellular distribution of the high-affinity receptor for IgE (FcεR1) on mouse cells differs from that on human cells.[27] As IgE dependent eosinophil-mediated ADCC is a possible effector mechanism of protective immunity in humans, the lack of FcεR1 on mouse eosinophils is of particular concern when attempting to model human immunity using the mouse.[27]

Immunodiagnostics

The accepted diagnostic standard of schistosomiasis is evidence of viable eggs in urine (*S. haematobium)*, faeces (*S. japonicum*, *S. mansoni*) or tissue biopsies. These microscope-based assays are relatively insensitive, especially in situations involving low level infections. Molecular techniques for schistosome DNA detection in faecal, urine or blood specimens increase sensitivity, but are expensive and still suffer somewhat from sampling limitations.[28] Serologic assays have proven useful clinically for diagnosis by the detection of antibodies against schistosomal antigens. This approach, with an extremely wide variety of reported immunodiagnostic assays, is particularly useful for symptomatic travellers or for serosurveys. However, for people in areas endemic for schistosomiasis, current serologic tests cannot discriminate between active infection and past exposure, although some isotypic assays can generally group active or inactive infections.[29] Circulating schistosomal antigen detection by monoclonal antibodies has been reported for decades and has the advantage of detecting active infections in a semi-quantitative manner. There is now a point of-contact circulating cathodic antigen (POC-CCA) assay commercially available for mapping of *S. mansoni* infections.[29]

This lateral flow cassette assay is performed on urine (Rapid Medical Diagnostics, Pretoria, RSA) and appears more sensitive than the Kato-Katz assay for mapping of *S. mansoni*-endemic areas, allowing on-site mapping of *S. mansoni* without stool collections. This will provide an important tool for introduction of control programmes into new areas. However, more sensitive and specific immunodiagnostic tools will be needed for field studies, vaccine and drug testing, elimination programmes, and in actual clinical diagnostics. Again, these efforts may be assisted by proteomic and metabolomic studies that may identify specific antigens or biomarkers for sensitive infection detection. Recent development of PCR diagnostic techniques are a welcome addition, but these assays still suffer from a sampling limitations of urine or stool, whereas a more useful diagnostic would utilize

serum or dried blood spots that could be multiplexed for assays for other infections. It also bears remembering that none of the literature or assays available provides an actual number of worms with which someone is infected.[30]

Control

The aims and strategies of schistosomiasis control have shifted fundamentally over the past few decades, since the introduction of modern schistosomicides, particularly praziquantel. Snail control with molluscicides, toxic chemicals, is expensive and logistically complex. Substantial human and material resources are needed for efficient application, as well as detailed epidemiological and malacological surveillance. Snail populations can be greatly reduced but rarely eliminated, so regular and long-term retreatment is necessary. The toxicity of molluscicides for other aquatic organisms, including fish, gives rise to ecological and economic concerns Snail control can also be pursued by physical measures or biological competitors, but such methods are not easy to put into practice.[28]

Schistosomiasis can in principle be eliminated by behavioural changes, sanitation, and safe water supply. Educational programmes can improve knowledge about the disease and healthcare seeking, but behaviour can be difficult to change without other options for water contact.[29] The provision of safe water supplies and latrines is obviously useful, but for the prevention of schistosomiasis, safe contact sites are also needed. In the case of *S japonicum*, transmission control necessitates interventions on the large and diverse animal reservoir.[31]

On the recommendation of WHO, population-based treatment with praziquantel is now the main component of most national control programmes. The fundamental aim is to reduce morbidity by keeping down intensity of infection. Various strategies can be applied, including indiscriminate mass treatment, active case finding, and treatment of particular risk groups such as school-aged children. 20 years of experience have shown that population-based treatment is feasible, safe, and effective[32]. In the absence of ecological or behavioral changes, however, it has little durable effect on transmission; regular retreatment is therefore needed for an unknown period. Sustainability is therefore a key requirement for chemotherapy-based control.[32]

CONCLUSION

Schistosomes are remarkable metazoan parasites that have co-evolved in concert with their mammalian hosts such that they are dependent on certain immune system components for their own biology. The immune system is largely incapable of resisting primary infection, and resistance to super infection takes years to develop. So, the survival of the host seems to depend on the ability to make an appropriately balanced TH response that is able to orchestrate granuloma development, prevent debilitating acute disease, and minimize fibrosis and severe morbidity during chronic infection.

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