Review Article

Immunology of human schistosomiasis

D. G. COLLEY¹ & W. E. SECOR²

¹Department of Microbiology, Center for Tropical and Emerging Global Disease, The University of Georgia, Athens, GA, USA, ²Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

SUMMARY

There is a wealth of immunologic studies that have been carried out in experimental and human schistosomiasis that can be classified into three main areas: immunopathogenesis, resistance to reinfection and diagnostics. It is clear that the bulk of, if not all, morbidity due to human schistosomiasis results from immune-response-based inflammation against eggs lodged in the body, either as regulated chronic inflammation or resulting in fibrotic lesions. However, the exact nature of these responses, the antigens to which they are mounted and the mechanisms of the critical regulatory responses are still being sorted out. It is also becoming apparent that protective immunity against schistosomula as they develop into adult worms develops slowly and is hastened by the dying of adult worms, either naturally or when they are killed by praziquantel. However, as with anti-egg responses, the responsible immune mechanisms and inducing antigens are not clearly established, nor are any potential regulatory responses known. Finally, a wide variety of immune markers, both cellular and humoral, can be used to demonstrate exposure to schistosomes, and immunologic measurement of schistosome antigens can be used to detect, and thus diagnose, active infections. All three areas contribute to the public health response to human schistosome infections.

Keywords: diagnosis, immune response, immunoregulation, pathology, resistance to reinfection, schistosomiasis

INTRODUCTION TO SCHISTOSOMIASIS

Schistosomiasis, or bilharzia, is a disease caused by trematodes of the genus Schistosoma (1) that afflicts at least 243 million people (2, 3). Adult male and female worms mate and produce fertilized eggs in veins of their human hosts, where they live for an average of between 3–10 years, with longevity records extending for several decades (4, 5). The eggs are excreted into the environment either in faeces or urine or are retained within the host where they induce inflammation and then die. Eggs that reach fresh water hatch and release free-living ciliated miracidia, which, if they infect a suitable snail host then reproduce asexually through mother and daughter sporocysts, producing thousands of cercariae which are released into the water and are infectious for humans. Cercariae penetrate through the skin and over 5–7 weeks migrate and mature to egg-producing adult male or female worms. Mature eggs, whether excreted or retained in the body, only live for 1–2 weeks. People can be infected by three main species of schistosomes: Schistosoma haematobium, S. mansoni and S. japonicum. Each species has a restricted range of appropriate snail hosts, so their transmission distribution is defined by their host snails habitat range. Adult worms live within either the perivesicular (S. haematobium) or mesenteric (S. mansoni, S. japonicum) venules. Schistosomes cannot excrete waste products, but rather regurgitate them into the blood stream. Some of the vomitus products are antigenic and are the basis of diagnostic assays (see below).

In areas endemic for schistosomiasis, in the absence of intervention, it is primarily a chronic disease lasting decades. This results from people being repeatedly exposed to cercariae and the longevity of adult worms. In these areas, a childs first infection often occurs by age two or three with the burden of infection increasing during the next 10 years as new worms successfully colonize the childs blood vessels (6, 7). Typical age prevalence and age intensity curves from all endemic areas show the highest
In contrast, experimental frame immunologic studies in people with schistosomiasis. the characteristics of human infection and has helped –

These responses continue to increase during chronic infection, and others are strongly down-regulated (14). Three main topics emerge when looking at human immune responses during schistosomiasis. (i) The most straight forward concerns immunodiagnostics, that is, what immune responses are mounted that can be used to determine whether someone has been exposed to schistosomes or if they have schistosomiasis? Many hundreds of immunodiagnostic assays have been reported and some of the more recent findings will be discussed below. (ii) Another area of immunology in schistosomiasis is that of resistance to (re)infection and responses against extant schistosomes. (iii) The third main aspect concerns immunopathogenesis and its immunoregulation. This area focuses on responses to eggs that are either exiting the body via the excreta or are trapped in bodily tissues such as the liver or bladder/urogenital wall. It is important to understand that because of the endemic and chronic nature of schistosomiasis, all three of these areas of immunologic research involve either repeated or continuous exposure to schistosome antigens over many years, thus implying ongoing changes due to antigenic exposures and the maturation of the immune responses to different levels of exposure to different antigens.

BACKGROUND BASED ON EXPERIMENTAL STUDIES

Much of our understanding of the human immune responses to schistosomes has been facilitated by the availability of murine experimental infection models. In particular, infection of mice with S. mansoni exhibits many of the characteristics of human infection and has helped frame immunologic studies in people with schistosomiasis. In contrast, experimental S. haematobium infections have been less instructive as adult worms do not migrate to the venous plexus and deposit eggs in the bladders of mice. However, the recent development of an S. haematobium egg injection model (18) has begun to yield insights into the pathogenesis of this infection (19). S. japonicum readily infects mice, but the challenges of working with the Oncomelania intermediate host have historically resulted in relatively fewer laboratories studying this species in experimental models than those working with S. mansoni.

Initially, the host must contend with penetrating cercariae in the skin and the subsequent larval stage, the schistosomula, as they migrate through the lungs, ending up in the mesenteric or perivesicular veins as adults. This migratory path and responses against migrating larvae and immature worms have been studied extensively in mice with the conclusion that most effective responses against incoming parasites occur in the lungs (20). Nothing is known about parasite migrations in humans, but they are assumed to be similar and they end up with the same result, adult worm pairs in specified locations. Adult worms, residing in those preferred venous environments, appear to be impervious to immune attack. Multiple mechanisms are likely to be responsible for their long-term survival in what amounts to a hostile (but impotent) immune environment. Some of these may be due, in part, in the schistosomes ability to continually regenerate its outer tegument through unique somatic stem cells (21), and perhaps their ability to masquerade through molecular mimicry (22) or by acquiring host antigens (23, 24). Some aspects of their survival may also involve manipulations of and by the hosts immune responses, such as isotypic shifts in antibody specificities (25, 26) and immunoregulation. Effective chemotherapeutic treatment of schistosomiasis does, however, depend on having established immune mechanisms that can kill the worms if they have undergone sufficient surface damage due to praziquantel (PZQ), the primary drug used to treat schistosomiasis (27–29).

Mouse models have been used extensively to investigate the protective immune response to schistosome infections, primarily with S. mansoni as the infecting species. Both antibodies and T cells are needed for maximal protection (30). The highest levels of protection are afforded by exposure to attenuated cercariae that die before maturity. A single exposure to attenuated cercariae induces partial protection, primarily associated with production of IFN-γ, while antibody responses become important in the protection of animals multiply exposed attenuated parasites (31). Attenuated cercarial vaccination is effective against invading larval parasites, but their susceptibility to immune attack wanes as worms mature and become adults. Whether the mechanism is a cytotoxic attack or simply...
death by delayed migration through the lungs has been questioned. Treatment of infected mice with praziquantel confers similar levels of resistance to reinfection if animals are also treated with anti-IL-10 receptor antibodies during treatment, suggesting that IL-10 ameliorates development of protective mechanisms (32).

Success with vaccination using attenuated cercariae in experimental animals led to attempts to identify individual vaccine antigen candidates based on reactivity of cells or sera from vaccinated mice. Both recombinant-protein- and DNA-based vaccines generate responses that can be enhanced by co-administration with cytokines or adjuvants that promote a Th1-type immune profile. Unfortunately, these vaccines have been less effective and less reproducible than immunization using attenuated cercariae. Nevertheless, this work provided the basis for the two schistosomiasis vaccine candidates currently being tested in humans (33, 34). Second generation vaccine candidates have focused more on generating immune responses to molecules that play a functional role in parasite homeostasis, such as membrane turnover, nutrient uptake or neutralization of reactive oxygen species (35–38). Vaccines in the latter category may even have therapeutic activity by disrupting adult worm immune evasion mechanisms and rendering them susceptible to host effector mechanisms.

The eggs produced by adult worms in their venous locations are intended (from the worms perspective) to be carried out of the body either by faeces or urine and released into the environment. However, the venous blood flow carries many of the eggs in the opposite direction or prevents their easy escape. The eggs contain a wide variety of proteases and other potentially toxic moieties, which once they are lodged in the tissues, can lead to necrosis (39, 40). The hosts defence against this tissue insult comes in the form of granuloma formation, to wall off and contain the egg and the proteolytic products it releases. The granulomas themselves can be detrimental lesions, and to prevent them from overwhelming the tissue sites or blocking venous blood flow, immunomodulation of the anti-egg antigen responses (granuloma formation) develops effectively in mice (41) and most people upon the establishment of chronic infections (42–44).

Key roles for the immune response in worm maturation and granuloma formation have been demonstrated through experimental S. mansoni infections of T-cell-deficient mice (40, 45). During the initial stages of infection, mice display a balanced or Th1-type immune response to parasite antigens. However, once egg deposition begins around 6 weeks of infection, a dramatic shift to a Th2-type response ensues. Specific schistosome egg antigens interacting with dendritic cells are responsible for this immunologic shift, partially through the action of certain carbohydrate epitopes (46). Unregulated production of the Th2 cytokine IL-13 eventually leads to widespread liver fibrosis, the functional cause of hepatosplenic disease in humans (47, 48). However, depletion of Th2 responses, particularly IL-4, results in tissue damage and host mortality due to pro-inflammatory Th1-type responses (49, 50). Thus, Th2 responses also perform a host protective function, and appropriate regulation minimizes overall host pathology. Alternatively activated macrophages and IL-10 are part of the regulatory feedback of Th2-type responses that limit the initial granulomatous inflammation that peaks in size and intensity at 8 weeks of S. mansoni infection (51, 52). As the infection continues, these and other immunomodulatory mechanisms further regulate granuloma formation such that newly deposited eggs at 12 or more weeks of infection induce smaller granulomas and less fibrosis than during the acute stage (53, 54). Failure to modulate the granulomatous response results in a hypersplenomegaly syndrome that shares many pathologic and immunologic characteristics with human hepatosplenic disease, greater fibrosis and shunting of worms and eggs to the lungs (55, 56). Mechanisms of immunomodulation include IL-10, T regulatory cells, B cells, antibodies, anti-idiotypic responses and T cell anergy (57, 58).

Egg excretion from mice is also dependent on the immune response, with T-cell-deficient mice demonstrating fewer faecal eggs (59). Recently, a predilection for schistosome egg deposition in Peyers Patches, which stimulated vascular remodelling and egg excretion, has been demonstrated (60).

HUMAN IMMUNE RESPONSES DURING SCHISTOSOMIASIS

When studying or reading about human immune responses during schistosomiasis, it is critical to consider the multiple facets of the host–parasite interface described above that involve different parasite life cycle stages. These are important distinctions for the immunologist, because they are important discriminations made by the hosts immune responses. Regardless of the endemic area in which studies are carried out, there is an overriding differential pattern of immune responses against worm-derived antigens vs. egg-derived antigens (61). In most studies, this is seen as early high-level responses to soluble egg antigens (SEA) that then decrease as infections become chronic (42–44, 62–64). Responses to soluble worm antigenic preparations (SWAP), in contrast, invariably rise during early infection and continue to be expressed throughout continuing chronic infections. This has long been true using these crude antigenic mixtures and is being shown now to be

© 2013 The Authors. Parasite Immunology published by John Wiley & Sons Ltd., Parasite Immunology, 36, 347–357 349
true for individual antigenic moieties expressed by different life cycle stages (65). It is also important to distinguish the status of people being studied beyond just whether or not they are currently harbouring schistosomes by considering how long they have been infected (66), whether their mother was infected while they were in utero (67, 68), and whether and how often they may have been treated for their schistosomiasis with PZQ (69–72). All of these situations and probably many others contribute to their immune status at the time they are being studied.

In addition, it should always be remembered that the study of human immune responses in schistosomiasis is almost exclusively based on the preformed circulating antibodies or cytokines or the responsiveness of lymphoid cells in the peripheral blood. These sources may or may not be representative of what is occurring in the micro-immunoenvironment of either the granulomatous lesion or against incoming schistosomula. Nevertheless, these are the specimens available to investigators, except in rare instances when spleens or other tissues can be obtained either at surgery or autopsy. Regardless of these stipulations, multiple investigators have successfully defined many aspects of the human humoral and cellular immune responses to schistosome antigens in relation to pathology, resistance to reinfection and diagnostics.

IMMUNOLOGY OF MORBIDITY AND REGULATION OF MORBIDITY IN HUMANS

As in experimental animal models, morbidity during human schistosomiasis results from chronic immune stimulation by schistosome eggs that are trapped in tissues and subsequent granula formation and fibrosis (73, 74). The vast majority of the burden of disease due to S. mansoni and S. japonicum, and possibly S. haematobium, appears to be caused by chronic inflammation, resulting in subtle morbidities such as anaemia, growth deficiencies, physical fatigue and diminished cognitive development (75–79). The inciting insults of this chronic inflammation are soluble egg antigens released from tissue-trapped eggs (80). While normal liver enzyme patterns are generally maintained during chronic schistosomiasis unless severe pathology develops (81), indicators such as increased levels of hepatic imply that inflammatory processes are at the heart of subtle morbidity due to these granulomatous lesions (76, 82, 83). In S. haematobium infections, the anaemia of chronic inflammation is aggravated by the blood loss seen as gross and micro-haematuria. Along with these examples of direct morbidity, schistosome infections can have indirect effects such as predisposing infected hosts to greater susceptibility to other pathogens. For example, the friable sandy patches

seen in female genital schistosomiasis caused by S. haematobium infections are associated with an increased risk of HIV acquisition (84, 85).

The immune process of granuloma formation, left unimpeded, would soon occupy vast amounts of tissue space, eventually shutting down return blood flow back to the heart through the portal system, creating portal hypertension, pulmonary hypertension and ultimately oesophageal varices, resulting in death. Prior to regular treatment with praziquantel of children and adults in high-risk occupations, this picture was seen in proportions of those infected with either S. mansoni or S. japonicum varying from 2 to 25% (86). The fact that it did not occur more frequently is in part attributable to immunomodulation of responses to SEA, as reflected in reduced lymphocyte proliferation in patients that do not develop hepatosplenomegaly (44). This phenomenon has been examined in human schistosomiasis by multiple groups, resulting in the consensus hypothesis that continuous exposure to SEA leads to the induction of regulatory mechanisms that dampen down granuloma formation, anti-IgE antibody production, and SEA-induced lymphocyte proliferation and cytokine production (44, 62, 87–89). A number of immunoregulatory mechanisms have been identified through investigations using cells and antibodies from chronically infected intestinal patients with subtle morbidity. These include adherent, macrophage-like cells (90); immune complexes (91); IL-10 (92); TGF-β (93); T regulatory cells (16, 71); and idiotypic interactions (94). It is impossible to ascribe an attributable fraction to each of these mechanisms, because they are demonstrated in vitro and with only correlations to states of morbidity. However, taken in the aggregate, and in the face of repeated findings by multiple groups in multiple endemic areas, down-regulation of SEA responses is occurring during chronic schistosomiasis and contributes to the establishment and ability to maintain chronic infections over decades without the development of hepatosplenomegaly by most infected individuals (44, 86). In addition, immunogenetics contributes to the ability of some people to better regulate (or not) their immune responses to schistosome infections (95, 96).

The concept that active schistosomiasis during pregnancy might impart an altered immune status on the offspring has been studied over a long span of time (58, 97, 98). There is evidence that this form of immune manipulation in utero actually occurs in humans because newborns of mothers with schistosomiasis already express IgM or and IgE antischistosome antibodies and have increased percentages of mature, CD5- B cells in their cord blood (68, 99). Also, it has long been known that their cord blood mononuclear cells proliferate strongly in response to SEA (but not Trypanosoma cruzi antigens,
unless the mother also has Chagas disease) and idiotypes on anti-SEA antibodies (67). In regard to the specificity of these responses, the cord blood mononuclear cells of babies born to mothers who have Chagas disease respond to T. cruzi antigens, but not to SEA (67). While this antigen and idiotypic sensitization occurs in utero, as do other influences on B cells (99), the impact of such perinatal influence is not known. It is hypothesized that it may result in an early immunoregulation against SEA, allowing the majority of children in an endemic area to establish regulated, chronic infections (58, 100). Other perinatal influences are noted in the article by Dr Alison Elliott in this issue.

It should be remembered that each of these interesting findings needs to be substantiated in various patient populations, and eventually mechanistic studies should be pursued to establish how the various phenomena fit together to provide the appropriately regulated responses that allow both host and parasite to survive. It is essential that individual findings be validated or compared based on different patient populations, exposure patterns, stage of infection, durations of infection and the like. It is hoped that reviewers and editors understand this necessity of having confirmatory evidence of any given finding or mechanism in such a complex relationship. The publishing of the first finding of high proportions of Treg in patients with schistosomiasis mansoni serves as an example (71). While interesting, it is critical that such findings be repeated both in the same populations and in other populations (16). Once substantiated, such observations need to be studied functionally in well-characterized subjects with different clinical forms or durations of infection as well as in other endemic settings. New cell subtypes are being defined almost constantly, diminishing the likelihood that pathology will be easily attributable to a given cell producing a given mediator in response to a given antigen. Even whether the most relevant antigens are secreted, located in membranes, or are somatic remains a topic of debate. Perhaps recent advances in schistosome proteomics will facilitate better definition of the critical antigens for human immunopathology.

IMMUNOLOGY OF RESISTANCE TO REINFECTION IN HUMANS

Whether a protective resistance to reinfection exists in people has long been discussed (101), but several lines of evidence now indicate that it does develop, although it may take a long time (17, 102) and perhaps rarely results in sterile immunity. A number of studies suggest that worm death, occurring either naturally or upon treatment, leads to the release of immunogens that stimulate protective responses, which after a sufficient number of occurrences are at a level to effectively react with antigens expressed by susceptible incoming schistosomula (17, 25, 69, 70, 72, 103–106) or lead to a decrease in fecundity (107). Despite the challenges of evaluating reinfection rates in people who have different exposure histories, encounter water bodies with differences in force of transmission and can be quite distinct genetically, epidemiologic data in endemic populations generally support age-associated decreases in infection as a result of development of anti-parasite immunity, as opposed to reduced water contact (108). However, while children in endemic areas are usually more susceptible to infection and reinfection than adults, this may not be entirely linked to histories of exposure and infection (15, 109). Part of developing an understanding of resistance to infection or reinfection, and how treatment may promote it, involves identifying immune responses that correlate with protection.

Unlike mice that demonstrate resistance in association with Th1-like responses, human immune responses that have repeatedly been linked with resistance to schistosomiasis reinfection are more Th2-associated. The association between parasite-specific IgE, eosinophils and resistance to reinfection has been observed across infecting schistosome species and in a variety of epidemiologic settings (26, 110–115). Mechanistically, both high- and low-affinity IgE receptors on eosinophils and B cells (or in soluble form), respectively, are associated with protection against reinfection (70, 116, 117). In contrast, susceptibility to reinfection has been associated with IgG4, which may serve as a blocking antibody, inhibiting the action of IgE (111–115, 118). Interestingly, the propensity of children and adults to produce IgG4 and IgE, respectively, matches their relative susceptibility to reinfection (119). Following treatment of adults, adult worm-specific IgG4 levels decrease, while worm-specific IgE is maintained at pretreatment levels or increases. In children, who more readily become infected, treatment is less likely to increase the IgE/IgG4 ratio. Recently, certain S. mansoni adult worm-associated tegumental-allergen-like (TAL) proteins have been characterized as important potential targets of protective IgE and reinfection-associated IgG4 (25, 120, 121).

Cytokine responses to schistosome antigens are also altered by treatment. IL-4 and IL-5, cytokines associated with stimulation of IgE and eosinophil production, respectively, generally increased following praziquantel treatment (122–127). Resistance to reinfection has been associated with these responses to the tegument antigen paramyosin in persons infected with S. japonicum, and soluble adult worm antigen preparations in persons infected with S. haematobium (14, 128). IFN-γ production following treatment is more commonly (although not exclusively)
linked with susceptibility to reinfection, as is IL-10 (129, 130). Interestingly, IL-10 is associated with IgG4 production (131), consistent with the observations that IgG4 responses are associated with susceptibility and the findings in mice that blocking IL-10 receptors is necessary for treatment to induce protection against reinfection (32). As with human immune correlates of immunopathogenesis and immunoregulation, critical antigens and immune cell correlates of resistance to reinfection need confirmation between different populations in a variety of epidemiologic situations to substantiate the relevance of any given response in host protection.

STATUS OF VACCINE CANDIDATES AND THE POTENTIAL ROLE IN ELIMINATION

There have been two schistosome candidate vaccines that have been produced by good manufacturing procedure and entered Phase I safety and immunogenicity trials – ShGST (Bilhvx) (33) and Sm14 (34). The results of the Bilhvx Phase I trial have been published, but those from the Sm14 trail are being analysed at this time. Bilhvx has also undergone Phase II and III trials in West Africa, and those results are also currently being analysed. Thus far, these candidates have not induced adverse reactions, but have induced immune responses. Other candidates that are in preclinical trials at various stages include tetraspanin-2 (132) and calpain (133) for S. mansoni and paramyosin (134), triose-phosphate isomerase (135), tetraspanin (136) and schistosome insulin receptor (137) for S. japonicum. Many of the vaccines for S. japonicum are being developed to help control the transmission contribution of zoonotic host species.

There are many questions that need to be addressed as research on schistosome candidate vaccines move forward (138). The first, and perhaps most contentious, question is, Do we need such a vaccine to control schistosomiasis? The debate has been further fuelled by the World Health Assembly Resolution 65.21 call to eliminate schistosomiasis. Perhaps the best answer to that is twofold: first, if we had an effective vaccine, we would use it. It is clear that in most endemic countries, mass drug administration with PZQ will not be sufficient to eliminate schistosomiasis; therefore, we need new tools to be used in combination with MDA such as snail control, behavioural change, water and sanitation. The second question might be, What is the ideal Target Product Profile is for a vaccine to protect against acquisition of schistosomiasis, or in fact could it be a vaccine that would simply reduce morbidity through control of egg production? In addition to the fundamental questions about the need or type of vaccine, there are other questions regarding how a vaccine should or could be safely tested. Even once additional antigens are ready for human testing, the design of clinical trials to evaluate them will produce its own challenges (138). Current experimental schistosomiasis vaccine candidates are evaluated by their ability to reduce worm burdens upon challenge infection and perfusion, but this approach cannot be used in humans because it is currently impossible to quantify human schistosome worm burdens. Egg output is another possible measure of vaccine efficacy, but we do not know the true correlation between quantitative egg output and worm burdens, and furthermore, it is likely not stable throughout infection. Challenge infections are not acceptable in a situation where adverse events such as transverse myelitis could occur prior to evaluation by egg output. Similarly, testing a vaccine on large populations of people in endemic areas when they could also be treated with PZQ might be ethically challenging and contentious. This is all ignoring the substantial cost investment needed to get through clinical testing and regulatory requirements. Nevertheless, the potential long-term role that an appropriate vaccine could play in the elimination of schistosomiasis, and the sustaining of that task makes continued studies on the discovery and development of antischistosome vaccines a worthy goal.

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 (139, 140). Molecular techniques for schistosome DNA detection in faecal, urine or blood specimens increase sensitivity, but are expensive and still suffer somewhat from sampling limitations (141, 142). Serologic assays have proven useful clinically (143) 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 (119, 144, 145). 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. 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 (140), 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. We are, instead, left with correlates of worm burden that are at best estimates and have little or no basis in data from people with active infections at different times after the establishment of their infections. This lack of a true gold standard is an impediment to many activities and studies on human schistosomiasis.

**WHAT IS LEFT?**

There is obviously much more information needed to truly understand the complex relationships between schistosomes and their human hosts. When discussing these interactions, it is important to keep in mind whether the topic is immunity against infection/reinfection or immunopathogenesis and to realize that there are almost certainly multiple responses and regulatory responses that play off against each other in support of a semi-balanced chronic infection. It is also useful to admit that the approaches and tools we have are not ideal. We are essentially restricted to the use of peripheral blood as our window into immune responses that are undoubtedly actually being played out in tissue microenvironments. Furthermore, without the option to infect and treat or to use manipulated parasites in controlled studies, we are confined to correlations rather than proofs. Finally, movement of *S. mansoni* into areas traditionally dominated by *S. haematobium* and of *S. haematobium* into areas endemic for *S. mansoni* complicates the epidemiologic, immunologic and diagnostic picture, especially with respect to the recent description of interspecies hybridizations between different human and animal schistosomes, which may alter the host–parasite interactions in both the mammalian and molluscan hosts (146, 147).

Still, there are many questions to be answered and careful correlative studies between various immune responses and well-documented cases or treated individuals will yield critical answers. Some of the immunologic questions that remain are obvious: What are the actual mechanisms of killing of invading schistosomula? Are there regulatory responses that hinder these mechanisms? How do adult schistosomes survive in an immunologically active environment? What level of granuloma formation is required to thwart the damaging effects of egg constituents and how much granuloma formation is too much, resulting anaemia of chronic inflammation or severe disease? What combination of regulatory mechanisms determines whether the outcome is anaemia or hepatosplenic or urinary fibrosis? Do the antischistosome immune responses induced by being born of an infected mother establish regulatory or protective status? Does having schistosomiasis effectively down-regulate someones ability to respond appropriately unrelated immunizations or co-infections? Does having schistosomiasis effectively down-regulate someones ability to respond inappropriately to other stimuli, such as allergens or auto-immunogens? Appropriate studies of people with schistosomiasis are yielding and will continue to yield answers to these critical questions.

**ACKNOWLEDGEMENTS**

The writing of this seminar received financial support from NIH grant R01 AI-053695 and the University of Georgia Research Foundation, Inc., which was funded by the Bill & Melinda Gates Foundation. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

**REFERENCES**

1 Basch PF. Schistosomes. Development, Reproduction and Host Relations. New York, Oxford University Press, 1991: 1–248.

2 World Health Organization. Schistosomiasis. Fact sheet N°115. Available at: http:// www.who.int/mediacentre/factsheets/fs115/en/ (accessed 4 December 2013)

3 Chitsulo L, LoVerde P & Engels D. Schistosomiasis. *Nat Rev Microbiol* 2004; 2: 12–13.

4 Warren KS, Mahmoud AA, Cummings P, Murphy DJ & House HB. Schistosomiasis *mansoni* in Yemeni in California: duration of infection, presence of disease, therapeutic management. *Am J Trop Med Hyg* 1974; 23: 902–909.

5 Chabasse D, Bertrand G, Leroux JP, Gauthier N & Hocquet P. Developmental bilharziasis caused by *Schistosoma mansoni* discovered 37 years after infestation. *Bull Soc Pathol Exot Filiales* 1985; 78: 643–647.

© 2013 The Authors. Parasite Immunology published by John Wiley & Sons Ltd., *Parasite Immunology*, 36, 347–357 353
6 Verani JR, Abudho B, Montgomery SP, et al. Schistosomiasis among young children in Usoma, Kenya. Am J Trop Med Hyg 2011; 84: 787–791.
7 Stothard JR, Sousa-Figueiredo JC, Betson M, et al. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. Parasitology 2011; 138: 1593–1606.
8 Sleigh AC & Mott KE. Schistosomiasis. In Gilles HM (ed.): Epidemiology and Control of Tropical Diseases (Clinics in Tropical Medicine and Communicable Diseases, Volume 1). London, UK, W.B. Saunders Co., 1986: 643–670.
9 Dalton PR & Pole D. Water-contact patterns in relation to Schistosoma haematobium infection. Bull World Health Organ 1978; 66: 417–426.
10 Wilkins HA, Goll PH, Marshall TF & Moore PJ. Dynamics of Schistosoma haematobium infection in a Gambian community. III. Acquisition and loss of infection. Trans R Soc Trop Med Hyg 1984; 78: 227–232.
11 Liu F, Lu J, Hu W, et al. New perspectives on host-parasite interplay by comparative transcriptomic and proteomic analyses of Schistosoma japonicum. PLoS Pathog 2006; 2: e29.
12 Verjovski-Almeida S, Leite LC, Dias-Neto E, Menck CP & Wilson RA. Schistosomes transcriptome: insights and perspectives for functional genomics. Trends Parasitol 2004; 20: 304–308.
13 Hokke CH, Fitzpatrick JM & HoffmanKF. Integrating transcriptome, proteome and glycome analyses of Schistosoma biology. Trends Parasitol 2007; 23: 165–174.
14 Leenstra T, Acosta LP, Wu HW, et al. T-helper-2 cytokine responses to SjTj predict resistance to reinfection with Schistosoma japonicum. Infect Immun 2006; 74: 370–38.1.
15 Vereecken K, Naus CW, Polman K, et al. Associations between specific antibody responses and resistance to reinfection in a Senegalese population recently exposed to Schistosoma mansoni. Trop Med Int Health 2007; 12: 431–444.
16 Naush N, Mida N, Mdluzwa T, Maizes RM & Mutapi F. Regulatory and activated T cells in human Schistosoma haematobium infections. PLoS ONE 2011; 6: e16860.
17 Fitzsimmons CM, Jones FM, Pinot de Moura A, et al. Progressive cross-reactivity in IgE responses: an explanation for the slow development of human immunity to schistosomiasis? Infect Immun 2012; 80: 4264–4270.
18 Fu CL, Odgegaard JL, Herbert DR & Hsieh MH. A novel mouse model of Schistosoma haematobium egg-induced immunopathology. PLoS Pathog 2012; 8: e1002655.
19 Ray D, Nelson TA, Fu CL, et al. Transcriptional profiling of the bladder in urogenital schistosomiasis reveals pathways of inflammatory fibrosis and urothelial compromise. PLoS Negl Trop Dis 2012; 6: e1912.
20 Wilson RA. The saga of schistosome migration and attrition. Parasitology 2009; 136: 1581–1592.
21 Collins JJ 3rd, Wang B, Lambrus BG, Tharp ME, Iyer H & Newmark PA. Adult somatic stem cells in the human parasite Schistosoma mansoni. Nature 2013; 494: 476–479.
22 Kemp WM, Damian RT, Greene ND & Lushbaugh WA. Immunochemical localization of mouse alpha 2-macroglobulin-like antigenic determinants on Schistosoma mansoni adults. J Parasitol 1976; 62: 413–419.
23 Goldring OL, Clegg JA, Smithers SR & Terry RJ. Acquisition of human blood group antigens by Schistosoma mansoni. Clin Exp Immunol 1976; 26: 181–187.
24 Keating HJ, Wilson RA & Skelly PJ. No overt cellular inflammation around intra-vascular schistosomes in vivo. J Parasitol 2006; 92: 1365–1369.
25 Walter K, Fullord AJ, McBeath R, et al. Increased human IgE induced by killing Schistosoma mansoni in vivo is associated with pretreatment Th2 cytokine responsiveness to worm antigens. J Immunol 2006; 177: 5490–5498.
26 Jiz M, Friedman JF, Leenstra T, et al. Immunoglobulin E (IgE) responses to paramyosin predict resistance to reinfection with Schistosoma japonicum and are attenuated by IgG4. Infect Immun 2009; 77: 2051–2058.
27 Fallon PG, Cooper RO, Probert AJ & Doenhoff MJ. Immune-dependent chemotherapy of schistosomiasis. Parasitology 1992; 105(Suppl): S41–S48.
28 Doenhoff MJ, Coli D & Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Curr Opin Infect Dis 2008; 21: 659–667.
29 Brindley PJ & Sher A. The chemotherapeutic effect of praziquantel against Schistosoma mansoni is dependent on host antibody response. J Parasitol 1987; 139: 215–220.
30 Jankovic D, Wynn TA, Kullberg MC, et al. Optimal vaccination against Schistosoma mansoni requires the induction of both B cell- and IFN-γ-dependent effector mechanisms. J Immunol 1999; 162: 345–351.
31 Kelly EA & Colley DG. In vivo effects of monoclonal anti-LT-4 antibody on immune responsiveness of mice infected with Schistosoma mansoni. Reduction of irradiated cercariae-induced resistance. J Immunol 1988; 140: 2737–2745.
32 Wilson MS, Cheever AW, White SD, Thompson RW & Wynn TA. IL-10 blocks the development of resistance to reinfection with Schistosoma mansoni. PLoS Pathog 2011; 7: e1002171.
33 Riveau G, Deplanque D, Remoué F, et al. Surveillance and immunogenicity of rSh28GST antigen in humans: phase 1 randomized clinical study of a vaccine candidate against urinary schistosomiasis. PLoS Negl Trop Dis 2012; 6: e1704.
34 Tendler M & Simpson AJ. The biotechnol- ogy-value chain: development of Sm14 as a schistosomiasis vaccine. Acta Trop 2008; 108: 263–266.
35 Tran MH, Freitas TC, Cooper L, et al. Suppression of mRNAs encoding tegument tetraspans from Schistosoma mansoni results in impaired tegument turnover. PLoS Pathog 2010; 6: e1000840.
36 Krautz-Peterson G, Camargo S, Huggel K, Verrey F, Shoemaker CB & Skelly PJ. Amino acid transport in schistosomes: characterization of the permease-heavy chain SPRM1hc. J Biol Chem 2007; 282: 21767–21775.
37 Krautz-Peterson G, Simoes M, Faghri Z, et al. Suppressing glucose transporter gene expression in Schistosoma mansoni impairs parasite feeding and increases survival in the mammalian host. PLoS Pathog 2010; 6: e1000932.
38 Cook RM, Carvalho-Queiroz C, Wilding G & LoVerde PT. Nucleic acid vaccination with Schistosoma mansoni antioxidant enzyme cytosolic superoxide dismutase and the structural protein filmarin confers protection against the adult worm stage. Infect Immun 2004; 72: 6112–6124.
39 Buchanan RD, Fine DP & Colley DG. Schistosoma mansoni infection in mice depleted of thymus-dependent lymphocytes. II. Pathology and altered pathogenesis. Am J Pathol 1973; 71: 207–218.
40 Byram JE & von Lichtenberg F. Altered schistosome granuloma formation in nude mice. Am J Trop Med Hyg 1977; 26: 944–956.
41 Colley DG. Adoptive suppression of granuloma formation. J Exp Med 1976; 143: 696–700.
42 Colley DG, Cook JA, Freeman GL Jr, Bartholomew RK & Jordan P. Immune responses during human schistosomiasis mansoni. I. In vitro lymphocyte blastogenic responses to heterogenous antigenic preparations from schistosome eggs, worms and cercariae. Int Arch Allergy Appl Immunol 1977; 53: 420–433.
43 Barsoum IS, Gamil FM, Al-Khaffaf MA, Ramzy RM, El Alamy MA & Colley DG. Immune responses and immunoregulation in relation to human schistosomiasis in Egypt. I. Effect of treatment on in vitro cellular responsiveness. Am J Trop Med Hyg 1982; 31: 1181–1187.
44 Colley DG, Garcia AA, Lambertiucci JR, et al. Immune responses during human schistosomiasis. XII. Differential responsiveness in patients with hepatosplenic disease. Am J Trop Med Hyg 1986; 35: 793–802.
45 Davies SJ, Grogan JL, Blank RB, Lim KC, Locksley RM & McKerrow JH. Modulation of blood fluke development in the liver by hepatic CD4+ lymphocytes. Science 2001; 294: 1358–1361.
relationship in Schistosoma mansoni-infected mice: the immunological dependence of parasite egg excretion. Immunology 1978; 35: 771–778.

60 Turner JD, Narang P, Coles MC & Mountford AP. Blood inflows exploit Peyer's Patch lymphoid tissue to facilitate transmission from the mammalian host. PLoS Pathog 2012; 8: e1003063.

61 Williams ME, Montenegro S, Domingues AL, et al. Leukocytes of patients with Schistosoma mansoni respond with a Th2 pattern of cytokine production to mitogen or egg antigens but with a Th0 pattern to worm antigens. J Infect Dis 1994; 170: 946–954.

62 Grogan JL, Kremsner PG, Deelder AM & Yazdanbakhsh M. Antigen-specific proliferation and interleukin-2 and interleukin-4 in regulating nitric oxide-mediated inhibition of T-cell proliferation and gamma interferon production in schistosomiasis. Infect Immun 2002; 70: 177–184.

63 Hoffman KF, Cheever AW & Wynn TA. IL-10 and the dangers of immune polarization: excessive type 1 and type 2 cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. J Immunol 2000; 164: 6406–6416.

64 Pesce JT, Ramalingam TR, Mentink-Kane MM, et al. Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. PLoS Pathog 2009; 5: e1000371.

65 Boros DL, Pelley RP & Warren KS. Spontaneous modulation of granulomatous hypersensitivity in schistosomiasis mansoni. J Immunol 1975; 114: 1437–1441.

66 Lundy SK & Lukacs NW. Chronic schistosome infection leads to modulation of granuloma formation and systemic immune suppression. Front Immunol 2013; 4: 39.

67 Henderson GS, Nix NA, Montesano MA, et al. Two distinct pathological syndromes in male CBA/J inbred mice with chronic Schistosoma mansoni infections. Am J Pathol 1993; 142: 703.

68 Fairfax KC, Amiel E, King IL, Freitas TC, Mboh M & Pearce EJ. IL-10R blockade during chronic schistosomiasis mansoni results in the loss of B cells from the liver and development of severe pulmonary disease. PLoS Pathog 2012; 8: e1002490.

69 Colley DG, Montesano MA, Freeman GL & Secor WE. Infection-stimulated or perinatally initiated idiotypic interactions can direct differential morbidity and mortality in schistosomiasis. Microbes Infect 1999; 1: 517–524.

70 Doenhoff M, Musallam R, Bain J & McGregor A. Studies on the host-parasite interaction of Schistosoma mansoni-infected mice: in human schistosomiasis mansoni infection. J Infect Dis 1986; 153: 779–790.

71 Wanatabe K, Mwinzi PNM, Black CL, et al. T regulatory cell levels decrease in people infected with Schistosoma mansoni on effective treatment. Am J Trop Med Hyg 2007; 77: 676–682.

72 Black CL, Mwinzi EM, Mwinzi PN, et al. Increases in levels of schistosome-specific immunoglobulin E and CD23(+)/B cells in a cohort of Kenyan children undergoing repeated treatment and re-infection with Schistosoma mansoni. J Infect Dis 2010; 202: 399–405.

73 Andrade A & Cheever AW. Alterations of the intrahepatic vasculature in hepatosplenic schistosomiasis mansoni. Am J Trop Med Hyg 1971; 20: 425–432.

74 Kamel IA, Elwi AM, Cheever AW, Mosmann JE & Danner R. Schistosomiasis mansoni and S. haematobium infections in Egypt. IV. Hepatic lesions. Am J Trop Med Hyg 1978; 27: 931–938.

75 King CH, Dickman K & Tisch DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet 2003; 365: 1561–1569.

76 Leenstra T, Acosta LP, Langdon GC, et al. Schistosomiasis japonica, anemia, and iron status in children, adolescents, and young adults in Leyte, Philippines 1. Am J Clin Nutr 2006; 83: 371–379.

77 Ellis MK, Li Y, Hou X, Chen H & McM-anus DP. sTNFR-II and sICAM-1 are associated with acute disease and hepatic inflammation in schistosomiasis japonica. Int J Parasitol 2005; 35: 717–723.

78 Bustinduy AL, Thomas CL, Fіasten JJ, et al. Measuring fitness of Kenyan children with polyparasite infections using the 20-meter shuttle run test as a morbidity metric. PLoS Negl Trop Dis 2011; 5: e1213.

79 Butter SE, Muok EM, Montgomery SP, et al. Mechanism of anaemia in Schistosoma mansoni-infected schoolchildren in Western Kenya. Am J Trop Med Hyg 2012; 87: 862–867.

80 von Lichtenberg F. Studies on granuloma formation. Ill. Antigen sequestration and destruction in the schistosome pseudotuber- cle. Am J Pathol 1964; 45: 75–93.

81 Mansour MM, Farid Z, Bassily S, Salah LH & Wattan RH. Serum enzyme tests in hepatosplenic schistosomiasis. Trans R Soc Trop Med Hyg 1982; 76: 109–111.

82 Ayoya MA, Spiekermann-Brouwer GM, Stoltzfus RJ, et al. Alpha 1-acid glycoprotein, C-reactive protein, and serum ferritin are correlated in anemic schoolchildren with Schistosoma haematobium. Am J Clin Nutr 2010; 91: 1784–1790.

83 Leenstra T, Coutinho HM, Acosta LP, et al. Schistosoma japonicum reinfection after praziquantel treatment causes anaemia associated with inflammation. Infect Immun 2006; 74: 6398–6407.

84 Kjetland E, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis

© 2013 The Authors. Parasite Immunology published by John Wiley & Sons Ltd., Parasite Immunology, 36, 347–357

355
and HIV in rural Zambian women. AIDS 2006; 20: 593–600.
85. Downs JA, Mguta C, Kaatano GM, et al. Urogenital schistosomiasis in women of reproductive age in Tanzania’s Lake Victoria region. Am J Trop Med Hyg 2011; 84: 364–369.
86. Richter J. The impact of chemotherapy on morbidity due to schistosomiasis. Acta Trop 2003; 86: 161–183.
87. Maizels RM & Yazdankhah M. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nat Rev Immunol 2003; 3: 733–744.
88. Malaguiça LC, Falcão PL, Silveira AM, et al. Cytokine regulation of human immune response to Schistosoma mansoni: analysis of the role of IL-4, IL-5 and IL-10 on peripheral blood mononuclear cell responses. Scand J Immunol 1997; 46: 393–398.
89. Shen L, Zhang ZS, Wu HW, et al. Down-regulation of specific antigen-driven cytokine production in a population with endemic Schistosoma japonicum infection. Clin Exp Immunol 2002; 129: 339–345.
90. Todd CW, Goodgame RW & Colley DG. Immune responses during human schistosomiasis mansoni. V. Suppression of schistosome antigen-specific lymphocyte blastogenesis by adherent/phagocytic cells. J Immunol 1979; 122: 1440–1446.
91. Goes AM, Gazzinelli R, Rocha R, Katz N & Doughty BL. Granulomatous hypersensitivities to Schistosoma mansoni egg antigens in human schistosomiasis. III. In vitro granuloma modulation induced by immune complexes. Am J Trop Med Hyg 1991; 44: 434–443.
92. King CL, Medhat A, Malhotra I, et al. Cytokine control of parasite-specific anergy in human urinary schistosomiasis. IL-10 modulates lymphocyte reactivity. J Immunol 1996; 156: 4715–4721.
93. Alves Oliveira LF, Moreno EC, Gazzinelli G, et al. Cytokine production associated with peripheral fibrosis during chronic schistosomiasis mansoni in humans. Infect Immun 2006; 74: 1215–1221.
94. Lima MS, Gazzinelli G, Nascimento E, Parra JC, Montesano MA & Colley DG. Immune responses during human Schistosoma mansoni. Evidence for antidiotype T lymphocyte responsiveness. J Clin Invest 1986; 78: 983–988.
95. Booth M, Shaw MA, Carpenter D, et al. Carriage of DRBl*13 is associated with increased posttreatment IgE levels against Schistosoma mansoni antigens and lower long-term reinfection levels. J Immunol 2006; 176: 7112–7118.
96. Rodrigues V Jr, Abel L, Piper K & Dessein AJ. Segregation analysis indicates a major gene in the control of interleukin-5 production in humans infected with Schistosoma mansoni. Am J Hum Genet 1996; 59: 453–461.
97. Lewert RM & Mandlowitz S. Schistosomiasis: prenatal induction of tolerance to antigens. Nature 1969; 224: 1029–1030.
98. Zhao F, Huang X, Hou X, et al. Schistosoma japonicum: susceptibility of neonate mice born to infected and noninfected mothers following subsequent challenge. Parasite Immunol 2013; 35: 157–163.
99. Seydel LS, Petelski A, van Dami GI, et al. Association of in vitro sensitization to Schistosoma haematobium with enhanced cord blood IgE and increased frequencies of CD5+ B cells in African newborns. Am J Trop Med Hyg 2012; 86: 613–619.
100. Djourdy Y, Wammes LJ, Supathi T, Sarteno E & Yazdankhah M. Immunological footprint: the development of a child immune system in environments rich in microorganisms and parasites. Parasitology 2011; 138: 1508–1518.
101. Warren KS. Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? J Infect Dis 1973; 127: 595–601.
102. Mutapi F, Billingsley PF & Secor WE. Infection and treatment immunizations for successful parasite vaccines. Trends Parasitol 2013; 29: 135–141.
103. Mutapi F, Ndhlovu PD, Hagan P, et al. Chemotherapy accelerates the development of acquired immune response to Schistosoma haematobium infection. J Infect Dis 1998; 178: 289–293.
104. Mutapi F, Ndhlovu PD, Hagan P & Woolhouse ME. A comparison of re-infection rates with Schistosoma haematobium following chemotherapy in areas with high and low levels of infection. Parasite Immunol 1999; 21: 253–259.
105. Wilson S, Jones FM, Fofana HK, et al. Rapidly boosted plasma IL-5 by induced treatment of human Schistosomiasis haematobium is dependent on antigen dose, IgE and eosinophils. PLoS Negl Trop Dis 2013; 7: e2149.
106. Pinot de Moreira A, Jones FM, Wilson S, et al. Effects of treatment on IgE responses against parasite allergen-like proteins and immunoglobulin E in children with childhood schistosomiasis and hookworm infections. Infect Immun 2013; 81: 23–32.
107. Mitchell KM, Mutapi F, Savill NJ & Woolhouse ME. Protective immunity to Schistosoma haematobium infection is primarily an anti-fecundity response stimulated by the death of adult worms. Proc Nail Acad Sci USA 2010; 109: 13347–13352.
108. Mitchell KM, Mutapi F, Savill NJ & Woolhouse ME. Explaining observed infection and antibody age-profiles in populations with uncontrolled schistosomiasis. PLoS Comput Biol 2011; 7: e1002237.
109. Kabatereine NB, Nnennvall BD, Ouma JH, et al. Adult resistance to schistosomiasis mansoni: age-dependence of reinfection remains constant in communities with diverse exposure patterns. Parasitology 1999; 118: 101–109.
110. Duhne DW, Butterworth AE, Fullford AJ, et al. Immunity after treatment of human schistosomiasis: association between IgE antibodies to adult worm antigens and resistance to reinfection. Eur J Immunol 1992; 22: 1483–1494.
111. Hagan P, Blumenthal UJ, Dunn D, Simpson AJ & Wilkins HA. Human IgE, IgG4 and resistance to reinfection with Schistosoma haematobium. Nature 1991; 349: 243–245.
112. Rihet P, Demeure CE, Bourgeois A, Prata A & Dessein AJ. Evidence for an association between human resistance to Schistosoma mansoni and high anti-larval IgE levels. Eur J Immunol 1991; 21: 2679–2686.
113. Demeure CE, Rihet P, Abel L, Ouattara M, Bourgeois A & Dessein AJ. Resistance to Schistosoma mansoni in humans: influence of the IgE/IgG4 balance and IgG2 in immunity to reinfection after chemotherapy. J Infect Dis 1993; 168: 1000–1008.
114. Satti MZ, Lind P, Vennervald BJ, Sulaiman SM, Daffalla AA & Ghalib HW. Specific immunoglobulin measurements related to exposure and resistance to Schistosoma mansoni infection in Sudanese canal cleaners. Clin Exp Immunol 1996; 106: 45–54.
115. Zhaosong Z, Haiwei W, Suchen C, et al. Association between IgE antibody against soluble egg antigen and resistance to reinfection with Schistosoma japonicum. Trans R Soc Trop Med Hyg 1997; 91: 606–608.
116. Gouni AS, Lamkhoudi B, Ochiai K, et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature 1994; 367: 183–186.
117. Ganley-Leal LM, Mwini PNM, Cetre-Sosah CB, et al. Higher percentages of circulating mast cell precursors correlate with susceptibility to reinfection with Schistosoma mansoni. Am J Trop Med Hyg 2006; 75: 1053–1057.
118. Oliveira RR, Figueiredo JP, Cardoso LS, et al. Factors associated with resistance to Schistosoma mansoni infection in an endemic area of Bahia, Brazil. Am J Trop Med Hyg 2012; 86: 296–305.
119. Grogan JL, Kremsner PG, van Dami GI, et al. Antischistosome IgG4 and IgE responses are affected differentially by chemotherapy in children versus adults. J Infect Dis 1996; 173: 1242–1247.
120. Webster M, Fullford AJ, Braun G, et al. Human immunoglobulin E responses to a recombinant 22.6-kilodalton antigen from Schistosoma mansoni adult worms are associated with low intensities of reinfection after treatment. Infect Immun 1996; 64: 4042–4046.
121. Pinot de Moreira A, Fullford AJ, Kabatereine NB, Ouma JH, Booth M & Dunne DW. Analysis of complex patterns of human exposure and immunity to Schistosomiasis mansoni: the influence of age, sex, ethnicity and IgE. PLoS Negl Trop Dis 2010; 4: e820.
122. Roberts M, Butterworth AE, Kimani G, et al. Immunity after treatment of human schistosomiasis: association between cellular responses and resistance to reinfection. Infect Immun 1993; 61: 4984–4993.
123 Scott JT, Turner CM, Mutapi F, et al. Dissociation of interleukin-4 and interleukin-5 production following treatment for Schistosoma haematobium infection in humans. Parasite Immunol 2000; 22: 341–348.
124 Joseph S, Jones FM, Laidlaw ME, et al. Impairment of the Schistosoma mansoni-specific immune responses elicited by treatment with praziquantel in Ugandans with HIV-1 confection. J Infect Dis 2004; 190: 613–618.
125 Joseph S, Jones FM, Walter K, et al. Increases in human T helper 2 cytokine responses induced by repeated treatment do not result in protective immunity to Schistosoma haematobium: interleukin (IL)-5 and IL-10 responses. J Infect Dis 2002; 186: 1474–1482.
126 Fitzsimmons CM, Joseph S, Jones FM, et al. Chemotherapy for schistosomiasis in Ugandan fishermen: treatment can cause a rapid increase in interleukin-5 levels in plasma but decreased levels of eosinophils and worm-specific immunoglobulin E. Infect Immun 2004; 72: 4023–4030.
127 Grogan JL, Kremsnner PG, Deelder AM & Yazdanbakhsh M. Elevated proliferation and interleukin-4 release from CD4+ cells after chemotherapy in human Schistosoma haematobium infection. Eur J Immunol 1996; 26: 1365–1370.
128 Medhat A, Shehata M, Bucci K, et al. Increased interleukin-4 and interleukin-5 production in response to Schistosoma haematobium adult worm antigens correlates with lack of reinfection after treatment. J Infect Dis 1998; 178: 512–519.
129 Shen L, Zhang ZS, Wu HW, et al. IFN-γ is associated with risk of Schistosoma japonicum infection in China. Parasite Immunol 2003; 25: 483–487.
130 van den Biggelaar AH, Borrmann S, Kremsnner P & Yazdanbakhsh M. Immune responses induced by repeated treatment do not result in protective immunity to Schistosoma haematobium: interleukin (IL)-5 and IL-10 responses. J Infect Dis 2002; 186: 1474–1482.
131 van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol 2013; 131: 1204–1212.
132 Pearson MS, Pickering DA, McSorley HJ, et al. Enhanced protective efficacy of a chimeric form of the schistosomiasis vaccine antigen Sm-TSP-2. PLoS Negl Trop Dis 2012; 6: e1564.
133 Ahmad G, Zhang W, Torben W, et al. Preclinical prophylactic efficacy testing of Sm-p80-based vaccine in a nonhuman primate model of Schistosoma mansoni infection and immunoglobulin G and E responses to Sm-p80 in human serum samples from an area where schistosomiasis is endemic. J Infect Dis 2011; 204: 1437–1449.
134 McManus DP, Wong JY, Zhou J, et al. Recombinant paramyosin (rec-Sp-97) tested for immunogenicity and vaccine efficacy against Schistosoma japonicum in mice and water buffaloes. Vaccine 2001; 20: 870–878.
135 Zhu Y, Si J, Harn DA, et al. Schistosoma japonicum triose-phosphate isomerase plasmid DNA vaccine protects pigs against challenge infection. Parasitology 2006; 132: 67–71.
136 Dai Y, Zhu Y, Harn DA, et al. DNA vaccine vaccination with recombinant proteins enhances the efficacy of DNA vaccines for schistosomiasis japonicum. Clin Vaccine Immunol 2009; 16: 1796–1803.
137 You H, Gobert GN, Duke MG, et al. The insulin receptor is a transmission blocking veterinary vaccine target for zoonotic Schistosoma japonicum. Int J Parasitol 2012; 42: 801–807.
138 Todd CW & Colley DG. Practical and ethical issues in the development of a vaccine against schistosomiasis mansoni. Am J Trop Med Hyg 2002; 66: 348–358.
139 De Vlas SJ, Engels D, Rabehlo AL, et al. Validation of a chart to estimate true Schistosoma mansoni prevalences from simple egg counts. Parasitology 1997; 114: 113–121.
140 Colley DG, Binder S, Campbell C, et al. A five-country evaluation of a point-of-care circulating cathodic antigen urine assay for the prevalence of Schistosoma mansoni. Am J Trop Med Hyg 2013; 88: 426–432.
141 Ibronne O, Koukounari A, Asaolu S, Moustaki I & Shiff C. Validation of a new test for Schistosoma haematobium based on detection of Dra1 DNA fragments in urine: evaluation through latent class analysis. PLoS Negl Trop Dis 2012; 6: e1464.
142 Wichmann D, Poppert S, Von Thien H, et al. Prospective European-wide multicentre study on a blood based real-time PCR for the diagnosis of acute schistosomiasis. BMC Infect Dis 2013; 13: 55.
143 Tsang VC, Hillyer GV, Noh J, et al. Geographic clustering and seroprevalence of schistosomiasis in Puerto Rico (1995). Am J Trop Med Hyg 1997; 56: 107–112.
144 Webster M, Fallon PG, Fulford AJ, et al. IgG4 and IgE responses to Schistosoma mansoni adult worms after treatment. J Infect Dis 1997; 175: 493–494.
145 Grogan JL, Kremsnner PG, van Dam GJ, Deelder AM & Yazdanbakhsh M. Anti-schistosome IgG4 and IgE at 2 years after chemotherapy; infected versus uninfected individuals. J Infect Dis 1997; 176: 1344–1350.
146 Huyse T, Webster BL, Geldof S, et al. Birectional retrogressive hybridization between a cattle and human schistosome species. PLoS Pathog 2009; 5: e1000571.
147 Webster BL, D Aws OT, Seye MM, Webster JP & Rollinson D. Retrogressive hybridization of Schistosoma haematobium group species in Senegal: species barrier break down between ruminant and human schistosomes. PLoS Negl Trop Dis 2013; 7: e2110.