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Immune Modulation by *Schistosoma mansoni* Infection and its Implication in Auto Immune Disorders and Allergic Diseases

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Abstract

The immune response during the acute phase of *schistosoma mansoini* infection is associated with type 1 helper T-cells (Th1) response with increased production of tumor necrosis factor (TNF-α) and interferon-γ (IFN-γ) while in chronic phase the immune response is associated with type 2 helper T-cells (Th2) type, with elevated levels of interleukin (IL)-4, IL-5, and IL-10 and decreased levels of IFN-γ. This down modulation is mediated by *S. mansoni* antigen driven IL-10 production. IL-10 modulates the expression of co-stimulatory molecules and the production of pro-inflammatory cytokines such as IFN-γ, TNF-α by acting on macrophages. IL-10 also inhibits the differentiation of dendritic cells and suppresses the production of Th1 and Th2 type chemokines and cytokines. Evidence indicates chronic exposure to *S. mansoni* to down regulate the type 1 immune response and prevents the onset of Th1 mediated diseases such as multiple sclerosis, diabetes mellitus and Cronh's diseases. Furthermore, chronic exposure to *S. mansoni* also down regulate Th2 mediated diseases such as atopic asthma and allergic rhinitis. This is mainly associated with diminished IL-5 production and increased IL-10 production by peripheral blood mononuclear cells in response to the parasite antigens. IL-10 induced by the parasite antigen interferes with allergic effector mechanisms either by inhibiting mast cell degranulation or by inhibiting Th2 cell proliferation. Generally, it seems that *S. mansoni* infection could mediate protection against allergic diseases and auto immune disorders. Identification of parasite molecules that induce protection and the way in which the parasite modulates immune response is critical to discover safe and effective drugs for the treatment of chronic inflammatory and allergic diseases.

Keywords: *S. mansoni*; Allergic diseases; Macrophages

Introduction

Schistosomiasis is one of the world's widespread parasitic diseases of man which is second only to malaria in socioeconomic and public health importance, mostly in tropical and subtropical areas. It is mainly found in Africa, South America, the Middle East, East Asia, and the Philippines [1].

In an attempt to measure the global burden of schistosomiasis, various estimates have been made. Recent systematic review integrating results of several independent studies by Steinmann *et al.* [2] suggested that 779 million people are at risk of schistosomiasis and 207 million people are infected worldwide. Africa is the continent most widely affected by the disease, caused mainly by *S. mansoni* and *S. haematobium*, which are the major causes of intestinal and urinary schistosomiasis, respectively. *S. japonicum* is transmitted in several Far Eastern countries (China, Philippines, and Indonesia). *S. intercalatum* and *S. mekongi* are geographically highly restricted to small areas of Africa and Southeast Asia, respectively.

There are five species of schistosomes that cause disease in humans, namely *S. mansoni, S. intercalatum, S. haematobium, S. japonicum and S. mekongi* [3]. Among these, *S. mansoni, S. japonicum* and *S. haematobium* cause significant public health problems [4]. *S. mansoni, S. japonicum* and *S. intercalatum* cause intestinal schistosomiasis whereas *S. haematobium* is responsible for urinary schistosomiasis. There are also other minor non-human shistosome species that may also cause accidental infections, or cercarial dermatitis (bird-infecting schistosomes e.g. Trichobilharzia spp.). Other schistosomes of veterinary importance include *S. bovis, S. matthei, S. hippopotami, S. sprinallis* and *S. rohhaini* [5]. In Ethiopia, *S. mansoni* and *S. haematobium* have significant medical and public health importance [6].

Fresh water snails of the genus *Bulinus, Biomphalaria* and *Oncomelania* serve as intermediate host of human *Schistosoma* parasites. Snails of the genus *Biomphalaria* serve as intermediate hosts of *S. mansoni*, Snails of the genus *Bulinus* serve as the intermediate hosts of *S. haematobiumi* and *S. intercalatumin*. *Oncomelania* serves as the intermediate host of S. japonicum [7]. In Ethiopia two species of the *genus Biomphalaria, B. sudanica* and *B. pfeifferi*, are known to transmit *S. mansoni* [8] whereas Bulinus abyssinicus and *B. africanus* are the only bulinid species found naturally transmitting *S. haematobium* [9].

Autoimmune disorders and allergic diseases

Immune-mediated diseases are diseases result from targeted tissue destruction due to chronic inflammation orchestrated by lymphocytes. Crohn's disease and ulcerative colitis together comprising Inflammatory Bowel Disease (IBD), asthma, Multiple Sclerosis (MS) and autoimmune (Type 1) Diabetes (T1D) are some examples of immune-mediated diseases.

Autoimmune diseases are the result of specific immune responses directed against structures of the self [10]. The acquired ability of the immune system to avoid responsiveness to self-antigens is defined as 'tolerance', and is obtained by the cooperative efforts of central and

peripheral mechanisms, which allow a rapid and efficient removal of pathogens (e.g. viruses or bacteria) in the absence of self-recognition. Occasionally, auto reactive cells may be activated, probably because of molecular mimicry between structures of the invading microorganism and the self. These auto reactive immune responses, however, are rapidly controlled and shut off by several immune regulatory mechanisms. Autoimmune diseases, on the other hand, originate from a sustained and persistent immune response against self-constituents, and require a breakdown in tolerance. The mechanisms responsible for this breakdown are so far poorly defined [11].

The incidence of autoimmune and idiopathic inflammatory disorders such as inflammatory bowel disease, diabetes and atopic disease has been increase exponentially during the past 40 years in Westernized societies, and a similar pattern is emerging in urbanized areas of developing countries [12]. This increase is too rapid to be driven mostly by genetic factors [13].

Epidemiologic studies have demonstrated that genetic factors are crucial determinants of susceptibility to autoimmune disease. Most autoimmune diseases are multigenic, with multiple susceptibility genes working in concert to produce the abnormal phenotype. In general, the polymorphisms also occur in normal people and are compatible with normal immune function. Only when present with other susceptibility genes do they contribute to autoimmunity [14]. Some of these genes confer a much higher level of risk than others; for example, the major histocompatibility complex makes an important contribution to disease susceptibility. Most autoimmune diseases are linked to a particular class I or class II human leukocyte anti-gens (HLA) molecule [15] but this association may require linkage with another gene such as that encoding TNF-a or complement. In the case of diabetes and rheumatoid arthritis, however, the reproduction of the disease in transgenic animals expressing particular human HLA antigens strongly indicates that the class I or class II molecule itself confers susceptibility to disease [16].

In addition to genetic factors, external environmental factors such as hormones, diet, drugs, toxins and/or infections are also contribute for the development of autoimmune diseases by amplifying autoimmunity in genetically susceptible individuals and to break tolerance in genetically resistant individuals, thereby increasing the risk of developing autoimmune disease. Therefore, the development of autoimmune diseases depends on a combination of genetic and environmental factors like hormones, diet, toxins, drugs and infections. Genetic predisposition accounts for only about one-third of the risk of developing an autoimmune disease, while none inherited environmental factors account for the remaining 70% risk [17].

Most autoimmune disorders are caused by the involvement of self-reactive immune cells such as autoantibodies, mononuclear phagocytes, auto reactive T lymphocytes and plasma cells (autoantibody producing B cells) [18].

Autoantibodies can induce damage to the body by binding to self-tissues, activating the complement cascade and inducing lysis and/or removal of cells by phagocytic immune cells. Self-antigen, autoantibodies and complement can combine to form injurious immune complexes that deposit in vessels or joints as is observed in lupus, inflammatory heart disease and arthritis [19].

Damage induced by cells of the immune system play a major pathogenic role in many autoimmune diseases. The predominant infiltrating cells include phagocytic macrophages, neutrophils, self-reactive CD4+ T helper cells and self-reactive CD8+ cytolytic T cells, with smaller numbers of natural killer cells, mast cells and dendritic cells. Immune cells damage tissues directly by killing cells or in directly by releasing cytotoxic cytokines, prostaglandins, reactive nitrogen or oxygen intermediates. Tissue macrophages and monocytes can act as antigen presenting cells to initiate an autoimmune response, or as effector cells once an immune response has been initiated. Macrophages act as killer cells through antibody dependent cell mediated cytotoxicity and by secreting cytokines, such as TNF or IL-1, which act as protein signals between cells. Macrophages and neutrophils damage tissues (and microorganisms) by releasing highly cytotoxic proteins like nitric oxide and hydrogen peroxide [18].

Allergic diseases such as allergic asthma, hay fever, eczema, and allergic rhinitis are mostly resulting due to allergic immune responses to common environmental antigens. Among allergic diseases, atopic asthma and allergic rhinitis are the most common diseases affecting the quality of life of patients. The immune pathogenesis of these diseases involves type 2 helper T-cells, with the production of IL-4, IL-5 and IL-13. IL-4 and IL-13 induce and maintain the synthesis of IgE by B cells and also the expression of FcεRI on mast cells and eosinophils, while IL-5 induces the recruitment, differentiation and infiltration of eosinophils in the bronchial mucosa [20]. Another cytokine, IL-9, by itself or together with IL-4 and IL-13, induces mucous production, airway remodeling and the activation and recruitment of mast cells [21]. Presence of mucus and bronchial hyper reaction as a result of activation of these various cell types, leads to the symptoms of asthma. Beside Th2 cells mediated reaction, subpopulations of activated Th1 cells also contribute to the inflammatory reaction associated with tissue [22].

In addition to Th2 and Th1 signature cytokines, some newly described cytokines such as Thymic Stromal Lymphopoietin (TSLP), IL-25 and IL-33 might participate in the pathogenesis of atopic asthma. TSLP is an epithelial cell derived cytokine, which induces Dendritic Cell (DC)-mediated CD4-T cell responses with a pro allergic phenotype. Recent studies have shown that TSLP, by induction of Th2 cytokines is able to initiate and maintain the allergic inflammatory process both in mice and humans [23].

The Immune Response against *Schistosoma mansoni* Infection and its Immune Modulation

Immune response against *Schistosoma mansoni* infection

The immune response to *S. mansoni* is characterized by a polarized Th2 responses including, the production of Th2 cytokines (IL-4, IL-5, IL-13, and IL-10), high serum titers of immune globuline (Ig) E antibodies and eosinophilia. The role of these cytokines in protecting humans against parasite infections is still not well understood. High levels of *S. mansoni* specific IgE correlated with protection against re infection in subjects living in an endemic area of *S. mansoni* [24]. IgE produced by B cells stimulates mast cells and basophils to release mediators which stimulate eosinophil differentiation and induce eosinophil cytotoxity. IgE can also directly affect eosinophils by binding to FcRI on eosinophils [25]. FcRI can mediate schistosomula specific eosinophil dependent cytotoxicity by signalling the release of Eosinophil Peroxidase (EPO). This provides the involvement of eosinophils in immunity against schistosomiasis. Experiments *in vivo* showed that eosinophils can kill *S. mansoni* in the presence of specific anti schistosome IgE antibodies. Furthermore, by using selective absorption of various isotypes or alternatively using competition with isotype matched irrelevant myeloma proteins, IgE was shown to

induce killing by mononuclear phagocytes, eosinophils, and platelets in both humans and rats [26].

Many studies have indicated that *in vitro* killing of cercariae and schistosomula can be initiated by host complement complexes [27,28] and Antibody Dependent Cell Mediated Cytotoxicity (ADCC) [29,30]. In some instances, the recognition of parasite glycans has been demonstrated to be involved in these immune processes [30,31]. The glycocalyx of cercariae seems to activate the alternative pathway of complement binding, leading to efficient killing of a majority of cercariae. Schistosomula on the other hand are less susceptible to killing via this complement pathway [32], but instead can be targeted via the classical pathway, which requires antigen specific antibodies for its initiation [33]. It was demonstrated that antibodies against glycan antigen in the presence of complement could mediate *in vitro* lysis of schistosomula, indicating that glycan epitopes on the surface of schistosomula could be targets for antibody mediated complement killing [31]. Killing of schistosomula, at least *in vitro*, can also be mediated by ADCC mechanisms, which involve eosinophils, macrophages or platelets that bind to antigen-specific IgE bound on the surface of the schistosomula [34]. The other mechanism of killing is antibody independent and the schistosomula are killed directly by IFN-γ activated macrophage (Figure 1).

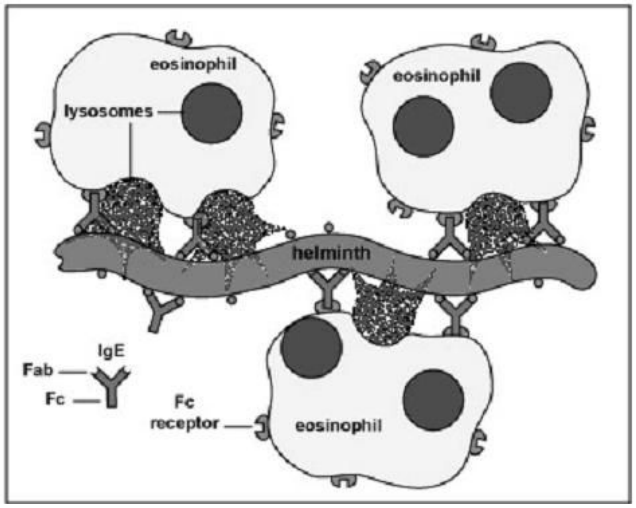

Figure 1: Opsonization of S. mansoni by IgE and Eosinophils. Cytokines and CD40 ligands expressed by Th2 cells function to stimulate B lymphocytes to express a class of antibodies called IgE. IgE acts as an opsonizing antibody to stick phagocytic eosinophils to parasite and allows the released major basic proteins and eosinophil cationic proteins to be focused on the targets for extracellular killing of the helminths. The Fab portion of IgE recognizes epitopes on the helminth, while the Fc portion binds to Fc receptors of activated eosinophils. The lysosomal proteases of eosinophils are able to destroy the tough integument of helminths (source: Doc Kaiser's Microbiology website).

Generally *S. mansoni* infection lead to an initial Th1 response with increased production of IFN-γ and TNF-α that is followed by a Th2 response induced by the parasite eggs' antigens that stimulates the production of Th2 cytokines such as IL-4, IL-5 and IL-10[35] (Figure 2).

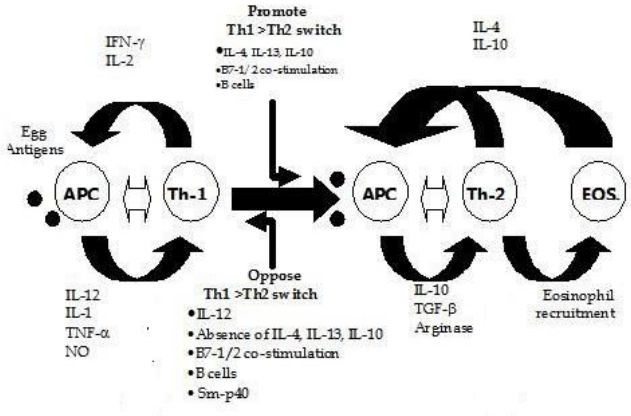

Figure 2: The immune response during infection with *S. mansoni*. The early response to egg antigens is of the Th-1 type, characterized by the indicated signature T cell and APC-derived cytokines; this response switches to a Th-2 type, also marked by typical cytokines. The upper box lists factors that facilitate the Th-1 to Th-2 switch. In contrast, conditions listed in the lower box oppose the Th-1 to Th-2 switch. [Modified from 20].

Immune modulation by *Schistosoma mansoni* infection

It is well known that the acute phase of S. mansoni infection is characterized by a strong Th1 inflammatory response and latter change in to a parasite antigen driven Th2 response chronically [36,37]. It is also known that this down modulation is mostly mediated by *S. mansoni* antigen driven IL-10 production [38].

Chronic *S. mansoni* infection induces a strong regulatory response with increased production of IL-10. IL-10, initially described by Pierz et al. [36], was first classified as a Th2-type cytokine but later considered the main cytokine of the regulatory immune response [37]. Besides T regulatory cells, a variety of cells, such as macrophages, Th2 cells, CD8+T cells, B cells, dendritic cells, Natural Killer (NK) and Natural killer T (NKT) cells also produce IL-10. Among the functions mediated by this cytokine are the inhibition of T cells and macrophage activation. Acting on macrophages, IL-10 modulates the expression of co-stimulatory molecules and the production of pro-inflammatory cytokines. IL-10 also inhibits the differentiation of dendritic cells and suppresses the production of Th1 and Th2 type chemokines and cytokines in some models [38]. IL-10 is able to inhibit the production of pro-inflammatory mediators such as IFN-γ, TNF-α and Nitric Oxide (NO) [39].

After encounter with *S. mansoni* antigens, different changes in the innate immune system such as modification of DC, macrophage (MΦ), and NKT cells, phenotype and cytokine secretion of the host are observed [40,41]. *S. mansoni* antigens can induce the secretion of regulatory cytokines from these cells as well as B1 B cells [42], resulting in the expansion of Th2 and regulatory T cells (Treg) populations that might be responsible for maintaining self-tolerance [38,43,44]. The induction and /or the expansion /recruitment of Treg and secretion of regulatory cytokines by these cells allow the parasite to evade both a sterilizing immune response and also suppress both Th1 and Th2 arms of the adaptive immune system [45,46].

DC and MΦ can direct the immune responses along either a tolerating or activating pathway based on the target receptors on these cells. *S. mansoni* has evolved strategies targeting receptors on these cells. Toll like receptors (TLRs) and C-type lectin receptors (CLRs) are broadly expressed on DCs and MΦs and they are the main parasite targets for evading immune surveillance [47]. More specifically, glycosylated molecules (expressed and secreted by *S. mansoni*) bind to the CLR and antagonize a TLR pro inflammatory pathway [48]. Numerous studies have shown that *S. mansoni* products induce IL-10 production by DCs and have a direct anti-inflammatory effect on DCs by controlling TLR ligand induced DC maturation [49]. *S. mansoni* has also been shown to induce alternatively activated MΦ (aa MΦ), which secrete anti-inflammatory mediators and inhibit T cell proliferation [50]. These macrophages require IL-4 for their development. Egg glycoproteins bind macrophage mannose receptors, and this allows alternatively activated macrophages to dampen inflammatory responses to schistosome eggs, results preventing organ damage [50].

Experimental study has shown that lysophosphatidylserine from helminth eggs activated TLR2 at the cell surface of DCs and influenced their functional maturation such that they induced IL-10-secreting regulatory T cells [49]. A schistosome egg glycoprotein has also been identified that induces the release of IL-4 and IL-13 from basophils, by none specifically binding and possibly crosslinking cell-surface IgE [51] NKT cells are also activated and stimulated to proliferate by glycolipids that are present in both eggs and worms [52].

The influence of *S. mansoni* products on the innate immune system also extended to NKT. These cells can direct the immune response in an appropriate direction by secreting a wide variety of pro and anti-inflammatory cytokines [53]. Schistosomes are rich in glycosylated molecules, which heavily decorate their integument or are actively secreted, and glycolipids presented by CD1d (a non-classical MHC molecule) on Antigen Presenting cells (APCs) may thus be able to activate regulatory NKT cells [54].

In addition to influence of *S. mansoni* antigens on the innate immune system, they induce the development of a population of $CD25^+$ $CD4^+$ T cells. These cells express the Treg cell transcription factor fork head box P3 (Foxp3), inhibit Tcell proliferation, make IL-10 but little of the signature Th2 cytokines, and potently suppress IL-12 production by CD40 agonist-activated DC [55].

Besides IL-10 and/or TGF-secretion/expression, there are also other possible regulatory mechanisms that would down-modulate the immune response during *S. mansoni* infection. Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), for example, is a molecule expressed on T cell surface that binds to the B7 molecule on antigen presenting cells and sends an inhibitory signal to the activated T cell limiting the production of the T cell growth factor IL-2 [56]. Thus, the linking of CTLA-4 molecules with B7 is essential in inhibiting the proliferative response of activated T cells [57].

In recent years, due to the immunomodulatory properties of IL-10 and its induction by helminthic infections, researchers have evaluated the influence of *S. mansoni* infection on the immune response and development of a number of infections and autoimmune diseases. Experimental study showed that Infection with *S. mansoni* affects the immune response to vaccine antigen. Individuals vaccinated with tetanus toxoid antigen and who were infected with *S. mansoni* produced the type 2 cytokine, IL-4, rather than IFN-γ in response to re stimulation in vitro, while uninfected vaccinated individuals in vitro, produced type 1 cytokine, IFN-γ [58].

There is evidence of regulation not only of Th1 but also of Th2 cell responses in individuals who are infected with *S. mansoni*, and infected individuals have been shown to have reduced allergic responses [45]. This is mainly associated with diminished IL-5 production and increased IL-10 production by peripheral blood mononuclear cells in response to antigens [59]. IL-10 induced by the parasite antigen interferes with allergic effector mechanisms either by inhibiting mast cell degranulation or by inhibiting Th2 cell proliferation [60]. Studies [61] have shown that *S. mansoni* infection and schistosome egg injection modulate allergic inflammation in ovalbumin (OVA)-sensitized mice by reducing eosinophil numbers and Lowering levels of IL-4 and IL-5 in *S. mansoni* infected and in parasite egg-injected mice than in asthmatic mice. In this study *S. mansoni* egg treated mice have increased IL-10 production in the lungs. IL-10 is an anti-inflammatory cytokine that seem to be involved in asthma modulation.

The ability of the recombinant *S. mansoni* antigens Sm22.6, Sm29 and PIII to modulate the inflammatory response have tested through *in vitro* experimental studies [62]. The Sm22.6 antigen is a soluble protein from the tegument, present in all life cycle stages of the worm with the exception of eggs [63]. Sm29 is a membrane-bound glycoprotein found on the tegument of the adult worm during the lung stage of S. mansoni infection [64], while PIII is a fraction of *S. mansoni* soluble adult worm antigen (SWAP) [65]. These antigens have been tested as vaccines to prevent schistosomiasis and/or liver pathology associated with the disease in murine models [66-68]. It was found that these proteins induce IL-10 in *S. mansoni* infected asthmatics [69]. Moreover, in a murine model of OVA-induced airway inflammation, immunization with Sm22.6, PIII and Sm29 leads to a reduction in the number of inflammatory cells, eosinophils and OVA specific IgE, compared to non-immunized mice. Also, the levels of Th2 cytokines in immunized mice are lower, while the levels of IL-10 and the frequency of Treg cells are higher in the immunized mice [70]. Sm14 is a fatty-acid binding protein from the adult worm [71] associated with down regulation of granuloma formation *in vitro* [66]. The ability of these proteins to down-modulate the *in vitro* Th2-inflammatory response in non-infected asthmatics is currently being tested with promising results [61].

The hypothesis that IL-10, highly produced by *S. mansoni* chronically infected individuals, suppresses the immediate hypersensitivity response to allergens and interfere with asthma severity has been also tested by Araujo et al. [59]. They have found higher levels of allergen-specific IL-10 production *in vitro* in *S. mansoni* infected asthmatics compared to asthmatics free of helminth infections. In the former patients the levels of Th2-cytokines IL-4 and IL-5 were higher than in infected asthmatics. Moreover, the addition of IL-10 to the cell cultures stimulated with mite allergen leads to a decrease in IL-5 production in asthmatics free of helminth infections.

These data together suggest that the mechanism behind the modulation of the immune response by the *S. mansoni* antigens involves regulatory cells, such as CD4+CD25+ Tcell, regulatory monocytes, regulatory cytokines such as IL-10 and also co-stimulatory pathways.

Protection and Therapeutic Prospects of *S. mansoni* Infection

There is sufficient evidence to emphasize that *S. mansoni* infection is driving responses that protect against autoimmune disorder and allergic disease. This has led to the number of studies aiming at identifying suitable *S. mansoni* molecules as immune modulators with therapeutic application for these diseases. Infection with *S. mansoni* or exposure to eggs from this helminth has inhibitory effect on the development of type 1 diabetes in Non Obese Diabetic (NOD) mice [51]. Another experimental study [72] showed that injection of *S. mansoni* eggs into 5 week old NOD mice totally inhibited the development of the disease, and later it was demonstrated that soluble extract of *S. mansoni* worm or egg completely prevented the onset of type 1diabetes in NOD mice.

It has been demonstrated that B cells induced by *S. mansoni* worms protect mice against allergic reactions in both anaphylaxis and allergic airway inflammation models in an IL-10–dependent manner. Both splenic B cells andCD4+ T cells isolated from chronically, but not acutely, infected mice protected against allergic airway inflammation via IL-10,revealing active roles for both IL-10 producing B cells and CD4 + T cells [73].

Helminth infections, particularly by *S. mansoni* also decreased tissue damage and clinical manifestation of other Th1-mediated autoimmune diseases such as multiple sclerosis and Crohn's disease. Using a mouse model to study Experimental Autoimmune Encephalitis (EAE), a multiple sclerosis like disease, it was demonstrated that infection with *S. mansoni* or injection of parasite eggs delays the onset of the disease and prevents inflammation in the central nervous system [74,75]. IFN-γ has been shown to exacerbate multiple sclerosis [76,77], and in mice model, the schistosome ova-induced Th2 response and consequent inhibition of IFN-γ production was, likely, responsible for the amelioration of EAE [75]. Moreover, the direct association between Th2 cytokines and *S. mansoni* ova induced protection from EAE was further suggested by the absence of any *S. mansoni* ova induced protection from EAE in signal transducers and activators of transcription 6 (STAT6)-deficient animals, which experience a more severe clinical course of EAE [78]. Signal transducer and activator of transcription (STAT)-6 is an important protein in the development of Th2 cells [64,79].

In the trinitrobenzesulfonic acid (TNBS) murine and rat model of colitis the colonic inflammation is due to an infiltration of over IFN-γ producing CD4+ T cells [80]. Concurrent infection with *S. mansoni* has been shown to significantly attenuate TNBS induced colitis in rats [81] and that exposure to eggs of *S. mansoni* protects mice from developing TNBS colitis [82-84].

Based on the information obtained in the above review, it can be suggest that *S. mansoni* antigen induces the production of regulatory cytokines such as IL-10 and TGF-B, regulatory cells such as Treg, CD4+CD25+ cell, regulatory monocytes such as aaMΦ, NKT cells and co-stimulatory molecules such as CTLA-4 which involved in immune modulation and this ability of the parasite antigens allow to provide protection for autoimmune disorders and allergic diseases in animal model. Although *S. mansoni* antigens provide protection for inflammatory diseases in animal model by modulating the immune response, the mechanism in which the parasite antigen modulate the immune response, suitable molecules of the parasite antigen that involved in immune modulation, the appropriate receptors that the antigens of the parasite used and signal transduction pathways that they trigger are still poorly under stood. So this knowledge might be critical for the development of novel therapeutic approaches for the treatment of autoimmune disorders and allergic diseases.

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