

Helminth Products as a Potential Therapeutic Strategy for Inflammatory Diseases

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Abstract: Helminths secrete several molecules that can modulate the immune responses, favoring their evasion and perpetuate their survival in the host. These molecules interfere with antigen presentation, cell proliferation and activation, antibody production, cause cell death, and stimulate regulatory responses. Here, we focus on some helminth products and address their immunomodulatory effects in the host immune system and, also, we describe some anti-inflammatory properties of an *Ascaris suum*-derived immunomodulatory molecule, named PAS-1. This protein is a 200-kDa molecule isolated by affinity chromatography using MAIP-1 (monoclonal antibody which recognizes PAS-1), coupled to Sepharose 4B. It suppresses the inflammatory responses in murine models of delayed-type hypersensitivity, lung allergic inflammation and LPS-induced inflammation into air pouches. PAS-1 also stimulates the secretion of regulatory cytokines such as IL-10 and TGF- β and primes IFN- γ -secreting CD8⁺ and IL-10/ TGF- β -secreting CD4⁺CD25⁺ cell clones that avoid the lung inflammation. Thus, this protein is a potent immunomodulatory component that may be used for therapeutic interventions in inflammatory diseases.

Keywords: Helminth products, immunomodulation, inflammation, antigen presentation, T cell response, cytokine production, regulatory responses.

1. INTRODUCTION

Helminths are known to cause widespread infections, mainly in the tropical and subtropical areas in the developing world, where the water supply and sanitation conditions are not adequate [1]. Although they do not cause high mortality, they tend to cause chronic infections in populations that live in the endemic area, leading to iron-deficiency, anemia, and malnourishment, and interference with physical and mental growth in children [2].

Helminth infections can impair immune response toward heterologous antigen [3], allografts [4], viral infections [5], and other helminth infections [6]. Helminths employ several immunomodulatory strategies in order to evade and/or modify the host immune response and, consequently, perpetuate their survival in the host [7], including suppression of antigen-specific immune responses and modulation and inactivation of the host protective immune response. The immunomodulation has been considered beneficial both for the host and the parasites, since it could avoid helminth eradication and protect the host from inflammatory responses that may damage the host's tissue [8].

Several immunomodulatory molecules and strategies have been identified, by means of which the helminths evade the host immune system, permitting the parasites to subvert the host protective responses. Some of these molecules include eotaxin metalloproteinase [9], calreticulin [10], antioxidants [11] and, neutrophil inhibitory factor [12]. They interfere with antigen processing and presentation [13], cell proliferation [14], cause T cell death [15], decrease IgE responses [16], reduce B cell activation [17] and, stimulate regulatory T cells [18]. Therefore, these immunomodulatory

factors can affect both the inductive and effector immune response.

In this review, we focus on some helminth products that have therapeutic potential toward inflammatory disorders and their strategies to induce immunomodulation in the host and also, we discuss the anti-inflammatory properties of PAS-1, an *Ascaris suum*-derived immunomodulatory molecule.

2. HELMINTH PRODUCTS AND THEIR STRATEGIES TO INDUCE IMMUNOMODULATION

Helminths produce and secrete several molecules that can modulate the immune response [19-20]. For instance, these molecules can degrade some host molecules such as eotaxin and antibodies, inhibit the formation of reactive oxygen and nitrogen intermediates, interfere with macrophage activation, down-modulate the antigen presentation by dendritic cell and macrophages, and mimic cytokines such as IFN- γ , TGF- β and mediators such as MIF [21]. In Table 1, we summarize the effects of some helminth products that might be used as therapeutic intervention in inflammatory responses.

2.1. Helminth Products that Cleave Host Immune System Molecules

Several helminth defense mechanisms that block host immune system have been described. The adult stage of *Nippostrongylus brasiliensis* releases in *in vitro* culture, a product with acetylhydrolase activity that promotes the cleavage of platelet-activating factor (PAF), a lipid-derived mediator that promotes bronchoconstriction and increases vascular permeability [22]. Moreover, excretory/secretory (ES) products from hookworm *Necator americanus* cleave eotaxin [9], and in this way, inhibit the recruitment of eosinophils.

Helminth serpins can interfere in the immune response by cleaving the immune factors. Serpins are an extensive family

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Table 1. Some Helminth Products and their Immunomodulatory Strategies

Helminth Products	Helminths	Immunomodulatory Strategies	Ref.
Worm extract	<i>Nippostrongylus brasiliensis</i>	Cleavage of PAF	[22]
ES products	<i>Necator americanus</i>	Cleavage of eotaxin	[9]
Serpins: Bm-SPN-2 Smpi56	<i>Brugia malayi</i> <i>Schistosoma mansoni</i>	Inhibition of serine proteinases, cathepsin G, elastase Inhibition of neutrophil elastase	[24] [25]
ES products	<i>Fasciola hepatica</i>	Cleavage of human IgG subclasses at hinge region	[26]
	<i>Spirometra erinacei</i> <i>Anisakis simplex</i> <i>Heligmosomoides polygyrus</i>	Suppression of the iNOS expression in LPS-activated macrophages	[29-31]
Trypsine-like proteinase or aminopeptidase	<i>Schistosoma mansoni</i>	Cleavage of IgG Fab fragment	[27]
Aspartic protease	<i>Schistosoma japonicum</i>	Cleavage human IgG	[28]
Cystatins:	<i>Brugia malayi</i> <i>Onchocerca lienalis</i> <i>Litomosoides sigmodontis</i>	Up-regulation of NO production in IFN- γ -activated macrophages Up-regulation of TNF- α production and decreasing of antigen-specific spleen cell proliferation	[32, 45] [45]
Onchocystatin	<i>Onchocerca volvulus</i>	Down-regulation of HLA-DR expression by human monocytes	[42]
Bm-CPI-1 Bm-CPI-2	<i>Brugia malayi</i>	Interference with cathepsins B, L, and S and asparagine endopeptidase. Blocking of the presentation of toxoid peptides by B cells	[43]
Nippocystatin	<i>Nippostrongylus brasiliensis</i>	Inhibition of cysteine proteases in endosomes/lysosomes of B cells	[44]
Glycans: Lacto-N-fucopentaose III and Lacto-N-neotetraose	<i>Schistosoma mansoni</i>	Induction of IL-10 production and suppression of T cell proliferation Inhibition of DC activation function Expansion of Gr1+ cells (CA suppressor macrophages), inhibition of CD4+ T cell proliferation via NO- and IFN- γ -dependent mechanisms Induction of IL-10 production and suppression of T cell proliferation	[52-58]
	<i>Taenia crassiceps</i>	Stimulation of Th2 response, recruitment of F4/80+ Gr1+ cells (AA macrophages) and enhancing of gene expression in AA macrophages	[59,60]
ES-62	<i>Acanthocheilonema viteae</i>	Inhibition of IFN- γ production by LPS-activated peritoneal macrophages Reduction of lymphocyte proliferation	[61,62]
Phosphorylcholine-containing glycosphingolipids	<i>Ascaris suum</i>	Inhibition of B cell proliferation, inhibition of anti-Ig-activation and LPS-induced activation of B cell proliferation	[63]
Lysophosphatidyl serine	<i>Schistosoma mansoni</i>	Interaction with DC by TLR-2 and induction of IL-10-producing regulatory T cells	[64]
TGF- β homologues: Tgh-2	<i>Brugia malayi</i>	Mimicry of human TGF- β and binding to TGF- β receptor	[65-67]
SmT β R1/SmRK1 and SmRK2	<i>Schistosoma mansoni</i>	Action as a receptor for host TGF- β .	[69,70]
Bp-trk-1	<i>Brugia pahangi</i>	Action as a receptor for host TGF- β .	[65]
IFN- γ homologues:	<i>Trichuris muris</i>	Binding of host IFN- γ receptor	[71]
MIF homologues: BM-MIF-1	<i>Brugia malayi</i> <i>Wuchereria bancrofti</i> <i>Onchocerca volvulus</i>	Stimulation of AA macrophages	[73,74]
PAS-1	<i>Ascaris suum</i>	Suppression of LPS-induced leukocyte migration and pro-inflammatory cytokines in air pouches and macrophage culture, stimulation of IL-10 and TGF- β production	[80]
		Inhibition of antibody production toward T-dependent antigens, not T-independent and T cell responses	[81]
		Down-modulation of cell recruitment and airway hyperresponsiveness in lung allergic inflammation	[82]
		Stimulation of IL-10/TGF- β -secreting CD4+CD25+ and IFN- γ -secreting CD8+ cells that inhibit the lung inflammation	Manuscript in preparation

of serine proteinase inhibitors, which regulate a wide variety of proteinase-dependent physiological functions, such as blood coagulation, fibrinolysis, activation of complement, and the inflammatory response [23]. A serpin produced by microfilarial stage of *Brugia malayi*, Bm-SPN-2, inhibits the enzymatic activity of serine proteinases, cathepsin G, and elastase from human neutrophils [24], suggesting that this parasite encode, the serpin Bm-SPN-2 in order to block defense mechanisms, triggered by the host immune system. In addition, Smp156, a serpin from *Schistosoma mansoni*, inhibits the neutrophil elastase [25], protecting the parasite from activated neutrophils during inflammation.

Besides promoting the cleavage of PAF, eotaxin, and neutrophil enzymes, helminth products can also cleave host immunoglobulins (Ig). Ig cleavage is critical for the parasite evasion, because it inhibits the antibody-dependent cell cytotoxicity and IgG degradation, which binds to IgG receptors and stimulate cytokine release. For instance, ES products from *Fasciola hepatica*, cleave all the human IgG subclasses at the hinge region [26]. In addition, *S. mansoni* schistosomula produces a trypsin-like proteinase or aminopeptidase that cleaves Fab fragment when Fc receptor of the worm binds with IgG [27]. Recombinant schistosome aspartic proteases from *Schistosoma japonicum*, specifically cleave human IgG, suggesting that these proteases may play a role in the degradation of host serum proteins ingested as a part of the schistosome bloodmeal [28].

2.2. Helminth Products that Modulate the Nitric Oxide Production

Nitric oxide (NO) is a potent microbicidal agent that plays a role in the host defense, against parasites. This effect has been demonstrated towards several helminths. It has been found that ES products, from parasites such as *Spirometra erinacei* [29], *Anisakis simplex* [30], and *Heligmosomoides polygyrus* [31] suppress the expression of iNOS in LPS-activated macrophages in a dose dependent manner. However, filarial nematode cystatins [32] up-regulate NO production from IFN- γ -activated macrophages. In spite of the susceptibility of parasites to NO, its stimulation in the host by helminth products is critical to promote nitration and oxidation of the host's molecules and damage several biological process. Moreover, in filariasis murine model, NO was associated with the suppression of T cell proliferation [33]. Thus, it is thought that the secretion of NO is linked to microfilariae killing and T cell response inhibition.

2.3. Helminth Products that Interfere with Antigen Presentation and T Cell Responses

The most important molecules that interfere with antigen presentation are cystatins. Cystatins constitute a family of cysteine protease inhibitors that are widely distributed and play essential roles in a spectrum of physiological processes [34]. Nematode cystatins can lead to severe changes in antigen processing, and inhibit the efficient generation of peptide-MHC class II molecule there by reducing the antigen presentation by APC. These molecules target cysteine proteases, which play a role in two catalytic processes [35]. First, cysteine proteases degrade proteins within the endosomal-lysosomal compartment of APC. Second, cysteine proteases are involved in the cleavage of the MHC class II-associated invariant chain, which leads to the formation of clip-

associated MHC-molecules. Synthesized CLIP molecules allow the binding of peptides to MHC class II molecules; subsequently, the cleavage process occurs that is promoted by cathepsins S in B cells and dendritic cells [36], cathepsins L in thymus epithelial cells [37] and cathepsins F in macrophages [38].

Nematode cystatins are homologous to mammalian cystatin C, which are highly expressed by immature dendritic cells and downregulated during dendritic cells maturation process to permit the transport of MHC II molecules to the cell surface [39]. These cystatins maintain dendritic cells in immature state, preventing the antigen presentation by these cells and they also down-regulate *in vitro* cellular proliferation [39].

Several helminth cystatins have been characterized. The first described parasitic cystatin was onchocystatin, derived from *Onchocerca volvulus* [40], that down-regulates the HLA-DR expression by human monocytes after 72 hours of co-culture [41, 42]. *Brugia malayi* nematodes secrete two homologues cystatins [43]: Bm-CPI-1, which is selectively expressed by L2 and L3 stage into the mosquito vector and Bm-CPI-2, which is constitutively expressed around the parasite life and interferes with two classes of proteases in the MHC class II antigen presentation: cathepsins B, L and S and asparagine endopeptidase. Also, Bm-CPI-2 blocks the presentation of peptide derived from tetanus toxoid by human B cells [42]. Nippocystatin, a cysteine protease inhibitor found in ES products of *N. brasiliensis*, modulates the antigen processing and interferes with the antigen presentation by inhibiting multiple cysteine protease activities found in the endosomes/lysosomes of B cells [44]. In addition, *Litomosoides sigmodontis* cystatins upregulate the production of tumor necrosis factor alpha (TNF- α) and diminish antigen-specific proliferation of the spleen cells in mice [45]. Besides inhibiting proteases from MHC class II pathway, cystatins can also modulate T cell proliferation and up-regulate IL-10 production [41, 42].

Several carbohydrate components derived from helminths also modulate the antigen presentation and T cell responses. In general, these components modulate the immune response by stimulating natural suppressors macrophages. The suppressor macrophages are categorized as classically activated (CA) macrophages, which are NO- and IFN- γ -dependent [46, 47] and alternatively activated (AA) macrophages, which are IL-4- or IL-13-dependent [48, 49]. These suppressor macrophages have been phenotypically characterized as Gr1+, CD11b+, and F4/80+ cells [50, 51].

Two glycans derived from *Schistosoma* eggs, lacto-N-fucopentaose III and lacto-N-neotetraose, have been related to induce IL-10 production, suppressing T cell proliferation [52]. SEA (soluble egg antigens) from *S. mansoni*, which are rich in lacto-N-fucopentaose III, suppress the LPS-induced inflammation by inducing Th2 responses [53], by enhancing the production of IL-10 and impairing dendritic cell (DC) activation. This latter property is due to the fact that SEA inhibit MyD88-independent, but not dependent-, pathways, which result in IL-10 production, although SEA block the production of IL-12 that can be stimulated by both MyD88-independent or dependent pathways [54]. This suggests that SEA regulate multiple signaling pathways downstream to TLR, and their effect could target the initiation signaling in

DC. The suppression of DC activation could be through the ligation of mannose receptor or DC-SIGN (DC-specific intercellular adhesion molecule-grabbing nonintegrin) that results in the inhibition of DC to secrete IL-12 in response to TLR ligands [55]. DC-SIGN ligation leads to IL-10 production, which has been implicated in the suppression of DC function [56]. It has been found that lacto-N-fucopentaose III likely presents an anti-inflammatory effect due to inducing Th2 response and functioning as an adjuvant [57]. High levels of IL-4, IL-5, IL-10, but not IFN- γ , are secreted by nasal lymphocytes of mouse, immunized with human serum albumin conjugated to lacto-N-fucopentaose III. Lacto-N-fucopentaose III is also able to expand peritoneal macrophages that bear Gr1+ marker and act as CA suppressor macrophages, inhibiting CD4+ T cell proliferation via NO- and IFN- γ -dependent mechanisms [58].

Carbohydrate components from *Taenia crassiceps* also favor Th2 responses, by stimulating IgG1 and polyclonal IgE responses, IL-4, IL-5, IL-10 production to a bystander antigen and are critical to induce gene expression in AA macrophages [59], indicating that these components enhance Th2 responses as an adjuvant and trigger anti-inflammatory responses by stimulating AA macrophages. Glycans from *Taenia crassiceps* in their conformational structure recruit F4/80+ Gr1+ peritoneal exudate cells and suppress proliferation of CD90+ cells (T cells) via cell-to-cell contact, not via IFN- γ and NO [60]. Moreover, *T. crassiceps* glycans do not activate F4/80+ Gr1+ cells through TLR-4 as has been proposed for synthetic and natural glycoconjugates [52, 58], and they are STAT-6 signaling independent. In addition, intact glycans are essential to recruit F4/80+ Gr1+ cells, since their treatment with sodium periodate decreases the recruitment of these suppressor cells.

Another helminth product that can affect the activity of antigen presenting cells is ES62, a phosphorylcholine-bearing filarial product, secreted by *Acanthocheilonema viteae*. This helminth product desensitizes LPS-stimulated mouse peritoneal macrophages to produce IFN- γ , by inhibiting the Th1 response [61]. ES-62 also reduces lymphocyte proliferation and stimulates anti-inflammatory properties [62]. Phosphorylcholine(PC)-containing glycosphingolipids from *Ascaris suum*, are immunomodulatory molecules, due to the fact that they inhibit anti-Ig-mediated B cell proliferation by causing apoptosis, inhibit LPS-induced activation of B cells by decreasing ERK phosphorylation, and modulate IL-12p40 production in LPS/IFN- γ -induced peritoneal macrophages [63], indicating that the PC moiety is important to induce the immunomodulatory effect although non-PC moiety can present modulatory properties in anti-Ig signaling.

Also, lysophosphatidylserine from *S. mansoni* can specifically target the immune system via TLR-2, interact with the dendritic cells and induce IL-10-producing regulatory T cells that are involved in immunosuppression [64].

2.4. Helminth Products that Mimic Cytokine and Other Mediators

Helminths can produce homologous proteins to immune system mediators, such as TGF- β R, IFN- γ , TNF- α R and

histamine, important substances in the regulation of anti-parasitic response.

Parasite-encoded TGF- β molecules have been characterized in filarial nematodes *Brugia malayi* and *B. pahangi*. These are two TGF- β homologues that are shown to be differentially regulated during the filarial life cycle: tgh-1 in *Brugia malayi* and *B. pahangi* [65], and tgh-2 in *B. malayi* [66]. Tgh-1 molecule is generally involved in developmental signaling; it has the maximum expression in maturation and moulting parasites within the human host, suggesting its role in filarial development events [65]. On the other hand, Tgh-2 is predominantly expressed in non-developing microfilarial and adult stages and binds to the human TGF- β receptor [67], mimicking human TGF- β and stimulating regulatory responses in the host. In addition to *Brugia* species, TGF- β immunoreactive molecules have been detected at the surface of cervical bodies, in tegument and subtegumental cells of other parasite, stages of *Schistosoma japonicum*, during the whole life cycle (eggs, cercariae, schistosomula and adult worms), and are distinctly regulated at each developmental stage [69].

Besides being described as TGF- β homologues, TGF- β receptor homologues have also been described in *Brugia* and *Schistosoma* species. SmT β R1 or SmRK1, a homolog of type I TGF- β receptor and a type of TGF- β family of receptor serine/threonine kinase, have been shown in *Schistosoma mansoni* surface, following its entry into the mammalian host [70]. In addition to expressing SmRK1, *S. mansoni* expresses another type I TGF- β receptor, SmRK2, from schistosomula and adult stages and it is located predominantly to the tegumental surface of parasite [70]. Type I TGF- β receptor (Bp-trk-1) has also been isolated from the filarial parasitic nematode *Brugia pahangi* in the three main stages of its life cycle: microfilariae, infective larvae and adults; although the ligand remains unknown, it may likely act as a receptor for host TGF- β rather than for parasite ligands [65].

Not only do helminths mimic the TGF- β ligands and receptor, but they also produce the homologs that mimic IFN- γ . *Trichuris muris*-derived molecules share cross reactive epitopes with the host IFN- γ . Moreover, these molecules can be shown to bind to IFN- γ receptor and induce change in lymphoid cells, similar to those induced by murine IFN- γ [71]. Thus, when the host immune system produces IL-4 to expulse the worms, the IFN- γ homolog production may perpetuate the parasite survival into the host.

Other types of molecules that mimic the host cytokines are macrophage-migration inhibition factors (MIFs), which are produced by several nematodes. Mammalian FIMs are small proteins produced by non-hematopoietic cells that act as pro-inflammatory cytokines and induce TNF production by macrophages in acute settings, such as septic shock [72]. The first MIF homologue to be characterized from a nematode was BM-MIF-1 identified in the filarial parasite *Brugia malayi*, but *Wuchereria bancrofti* and *O. volvulus* also encode MIF family proteins [73]. It might play multiple roles in host-parasite interaction, due to the fact that it is located in several tissue types and is found in both cell-associated and secreted forms. Probably, helminths may secrete MIF molecules to down-modulate the inflammatory response, mainly by stimulating the alternatively activated macrophages that

have been found to play down-regulatory functions in the helminth infections, such as T cell proliferation inhibition and IL-10 and TGF- β release [74].

3. THE ANTI-INFLAMMATORY EFFECT OF PAS-1, AN IMMUNOMODULATORY PROTEIN FROM *ASCARIS SUUM*

Previously, it has been demonstrated that components from *Ascaris suum* body extract modulate the antibody response and the cell-mediated response in mice. Soares *et al* (1987) have demonstrated that, besides inhibiting the IgE production, *A. suum* extract suppresses the IgG1 and IgG2a antibody production [75]. Ferreira *et al* (1995) have shown that DBA/2 mice immunized subcutaneously with OVA + *A. suum* extract and challenged with OVA in the footpad, present suppression of immediate (3 hour after challenge) and late (24 hours after challenge) type IV hypersensitivity reaction [76]. The isolation of protein fractions from *A. suum* extract by Sephacryl S-300 gel filtration chromatography, yields three peaks (PI, PII, and PIII). PI is constituted of high weight components that suppresses anti-OVA IgE antibody production in mice immunized with OVA + PI [77, 78] indicating that the suppressive effect observed in *A. suum* extract is due to high molecular weight components. PI protein fraction was used to obtain the monoclonal antibody MAIP-1, which recognizes one of the suppressive components in the *A. suum* extract; it is a 200-kDa-protein named PAS-1 [79].

PAS-1 suppresses the LPS-induced leukocyte migration and pro-inflammatory (IL-1 β , IL-6 and TNF- α) cytokine production in air pouches exudates and macrophage culture supernatant; moreover, it stimulates the production of IL-10 and TGF- β [80], indicating that the modulatory effect of PAS-1 in LPS-induced inflammation is likely due to these two cytokine. Furthermore, PAS-1 was demonstrated, modulating the humoral and cellular immune response against OVA. It inhibits the production of IgM, IgG1, IgG2a, IgE and anaphylactic IgG1 toward T-dependent, but not T-independent, antigens and anti-OVA type IV hypersensitivity reaction in mouse footpad injected with carrageenan [81], suggesting that PAS-1 suppresses B and T cell responses.

PAS-1 is also able to down-modulate antibody production, Th2 cytokine secretion, cellular recruitment and airway hyperresponsiveness induced by APAS-3, an allergenic protein from *A. suum* [82]. Recently, we have demonstrated that regulatory T CD4+CD25+ cells and T CD8+ cells secrete IL-10/TGF- β and IFN- γ , respectively, and they are involved in the mechanisms by which PAS-1 down-modulate the lung allergic inflammation in mice, since OVA-induced inflammation is reverted when PAS-1-primed regulatory T CD4+CD25+ cells or T CD8+ cells are adoptively transferred to OVA-immunized mice (manuscript in preparation).

CONCLUDING REMARKS

In conclusion, helminths secrete several factors that can modulate the immune response. Some helminth products can cleave the host molecules, such as chemokines, Ig, enzymes; modulate the NO production; interfere with the antigen presentation and T cell responses by down-modulating DC functions; and mimic the cytokines such as IFN- γ and TGF- β and other mediators such as MIF. Here we demonstrated the potent immunodulatory molecule from helminth is PAS-1, a

protein from *A. suum*, that down-modulates inflammatory responses inasmuch as PAS-1 inhibits B and T cell responses, cellular recruitment to the lungs, airway hyperresponsiveness. Thus, due to their capacity to induce immunomodulation, these helminth products might be used for therapeutic interventions in inflammatory diseases.

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