ANTI – ARTHRITIC ACTIVITY OF SCHISTOSOMA MANSONI DERIVED ANTIGENS IN ADJUVANT INDUCED ARTHRITIS IN RATS

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Abstract

Schistosoma is a waterborne infection that can pose a serious health consequence for all living things in general and humans in particular. High S. mansoni infection of rodents was recorded among those found in human sewage contamination around home ranges, in high local snail abundance areas and a high movement pattern of rodents between transmission sites. The schistosome life cycle occurs in 2 hosts: snails and mammals. Either asexual or sexual reproduction occurs, depending on the type of host. Schistosomiasis is caused by infection with blood flukes of the genus Schistosoma. parasites can induce an immunosuppressive environment to evade the immune system. This also benefits the host, as a reduced inflammatory response limits tissue damage. The most well-known S. mansoni proteases are cysteine and aspartic proteases, as well as the serine proteases (SP)s. The Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the lining of the synovial joints, resulting in both cartilage destruction and bone erosion. The CIA autoimmune mouse model is widely used to study RA. Infection of mice with either S. mansoni or S. japonicum prior to collagen immunization reduced the severity of CIA. Autoclaved antigen, derived from S. mansoni cercariae (ASMA), has been tested for a potential protective effect on adjuvant arthritis (CFA-induced AA) induced in rats by subcutaneous and intradermal injections of complete Freund's adjuvant into the paw and tail, respectively.

Keywords: Schistosoma mansoni, Rheumatoid arthritis (RA), Human sewage contamination, Autoimmune disease

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Introduction

Schistosoma is one of the most recurrent water-contact parasitic pathogens that affects humans and animals. Schistosomiasis is one of the most common in areas where sanitation is inadequate and water supplies are unsafe **(1)**.

The disease burden caused by schistosomiasis alone is estimated at 4.5 million disability-adjusted life years. According to the WHO more than 220 million people from low-income countries are at risk of schistosomiasis. It is the most killer parasitic infection next to malaria in the African region alone **(2)**.

In Ethiopia, schistosomiasis is one of the major ongoing public health problems reported in the different parts of the country. Relatively, S. mansoni species was reported in most parts of the country and S. haematobium was reported in some low altitude areas of the country **(3)**.

The increasing human and livestock population leads to increased agricultural production through expansion in the natural ecosystem and intensification by using irrigation that increases contact between humans and animals. Increasing the exchange in animal–human ecosystem interfaces increases the transmission of infections like schistosomiasis **(4)**.

Schistosoma is a waterborne infection that can pose a serious health consequence for all living things in general and humans in

particular. Depending on different factors; it causes schistosomiasis ranging from mild to severe life-threatening infections in humans. It affects primarily women and school-aged children. Schistosomiasis in children is particularly serious and results in liver and spleen enlargement, anemia, stunting, reduced ability to learn and can result in death **(5)**.

Intestinal schistosomiasis also infects rodents. Different studies show that the high prevalence and parasitic burden of S. mansoni are confirmed in rodents. Rodents preferred areas of dense herbaceous vegetation near the ground, as well as courses and waterbodies. High S. mansoni infection of rodents was recorded among those found in human sewage contamination around home ranges, in high local snail abundance areas and a high movement pattern of rodents between transmission sites **(6)**.

The level of S. mansoni infection in rodents increased with proximity to human habitations, which is also related to the level of infection in humans. Thus, rodents might be an important reservoir of schistosoma and a source of infections for other groups of animals and humans. New phenomena concerning that the spillover of hybrids can generate from rodents a higher risk of infection for humans. Hybridization of different animal schistosomes causes the emergence of virulent species for human infection **(7)**.

Effective schistosomiasis prevention and control is no longer a matter of heavy application of molluscicides and mass drug administration blindly; rather, scientific information about the disease distribution/burden, presence of intermediate host and the burden in other possible reservoir hosts (like rodents) are paramount important. Knowing the epidemiology of snails and cercariae is an indispensable tool for intervention measures against schistosomiasis. The species of schistosomiasis varies with the type of snail intermediate host **(8)**.

Adult S. mansoni worms reside deep within the mesenteric veins of the intestine, where they feed on blood and acquire nutrients necessary for growth, development, and egg production. Each worm pair produces ~300 eggs daily, which exit the host by moving from the depths of the mesenteric vessels, across the intestinal wall and into the intestine lumen **(9)**.

Importantly, as schistosome eggs are not in possession of any obvious motility mechanisms themselves, their expulsion is likely to be heavily reliant on host-driven processes. However, successful egg passage is not guaranteed. Approximately half of all deposited eggs never reach the intestine, but instead are swept to the liver, where they evoke strong granulomatous inflammation, as characterized by the infiltration of alternatively activated (AA) macrophages, eosinophils and T-helper 2 (Th2) cells, with additional fibroblast proliferation and generation of extracellular matrix **(10)**.

For the remainder of intestinally-bound eggs, success is still not certain. Firstly, eggs remain viable for a mere 2–3 weeks following oviposition, providing them with a relatively short timeframe to make this journey. Secondly, due their high antigenicity and continual release of antigens and other metabolites, transiting eggs are easily detected by the host immune system, becoming the focal point of inflammatory granulomatous reactions. If these responses are too extreme, a variety of immune-pathologic sequelae will follow **(11)**.

It has become increasingly obvious that schistosomes implement a variety of strategies to ensure efficient egg transit. Within the vasculature, egg extravasation is promoted by angiogenesis, endothelial activation, and interactions with blood clotting components **(12)**.

In the intestinal tissues, schistosomes exert a variety of immunomodulatory influences to support granuloma formation around transiting eggs, which is an essential process in egg excretion. Directly related to this, and to prevent overwhelming immunopathology, schistosomes guide the immune response toward a more regulatory phenotype during chronic disease (13).

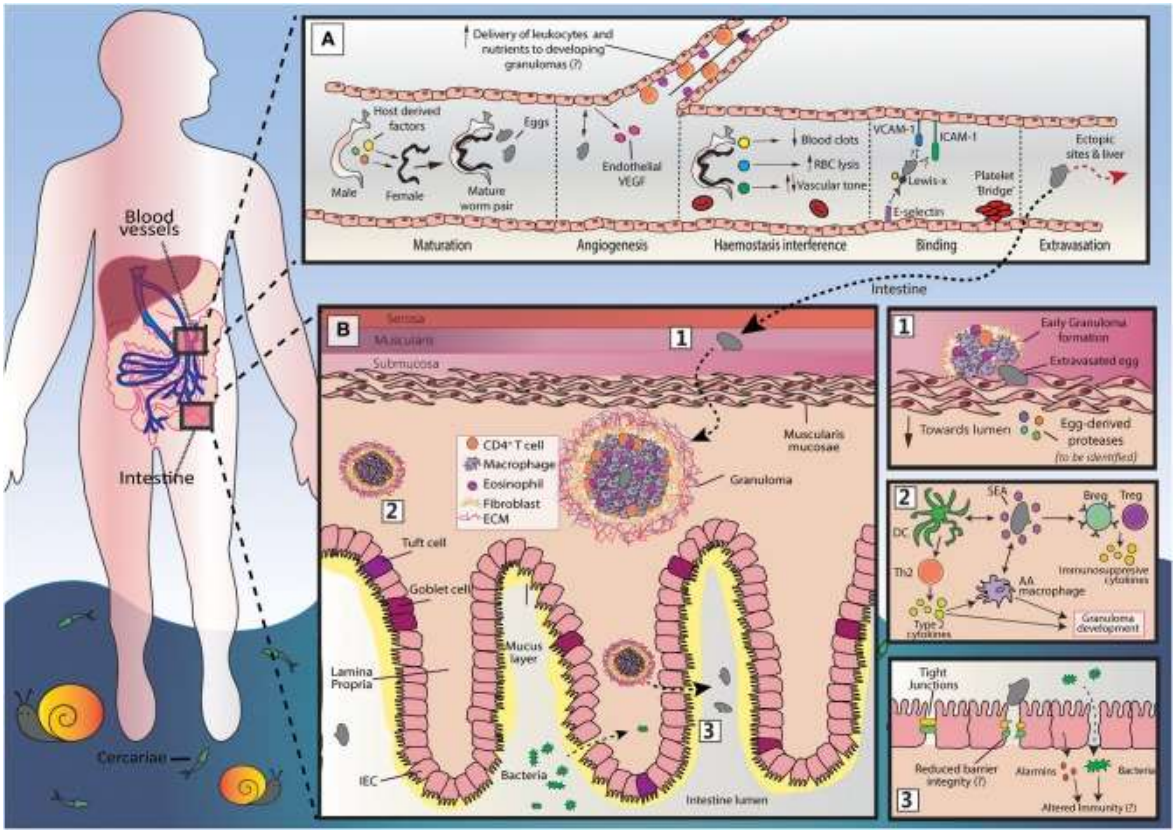

Figure 1. An overview of S. mansoni egg migration. Schistosome egg transit is facilitated by a series of host interactions at the intestinal and vascular interface.

(A) The development of schistosomes into sexually mature, egg-producing adults occurs within the portal vein (~3–5 weeks post infection) and requires the transduction of host-derived signals (including those from the innate and adaptive immune system) to the developing worm pair. Once sexual maturity is reached, worm pairs migrate toward the mesenteric vessels, where the females lay approximately 300 eggs per day and actively modulates the intravascular environment to support their long-term survival. The production of eggs at ~5–6 weeks post infection is a milestone event in the schistosome life cycle, that is characterized by induction of a marked Th2 response and angiogenesis. Notably, the generation of a Th2 response by the host is critical for egg passage, and new vessel formation may favor egg transit, promoting the recruitment of immune cells and nutrients to developing granulomas. Freshly deposited eggs cannot move by themselves and must somehow attach and extravasate the endothelium. Although yet to be fully defined, this process may involve E-selectin: -Lewis-x interactions, and participation from platelets, ICAM-1 and VCAM-1. While a large proportion of eggs successfully penetrate the endothelium and reach intestinal tissue, many are swept to the liver or other distal locations (e.g., brain or spinal cord). Since schistosome eggs are unable to transit through these organs, overwhelming tissue pathology and inflammation may ensue. **(B)** Once schistosome eggs have passed across the host endothelium and out of the vasculature, they must cross the multi-layered intestinal wall. The host immune system responds to transiting eggs via an inflammatory granuloma response, in which individual eggs are encapsulated by immune cells [including alternatively activated (AA) macrophages, Th2 cells and eosinophils] and extracellular matrix (ECM), which protects host tissues from egg-derived toxins, but ultimately leads to formation of fibrotic lesions. For unknown reasons, granulomatous responses need to successfully develop for effective egg excretion from the host. Accordingly, schistosomes and their host have co-evolved a wide range of mechanisms to skew the host immune response toward granuloma-inducing Th2 profile. These include the ability of soluble egg antigens (SEA) to promote alternative activation in macrophages and to condition dendritic cells (DCs) for Th2

polarization. However, to prevent unwanted bystander tissue damage and potentially fatal immunopathology, schistosomes also implement various strategies to dampen host immunity and expanded regulatory networks (Bregs and Tregs). There remain many unknowns surrounding egg migration. This includes the molecules secreted by eggs to disrupt host barriers and modulate immune responses and, importantly, how egg penetration and intestinal 'leakiness' may influence local and systemic immune reactions **(13)**.

The schistosome life cycle occurs in 2 hosts: snails and mammals. Either asexual or sexual reproduction occurs, depending on the type of host. Asexual reproduction occurs in freshwater snails. In the snail, this begins with the development of miracidia into a sporocyst. Sporocysts multiply and grow into cercariae. In the mammalian hosts, parasites grow to become mature, mate, and produce eggs. Mammalian hosts include humans, mice, and dogs **(14)**.

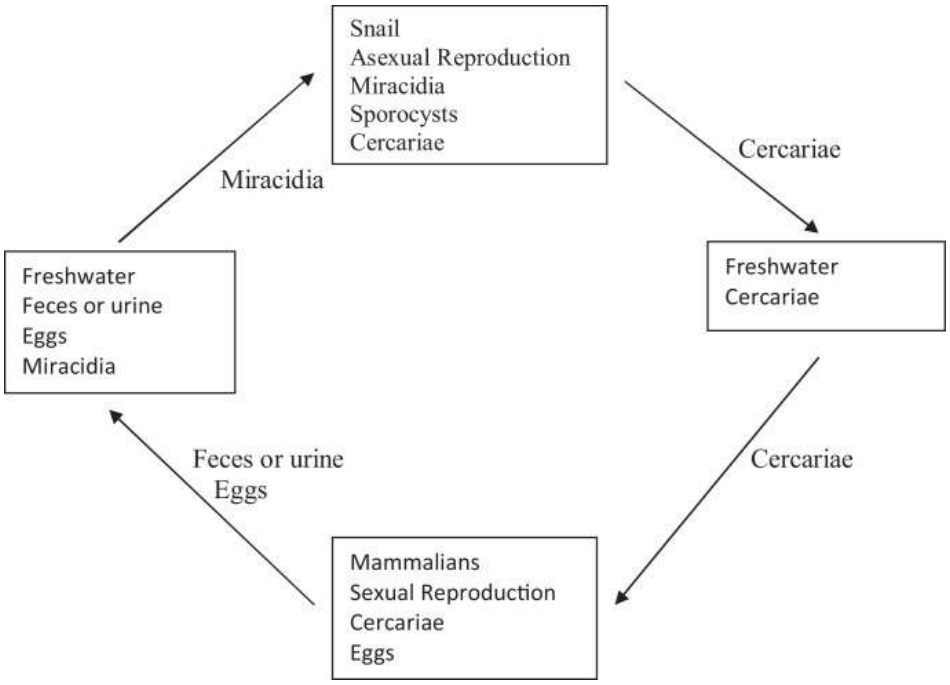

Figure 2. Schistosomiasis life cycle. Asexual reproduction in snails and sexual reproduction in mammals **(15)**.

Schistosomiasis is caused by infection with blood flukes of the genus Schistosoma. At least 5 trematode species are known to infect humans. These are S. haematobium, S. intercalatum, S. japonicum, S. mansoni, and S. mekongi. Schistosomiasis infects more than 230 to 250 million people annually and 779 million people are at risk of infection **(16)**.

This disease causes 280,000 deaths annually, and a worldwide burden of 3.3 million disability-adjusted life years. Human schistosomiasis is among the most prevalent human parasitic infections **(17)**.

The disease ranks second beneath malaria on the list of parasitic diseases, and exists in 75 to 76 countries, Schistosomes exists in many developing countries in Africa, Asia, South America, and several Caribbean islands. Schistosomiasis can also occur in nonendemic areas. It can be spread through water-based development projects and immigration **(18)**.

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 host's 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 **(19)**.

In most studies, this is seen as early high-level responses to soluble egg antigens (SEA) that then decrease as infections become chronic. Responses to soluble worm antigenic preparations (SWAP), in contrast, invariably rise during early infection and continue to be expressed throughout continuing chronic infections **(19)**.

This has long been true using these crude antigenic mixtures and is being shown now to be true for individual antigenic moieties expressed by different life cycle stages. 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, whether their mother was infected while they were in utero, and whether and how often they may have been treated for their schistosomiasis with PZQ. All of these situations and probably many others contribute to their immune status at the time they are being studied **(20)**.

Immune Modulation by S. mansoni

It is well-known that parasites can induce an immunosuppressive environment to evade the immune system. This also benefits the host, as a reduced inflammatory response limits tissue damage. Murine studies have shown that repeated infections with S. mansoni lead to the suppression of the immune response, promoting survival of the adult worms **(21)**.

Early Immune Responses Induced by Proteases

Proteases are crucial for the survival of parasites. A range of different proteases assist in invasion, nutrient uptake, hatching, evasion of the immune system, and modulation of the host's physiology. S. mansoni proteases have been shown to regulate vascular functions, causing vasodilation, which allows the relatively large adult worms to move more freely to the narrow blood vessels and deposit their eggs there **(22)**.

The most well-known S. mansoni proteases are cysteine and aspartic proteases, as well as the serine proteases (SP)s. The best studied protease, the 28kDa S. mansoni cercarial elastase (SmCE) is largely responsible for skin penetration. Once cercariae come into contact with the human host, they can enter the skin within 1.5 min, with the help of SmCE **(22)**.

SmCE is capable of degrading a large variety of human skin macromolecules. Importantly, this protease is also able to elicit an immune response in the host. SmCE induces the production of anti-elastase IgG2a antibodies, which induce macrophage-mediated cytotoxicity against schistosomula and cercariae, resulting in effective killing of the parasite at this stage. In addition, both the alternative and classical complement-mediated pathways contribute to the clearance of the parasite during early infection **(23)**.

Although SmCE plays a key role in eliciting this response, it is also involved in resistance against complement-mediated killing. During the transformation of cercariae into schistosomula, SmCE assists in remodeling the outer layer of the tegument (i.e., the outer surface of schistosomula and adult worms) and shedding of the glycocalyx which is a potent inducer of the complement system **(24)**.

Next to shedding the glycocalyx, the transforming cercariae remodel the single membrane surface into a complex bi-layer membrane structure, incorporating different host molecules, multi-layered vesicles and glucose transporters. Interestingly, the outer surface of the bi-membrane structure can adsorb human blood molecules, therefore masking it from recognition of the immune cells. However, several tegument proteins are targeted by the immune system, as can be shown by the production of specific IgE against members of the Tegumental allergen-like (TAL) family **(25)**.

Although the early antigens discussed in this section are crucial for evading initial immune responses during and after invasion, they do not actively modulate the immune response. These proteins are attractive candidates for vaccine development, but are not suitable for immunomodulatory therapy. The processes that lead to immunosuppression by S. mansoni will be covered in more detail in the following sections, highlighting the role of dendritic cells and macrophages as these cells largely determine whether a Th1 or Th2 dominant immune response will be initiated **(26)**.

Dendritic Cells

Dendritic cells (DCs) are crucial for connecting the adaptive and innate immune responses. Depending on the stimuli DCs receive, they can adopt either a tolerogenic or an immunogenic activation state, which in turn affects the differentiation of T-cells. The maturation of dendritic cells begins with the uptake of an antigen via pattern recognition receptors

(PRRs) such as Toll-like receptors (TLRs) and C type lectin receptors (CLRs) **(26)**.

PRRs recognize the so-called pathogen-associated molecular patterns (PAMPs) on infectious agents, which leads to internalization of the pathogen. Whereas, immunogenic DCs develop in response to "danger" signals in the form of PAMPs, cytokines or other signals from activated T-cells, tolerogenic DCs usually arise in response to apoptotic cells or commensal bacteria, in the absence of "danger" signals. These DCs do not exhibit markers of activation such as MHC and CD86 upregulation **(26)**.

The tolerogenic DC induce Th2 and Treg responses, as seen in helminthic infections. Importantly, tolerogenic DCs have been shown to prevent the development of autoimmunity. Therefore, helminthic products that promote the development of tolerogenic DCs have therapeutic potential for treating autoimmune disorders **(26)**.

Indeed, certain helminthic products have been found to direct naïve DCs toward the tolerogenic profile by binding to TLRs or CLRs (such as DC-SIGN). In particular, soluble components secreted by S. mansoni eggs, called soluble egg antigen (SEA), and egg-derived dsRNA have shown immunoregulatory properties through induction of tolerogenic antigens. SEA comprises all soluble components of the S. mansoni eggs, of which only few have been identified and characterized **(27)**.

Studies with murine bone-marrow derived DCs have found that the presence in vitro of SEA prevents TLR-dependent conventional activation of DCs. The tolerogenic profile of SEA-exposed DCs was confirmed by minimal upregulation of MHC, absence of CD80/CD86 upregulation and lack of Th1 and Th17-type cytokine production, such as IL-6, TNF and IL-12, and maintain their ability to endocytose, which is lost during conventional maturation of DCs **(28)**.

To confirm that these unconventional DCs effectively drive a Th2 response, SEA-treated DCs were transferred to mice. Indeed, when murine SEA-treated DCs were transferred into live animals, they induced the differentiation of naïve T-cells into Th2 cells and the production of IL-4, IL-5, and IL-10. Furthermore, the induction of a tolerogenic DC profile by SEA has been found to be dependent on CD40. Although SEA does not upregulate CD40, absence of CD40 leads to failure to develop Th2 responses by SEA-exposed DCs **(28)**.

On a molecular level, SEA has been found to inhibit pro-inflammatory responses by interacting with the nuclear factor κ B (NFκB) family member B-cell lymphoma 3-encoded protein (Bcl3). Klaver et al. showed that the glycosylation of SEA is essential for the Th2-driving of DCs by suppressing lipopolysaccharide (LPS)-induced, TLR-mediated production of pro-inflammatory cytokines **(27)**.

It is still unclear how exactly DCs drive Th2 differentiation after activation by SEA, but it is known that CD40, OX40L and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB1) expression are required. However, it is certain that unconventional activation profiles of DC induced by SEA can actively promote Th2 response development **(29)**.

Non-SEA components have also been found to induce tolerogenic DCs. One of the tegumental antigens, Schistosoma mansoni protein 29 (Sm29), has been shown to induce tolerogenic DCs in vitro. Sm29 is located in the tegument of adult S. mansoni and constantly exposed to the immune system, which would explain its immunosuppressive characteristics **(30)**.

DCs treated with Sm29 exhibited several characteristics of a tolerogenic profile: higher expression of HLA-DR, CD83, CD80, and CD86 as well as of IL-10 and IL-10R, and increased the frequency of CD4+ T-cells expressing the regulatory molecules CTLA4 and CD25. Taken together these findings suggest Sm29 contributes to the differentiation of naïve T-cells into Treg, unlike the SEA that is a potent Th2 inducer **(30)**.

Macrophages

Schistosoma mansoni also affects macrophage activity. Macrophages can either be activated via the classical pathway (M1) or the alternative pathway (M2). M1 activation occurs in response to TLR ligands or IFNγ, M2 activation occurs in response to IL-4/IL-13. M2 macrophages, in contrary to M1 macrophages, have low expression of IL-12, but high expression of IL-10, TGFβ and arginase 1. M2 macrophages are present in granulomas and have been found to play a key role in the immunomodulation during schistosomiasis **(31)**.

They have anti-inflammatory functions and play a direct role in modulating fibrosis and survival of the host by downregulating

inflammation. Interleukin-4-inducing principle from Schistosoma mansoni eggs (IPSE/alpha-1), a major component of SEA, is the main driver of M2 differentiation. IPSE/alpha-1 binds to immunoglobulins, with a high affinity for IgE **(32)**.

Once it binds to IgE bound to FceRI receptors on the surface of basophils, it triggers the release of IL-4 and IL-13, which directly induces the differentiation of monocytes into alternatively-activated-macrophage-like phenotype and inhibits the secretion of pro-inflammatory cytokines by LPS-stimulated monocytes **(32)**.

Next to SEA, the lipid lysophosphatidylcoline (LPC) can also induce macrophage differentiation into an M2 phenotype. LPC is excreted by the worm as a degradation product. It has anti-inflammatory properties such as increasing the immunosuppressive function of Treg cells, promoting eosinophil recruitment and stimulating Th2 polarization through Toll-like receptor 2 (TLR2) dependent mechanisms **(33)**.

LPC activates peroxisome proliferator-activated receptor gamma (PPARγ), a transcription factor required for M2 polarization, which in turn increases Major Histocompatibility Complex, Class I-Related (MR1), chitinase 3-like 3 (Ym1), IL-10 and TGFβ, but not Nitric Oxide Synthase 2 (NOS2), gene expression, which is characteristic for M2 macrophages **(33)**.

Additionally, LPC induces IL-10 production by macrophages. Thus, SEA and LPC, amongst others, drive M2 differentiation of macrophages, which contributes to the immune shift to Th2 response observed in schistosomiasis **(33)**.

B-Cells and IgE

As the source of the IgE which protects the host, B-cells play an important part in the immune response against S. mansoni. In S. mansoni infected individuals, T helper 2 (Th2) responses and their associated characteristics (IL-4, IL-5 cytokines, eosinophilia, and specific IgE secretion) have been associated with resistance against re-infection **(34)**.

S mansoni has developed mechanisms to interfere with IgE signaling to evade the immune system. S. mansoni antigens are able to cleave the surface-bound low-affinity IgE receptor CD23, which could potentially interfere with T-cell activation. Additionally, S. mansoni was found to secrete a homologue of soluble CD23 acting as a decoy receptor by binding IgE and inhibiting activation of the high-affinity IgE receptor FcεRI. This in turn prevents degranulation of basophils and mast cells, inhibiting the release of cytotoxic molecules and inflammatory mediators, which usually contribute to killing of the parasite **(35)**.

In addition to conventional B cells, a small subset of B-cells, B regulatory cells (Bregs), are also involved in the response to S. mansoni. Bregs have recently been identified, as a subset of B-cells capable of producing IL-10, which induces Treg differentiation in vitro. Furthermore, Bregs can downregulate immune responses through direct interaction with effector T-cells **(36)**.

IPSE/alpha-1 can induce production of IL-10 in naïve B cells and stimulate the differentiation of Breg cells Additionally, B cells bind SEA and internalize it, leading to a 3-fold upregulation in the production of IL-10 **(36)**.

Bregs have been implicated as important players in autoimmunity, and helminth infections have been shown to affect their function in autoimmunity, potentially altering the course of disease. Therefore, stimulation of these cells by S. mansoni products warrants further investigation **(37)**.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily affects the lining of the synovial joints, resulting in both cartilage destruction and bone erosion. The disorder may lead to progressive disability and premature death, contributing to a significant clinical and economic burden on society. Some biologic agents such as cytokine antagonists that inhibit TNF-α, IL-1β, or IL-6 (anti-TNF-α, anti-IL-1, or anti-IL-6) have shown preventive effects that can substitute for conventional disease-modifying anti-rheumatic drugs **(38)**.

However, no clinically useful biologic therapy is available for the individually tailored treatment of RA, and patients with RA usually require a long-term treatment plan, in which side effects are generally inevitable. Thus, the development of an innovative prophylactic or therapeutic strategy is critical, and there has been considerable interest in developing recombinant immune-modulating drugs for RA treatment **(39)**.

Collagen-Induced Arthritis Autoimmune Mouse Model for Rheumatoid Arthritis

The CIA autoimmune mouse model is widely used to study RA. Infection of mice with

either S. mansoni or S. japonicum prior to collagen immunization reduced the severity of CIA. In CIA mice, a prior S. mansoni infection was found to down-regulate the splenic production of Th1 (IFN-γ), and pro-inflammatory cytokines (TNF-α, and IL-17A), and this was accompanied by the up-regulation of anti-arthritic cytokines (IL-4 and IL-10) **(40)**. Subsequently it was demonstrated that the protective effect of a S. japonicum infection against CIA is infection stage-dependent, i.e., protection was only provided in the ASCIA group {when the first injection of type II collagen (CII) was given at the acute stage [7 weeks post infection (p.i.)]}, but not in the ESCIA group [when the first injection of CII was given at an early stage (2 weeks p.i.)] **(41)**. The protective effects in the former group were associated with increased production of IL-4 and IL-10 and reduced production of IFN-γ in the spleen. As a result, the importance of a dominant and long-lasting Th2 response in suppressing autoimmune joint inflammation was suggested by these authors **(41)**.

Another group then explored the effects of S. japonicum infection on CIA by challenging DBA/1 mice with unisexual or bisexual cercariae 2 weeks prior to CII injection or at the onset of CIA. This study showed that S. japonicum infection (unisexual or bisexual) 2 weeks prior to CII immunization significantly reduced the severity of CIA **(42)**.

This outcome was consistent with earlier results obtained with a S. mansoni infection by Osada et al. but not with previous observations by He et al. In the protected mice, significant down-regulation of Th1 (IFN-γ) and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), and up-regulation of Th2 (IL-4) and the anti-inflammatory cytokine IL-10 were observed **(43)**.

Song et al. also demonstrated that when the established CIA mice were challenged with bisexual S. japonicum cercariae, exacerbating effects on the disease were elicited at 1-week p.i. Notably, S. mansoni infection exhibited both ameliorating and exacerbating effects on spontaneous autoimmune arthritis in IL-1 receptor antagonist (IL-1Ra)-deficient mice **(42)**.

While S. mansoni infection partially protected the IL-1Ra-deficient mice from arthritis with reduced IL-17 and TNF-α and enhanced IL-4 and IL-10 splenic responses, the infected mice had increased levels of IgG rheumatoid factor and anti-dsDNA IgG in serum which likely contributed to the exacerbating autoimmune effects **(44)**.

By employing signal transducer and activator of transcription 6 (STAT6) knock-out (KO) and IL-10 KO mice, Osada et al. later demonstrated that STAT6-related cytokines (IL-4, IL-13) and IL-10 are essential for the suppression of CIA by a S. mansoni infection **(45)**.

Adjuvant Arthritis (CFA-Induced AA) Induced Rat Model

Schistosome antigenic components have been employed to circumvent the potential deleterious effects caused by a live worm infection. Autoclaved antigen, derived from S. mansoni cercariae (ASMA), has been tested for a potential protective effect on adjuvant arthritis (CFA-induced AA) induced in rats by subcutaneous and intradermal injections of complete Freund's adjuvant into the paw and tail, respectively **(46)**.

Intradermal injection of ASMA, after CFA-induced AA, attenuated the progression of clinical signs of polyarthritis, and improved the gait and increased the body weight of animals, with reduced production of IL-17 and increased serum levels of both IL-10 and IFN-γ. The authors suggested that up-regulation of $Foxp3^+$ Tregs, with subsequent modulation of both pro- and anti-inflammatory cytokines, contribute to the anti-arthritic activity **(46)**.

Unlike the CIA model, in which it has been proposed that the anti-arthritic effect of schistosome infection is induced by Th2-polarization with increased levels of protective Th2 cytokines and suppression of the pathogenic Th1 cytokines, in the CFA-induced AA rat model, IFN-γ (the cytokine strongly associated with a Th1 response) increased after ASMA treatment; this may have been due to the presence of mycobacteria, constituting the main antigenic component in the CFA adjuvant, inducing the high level of endogenous IFN-γ recorded **(46)**.

Conclusion

The findings could have implications for the development of new arthritis treatments, potentially involving further investigation in humans. Future research may include further elucidating the mechanisms of action, optimizing antigen formulations, and conducting clinical trials in humans.

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