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Interaction and involvement of cellular adhesion molecules in the pathogenesis of *Schistosomiasis mansoni*

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ABSTRACT

Parasites from genus *Schistosoma* currently infect more than 200 million people worldwide. Infection with *Schistosoma mansoni* causes intestinal schistosomiasis with geographical distribution across Africa, Middle East, Caribbean, Brazil, Venezuela and Suriname. People with *Schistosomiasis mansoni* suffer from a chronic disease as result of an exacerbated immune response to the eggs deposited in hepatic tissue. The presence of eggs in the tissue triggers the recruitment and activation of immune cells to wall off and isolate them from the rest of the organism. In this context, immune cells turn activated and increase the expression of cellular adhesion molecules (CAM), such as L-selectin and LFA-1, and DC-SIGN which through interaction with CAM expressed on activated endothelial vessels, help moving leukocytes quickly to the sites of infection (inflammation around the eggs), as a strategy to defend the organism from foreign invaders. Since the vertebrate host is not able to eliminate the foreign invader a granuloma formation take place in the tissue where the eggs are trapped, originating granulomas. Patients and mice with chronic schistosomiasis have increased levels of CAM in their circulation and egg-trapped tissue, which may contribute to the inflammatory process, granuloma formation and pathology aggravation. Here we systematically reviewed the findings raised over the last two decades that addressed the involvement of cellular adhesion molecules in the intestinal and hepatic inflammatory response and liver granuloma formation during *Schistosomiasis mansoni*. This review intends to contribute to the understanding of *Schistosomiasis mansoni* pathogenesis by discussing alterations and interactions in cellular adhesion molecules during the disease.

1. Introduction

Schistosomiasis is a widespread parasitic disease caused by trematodes of the genus *Schistosoma*. It is estimated that at least 200 million people in the world have schistosomiasis. This disease is prevalent in tropical and subtropical areas, mainly in Africa and Asia; however, it is also endemic in South America (particularly in Brazil). The main affected population lives in poor communities without adequate sanitation. It is estimated that the *Schistosoma mansoni* is currently responsible for infecting 4–6 million people in Brazil [1].

During the infection by *S. mansoni*, although the eggs are eliminated with feces, the parasite lives inside blood vessels, where the adult organisms copulate, and the females release eggs. When the eggs adhere to the endothelium of mesenteric vessels, they are dislocated to the mucosa. A periovular granulomatous reaction occurs in intestinal tissue, and after a few days, many of them are expelled to the intestinal lumen. Nevertheless, only some of the eggs adhere to the endothelium tissue, and others are embolized to the portal system where they reach the liver. There, the development of hepatic periovular granulomas takes place. The granulomatous response to parasite eggs deposited in the liver is both a primary immune response to this parasite stage and a central mechanism of the disease pathology. The granulomatous inflammation in the liver ultimately leads to periportal fibrosis and portal hypertension.

Cellular adhesion molecules (CAM) are distributed throughout regions of plasma membranes in contact with other cells and extracellular matrix. The classes of CAM include cadherins, selectins, integrins and the immunoglobulin (Ig) superfamily. While cadherins are stably expressed during cell life, participating in tissue differentiation, the expression of other CAMs varies according to the maturation and

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functional states of various cell types. Immune cells, for example, after sensing the presence of inflammatory mediators, move quickly to sites of infection or inflammation, because the movement of leukocytes into injured tissue is particularly important in defense against foreign invaders. The adhesion of leukocytes to the endothelium close to sites of inflammation depends on the sequential activation of several CAMs on the surface of the interacting cells [2]. The extravasation of leukocytes from the blood to the inflamed tissue is a dynamic process involving formation and breakage of cell-cell contacts between leukocytes and endothelial cells of the vessels [3]. The leukocyte/endothelial interactions promoted by CAMs are key processes in promoting inflammatory responses in a variety of diseases. CAM-mediated leukocyte recruitment contributes to chronic inflammation (as in rheumatoid-arthritis [4]) inflammation severity during infection diseases (as in malaria [5]), and its inhibition is of increased interest for the treatment of diseases driven by inflammation [6]. Furthermore, adhesion molecules are involved in the inflammatory processes that initiate and maintain hepatic granuloma formation during *S. mansoni* infections [7].

Expression of CAM constitutes an essential element in cell recruitment and inflammation during infection by *S. mansoni*. Initially, the involvement of selectin during development of the schistosomula stage [8] and the expression of ICAM-1 in intestinal granulomas of mice infected with *S. mansoni* [9,10] highlighted its role as a major adhesion molecule involved in the inflammatory process related to parasite recognition and granuloma formation. A review published 20 years ago initially addressed the role of these CAMs in schistosomiasis pathogenesis [11]. Since then, additional knowledge regarding the participation of these CAMs in intestinal disease and liver inflammation, as well as a description of additional molecules has arisen in this field. More recently, the ICAM-3/DC-SIGN axis has been proposed to play an important role in the inflammatory process during schistosomiasis [12]. Here, we review the findings raised over the last two decades that had shed light upon adhesion molecules that constitute important elements in schistosomal intestinal inflammatory response and liver granuloma formation.

2. Immune responses during *Schistosomiasis mansoni*

The inflammatory reaction against the eggs transported by the portal system to host organs, primarily the liver, causes most of pathological manifestations of schistosomiasis. The eggs of *S. mansoni* may also deposit at ectopic sites, most frequently the lung, occurring at 29% of the cases of *Schistosomiasis mansoni* [13]. A granulomatous reaction that depends on the infiltration of many cell types including eosinophils, neutrophils, lymphocytes, monocytes, takes place in response to the antigens secreted or released by eggs deposited in the tissue. At least three major schistosome-soluble egg antigens (SEA) have been identified with immunomodulatory features in infected patients: omega-1, IPSE/alpha-1 and kappa-5 [14–16]. These antigens are recognized by immune cells and induce secretion of inflammatory cytokines by the host, including IL-4, a known activator of basophils that acts as an inducer of the Th2-type response. SEA antigens may also present hepatotoxicity [17], contributing to hepatic damage and fibrosis during *Schistosomiasis mansoni*.

Immune cells leave the peripheral circulation and reach inflammatory sites via a mechanism mediated by adhesion molecules [18]. Like many helminthic infections, the predominant immune response during *Schistosomiasis mansoni* is mediated by T helper (Th) 2, although Th1 responses are relevant in the acute phases of infection [19]. $CD4^+$ T cells produce IL-17, called Th17, and are associated with tissue injuries and granuloma formation during human schistosomiasis [20] as well as a murine model of colitis [21]. The cytokines IL-23 and IL-1β produced in response to SEA are the main immune mediators driving the generation of pathogenic Th17 cells in mice [22]; however, this aspect is not quite clear for human infections with the parasite.

The expression of CAM on T cells can be positively regulated by inflammatory cytokines. TNF-α, a Th1 cytokine, increases the expression of ICAM-1, VCAM-1 and E-selectin [23] and plays an important role in the initiation of granulomas and liver fibrosis during *Schistosomiasis mansoni* [9]. Nevertheless, expression of CAM does not cause substantial changes in Th1, Th2 and Th17 immune responses, even though the cells involved in these Th-mediated immune responses are phenotypically different [24,25]. For example, in Th1 and Th2 immune responses, there is downregulation of leukocyte (L)-selectin (CD62 L) expression that reduces the homing of lymphocytes to the peripheral lymph nodes and contributes to their migration to the inflamed tissue [24,26].

In schistosomiasis, the primary cytokines responsible for chemotaxis of leukocytes, by upregulating the expression of surface receptors and CAM on leukocytes and endothelial cells, are IL-4 and IL-5 [24,18], mainly produced by Th2 immune cells, because the chronicity of the disease is related to Th2 immune responses [27,28]. In turn, IL-13 is the dominant Th2 cytokine regulating fibrosis during chronic schistosomiasis [29]. IL-4 is also increased in pulmonary hypertension (PH) in mice chronically infected with schistosomes, and its levels correlate with inflammatory responses in pulmonary peri-egg granulomas and vascular remodeling [27]. IL-5 is the major cytokine related to chemotaxis and activation of eosinophils [18], cells frequently found at increased levels in the peripheral blood and affected tissues of patients with schistosomiasis [30,31]. This cell type directly kills *S. mansoni* schistosomules [32] and may down-modulate production of schistosome-specific Th-2 type cytokines by peripheral blood mononuclear cells in response to the *Schistosoma* adult worm [33,34]. The mechanism of IL-5 signal transduction and eosinophil activation was reviewed by Adachi and Alam (1998) [35]. In schistosomiasis, eosinophil migration to tissues is mediated by a series of molecules. For example, the C-C chemokine receptor (CCR) 5 that is activated by eotaxin CCL3 is involved in the maturation, recruitment and chemotaxis of eosinophils [36]. In a murine model of schistosomiasis, eosinophils were shown to place in pathology in check: mice with eosinophil-deficiency had normal disease progression [37]. Further studies are necessary to properly determine the role of eosinophils in human schistosomiasis. Because CAM plays a very important role in cellular interactions and signaling in the immune response against *S. mansoni* and in granuloma formation, we need to understand these complex interactions to clearly realize the pathological consequences.

3. Selectins

An early step of leukocyte recruitment to injured tissue is mediated by selectins, a class of CAM specifically expressed on leukocytes and endothelial cells. Selectins correspond to a group of calcium-dependent single-transmembrane proteins involved in the early steps of cellular adhesion, promoting deacceleration of circulating cells and cell rolling on the endothelium. This initial intercellular interaction allows rolling of leukocytes over the endothelial surface [38]. Selectins are named according to the cells where they are expressed. E-selectin is on the plasma membrane of endothelial cells under inflammatory stimulation, and can bind to its ligand, the oligosaccharide sequence, called the sialyl Lewis-x (sLex: Siaα2,3Galβ1,4[Fucα1,3]GlcNAc) antigen, broadly present on leukocyte glycoproteins and glycolipids. P-selectin is expressed in platelets and endothelial cells and L-selectin on leukocytes, where it participates not only in homing to the lymph nodes but in the recruitment of leukocytes to sites of inflammation. In addition to the traditional interaction between selectins and glycoprotein ligands, L-selectin and P-selectin can be ligands for leukocytes to bind to E-selectin [39]. The expression and participation of selectins during schistosomiasis has been addressed by a few research groups. Though no differences were observed in terms of levels of soluble endothelial (sE)- or soluble leukocyte (sL)-selectin in the sera of patients with *Schistosomiasis mansoni* and normal controls [40], the expression of P- and E-selectin was upregulated in the murine liver following infection with *S.*

mansoni [41]; they may play important roles in recruitment of immune cells and granuloma formation in the liver. L-selectin expression was observed not only localized in liver tissue leukocytes after infection with *S. mansoni* but was also bound to carbohydrate ligands on the surface of miracidium inside hepatic eggs in mice. L-selectin ligands include GlyCAM-1, CD34, and MadCAM-1, but none of these ligands have yet been studied during *Schistosomiasis mansoni*. The soluble form of L-selectin shed from surface of activated leukocytes has been found active in human sera [42]. Its interaction with *S. mansoni* miracidia was proposed to act to prevent miracidia release of the tissue-trapped egg, and downregulating granulomatous inflammatory infiltrates [43]. Nevertheless, the contribution of these interactions to granuloma formation has not been addressed. Furthermore, the expression of selectins in human lung endothelial cells can be negatively modulated by the larval stage of *S. mansoni*. Trottein et al. (1999) [8] demonstrated that substances secreted by the schistosomula reduce gene expression of E-selectin induced by TNF-a [8], suggesting that *S. mansoni* schistosomula negatively regulates the recruitment of leukocytes to host tissue.

Binding of P-selectin to its ligand expressed in leukocytes, P-selectin glycoprotein ligand-1 (PSGL-1), mediates contact between platelets and leukocytes that facilitates the crawling of these cells in the lumen and migration between endothelial cells to the perivascular tissues [44]. The expression of P-selectin was found to be upregulated in activated platelets from patients with *S. mansoni* and can influence the function of T cells during the inflammatory process. Alongside alterations in P-selectin expression, the frequency of platelets expressing activation markers was higher in patients with liver fibrosis caused by *S. mansoni*, although it remains unclear as to whether this activation has any impact in leukocyte recruitment. Because platelet/T cells interactions facilitate T cell adhesion and may act to inhibit the proliferation of non-regulatory T cells (CD4 +/CD25-), stimulating the proliferation of T-reg cells (CD4 +/CD25 +) [45], it is likely that alterations in platelet activation may impact the migration and the phenotype of T lymphocytes during *Schistosomiasis mansoni*. In a murine model, the expression of P-selectin decreased liver inflammation and fibrosis that resulted from chronic Th2 inflammation. In this context, the inhibition of Th2 immune responses was mediated by suppression of IFN-g and upregulation of decoy IL-13R. Along with IL-4, IL-13 secreted by Th2 cells play a central role in liver fibrogenesis during schistosomiasis, and decoy IL-13R acts as an inhibitor of IL-13 signaling [41]. Hence, selectins may interfere with regulating the polarization of immune responses and may play a crucial role in the pathological consequences of schistosomiasis.

4. Integrins

4.1. LFA-1/ICAM-1 interaction

Formation of a cellular granuloma in response to an infectious agent requires the participation of a variety of cells that, because of their adherence and inflammatory abilities, serve to wall off foreign agents from surrounding tissue and ultimately to destroy them. Tighter adhesion between circulating leukocytes and activated endothelial cells is provided by β-containing integrins on the surface of leukocytes that leads to efficient tissue infiltration of leukocytes. Activated integrins bind intercellular adhesion molecules (ICAM)-1 and ICAM-2, that are Ig-superfamily CAMs expressed constitutively on the surface of endothelial cells. Finally, the adhered T lymphocytes move between adjacent endothelial cells and gain access to the underlying tissue [46]. Lymphocyte function-associated antigen-1 (LFA-1), expressed in lymphocytes and other leukocytes, is the integrin most studied in the context of infection by *S. mansoni,* primarily through its interaction with ICAM-1. In a study to clarify the role of TNF-a during inflammatory granuloma formation, Lukacs and colleagues [47] found that the pro-inflammatory effect of TNF-a was in part mediated by induction of ICAM-1 expression in response to antigens secreted by the eggs *S. mansoni* trapped in the lung of CBA/J mice. Ritter and colleagues [9], and the Jacobs group [7] were pioneers in studying the involvement of CAM in the process of granuloma formation. They demonstrated that expression of ICAM-1 in hepatic granulomas in mice was induced by SEA, and that ICAM-1 levels paralleled granuloma size and cellularity, highlighting a potential correlation between ICAM1 expression and the pathology of *Schistosomiasis mansoni*. The upregulation of both ICAM-1 and LFA-1 was detected along the sinusoidal walls of small blood vessels in hepatic sections during early stages of infection, before granuloma formation, implying their participation in the initiation of granuloma formation [48]. The induction of ICAM-1 expression was important for lymphocyte recruitment to the inflamed tissue through LFA-1 expression [49]. Levels of ICAM-1 were found upregulated not only in lymphocytes at the site of egg deposition and formation of liver granuloma, but also in splenic lymphocytes in mice acutely and chronically infected with *S. mansoni* [50]. Thus, ICAM-1 upregulation in lymphocytes is dictated by antigen presenting cells in lymphoid organs, whereas the inflammatory environment in liver granulomas may help to sustain increased levels of CAM in the inflamed tissue. In fact, the use of neutralizing antibodies against adhesion molecules ICAM-1 and LFA-1 inhibited proliferation and production of IL-2 and IL-4 by splenic lymphocytes from mice acutely infected with *S. mansoni* [50]. In a more recent study using pulmonary granuloma model of schistosomiasis, ICAM-1 expression correlated with the size of the *Schistosoma* granuloma [51]. This model is based on the injection of *S. mansoni* eggs into mice to study the granulomatous reactions around the eggs bypassing variations caused by additional factors related to the previous steps of the vertebrate infection, including the egg-producing capacity of females. Because increased expression of ICAM-1 in the lung parenchyma outside the granuloma area was observed in larger granulomas, reduced ICAM-1 expression followed smaller lung granulomas in mice orally-tolerant to ovalbumin [51]. Importantly, nitric oxide (NO) constitutively produced by endothelial cells inhibited the expression of ICAM-1 [52] to avoid leukocyte attachment to the endothelium in the steady-state, and variations in NO production played a role in leukocyte recruitment during schistosomiasis. Endothelial cells from mesenteric vessels of infected animals have enhanced leukocyte-mesenteric endothelial cell adhesion due reduction in NO levels and in expression of endothelial nitric oxide (NO) synthase (eNOS), an enzyme responsible for NOS metabolism in the endothelium [53]. This reduction in endothelial NO may promote the up-regulation of ICAM-1 observed in infection with *S. mansoni*.

The soluble ICAM-1 (sICAM-1) is a free fragment of this adhesion molecule that maintains the ability to combine with its ligand. The levels of sICAM-1 were increased in the serum of patients with more severe forms of schistosomiasis [54,55], despite comparable levels of soluble endothelial (sE)- and soluble leukocyte (sL)-selectin, in the sera of patients with *Schistosomiasis mansoni* and normal controls [40]. In other studies, plasma levels of sICAM-1 were associated with hepatosplenomegaly [56] and correlated with serum markers of fibrosis in patients with hepatosplenic *Schistosomiasis mansoni* [57]. Secor et al. [25] demonstrated that levels of sICAM-1 were correlated with negative modulation of T cells and natural killer activation, once this molecule acts as a competitive inhibitor of cell-cell interactions via ICAM-1/LFA-1, and ultimately downregulates granuloma formation during schistosomiasis. Then, an increase in sICAM-1 levels in patients with *Schistosomiasis mansoni* could be an evolutionary strategy of the human immune system to limit an exacerbated immune response in inflamed tissue.

Silveira-Lemos et al. [26] studied expression of activation markers and ICAM-1 in peripheral blood eosinophils from chronic *S. mansoni*-infected patients. Such eosinophils present a chronic activation status, with dichotomic expression of beta-chemokine receptors and enhanced expression of CAM and co-stimulatory receptors. These findings demonstrate the dynamic expression of activation markers and CAM during chronic *S. mansoni* infection and reinforce the importance of CAM expression in the recruitment of eosinophils during human

schistosomiasis. Furthermore, macrophage migration inhibitory factor (MIF) participates in the IL-5-driven maturation of eosinophils and in tissue eosinophilia associated with *S. mansoni* infection [58]. This factor is secreted by T cells, macrophages, eosinophils, hepatocytes, and Kupffer cells among others, and can also directly mediate the upregulation of CAM on immune cells [28].

4.2. ICAM-1 and Mac-1 recognition of parasite Lewis^x

Many helminths, including *Schistosoma* spp. express glycan antigens that share structural similarities with those expressed by the host. Their expression in helminths occurs as an evolutionary adaptation to the host, and may provide the parasite with advantages in modulating the host defense to successfully infect the host. The Lewis^x expressed in *Schistosoma* is one host-like glycan, and though not sialated as is the Lewis^x expressed by leukocytes, it can be recognized by immune cells. The interaction between ICAM-1 and Mac-1 (CD11b/CD18), a β2-integrin expressed by macrophages, eosinophils and neutrophils, also mediates the adhesion of leukocytes to stimulated endothelial cells. In addition to this interaction, Mac-1 and ICAM-1 participate in the recognition of Lewis^{-x} antigens expressed by *Schistosoma*. The interaction of Mac-1 with Lewis^x expressed by the schistosomula stage of *S. mansoni* is required for a successful antibody-dependent cell-mediated cytotoxicity in murine macrophages [59,60]. The binding of Lewis^x to endothelial CAM can also be necessary for the deposition of *S. mansoni* eggs into different tissues. It has been demonstrated that Lewis^x antigens expressed by *S. mansoni* egg, and ICAM-1 expressed by human umbilical vein endothelial cells is necessary to promote adhesion between live eggs and endothelial cells treated with interleukin (IL)-1β, a pro-inflammatory cytokine [61]. Therefore, there is a need for further studies to clarify whether the recognition of Lewis^x antigens expressed on *S. mansoni* by CAM expressed on immune cells is an important mechanism for the immune system to recognize and mount an efficient immune response against the parasite, or for the parasite to gain entrance into various tissues. Data published by el-Ahl et al. [62] however, demonstrated that mice vaccinated with ultraviolet-attenuated *S. mansoni* cercariae had increased ICAM-1 expression in granuloma cells, suggesting that this CAM ultimately help the vertebrate host to fight against the infection and modulate granuloma formation.

4.3. VLA-4/VCAM-1

In addition to the role of ICAM-1, other CAMs are certainly involved in the generation of granulomas, because ICAM-1 knockout mice infected with *S. mansoni* normally developed liver granulomas; however, they did so with increased expression of vascular cell adhesion protein 1 (VCAM-1) [9]. VCAM-1 is a protein that mediates the interaction of various immune cells, through interaction with very late antigen-4 (VLA-4) present in lymphocytes, monocytes and eosinophils. It is not expressed in the resting vascular endothelium but is upregulated in response IL-1 and TNF-a in a NF-kb-mediated manner. Alterations in expression of VCAM-1 and other CAMs during infection with *S. mansoni* is summarized in Table 1. The interaction between VCAM-1 and VLA-4 has been shown involved in the infiltration of lymphocytes into the liver and intestine during inflammation [63,64]. VCAM-1 expression in a human endothelial cell line has been demonstrated to promote adhesion of *S. mansoni* eggs to the endothelium [61] and could contribute particularly to the deposition of eggs into intestinal tissue. From the host perspective, egg deposition in the intestine and its translocation to the intestinal lumen works as an attempt to get rid of the infectious agent. Corroborating with the anti-parasite role played by VCAM-1, its expression in liver granuloma of *S. mansoni* has been shown to be directly correlated with resistance to infection by this parasite in mice vaccinated with ultraviolet-attenuated *S. mansoni* cercariae [62]. In turn, the parasite developed mechanisms to evade host elimination, because its schistosomule is able to reduce endothelial cells-adhesion VCAM-1/VLA-4, probably trough the action of schistosomule-derived lipophilic factor on peroxisome proliferator-activated receptors (PPAR) [8]. These data suggest that VCAM-1 may play a dual role during infection by *S. mansoni*, promoting egg adhesion to sites of egg deposition as well as parasite elimination.

A few studies have addressed the contribution of CAM to the immune cell recruitment and activation during infection by other species of *Schistosoma*, including *S. haematobium* and *S. japonicum*. Despite the fact that the study of CAM during disease caused by these two species of *Schistosoma* is in its initial stages, the expression of CAM appears to follow similar patterns described for infection by *S. mansoni*. Increased levels of ICAM-1, LFA-1 and VLA-4 were found in liver tissue and periovular granulomas in Swiss mice infected with *S. haematobium* [65]. Furthermore, infection with S. *japonicum* led to increased ICAM-1 and VCAM-1 levels in liver tissue of C57BL/6 mice [66]. Ellis and McManus [67] showed an increase of sICAM-1 in patients in the acute and advanced chronic phases of schistosomiasis japonica, and a positive correlation of sICAM-1 with the intensity of the infection and the number of eosinophils in the patients in acute stage. Since, human *Schistosoma* are very similar in terms of secretion of effector molecules involved in host-parasite interactions, it is likely that CAM also plays an important role in the establishment of chronic inflammation in patients with schistosomiasis caused by different species.

4.4. ICAM-3 interaction with LFA-1 or DC-SIGN

Infection with *S. mansoni* results in a CD4 T lymphocyte-mediated inflammatory reaction against the parasite eggs in humans as well as in mice. LFA-1 mediates adhesion and migration of leukocytes, including lymphocytes and dendritic cells into inflamed tissue by binding to one of its ligands: ICAM-1, ICAM-2 or ICAM-3. As discussed above, LFA-1 is likely to coordinate leukocyte recruitment to granulomas and immune cell activation during schistosomiasis through interaction with ICAM-1. Although ICAM-1 and ICAM-2 are constitutively expressed on the endothelial cells surface, ICAM-3 is absent in endothelial cells in normal tissue, being the predominant ICAM molecule expressed in resting lymphocytes, where it is implicated in both adhesion and signal transduction events. In contrast to ICAM-1 and ICAM-2, ICAM-3 is exclusively expressed in human cells and studies on ICAM-3 have been performed in human primary cells or cell lines. Though the participation of ICAM-3 in the process of T cell activation has yet to be further elucidated, blocking of ICAM-3 have been shown to inhibit T cell proliferation [68], and antibody engagement of ICAM-3 results in elevation of intracellular calcium levels and induction of tyrosine phosphorylation, both crucial signals in T-lymphocytes activation [69]. ICAM-3 participates in T cell activation trough interaction with LFA-1 expressed in DC—potent antigen-presenting cells (APC) with the ability of activating T-lymphocytes—and its contribution to the immune synapse stabilization [70]. Initially, the low affinity between LFA-1 and ICAM-3 ruled out the role of their interaction in mediating strong adhesion between DC and lymphocytes [71]; however, a more recent study demonstrated that LFA-1 expressed on human DC has its ligand binding capacity promoted by exposure to chemokine [72]. In addition to the common ICAM-3 receptors, LFA-1 and αDβ2 integrins, a dendritic cell (DC)-specific ICAM-3-grabbing non-integrin (SIGN)/CD209, binds ICAM-3 with high affinity. This binding promotes important signals in the first contact of resting T cells with DC stabilizing the DC–T cell contact zone and enabling proper T cell receptor engagement [71]. Based on these findings, it may be the case that the interaction between ICAM-3, expressed in resting T lymphocytes, and LFA-1 or DC-SIGN expressed in DC, could occur in lymphoid organs and substantially participate in the T cell proliferation phenomena that promotes T cell generation in response to infection with *S. mansoni*. Studies are necessary to understand whether ICAM-3 interactions with its ligands can play a role in CD4$^+$ T lymphocyte-mediated inflammatory reactions during *Schistosomiasis mansoni*.

Table 1
Expression of membrane bound cellular adhesion molecules during infection with *S. mansoni* in humans and mice.

Cellular adhesion molecules	Alterations in expression during infection with *S. mansoni*
Selectins	
P-selectin	Upregulated in hepatic granuloma in C57BL/6 mice following infection with eggs of *S. mansoni*
	Upregulated on activated platelets from patients with *Schistosomiasis mansoni*
E-selectin	Upregulated in hepatic granuloma in C57BL/6 mice following infection with eggs of *S. mansoni*
L-selectin	Upregulated in liver tissues leukocytes surrounding eggs of *S. mansoni* and surface of miracidia in BALB/c, CBA/J, C57BL/6 and Swiss mice
Integrins	
ICAM-1	Expression correlates with granuloma formation in hepatic endothelial cells of mice infected with *S. mansoni*
	ICAM-1 expression correlated with the size of the pulmonary granumola in C57BL/6 mice
	Upregulated by TNF-a in response to antigen secreted by *S. mansoni* trapped in the lung of CBA/J mice
LFA-1	Upregulated in spleen lymphocytes during acute and chronic infection in CBA/J mice
	Upregulated in lymphocytes in the site of hepatic egg deposition and granuloma in CBA/J mice
VCAM-1	Upregulated during formation of hepatic granuloma in mice lacking ICAM-1

5. DC-SIGN

In addition to its interaction with ICAM-3, DC-SIGN is a C-type lectin receptor (CLR) that works as a potent pathogen-recognition receptor by way of its affinity for carbohydrate structures on pathogens. A pioneer study performed by Appelmelk and collaborators (2003) [73] showed that DC-SIGN binds with high affinity to synthetic mannose- and fucose-containing glycoconjugates, structures that are abundantly expressed by such pathogens as *Mycobacterium tuberculosis*, *Leishmania mexicana*, and *S. mansoni* [73]. The *S. mansoni* worm glycolipids and egg glycan antigens, as Lewis^x, can be sensed by DC-SIGN in DC [74]. DC-SIGN binding induced an inflammatory phenotype in human dendritic cells [75]. DC-SIGN also recognized Le^x glycan expressed in *S. mansoni* cercariae, suggesting that surveying DC in the skin may respond to schistosome-derived glycolipids immediately after infection [76]. In DC, SEA internalization and translocation to MHCII-positive lysosomal compartments was mediated by DC-SIGN and may be implicated in regulating the response of DC to signals induced by TLR triggering [77]. Mice express eight homologs of the human DC-SIGN (SIGNR1-8) [78] and the initial study addressing the participation of DC-SIGN in the infection by *S. mansoni* was published by Saunders and collaborators (2009) [79], where they reported that SIGNR1 bound *in vitro* to *S. mansoni*. Nevertheless, it does not play an important role in the *in vivo* immune response against the parasite or in granuloma formation. On the other hand, the expression of other murine homolog, SIGNR5 was upregulated in CBA mice, that develop severe liver inflammation when infected with *S. mansoni,* and gene silencing of SIGNR5 in CBA bone-marrow-derived DC (BMDC), and its overexpression in the same cell type from BL/6 mice demonstrated that SIGNR5 is an essential player in the induction of IL-1β and IL-23 cytokines and generation of immunopathogenic Th17 [12,80]. DC-SIGN triggering in human monocyte-derived DC favors Th2 immune response via activation of atypical NF-κB family member Bcl3, and suggested that recognition of *S. mansoni* by DC-SIGN could also mediate Th2 immune responses during schistosomiasis [81]. A follow-up study by Kalantari et al. (2018) [82] demonstrated that abrogation of SIGNR5 expression in mice infected with *S. mansoni* protected from hepatic damage and presented reduced levels of Th17 cytokines, IL-1β, IL-23 and IL-17, with concomitant decrease in Th2 cytokines. This study also demonstrated the interaction of SIGNR5 with other receptor for pathogens. Interestingly, the SIGNR5 expressed on DC worked in conjunction to two other CLR, Dectin-2 and Mincle, to activate the production of such cytokines and ultimately induce the Th17 immune response [82] (Fig. 1). In addition to binding to ICAM-3, DC-SIGN also supports tethering and rolling of DC on the vascular ligand ICAM-2 under shear flow, regulates chemokine-induced transmigration of DC across both resting and activated endothelium and can be involved in the migration of immature DC from blood to peripheral tissue in steady state or during infection [83]. Nevertheless, the characterization of the role of DC-SIGN in immune responses during schistosomiasis and granuloma formation is quite incomplete at the present moment. The impact of other SIGNR homologs during *S. mansoni* infection remain elusive. Additional experiments using inhibitors or antibodies against the SIGNR in order to block SIGNR signaling in a specific time point during the infection (chronic stage) are needed to determine the nature of SIGNR involvement in the chronic immune response against *S. mansoni* and the participation of ICAM-3/DC-SIGN axis in the DC-T cell interaction during infection by *S. mansoni* (Fig. 1). Experimental strategies aiming to clarify the role of DC-SIGN in cell rolling and recruitment during human schistosomiasis may also be of great importance to understand the pathogenesis of *Schistosomiasis mansoni*.

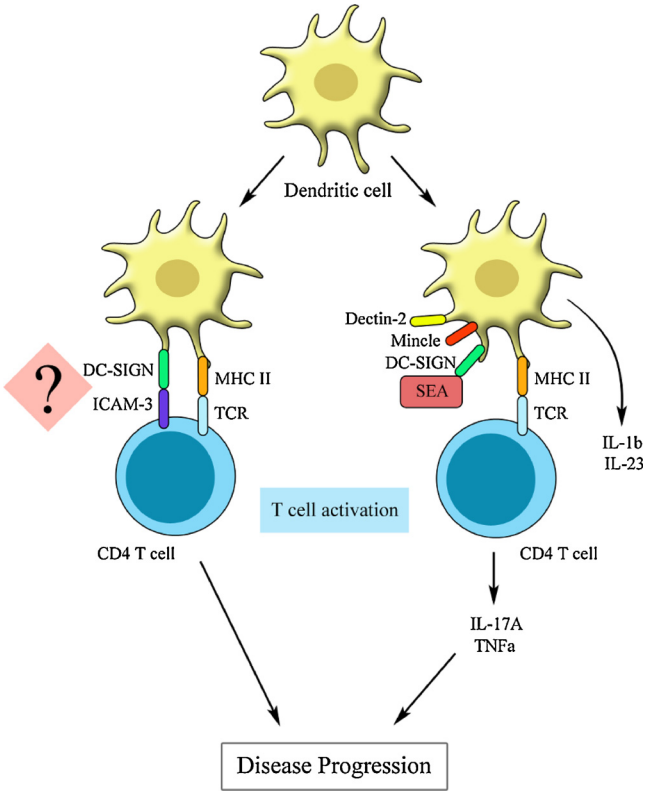

Fig. 1. DC-SIGN recognition of soluble eggs antigen from *S. mansoni* contribute to T cell activation and disease progression. When sensed by DC-SIGN expressed on DC in conjunction to Dectin-2 and Mincle, the *S. mansoni* egg glycan antigens (SEA) are internalized and presented to T cells. The T cell receptor (TCR) triggering in T cells in presence of IL-1b and IL-23a, produced by DC in response to antigen exposure, induces generation of IL-17A + TNF-a + T CD4 cells that contribute to the inflammation, granuloma formation in the liver and the disease progression. It is likely that interaction between DC-SIGN and ICAM-3 stabilizes the DC–T cell contact zone and enables proper engagement of TCR during T cell activation and disease progression during *Schistosomiasis mansoni*.

6. L-SIGN

Liver/lymph node-specific ICAM-3-grabbing non-integrin (L-SIGN) is a human homologue of DC-SIGN, expressed in liver sinusoidal endothelial cells. Similarly, L-SIGN recognizes ICAM-3 as well as high mannose- and fucose-containing oligosaccharides although with different specificity from that of DC-SIGN. Liver sinusoidal endothelial cells function as liver-resident APCs and their activation occurs during egg-induced granuloma formation in the liver is commonly observed in schistosomiasis [9]. Glycosylation of schistosome antigens plays an important role in immunological processes during infection by *S. mansoni* [84], including induction of hepatic granuloma formation by *S. mansoni* SEA that leads to severe fibrosis, as well as hepatosplenomegaly and portal hypertension associated with schistosomiasis [19,85]. In an attempt to investigate whether L-SIGN plays a role in the recognition of glycosylated schistosome egg antigens from eggs trapped in the liver of hosts infected with *S. mansoni*, Van Liempt and colleagues [86] tested the interaction between L-SIGN and various glycan epitopes of SEA. L-SIGN interacted with *S. mansoni* SEA but recognized different glycoprotein fraction when compared to DC-SIGN. While DC-SIGN preferentially bound to the major glycan from SEA, epitope Galβ1,4 (Fucα 1,3) GlcNAc Lewis (Le^x) expressed in all parasite life stages, probably through Val^{351} residue, L-SIGN recognizes other fucosylated glycans, such as Le^a, Le^b, and Le^y [86]. Markedly, L-SIGN binds to schistosomal egg glycosphingolipids via fucosylated carbohydrate, utilizing a binding mode that may be different from the way it binds to Lewis antigens [87]. In this way, the manipulation of the host immune response by glycoconjugates may modulate the immune response throughout the various parasite states during vertebrate infection through interaction with L-SIGN, contributing to the immunobiology and/or liver pathology during schistosomiasis. Nevertheless, much remains elusive about the immunological events and disease outcomes triggered by L-SIGN recognition of the various schistosomal glycoconjugates. Furthermore, the impact of the differential recognition of *S. mansoni* glycoconjugates by APC on T cell activation and leukocyte recruitment to the liver requires further study.

7. Mac-1/DC-SIGN interaction between neutrophils and dendritic cells may dictate cellular activation and migration in inflamed tissue

Neutrophils count for a significant percentage of the immune cells found in granulomas and can play important roles in the immune response involved in granuloma formation. The incubation of eggs of *S. mansoni* with human granulocytes (96% neutrophils) reduces the egg activity and posterior granuloma formation in mice after intravenously injection with the eggs [88]. Furthermore, IL-17, an inflammatory cytokine that mediates neutrophil recruitment [89], when secreted by Th17 cells during an immune response to *S. mansoni* [21], might primarily sustain the recruitment of neutrophils to *S. mansoni* granulomas, regardless of the inhibitory effect of chemokine-binding protein (smCKBP) on this phenomenon, because it can increase the expression of CAM [90]. Neutrophils leave the blood stream and reach inflamed tissues through the interaction of LFA-1 and Mac-1 with their counter-receptor ICAM-1 and ICAM-2 expressed on endothelial cells. These interactions are important for neutrophil recruitment across the intestinal epithelium [91]. Furthermore, Mac-1 mediates the interaction between neutrophils and DC that accumulate at sites of infection [92]. If on the one hand, the Mac-1/DC-SIGN interaction induces DC maturation and primary Th1-based responses [93], on the other hand it promotes neutrophil migration to inflamed tissues [94]. In the infectious context, neutrophil interactions with DC-SIGN expressed in DC during *in vitro* exposure to *Aspergillus* greatly enhanced DC maturation [95]. If Mac-1 mediates neutrophil recruitment to granuloma sites and if the interaction between Mac1 and DC-SIGN expressed on neutrophils and DC participates in inflammation during infection with *S. mansoni*, this is not known; however, because both cell types are observed in liver granuloma [96], a likely interaction between Mac-1and LC-SIGN or DC-SIGN should be addressed in future studies.

In summary, CAM expression correlates substantially with schistosomula immune destruction, parasite egg adhesion to endothelium, cell recruitment to the granuloma formation and possibly development of fibrosis and portal hypertension. CAM and its interactions are certainly important pathways in *S. mansoni* pathogenesis. Therefore, further studies are crucial to clarify all intriguing roles of CAM in this important parasitic disease, to explore the therapeutic aspects of modulating CAM expression during *Schistosomiasis mansoni*.

8. Conclusion

Overall, increased expression of CAM on the surface of activated leucocytes and endothelial cells is associated with the activation state of immune cells, granuloma formation and tissue damage in humans and mice infected with *S. mansoni*. Further studies on expression of CAM in plasma and inflamed tissue may contribute to prediction of liver inflammation and clinical outcomes in patients with *Schistosomiasis mansoni*. Furthermore, inhibiting CAM function with neutralizing antibodies to various adhesion molecules during life cycle of *S. mansoni* in its vertebrate host may be employed to better determine the cause-effect relationship between expression of CAM and disease progression. Future studies targeting the inhibition of cellular adhesion molecules may contribute to the knowledge of schistosomiasis immunopathogenesis and to the development of a supplementary therapeutic tools for treatment with anthelmintics, with the purpose of controlling tissue inflammation, granuloma formation, tissue damage and fibrosis, primarily in the liver.

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