

Role of *Schistosoma Mansoni* Antigens in Type 1 Diabetes

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Abstract:

Infection with *Schistosoma mansoni* (*S. mansoni*) or exposure to eggs from this helminth inhibits the development of type 1 diabetes in NOD mice. The soluble extracts of *S. mansoni* worm or egg completely prevent onset of type 1 diabetes in these mice but only if injection is started at 4 weeks of age. T cells from diabetes-protected mice make IL-10 in recall responses to parasite antigens. These cells are furthermore impaired in their ability to transfer diabetes to NOD-SCID recipients. Bone marrow dendritic cells derived from NOD mice are found to make more IL-10 and less IL-12 following culture with *S. mansoni* soluble egg antigens in conjunction with lipopolysaccharides. NOD mice are deficient in NKT cells. Soluble worm and egg antigens increase the numbers of V α 14i NKT cells in NOD mice. These effects of schistosome antigens on the innate immune system provide a mechanism for their ability to prevent type 1 diabetes in NOD mice.

Keywords: *Schistosoma Mansoni*, Antigens, Type 1 Diabetes

Introduction:

Schistosomes are trematode worms (flukes) belonging to the phylum Platyhelminthes. The adult worms live in the vascular system of birds and mammals (blood flukes) (1).

All the schistosomes that mature in man belong to the genus *Schistosoma* of the family Schistosomatidae, which contains 11 other genera, some of which cause cercarial dermatitis. The genus *Schistosoma* contains 19 species, five of which (*Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. mekongi* and *S. intercalatum*) are of major pathological importance, while the others are essentially parasites of non-human mammals, although some zoonotic transmission to man does occur. An estimated 600 million people are at risk for schistosomiasis; 200 million are currently infected in 74 countries. Probably more than 95% of human infections are due to *S. mansoni* and *S. haematobium* (2).

Adult worms of *S. mansoni* are found in the mesenteric veins. They live for up to 30 years, with a mean lifespan of 3–6 years. They produce large numbers of eggs: 300 per day per female *S. mansoni*. About one-half of the eggs transit to the intestine, from where they leave the body in the faeces. The main number of eggs are retained in the tissues, where they survive for a further three weeks; these are responsible for inducing most of the pathological manifestations of disease (3).

Within the tissues of the snail, the miracidium is transformed into the mother sporocyst, within which are formed several hundred daughter sporocysts. These migrate from the site of penetration to the digestive gland and reproductive tract of the snail, in which they proliferate internally to produce cercariae, the stage that infects

man. This process takes about one month, and from one miracidium several million genetically identical cercariae may be produced by this asexual process during the lifetime of the infected snail (3).

The cercariae are shed from the snail in response to temperature and light and aggregate at the surface of the water, ready to infect the definitive human host. Cercariae penetrate intact skin rapidly, using proteolytic enzymes produced by the paired penetration glands at their anterior ends; the tail is discarded in the water (2).

Once they are within the skin, the cercaria is transformed into the skin-stage schistosomulum (2).

The schistosomulum then penetrates the basement membrane of the epidermis, the schistosomulum enters a lymphatic vessel or capillary in the dermis and is carried passively to the lungs via the right side of the heart. The young schistosomula embolize in the capillaries being too large to pass through the pulmonary veins. Schistosomula are then distributed all over the body via the left ventricle, in proportion to cardiac output. Those that embolize in various capillary beds migrate through these to regain the heart and recirculate until they reach the hepatic portal system, a process usually completed within three recirculations (1).

Primary infection usually occurs at a very young age, when children are exposed to contaminated water while bathing or playing. However, acute schistosomiasis is rarely observed in children, most likely due to B and T cell imprinting of children born to infected mothers (4).

Therefore, acute infection is most often observed in travelers from non-endemic areas. Since schistosomiasis begins with cercaria entering the skin, the first reaction to infection occurs there, usually within 24–48 h after invasion (5).

Dying cercariae in the skin trigger an innate immune response, which leads to a hypersensitivity response and the resulting cercarial dermatitis which presents as urticaria or angioedema (6). Cercarial dermatitis is the result of an inflammatory reaction to a variety of excretory/secretory (ES) proteins that facilitate skin penetration (7).

Late chronic infection causes intestinal disease and hepato-splenic schistosomiasis, Chronic infection is established once the mature worms start producing eggs that are then secreted in the stool by the human host. Adult worms do not induce an inflammatory response and therefore do not cause any direct symptoms, They are equipped with a variety of strategies that allow them to evade an immune response. In contrast, the eggs are well-capable of inducing an inflammatory response on which they rely to pass from blood vessels into the lumen of the gut so they can be excreted and continue the life cycle (8).

However, approximately half of the eggs become trapped in the tissues and attract inflammatory cells, leading to the formation of granulomas and fibrosis. Resulting complications of the chronic infection include organ obstruction, portal hypertension and hepatosplenomegaly with potential gastrointestinal bleeding (1).

Role of *Schistosoma mansoni* antigens (either egg or adult antigens) in preventing autoimmune disease:

The immunosuppressive capacity of *S. mansoni* has become of interest in the context of autoimmune disorders (9). Since autoimmune disease are characterized by an overactive immune system and predominant Th1 and/or Th17 responses, it seems plausible that infection with these immunosuppressive helminths could potentially be beneficial in preventing or treating autoimmune inflammatory disorders. However, despite the extensive amount of in vitro and in vivo studies investigating the effects of *S. mansoni* in autoimmunity, there are no clinical trial reporting use of *S. mansoni* products in autoimmune disorders so far. A recombinant protein of the closely related *S. haematobium* has recently entered clinical trials for the use in IBD. Based on the data regarding its effects discussed in the previous and in the following sections it could be argued that *S. mansoni* is an eligible candidate for future clinical trials (10).

S. mansoni excretory/secretory products have also been extensively studied, and the immunological effects of these products has been investigated repeatedly. In summary, the promising results of hookworm clinical studies and the knowledge of *Schistosoma* immunomodulation provide a steppingstone for further trials using *S. mansoni* and its products as a treatment option in treatment-unresponsive patients (11).

It was showed that infection with *S. mansoni* or injection of the parasite's soluble extracts of *S. mansoni* eggs (SEA) or worms (SWA) could completely prevent diabetes onset in NOD mice (12). Moreover, SEA increased IL-10 production from NOD bone marrow-derived dendritic cells (DC) and correspondingly diminished IL-12 production (13).

Exposure to SWA and SEA able to increase IL-10 production by T cells. Produced IL-10 has been shown to potently regulate diabetes development. The ability to prevent onset of DM1 may be through a range of mechanisms including those initially acting on the innate immune response but subsequently on T cell function (13).

The production of IL-10 at this time point is of considerable interest as it may indicate the presence of regulatory T cells and a potential role for such cells in the reinforcement of regulatory circuits to prevent DM1 (14).

T cell IL-10 production, suggests that tolerance may be maintained by regulation. The fact that SWA and SEA have differential effects on DC function furthermore suggests that SWA may exert its influence on the evolution of diabetes in NOD mice in a different way than SEA. NOD mice are deficient in NKT cells and injection of NKT cells into NOD mice prevents DM1 development (15).

It was found that SEA and SWA not only prevent diabetes in NOD mice but both significantly increase NKT cells in the liver. This strongly suggests that this may be an additional mechanism by which *schistosome* antigens can prevent onset of diabetes in NOD mice (16).

Role of *Schistosoma* TH2 response in DM1

As DM1 is a Th1-mediated autoimmune disease, any skewing or correction of the immune response towards Th2, would result in diabetes prevention. *S. mansoni* soluble egg antigens have the potential to profoundly regulate the immune system of the infected host and prevent DM1 in non obese diabetic (NOD) mice. These responses are thought to occur due to prolonged production of immunoregulatory cytokines such as IL-4, IL-5, IL-10 and TGF β . Moreover, it is thought that regulatory T cells (Tregs) may also affect glucose metabolism through their long-term secretion of IL-10 or transforming growth factor β (TGF- β), which inhibit the production of inflammatory cytokines or counteract the TNF-mediated inhibition of insulin signalling in adipocytes. Hence, the comorbidities of DM1 and schistosomiasis may affect the consequences of both diseases (17).

The role of the *Schistosoma* TH2 response in DM1 involves the modulation of the immune system by shifting the dominant Th1 profile, which drives the autoimmune destruction of insulin-producing beta cells, towards a Th2 profile that promotes anti-inflammatory responses (18).

Schistosoma infections enhance the production of Th2 cytokines such as IL-4, IL-5, and IL-10, while suppressing Th1 cytokines like IFN- γ . This shift not only reduces inflammation but also promotes the activation of regulatory T cells (Tregs), which further inhibit pathogenic Th1 activity. The presence of *Schistosoma* antigens has been linked to increased Treg activity and a favorable cytokine environment that maintains immune tolerance. These findings suggest that *Schistosoma*-derived products could be explored as potential therapeutic agents to induce a Th2 response and enhance regulatory mechanisms, offering a novel approach to managing autoimmune diabetes by leveraging the immunomodulatory properties of these parasites (4).

Parasitic helminths regulate the host's immune system and induce Th2 as well as regulatory immune responses, which may prevent the onset of diabetes (19).

It has been speculated that the immune response to Th2 and regulatory axes can inhibit the Th1 response in diabetes (20).

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