A double edged sword: *Schistosoma mansoni* Sm29 regulates both Th1 and Th2 responses in inflammatory mucosal diseases

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Parasitic helminths develop the capability to live for decades in the human host. Besides that, parasites acquire the ability to modulate human immune responses, what has always called the attention of many scientists worldwide. Among these helminths is *Schistosoma mansoni*, one of the main agents of schistosomiasis, which lives for years within human blood vessels. Schistosomiasis is the most important human helminthic infection in terms of global morbidity and mortality,[1] representing a major public health problem in endemic countries, debilitating infected people due to abdominal pain, portal hypertension, and hepatic and intestinal fibrosis in chronically infected patients.[1,2] On the other hand, evidence reveals that *S. mansoni* and other helminths down-regulate inflammatory responses in immune-mediated mucosal diseases.[3–6] Fortunately, the control of the host inflammatory response appears not to be strictly dependent on parasite infection, but can be extended to pathogen-derived antigens,[3,5–7] suggesting that some *S. mansoni* molecules are useful weapons to control inflammation.

Among helminths that regulate inflammation, *S. mansoni* appears to induce particularly strong downmodulation of inflammatory responses.[8] *S. mansoni* acute phase of infection is characterized by a strong T-helper (Th)1 inflammatory response, which is regulated by interleukin (IL)-10 production and evolves to a parasite antigen-driven Th2 response.[8,9] IL-10 is able to inhibit the production of proinflammatory mediators such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and nitric oxide (NO).[8] Particular functions mediated by this cytokine are the inhibition of T cells, inhibition of dendritic cell (DC) differentiation, activation of macrophages, and regulation of the Th1- and Th2-type cytokines.[10] Some *S. mansoni* proteins have the ability to increase the production of IL-10 *in vitro* and *in vivo*. Among them, Sm29 (Genbank acession number AAC98911.1) has been studied as a potential immunoregulatory molecule.[3–5,11] Sm29 is a membrane-bound glycoprotein found on *S. mansoni* tegument that seems to be important in the surface biology of this parasite.[11] Sm29 amino acid sequence shows homology to some unknown *S. japonicum* proteins: SJCHGC03008, SJCHGC05668, SJCHGC05578, and SJCHGC02532 (53, 53, 49, and 37% identity, respectively). Besides *S. japonicum* proteins, Sm29 shows no similarity to any other protein deposited in databases.[12] On stimulation with Sm29 *in vitro*, increased IL-10 production was observed in both splenocytes of Sm29-vaccinated mice and in peripheral blood mononuclear cell (PBMC) of *S. mansoni*-infected individuals.[11] This report aims to discuss the available evidence regarding Sm29 importance as a potential therapeutic agent against two important mucosal inflammatory diseases: leishmaniasis and asthma.

LEISHMANIASIS

Leishmaniasis is a public health problem in at least 88 countries, in which ~350 million people are at risk, and 1.5 million cases emerge per year.[13] Cutaneous leishmaniasis (CL) is the most common clinical manifestation of leishmaniasis, causing several skin lesions that can be destructive and disfiguring, and that occasionally advance to involve the mucosa.[14] Early in the establishment of infection in skin and lymphoid organs, *Leishmania* parasites have multiple effects on macrophage and DC functions, inhibiting host innate anti-microbial defenses and impairing their capacity to initiate Th1 cell immunity.[15] The Th1-type immune response is crucial in leishmania infection control, by releasing IFN-γ necessary for activation of macrophages, leading to NO-

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mediated killing of the intracellular parasite.[15] Nevertheless, considerable evidence suggests that the excessive inflammation triggered by Th1 cytokine release is implicated in the pathogenesis of leishmaniasis. High levels of TNF-α and IFN-γ are associated with increase in lesion size in cutaneous leishmaniasis.[16] Moreover, patients positive for leismaniasis without clinical manifestations (subclinical individuals) shown low IFN-γ production and an equilibrium between IFN-γ and IL-10 production.[15]

Current evidence supports an interaction between helminths and a co-*Leishmania* infection.[17] Patients with CL and infected with helminths have smaller skin lesions and increased IL-5 compared with those with no helminth co-infection.[17] In another study conducted by our research group with leishmaniasis patients, PBMC cultures were stimulated with *Leishmania* soluble antigen (SLA) and then, exposed or not to *S. mansoni* antigen Sm29. We observed reduction in IFN-γ and TNF-α production and increased levels of IL-10 and IL-5 in Sm29-treated cells.[4] This cytokine profile change coincides with an enhanced CD4+ T cell frequency detected in CL patients. Therefore, Sm29 used in this study downregulated the *in vitro* proinflammatory responses induced by SLA in a group of CL patients. Together with Th1 immune response, monocytes and macrophages are key cells to control *Leishmania* sp. infection but also can lead to immunopathology. In another study with a different cohort, we observed that Sm29 caused a decrease in HLA-DR expression in monocytes from cutaneous leishmaniasis patients after SLA stimulation which may interfere with antigen presentation during infection, reducing the magnitude of the immune response.[3] However, the effect of MHC class II expression in regulation of inflammatory responses in CL patients requires further investigation. As DCs are critical to orchestrate the initial immune response during leishmaniasis, we tested the ability of Sm29 to modify DCs activation profile. We observed that Sm29 led to an increase in the frequency of DCs expressing IL-10 and IL-10 receptor (IL-10R) in patients with CL.[18] IL-10 may act in the control of cell-mediated lesion development in leishmaniasis. In mucosal leishmaniasis (ML) there is a lack of IL-10 response, in part explained by the downregulation of the IL-10R.[19] These authors demonstrated that impaired expression of IL-10R in lesions from ML patients was associated with the exacerbated immune response observed in this clinical form of disease.

The potential mechanisms used by Sm29 to regulate inflammatory responses during human leishmaniasis are summarized in **Figure 1**. In addition to the regulatory effect of Sm29 on Th1 responses, this antigen was also reported to modulate inflammatory Th2 immune responses involved in allergic disorders.

ASTHMA

Asthma is a chronic inflammatory disorder in the airways that affects as many as 300 million people worldwide, with a predicted increase in asthmatic patients living in urban areas.[20] Genetic factors contribute to the development of asthma, although the environmental factors are also surely important in this disease and is the main cause of high prevalence, especially in developed countries.[20] In asthmatic individuals, exposure to certain allergens triggers a dysregulated Th2-mediated immune response, with the secretion of characteristic cytokines, such as IL-4, IL-5 and IL-13, and also IgE antibodies.[21,22] IL-10 together with regulatory T cells, participate in balancing Th2-type inflammation, leading to suppression of the allergic response and asthma resolution.[23]

Chronic helminth infections are characterized by skewing towards Th2 and regulatory immune responses. This regulatory network is thought to also temper responses to non-helminth antigens, like allergens, possibly leading to lower prevalence of allergies in subjects that are chronically infected with helminths.[24] The hygiene hypothesis postulates that decreased exposure to certain infectious agents is associated with changes in the immune system which predispose

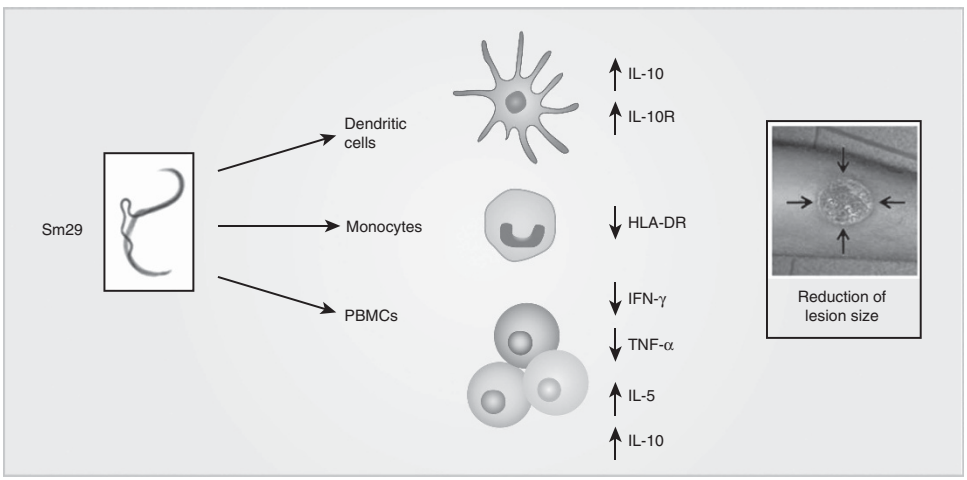

Figure 1 Schematic illustration of the effect of Sm29 regulation in human cutaneous leishmaniasis (Th1 response). Sm29 treatment *in vitro* leads to an increase in IL-10 production and in IL-10R expression in dendritic cells and decrease in HLA-DR expression in monocytes from leishmaniasis patients. Sm29 also promotes a reduction in IFN-γ and TNF-α levels and an increase in IL-10 and IL-5 production in PBMC of cutaneous leishmaniasis patients. PBMC, peripheral blood mononuclear cell.

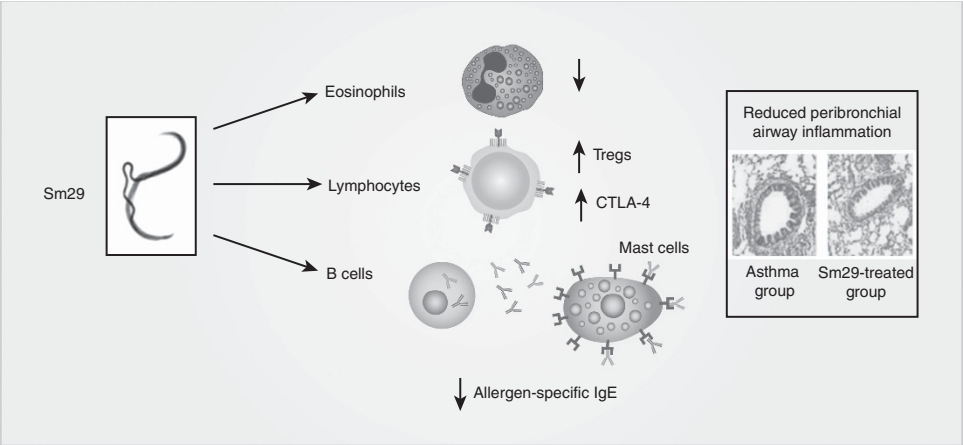

Figure 2 Working model of the Sm29 triggers regulation of OVA-induced AAI in mice (Th2 response). Sm29 immunization reduces the number eosinophils in the lungs, decreases OVA-specific IgE levels, leading to lower mast cell activation and reduced bronchial airway inflammation. In addition, Sm29 triggers increase in the frequency of T regulatory cells and CTLA-4 expression in lymphocytes. Taken together, these Sm29 effects on cells of the immune system can improve the resolution of asthma induced inflammation. AAI, allergic airway inflammation.

subjects to allergy.[25] Although there is a reduced IL-10 production in asthma patients,[26] during chronic schistosomiasis, IL-10 production is crucial in the regulation of granuloma around parasites' eggs deposited in the host's liver.[8] IL-10 production that occurs during long-term helminth infections are inversely correlated with allergy. A pioneering study performed in Brazil revealed that *S. mansoni*-infected asthmatic patients from a rural area presented a milder course of asthma when compared with non-infected asthmatic subjects living in rural or urban areas with the same socioeconomic conditions.[27] Further, asthmatic patients infected with *S. mansoni* were investigated for IL-10 production. The authors observed that PBMCs from these patients produced higher levels of allergen-specific IL-10 when compared with non-infected asthmatic cells.[28] In another study, the expression of CTLA-4 was also significantly higher in lymphocytes of *S. mansoni*-infected asthmatic patients when compared to non-infected ones.[29] CLTA-4 has an important role in inflammatory asthma modulation through the reduction of IL-4 and IL-5 secretion, and controlling Th2 immune responses.[30]

A study performed by our group using laboratory animals demonstrated that mice infected with *S. mansoni* or exposed to parasite's eggs became more resistant to experimental OVA (OVA)-induced allergic airway inflammation (AAI). AAI protection was associated with increased frequency of $CD4^+$ $CD25^+$ $Foxp3^+$ T cells independent of IL-10 activity, which is consistent with the hypothesis that parasite-induced regulatory T cells (Tregs) can down-modulate Th2 allergic inflammation via cell–cell contact-dependent mechanisms. Proteins secreted or localized on the surface of *S. mansoni*, that are in intimate contact with host tissues, may be more effective in triggering immunoregulatory processes. Among them is Sm29, which was used in immunization of mice before AAI induction with OVA. Immunization with Sm29 reduces the number of inflammatory cells in the lungs and the OVA-specific IgE levels. Sm29 immunized mice also presented a higher percentage of regulatory T cells, that lead to a consistent reduction in peribronchial airway inflammation and improved asthma resolution. It is also possible that IL-10 induced by Sm29 inhibits mast cell migration and activation interfering with allergic responses as previously demonstrated.[31] However, further studies are required to confirm the modulatory effect of Sm29 in allergic asthma in humans. The potential mechanisms used by Sm29 to modulate experimental AAI are shown in **Figure 2**.

OTHER INFLAMMATORY DISEASES

Evidences presented here demonstrate that *S. mansoni* antigens seem to be protective against leishmaniasis and asthma. Although not the focus of this commentary, it has also been found that Sm29 can modulate Th1 responses induced by human T cell lymphotropic virus type 1 (HTLV-1) infection, which is the causal agent of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[6] This regulatory effect was associated with increased levels of IL-10 induced by this antigen. Other studies, using *S. mansoni* infection or schistosome antigens have demonstrated that this parasite seems to also protect against the development of autoimmune diseases, such as diabetes[32–35] and inflammatory bowel diseases (IBDs).[36–38] *S. mansoni* infection results in long-lasting prevention of diabetes and IBDs characterized by a string Th2 response.[34,36] *S. mansoni* protection appears to stem largely from a shift to non-pathological Th2 response, although there is also evidence for the generation of immunosuppressive regulatory cells (Treg).[35,38] So far, we have not tested Sm29 ability to modulate autoimmune diseases. However, the capacity of Sm29 to induce IL-10 production and expansion of Treg cells might influence the outcome of autoimmune conditions. The mechanisms by which whole parasite, helminth extracts, or defined schistosome products modulate the immune responses and inhibit inflammatory diseases are summarized in **Table 1**.

Table 1 Schistosome antigens involved in modulation of inflammatory diseases

Antigen	Model	Putative mechanisms of protection	References
Leishmaniasis			
Sm29	PBMC of CL patients	Decreases IFN-γ and TNF-α production and induces IL-10 and IL-5 Increases IL-10 and IL-10 receptor expression in DCs	3,4,18
SmTSP-2	PBMCs of CL patients	Decreases IFN-γ and TNF-α production and increases IL-5 Induces the expression of CTLA-4 on CD4 + T cells and the frequency of CD4 + FoxP3 + T cells	3,4
PIII	PBMCs of CL patients	Decreases IFN-γ and TNF-α production and induces IL-5 Induces the expression of CTLA-4 on CD4 + T cells and the frequency of CD4 + FoxP3 + T cells	3,4
S. mansoni infection	*Leishmania* and *Schistosoma*-coinfected patients	Reduces the lesion size Induces high levels of IL-5 and IgE	17
Asthma			
Sm29	Murine model of OVA-induced airway inflammation	Reduces peribronchial airway inflammation and improves asthma resolution Decreases OVA-specific IgE levels and increases frequency of CD4 + FoxP3 + T cells	5
Sm22.6	Murine model of OVA-induced airway inflammation PBMCs of asthmatic *S. mansoni*-infected patients	Decreases OVA-specific IgE levels and EPO in lung tissue and increases frequency of CD4 + FoxP3 + T cells Induces IL-10 production by PBMCs of asthmatic patients infected with *S. mansoni*	5,41
SjP40	Murine model of OVA-induced airway inflammation	Induces Th1 responses	42
SEA	Murine model of OVA-induced airway inflammation	Reduces eosinophils in BAL and Th2 cytokines Increases frequency of CD4 + FoxP3 + T cells and IL-10 production	7
S. mansoni infection	*Schistosoma*-infected asthmatic patients	Milder course of asthma	27
	PBMCs of asthmatic *S. mansoni*-infected patients	Monocytes and CD4 + CD25 + T cells produce IL-10 Increases CTLA-4 and CD40L expression in CD4 + T cells	28,29
HTLV-1			
Sm29	PBMCs of HTLV-1 infected patients	Increases IL-10 levels and reduces IFN-γ	6
SmTSP-2	PBMCs of HTLV-1 infected patients	Increases IL-10 levels and reduces IFN-γ	6
Inflammatory bowel diseases (IBDs)			
SWAP	Adoptive transfer T cell model	Reduces IFN-γ and IL-17A production and increases IL-4 levels in the colon	36
SEA	Adoptive transfer T cell model	Downregulates IL-17A-producing cells and upregulates IL-4-production in the colon	37
SEA	DSS-induced colitis	Increases Th2 cytokines and CD4 + FoxP3 + T (regs) cells	38
Sjcystatin	TNBS-induced colitis	Reduces IFN-γ and increases IL-4, IL-13, IL-10 and TGF-β in colon tissues	43
Type 1 diabetes (T1D)			
Omega-1	Non-obese diabetic (NOD) mice	CD4 + FoxP3 + T (regs) cells inducing factor	32
LNFPIII	Insulin sensitivity in diet-induced obese mice	Induces IL-10 production by macrophages and dendritic cells	33
S. mansoni infection and SEA	Insulin sensitivity in diet-induced obese mice	Induces M2 macrophage activation and shift to Th2 responses	34
SEA	Non-obese diabetic (NOD) mice	Induces Th2 and Treg cells expansion	35

Abbreviations: BAL, bronchoalveolar lavage fluid; OVA, ovalbumin; PIII, a fraction of *S. mansoni* soluble adult worm antigen (SWAP) obtained by anionic chromatography (FPLC); SEA, *S. mansoni* soluble egg antigens; SWAP, *S. mansoni* soluble worm proteins; TSP, tetraspanin.

CONCLUDING REMARKS

Helminth infections affect the host immune system at several levels and the regulatory effects of the parasite and its secretions may not be restricted to the sites of infestation, but may extend to distal mucosal sites.[39] For these reasons, the identification of one or more products with therapeutic potential, from all the genes that a single helminth can express, is a challenging task.[40] The possibility of specific molecules from helminth parasites having potent modulatory effect may be an important resource for the development of future immunotherapies to control inflammatory diseases. Here, we focused on Sm29 function as an immunoregulatory molecule and reported studies in which this protein was able to control inflammatory mucosal diseases with both Th1 and Th2 immune response profiles. Promising results have been obtained by Sm29 treatment of cells from *Leishmania* infected patients *in vitro* and also by Sm29 treatment of OVA-induced AAI mice. In summary, Sm29 protein acts like a double edged sword affecting both Th1 and Th2 branches of inflammatory mediated-diseases by IL-10 production and Treg cells expansion. Future studies should focus on better understanding of the mechanisms by which Sm29 regulates inflammatory reactions in autoimmune diseases. The Sm29 molecule is a potential therapeutic agent in the resolution of mucosal inflammation, possibly helping patients to improve their conditions without paying the price of becoming infected with noxious pathogens. Our group is now working with regulatory agencies in Brazil to produce Sm29 in good manufacturing practices conditions to a begin phase 1 clinical trial using this molecule.

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AUTHOR CONTRIBUTIONS

S.C.O., B.C.F., L.S.C., and E.M.C. wrote the manuscript.

DISCLOSURE

The authors declared no conflict of interest.

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