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After due consideration, the editors of the journal and the authors of the paper agree that the paper be retracted from Microbiology Australia.

Reason: irresolvable authorship dispute.
Chronic parasitic disease affects millions of people worldwide. Helminth infections are usually asymptomatic or cause chronic disease that may range from mild to debilitating. One of the hallmarks of the immune response to parasitic infections is the tendency to suppress inflammation and control tissue damage. The net effect of this is not only to reduce or inactivate the activities of the parasite, but even to skew immune responses to other infectious agents. This article discusses the state of our understanding of the complex regulation and control of immune responses induced by schistosomes.

Biography

Zin Naing joined the Virology Research Lab (VRL) in 2007 and completed a year of honours with research into determination of viral and host factors influencing the outcome of human cytomegalovirus (CMV) infection in liver transplant recipients. After completion of his degree, he worked as a full-time research assistant for 3 years at VRL until commencing his PhD. Zin’s research is focusing on the role of CMV genetic variation on infection of the human placenta and alteration of immune response within placental tissue. This research will (i) determine the role CMV cellular tropism genes on infection of placental trophoblast cells, and (ii) determine the role of CMV (immediate-early, early, late) gene products on induction of inflammatory cytokines during infection.
Schistosomiasis ranks fourth among the most prevalent helminthic diseases\(^1\), and is included in the London Declaration. Schistosomiasis (bilharziosis) is caused by blood flukes of the genus *Schistosoma* (Figure 1) and is one of the most severe and chronic parasitic diseases worldwide, affecting ~250 million people with illness, disfigurement or death. The disease is endemic in 76 countries and more than 280,000 deaths occur annually due to schistosomiasis, mainly in rural areas of the developing world, which is testimony to its public health significance\(^1,6\). The infection is not endemic in Australia despite the fact that infected travellers and immigrants enter the country each year. The absence of an appropriate snail vector in Australia means that the life cycle cannot be completed, and effectively limits its transmission beyond an infected individual. In endemic countries, the overwhelming burden of disease is on children.

**Pathogenesis of schistosomiasis**

One of the most intriguing aspects of schistosome biology is the interaction of the parasites with the host immune system. The immune response enables the host to survive while infected, and to eventually develop resistance or immunity to subsequent reinfection. However, it is also central to the development of disease due to its role in orchestrating granuloma formation around tissue-trapped parasite eggs. While schistosomes have clearly evolved mechanisms for evading host immune responses, their normal development is, paradoxically, also dependent on the presence of a normal immune system\(^7\). It been shown that worms in experimental animals that lack T helper cells do not develop normally\(^8\). Further, inflammation is required to permit access of eggs to the gastrointestinal tract to enable the parasite to complete the lifecycle\(^7\).

Immune responses to schistosome infection in humans (and animal models) differ between the acute and chronic stage of the disease\(^9,10\). The early immune response is stimulated by cercariae migrating through the skin and schistosomulae migrating through the lungs. This induces innate (macrophage) and T-cell mediated inflammatory immune responses (termed TH1 responses). The symptoms are also known as Katayama syndrome, emerge from 14 days after infection\(^1,11,12\) and may include fever, coughing, fatigue, diarrhoea and anorexia.
As the disease develops, the immune response shifts toward the production of cytokines that reduce inflammation and promote the formation of granulomas. This anti-inflammatory response (termed TH2) is actively induced by antigens secreted by the eggs that start to be released by the adult worms in the portal circulation (Figure 2). This shift to TH2 type responses is orchestrated by the secretion of IL-4 and later IL-5 and IL-13. Following primary infection with schistosomes, an IgE-mediated hypersensitivity response can also develop against penetrating cercariae (cercarial dermatitis), which is often seen in visitors to endemic areas. The TH2 response, especially the presence of IL-4, leads to the formation of granulomas surrounding the eggs particularly in the liver, but also in the lung, pancreas and lymph nodes. Developing granulomas consist predominantly of eosinophils, granulocytes, T cells and macrophages. TH2 cells also make IL-13, and this cytokine stimulates myofibroblasts to make collagen, which can lead to excessive fibrosis associated with granuloma formation and resolution.

As the infection enters the chronic phase, the TH2 response is downregulated and modulated largely by IL-10 that results in reduced cellular responsiveness to schistosome antigens (Figure 2). This regulation keeps tissue damage in check and is mediated by regulatory T-cells (Treg). As a result, most chronically infected patients remain asymptomatic. However, in chronically infected and untreated patients the severe persistent granulomatous inflammation against deposited eggs results in excessive collagen deposition in affected tissues and therefore leads to fibrosis. This is especially severe where eggs are trapped in liver sinusoids causing periportal fibrosis and occlusion of the portal veins, which, in turn, results in portal hypertension, hepatosplenomegaly, ascites and gastrointestinal bleeding.

Schistosome eggs are remarkable for their ability to polarize the immune response. Given the importance in disease progression during schistosome infection, a major focus has been on the investigation of the schistosome egg and its components that might be involved in the induction and modulation of immune responses.

**Eggs as a major driver of immune suppression**

Proteins of schistosome eggs have been classified into two groups: soluble egg antigens (SEA) and egg secretory proteins (ESP). ESP consists solely of secreted proteins from mature eggs containing live larvae and, therefore, represents the ‘secretome’ of the egg. A proteomic analysis has revealed that ESP comprises at least 188 proteins. The predominant components of this mixture are omega-1
and the ‘IL-4-inducing principle’ of *S. mansoni* (IPSE). These two molecules have been characterised on the molecular level and described as being heavily glycosylated proteins that are exclusively expressed by the sub-shell area of mature eggs.

**Omega-1: a hepatotoxin that drives TH2 activation in dendritic cells.** In an early paper, Doenhoff and colleagues reported that T-cell-deprived and immuno-suppressed mice suffered from severe tissue damage during *S. mansoni* infections that could be prevented by monospecific antibodies against a highly immunoreactive egg antigen. Interestingly, the presence of cytotoxic products in *S. mansoni* eggs indicates that granuloma formation protects the host against tissue damage. This hepatotoxic protein was isolated from ESP and named omega-1. Further investigation revealed that omega-1 is a member of the RNase T2 family with ribonuclease activity. Later studies demonstrated that omega-1 is one of the major molecules that induces/drives TH2 responses on activation of DCs, with similar characteristics as whole ESP in *vitro* and *in vivo*. Depletion of ESP of omega-1 decreases TH2 inducing capacity *in vitro* substantially (by 70%)..

**IPSE: a selective inducer of IL-4.** Stimulation studies using human basophils demonstrated that IPSE is a bioactive protein in ESP, leading to activation of basophils and expression of IL-4 and, more importantly, IL-13. The IL-4 inducing capacity of IPSE strongly suggests a role in initiating TH2 responses, whereas IL-13 has been emphasised as a key mediator of the progression of hepatic fibrosis.

As our understanding of the role of these proteins in immune modulation expands, another interesting possibility is raised – could such proteins be used to treat other inflammatory conditions?

**Parasite antigens as potential modulators for immune-mediated disease**

To date, little work has been done to investigate the possible applications of these immunomodulatory proteins in other systems. However, in a recent study IPSE was found to skew immune responses in a xenograft tumour model and was proposed as a potential approach to prevent transplant rejection.

However, the immunomodulatory effects of infections with other helminth parasites have been explored in more detail and an interesting application of this idea has been the successful use of infection with nematodes to treat Crohn’s disease (a severe chronic inflammatory disease of the colonic mucosa that is intractable to other therapy). Several studies have been reported where patients who were infected with embryonated eggs of the pig whipworm (*Trichiuris suis*) displayed significant improvements in symptoms. Given the encouraging results using the IPSE protein, schistosoma egg antigens might also have potential as therapeutics for inflammatory diseases.

**Schistosomiasis and co-infections**

In areas where schistosomiasis is endemic, other infectious diseases are also of serious concern. There are surprisingly few data on the impact of co-infections; however, there is evidence that in infections with schistosomes concurrent with malaria, for example, synergies exist and the severity of effects such as anaemia and low birth weight are increased. A study by Flores et al. investigating the parasite burdens in a rural Kenyan population revealed that not only were children 9.3 times more likely to be co-infected with *S. haematobium* and malaria, but also increased malaria infection intensity correlated with increased schistosome infection. This study highlights the need for further studies on the interactions between parasites and other co-infections.

Co-infection is also an important consideration for vaccination campaigns and may explain why some vaccines are less effective in the field than predicted. The immunological basis for this may also relate to immunomodulation. For example, a recent study showed that antibody responses in mice to a hepatitis B vaccine were significantly reduced in mice infected with *S. japonicum*. However, this effect was reversed when mice were treated with anthelmintics to cure the infection.

**Concluding remarks**

Schistosomes and other helminth parasites manipulate the immune response of the host, a necessity that has evolved to ensure their survival and reproductive success in long-term infections. With the development of modern techniques and the availability of genome data for many of these parasites we are now beginning to understand the molecular mechanisms that underlie this complex relationship, which might lead to new therapeutic approaches.

**References**


**Biographies**

**Bernd Kalinina** is a Principal Research Fellow at the Centre for Animal Biotechnology, Faculty of Veterinary Science, The University of Melbourne. He has had a long-standing interest in schistosome infection with the recent completion of the *S. mansoni* genome project and emerging abundance of molecular information, his group is focussed on functional genomics in schistosomes to discover novel genes and biochemical pathways involved in pathology, growth, reproduction and survival of the parasite as potential intervention targets. Bernd is also Editor-In-Chief of *Experimental Parasitology* (Elsevier), one of the leading parasitology journals.

**Anna Walduck** is a Senior Lecturer in applied microbiology at RMIT University. Her laboratory studies the pathogenesis of chronic and acute bacterial infections, including *H. pylori* infection and the immunology of sepsis. She has a strong interest in vaccine development and in the regulation of mucosal immune response.

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