

CHAPTER

Helminth-Derived Immunomodulatory Molecules

Poom Adisakwattana, Sean P. Saunders, Hendrik J. Nel
and Padraic G. Fallon*

Abstract

Infection of man with parasitic helminths leads to potent activation and modulation of the host immune response. This modulation of immunity by helminth infections may have bystander effects in altering, either suppressing or exacerbating, unrelated inflammatory processes. Various ongoing clinical trials are testing the therapeutic application of helminth infection of patients with inflammatory diseases, including inflammatory bowel disease and allergic disorders. Rather than the use of live helminth infection, with the potential for side effects, an alternative approach is to identify the immune modulatory molecules (IM) produced by helminths that can alter immune functions. In this review, we will focus on characterized helminth-derived IMs that may have potential to be developed as novel therapeutics for inflammatory diseases.

Introduction

Helminth parasites infect a broad range of species, including man and it is estimated that a third of the global population is infected with parasitic worms. In this chapter, we focus solely on parasitic helminths, which have a medical significance to humans. These species include the Digenean flukes of the Class Trematoda (Flatworms) and the Class Cestoda (Tapeworms), both of the phylum Platyhelminthes and the phylum Nematoda (Roundworms). Some of the major species of helminths of medical importance to humans are outlined in Table 1, presented with an arbitrary ranking based on prevalence of worldwide infections.

Helminth infections of man are often characterized by long-term chronic infections, frequently for decades, without overt morbidity and relatively few deaths. In helminth-infected individuals, the number of worms present in the host determines the levels of morbidity and pathology. Higher worm burdens result in more severe pathology and potential death. This propensity of parasitic helminths to chronically infect the human host without severe morbidity is indicative of co-evolution whereby the parasite has adapted to infect the host without killing all infected individuals. In response to infection with a foreign pathogen, such as helminths, the host will initiate a potent immune response against the parasites. Despite the attrition from the hosts immune system, parasitic helminths achieve long-term survival in the host as they have evolved multiple mechanisms to suppress immune responses and promote tolerizing regulatory responses to down-modulate inflammation. Rather than focus on the modulation of host immunity for the benefit of the parasites survival, there is a growing awareness that these processes may protect against the more deleterious aspects of pathology in unrelated inflammatory diseases. Table 2 summarizes a number of human diseases reportedly modulated by natural helminth infections. In the context of human atopy, we have postulated that the immunomodulatory

*Corresponding Author: Padraic G. Fallon—Inflammation and Immunity Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin 8, Ireland. Email: pfallon@tcd.ie

Table 1. Medical important diseases caused by parasitic helminths

Disease	Helminth
Nematode	
Ascariasis	<i>Ascaris lumbricoides</i>
Trichuriasis	<i>Trichuris trichiura</i>
Ancylostomiasis (Hookworm infection)	<i>Ancylostoma duodenale</i> <i>Necator americanus</i>
Lymphatic filariasis (Elephantiasis)	<i>Wuchereria bancrofti</i> <i>Brugia malayi</i>
Enterobiasis	<i>Enterobius vermicularis</i>
Toxocariasis (Ocular/visceral larva migrans)	<i>Toxocara canis</i>
Onchocerciasis (River Blindness)	<i>Onchocerca volvulus</i>
Strongyloidiasis	<i>Strongyloides spp.</i>
Angiostrongyliasis	<i>Angiostrongylus cantonensis</i>
Anisakiasis	<i>Anisakis simplex</i>
Trichinellosis or Trichinosis	<i>Trichinella spiralis</i>
Trematode	
Schistosomiasis (Bilharzia or snail fever)	<i>Schistosoma haematobium</i> <i>Schistosoma mansoni</i> <i>Schistosoma japonicum</i>
Paragonimiasis	<i>Paragonimus westermani</i>
Opisthorchiasis	<i>Opisthorchis viverrini</i>
Cestode	
Taeniasis	<i>Taenia spp.</i>
Cysticercosis (Neurocysticercosis)	<i>Taenia solium</i>
Alveolar Echinococcosis (Hydatid disease)	<i>Echinococcus multilocularis</i>

*The worldwide incidences of medically important helminth-induced diseases vary greatly. From 1.221 billion *Ascaris* infections to <1000 *Trichinosis* cases/year.

mechanisms employed by helminths to alter host immunity may induce regulatory responses that down-modulate inflammatory allergic processes in the infected host.¹ The potent immunosuppressive capabilities of certain parasitic helminth species has promoted research on exploiting helminths as therapeutics to treat unrelated inflammatory disease in patients. Immune modulation by helminth parasites has recently been extensively reviewed.¹⁻⁵ Therefore, the role of helminth infections in modulation of unrelated disease in humans and experimental animal models will not be covered here.⁶ In this chapter we review the known helminth immunomodulatory molecules (IM), which have been shown to have a defined effects on immunity and may have therapeutic potential.

Therapeutic Use of Helminth Infections

The data in support of a protective role for helminth infections in modulating inflammation poses the clinically relevant question, “Will a worm a day keep the doctor away?” To address this question, there are a number of completed and ongoing clinical trials that involve the deliberate infection of patients with live helminth infections (Table 3). In recent clinical trials, patients with inflammatory bowel disease (IBD) have been infected with two different parasitic helminth species.

Table 2. Studies showing that infection with helminths may modulate selected human diseases

Diseases	Helminth	Effect of Infection	Ref.
Allergic sensitization	<i>Schistosoma haematobium</i>	Lower skin-prick test positives to different allergen	7
	<i>Schistosoma mansoni</i>	Low skin-prick test responsiveness to inhaled allergen	8
	<i>Ascaris lumbricoides</i> and <i>Necator americanus</i>	Low risk of sensitization to dust mite allergen	9
Multiple sclerosis (MS)	<i>Hymenolepis nana</i> <i>Trichuris trichiura</i> <i>Ascaris lumbricoides</i> <i>Strongyloides stercoralis</i>	Improved clinical profile	10,11
Tuberculosis	<i>Trichuris trichiura</i> <i>Ascaris lumbricoides</i> <i>Strongyloides stercoralis</i>	Deleterious effects on immune response to mycobacterial infection Increased pathological damage following anti-mycobacterial treatment with a poorer clinical outcome. Decreased immunogenicity of BCG vaccination against mycobacterial infection	12

Repeated administration of *Trichuris suis* ova, the porcine whipworm, has been reported to be a safe and an effective treatment for IBD.^{13,14} In separate studies, infection of IBD patients with the human hookworm *Necator americanus* has also been shown to have therapeutic potential.¹⁵ Furthermore, *N. americanus* has also been utilized to treat volunteers with allergies.¹⁶

Table 3. Clinical trials involving helminth infections of patients with defined human inflammatory diseases

Disease	Helminth	Therapeutic Effect
Inflammatory bowel disease/ Irritable bowel disease		
Crohn's disease	<i>Trichuris suis</i> Ova	Decreased disease symptoms. ^{13,22}
Crohn's disease	<i>Necator americanus</i>	Decreased disease symptoms. ¹⁵
Ulcerative colitis	<i>Trichuris suis</i> Ova	Regresses clinical symptoms. ^{13,22}
Autoimmunity		
Celiac disease	<i>Necator americanus</i>	Ongoing trial; recruiting Phase II ^A
Multiple Sclerosis	<i>Necator americanus</i>	Ongoing trial; not yet recruiting Phase II ^B
Allergic diseases		
Allergic Rhinoconjunctivitis	<i>Necator americanus</i>	Completed trial ^C
Asthma	<i>Necator americanus</i>	Completed trial ^D (17, 23) (16)

^AClinicalTrials.gov Identifier: NCT00671138; ^BClinicalTrials.gov Identifier: NCT00630383;

^CClinicalTrials.gov Identifier: NCT00232518; ^DClinicalTrials.gov Identifier: NCT00469989.

All studies using live helminth infections to-date have been promising, but there is a need for caution when considering such approaches with potentially virulent pathogens beyond the controlled conditions of clinical trials. Indeed, evidence in support of a protective role for helminths in unrelated inflammatory conditions is conflicting and differs between worm species. A recent meta-analysis of humans naturally infected with various helminths showed that certain species had no influence on response associated with unrelated diseases (asthma and wheeze), while infection with *Ascaris* led to potentially deleterious effects and, in contrast, hookworm infections have a strong dose-dependent protective effect.¹⁷ Furthermore, in animal studies there is data reporting that various helminths can exacerbate the severity in models of inflammatory bowel disease^{18,19} and allergic lung inflammation.²⁰ Alarming, a recent study reports that a patient with Crohn's disease, treated with *T. suis*, developed an iatrogenic infection despite the parasite being considered a nonhuman pathogen.²¹ Considering the potential side effects posed by such treatments with live worms, we believe a more logical approach is to identify and investigate the IMs expressed by helminths that may be used as anti-inflammatory therapeutics. For the remainder of the chapter, we describe helminth IMs that have been identified to-date.

Helminth IMs

The development of therapeutic IMs from bacteria and viruses is a widely investigated area of research, for reasons previously discussed.⁵ In comparison, though less helminth IMs have been described to-date, there are some aspects of the interplay between helminths and the human host that would suggest they are an IM source of significant promise. A fundamental feature of worm infections is that rather than being typified by transient acute infections, they modulate host immunity via the synthesis and secretion of various parasitic IMs that chronically usurp the immune response for years to decades. It is this capacity for long-term immune suppression that suggest a potential for use of helminth IMs as treatments in chronic inflammatory conditions.

As helminth parasites have large genomes compared with bacteria and viruses (Fig. 1), they represent a potentially greater source of diverse IMs. The large genome of helminths, with 10-20,000

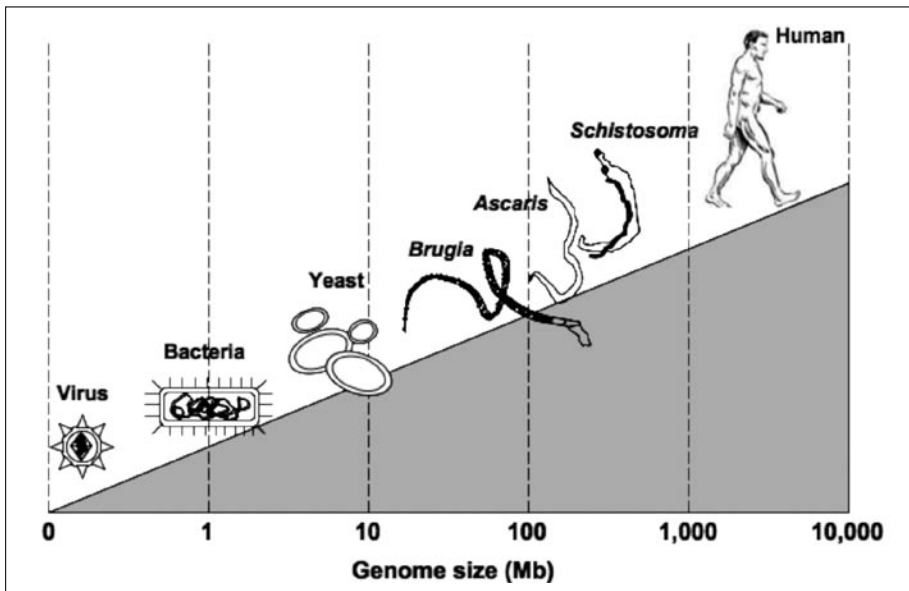


Figure 1. Comparison of genome size in different organisms. The figure illustrates the relatively large genome size (90-270 Mb) of the helminth species shown (*Brugia*, *Ascaris* and *Schistosoma*) relative to other organisms.

Table 4. Comparative biological differences between certain parasitic helminths and viruses

	Parasitic Helminth			Viruses
	<i>Schistosoma</i>	<i>Brugia</i>	<i>Ascaris</i>	
Genome size	270 Mb	85-95 Mb	230 Mb	2-200 kb
Expressed proteins (estimates)	15-20,000	~18,500	15-20,000	Encoding up to 200 proteins
Location	Vasculature	Lymphatics	Intestinal lumen	Obligate intracellular
Infection	Skin penetration	Insect bite	Ingesting eggs	Respiratory, alimentary or urogenital tract, skin or eye
Intermediate host/vector	Snail	Mosquito	None	Generally none, some transmit through insects
Resident	Vasculature	Lymphatics, Vasculature	Gastro-intestinal tract	Systemic

expressed proteins, is possibly a prerequisite for the complexity of their life-cycles, with stage- or tissue-specific expression of genes in the multiple life-cycle stages of sexual maturation that occur in the definitive mammalian host. As many worms have intermediate hosts or vectors, this further necessitates genes that function as IMs to modulate the intermediate host's immunity (Table 4). In the mammalian host, the major interface between the immune system and the adult parasitic worms, their larvae or eggs, are molecules expressed on the surface or those that are secreted or excreted by the parasite. However, despite the known potent immunomodulatory activity of helminth parasite infections or extracts from the parasite, relatively few IMs from parasitic worms have been characterized to-date. In this chapter, we have restricted helminth IMs to only recombinant proteins or characterized native molecules with proven bioactivity (Table 5). We will describe some aspects of the modulatory activity of these helminth IMs.

ES-62

The molecule was first discovered as a 62 kDa molecules in excretory/secretory products (ES-62) of *Acanthocheilonema viteae*, a filarial nematode of rodents in 1989 by Harnett et al.⁴⁰ It was also identified in other filarial nematode species that can cause severe human morbidity, such as *Wuchereria bancrofti*, *Brugia malayi* and *Onchocerca volvulus*. ES-62 is a phosphorylcholine (PC) containing glycoprotein that has been widely investigated as an immunomodulatory molecule. The active native molecule of ES-62 contains PC moieties that are modified by posttranslational processes.⁴⁰

ES-62 exhibits immunomodulatory effects that can lead to downregulation of immunity, as well as inducing the maturation of Th2-inducing dendritic cells (DC) with a resulting Th2 cell polarized immune response.⁴⁰ In addition, it is broadly anti-inflammatory and mediates diverse effects on various cells of the immune system.⁴⁰ Functional studies of ES-62 suggested that immunomodulatory activity may rely on the PC moiety.⁴¹ Indeed, in a recent study, PC conjugated with other carrier proteins mimics the function of native ES-62, whereas recombinant ES-62 without PC did not display immunomodulatory activity.⁴² ES-62 modulates macrophages and DCs by first binding with TLR4 on their surface.⁴³ In addition to modulating macrophages and DCs, ES-62 forms a complex with TLR4 on the surface of human mast cells, triggering a downstream signal cascade.²⁷ The downstream product triggered by the ES-62/TLR4 complex directly inhibits the FcεRI-related allergic response of mast cells and blocks mast cell degranu-

Table 5. Examples of IM from helminths that modulate immune responses

IM	Helminth	Modulatory Activity	Ref.
Cystatin	<i>Onchocerca volvulus</i> <i>Acanthocheilonema viteae</i>	1. Induces cell hyporesponsiveness	24
		2. Induces IL-10-producing macrophages	25
ES-62	<i>Acanthocheilonema viteae</i>	1. Anti-inflammatory (prevents collagen induced arthritis)	26
		2. Protects against allergic airway hyperresponsiveness and skin hypersensitivity	27
LNFPIII	<i>Schistosoma mansoni</i>	Th2-inducing adjuvant	28,29
Lyso-PC	<i>Schistosoma mansoni</i>	Stimulates IL-10 producing regulatory T-cells	30
Sm16	<i>Schistosoma mansoni</i>	Suppresses cutaneous inflammation	31
SmCKBP	<i>Schistosoma mansoni</i>	Chemokine binding protein (suppresses acute inflammation)	32
Thioredoxin peroxidase	<i>Fasciola hepatica</i>	Induces alternatively-activated macrophages	33,34
	<i>Schistosoma mansoni</i>		

lation.²⁷ In terms of therapeutic potential, ES-62 reduces articular inflammation in a model of collagen-induced arthritis in the DBA-1 mouse.²⁶ Moreover, ES-62 efficiently protected against hypersensitivity, mediated by mast cells in the skin and lungs of a hyperresponsive allergic mouse model.²⁷ The data provides compelling evidence in support of further research into the therapeutic potential of ES-62, or small molecule derivatives/peptides, in a variety of immunological diseases and disorders.

Sm16

In countries where *Schistosoma mansoni* is endemic, water can contain the infective stage, the cercariae, which can attach to the skin of a human host. The cercariae penetrates the skin following the secretion of a proteolytic cocktail to gain entry into the epidermis from where they can transform into schistosomula, a larval stage, which migrate to the vasculature. Previous studies suggest that *Schistosoma mansoni* larvae utilize an immunomodulatory mechanism during penetration and migration through the skin of rodent host by suppressing inflammatory responses.^{31,44} Thus ES products from *S. mansoni* cercariae and schistosomula could activate production of IL-1 receptor antagonist from human keratinocytes in vitro⁴⁵ and cercariae also stimulate mouse skin and cultured keratinocytes to produce IL-10 that is a crucial regulatory cytokine.⁴⁶ An analysis of the bioactivity in cercariae ES products of the parasite found that a 16.8 kDa protein, designated Sm16, has partial homology with human stathmin and exerts an anti-inflammatory activity.⁴⁷ In vitro studies support a role for Sm16 in reducing expression of IL-1 α in human keratinocytes, suppressing lymphocyte proliferation and down-regulating expression of ICAM-1.⁴⁸ Furthermore, consistent with a role in suppression of inflammation, intradermal delivery of Sm16 cDNA reduced cutaneous inflammation in mice.⁴⁸ Sm16 efficiently binds to the lipid bilayer presented on the cell membrane of diverse cell types that probably play a crucial role during skin penetration, which may account for its modulatory activity.⁴⁹

S. mansoni Chemokine Binding Protein (smCKBP)

Production and secretion of cytokine and chemokine binding proteins (CKBP) is an immune-modulation strategy widely employed by a range of viruses.⁵⁰ SmCKBP is the first CKBP described in a parasite and is secreted solely from the eggs of *S. mansoni*, *S. heamatobium* and

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S. japonicum.³² SmCKBP selectively binds to certain members of the chemokine subfamilies as well as the glycosaminoglycan heparan. Recombinant smCKBP suppresses inflammation induced in a mouse contact hypersensitivity model and blocked CXCL8-induced pulmonary inflammation.³² The smCKBP gene has also been cloned by Hass and colleagues and is reported to be an inducer of degranulation of basophils.⁵¹

Thioredoxin Peroxidase (TPx)

Thioredoxin peroxidase (TPx) was first described in the yeast, *Saccharomyces cerevisiae*.⁵² The enzyme is classified into the peroxiredoxin family which protects cellular components from oxidative damage by reactive oxygen species (ROS; O_2^- , H_2O_2 and $HO^\bullet$).⁵² TPx is a ubiquitous enzyme that can be found in various organisms in the whole animal kingdom. In different organisms, TPx has a conserved amino acid sequence homology and a conserved TPx activity motif.^{53,54} Among helminths, TPx has been identified in both trematode, nematode and cestode species, examples of which include *Fasciola hepatica*, *S. mansoni*, *Onchocerca volvulus* and *Echinococcus granulosus*.^{33,53-55} Consistent with other aerobic organisms, parasites require antioxidant enzymes for protection from cell damage caused by ROS that are produced during cellular metabolic oxidation. In addition, they need antioxidant enzymes, such as TPx, for protection against ROS released from infection-stimulated host phagocytes (neutrophils, eosinophils and macrophages).⁵⁶

Functional characterization of TPx in helminths suggests that it plays a significant role in host-parasite interaction as an antioxidant enzyme against host ROS.⁵⁷ Recombinant *F. hepatica* TPx has shown immunomodulatory activity and was demonstrated to be an inducer of alternatively activated macrophages, including the inducement and recruitment of such macrophages to the peritoneum in a mouse model.³³ Recombinant TPx directly activates a mouse macrophage cell-line to induce a polarized Th2 cell response.³³ A recent study argues that the role of TPx on alternative activation of macrophages, is not only independent of antioxidant activity, but IL-4 and IL-13 independent as well.³⁴ This suggests that helminth TPx activates macrophage as an initial step to developing a Th2 response.³⁴

Onchocystatin

The Cystatins are ubiquitous proteinase inhibitors of cysteine proteases that regulate various biological and pathological processes by inhibition of cysteine protease activity.⁵⁸ Cystatin is secreted by human mononuclear phagocytes and during inflammatory processes its expression is down modulated which, in turn contributes to increased cysteine protease activity.⁵⁸ In addition, the study of cystatin in DC maturation and MHC molecule processing suggested that cystatin plays a role in the intracellular control of invariant chain degradation and antigen presentation.⁵⁸

In parasites, cystatin was first described in the filarial parasite *Onchocerca volvulus*, hence termed onchocystatin, which causes river blindness.⁵⁹ The cellular hyporeactivity induced by secreted onchocystatin when added to human peripheral blood mononuclear cells (PBMC) in vitro, is comparable to some aspects of the state of immune hyporesponsiveness seen in patients infected with *O. volvulus*.²⁴ In addition, onchocystatin stimulated human PBMCs to produce significant levels of IL-10 compared to unstimulated PBMCs and down-regulated the expression of HLA-DR proteins and costimulatory molecules on human monocytes.⁶⁰ Interestingly, an in vivo study with the administration of filarial cystatin (*Acanthocheilonema viteae*) to an allergic airway hyperresponsive mouse model supported the role of cystatin in suppression of allergic hyperreactivity by induction of IL-10-derived macrophages.²⁵ Furthermore, in a chemically-induced colitis mouse model, cystatin regressed the macrophage-mediated inflammatory infiltration and epithelial damage in the colon.²⁵ Immunomodulatory cystatins are present in other parasitic nematodes, which contrast with the absence of such activity in cystatins from free-living nematode *Caenorhabditis elegans*.^{58,61} Cystatin has been also identified in the blood fluke *S. mansoni*, with a potential function as a cysteine protease inhibitor.⁶² However, the immunomodulatory potential of schistosome cystatin has yet to be fully addressed.

Helminth Glycans and Glycolipids as IMs

Recent studies demonstrate that carbohydrate and lipid determinants within cell surface and secreted glyco- or lipo-conjugates are capable of eliciting an immunomodulatory potential.^{12,63-65} In parasitic helminths, several different carbohydrate and lipid molecules from the parasitic surface or ES product are potent modulators of the host immune response. The most widely investigated helminth carbohydrate is Lacto-N-fucopentaose III (LNFPIII)⁶⁴ and, while with respect to helminth lipid IMs, schistosomal lysophosphatidylserine (lyso-PS) is the best characterized.³⁰

LNFPIII

Previous studies on the role of carbohydrates in schistosome eggs demonstrated that glycans in soluble egg antigen promoted an enhanced Th2 response.²⁸ LNFPIII is one such glycan that is present in schistosome soluble egg antigens with potent modulatory activity. Administration of LNFPIII conjugated with carrier molecule into a mouse model demonstrated strong Th2 responses, thus functioning as a potent Th2-inducing adjuvant.²⁸ In addition, LNFPIII induces in mice expansion of IL-10-producing B-1 cells^{66,67} a peritoneal macrophage population that can suppress CD4⁺ T-cell,^{68,69} evoke alternative activation of macrophages *in vivo*⁷⁰ and also induces DC to develop into a DC2 phenotype.^{29,71} With its potent *in vivo* modulatory activity, it will be of interest to further evaluate the effects of LNFPIII administration in animal models of inflammatory diseases.

Lyso-PS

Lyso-PS was identified in a screen for innate interactions between human DCs and different classes of lipids from schistosome worms or eggs.^{30,72} Human DCs treated with schistosome phosphatidylserine (PS) were modulated such that they primed naive T-cells to suppress proliferation of autologous T-cells, via the production of IL-10 in a TLR2-dependent manner.^{30,72} The specific factor that induced IL-10-producing regulatory cells was shown to be lyso-PS.³⁰

Helminth Cytokine and Chemokine Homologues as IM

The host immune response to helminths is partially controlled by cytokines, as immune cell signaling molecules and chemokines, to induce cell-specific chemotaxis, in order to elicit the appropriate anti-helminthic response. Prolonged co-existence of helminths and their hosts have resulted in parasite developing homologues to human cytokines and chemokines that manipulates the host immune response in such a way as to prolong parasite infestation. Examples of helminth cytokine and chemokine homologues are shown in Table 6 and described herein.

Table 6. Helminth-derived cytokine and chemokine homologues

Cytokine and Chemokine Homoloques	Helminth	Modulatory Activity	Ref.
IFN- γ	<i>Trichuris muris</i>	Polarizes Th-1 immune response (inappropriate anti-helminthic immune response)	35
HMGB1	<i>Schistosoma mansoni</i>	Probably modulates host immune responses to promote helmith egg dissemination	36
MIF	<i>Trichuris muris</i>	Probably controls migration of immune cells and the infection site	37
TCTP	<i>Brugia malayi</i>	Antioxidant (prevent oxidative damage)	38
TGF- β	<i>Brugia malayi</i>	Binds to human TGF- β receptor (Possibility of immuno-modulation)	39

Interferon (IFN)- γ

The generation of a type 2 immune response by the hosts expels infections by many helminths, thus it would be advantageous for the helminth to evoke a counter regulating type 1 response. Research on *Trichuris muris*, a mouse model of human infecting nematode *T. trichiura*, a homologue to a type 1 immune response driving cytokine, IFN- γ , was uncovered.³⁵ This protein had the capacity to bind to the mouse IFN- γ receptor with similar downstream effects as the host cytokine, including Th1 lymphocyte differentiation and function.³⁵ The secretion of a IFN- γ homologue by a helminth could alter the local cytokine milieu and facilitate its survival in the host.

Macrophage Migration Inhibition Factor (MIF)

Many other helminths, such as *Trichinella spiralis*, *Brugia pahangi*, *Ancylostoma ceylanicum*, have an orthologue MIF.⁷³ MIF was one of the first cytokines discovered and has been shown to play a role in promoting inflammation through macrophage and T-cell activation as well as IgE synthesis.⁷⁴ It has also been shown to play a central role in host protection against some helminths, specifically *Taenia crassiceps*.⁷⁵ Using recombinant helminth MIFs, it has been shown that many of these orthologs have the ability to be chemoattractant to human monocytes in vitro and thus might have the ability to control the influx of immune cells and the egress of primed antigen presenting cells from the infection site.^{37,76} Some helminth MIFs also have the ability to interact with the human MIF receptor (CD74), resulting in monocyte activation and their subsequent cytokine production, capable of affecting appropriate anti-helminth immune responses.³⁷

Transforming Growth Factor- β (TGF- β)

TGF- β homologues, or TGF- β -like protein or TGF- β -like ligand, have been observed in all subgroups of helminths. The filarial worm, *B. malayi*, secretes a TGF- β -like protein that is capable of binding to the mammalian TGF- β receptor³⁹ with possible immune modulation. Several in vivo and in vitro studies have demonstrated the interaction of *S. mansoni*-derived TGF- β receptors, SmT β RI and SmT β RII, with the human TGF β 1 ligand that is ultimately capable of resulting in gene specific transcription.⁷⁷⁻⁸¹ This provides evidence for a possible involvement in the regulation of early schistosome development in response to host-derived factors. In the cestode *Echinococcus multilocularis*, 2 Smad protein family members have been identified that are crucially involved in intracellular TGF- β signaling⁸² providing further evidence for a TGF- β -like signaling cascade within helminths as a mechanism of host-parasite interaction.

Translationally Controlled Tumor Protein (TCTP)

TCTP, also known as tumor protein, translational-controlled 1 (TPT1), is expressed in various organisms, including helminths and has broad biological activities.⁸³ TCTP homologues from the human filarial parasites *Wuchereria bancrofti* and *Brugia malayi*, have been shown to possess both histamine-releasing function as well as calcium-binding properties in vitro.⁸⁴ Their precise function in helminths do not seem clear, but in vivo injection of isolated helminth TCTP into mice induced the accumulation of eosinophils implying a role in the induction of host pathology as a possible survival strategy.⁸⁴ A recent study on the Bm-TCTP homologue has implicated a role as an antioxidant protein that could provide protection against oxidative damage brought on by a host anti-helminthic immune response.³⁸

High-Mobility Group Box 1 (HMGB1)

HMGB1 is an abundant nuclear protein released from dying mammalian cells, as well as being secreted from activated macrophages, that can induce the production of TNF- α and lead to inflammation and tissue repair (reviewed in ref. 85). Homologues of HMGB1 have been identified among the *Schistosoma* species.³⁶ SmHMGB1 is expressed in large quantities in adult female, or in schistosome eggs and egg-secreted antigens, prompting speculation that the molecule plays a role in modulating host immune responses to promote helminth egg dissemination.³⁶ Recombinant *S. mansoni* HMGB1 has been shown to induce the release of pro-inflammatory cytokines from macrophages in vivo implying a significant role for this cytokine-like molecule in eliciting host immune responses.³⁶

Summary

A rational approach to exploit the immune modulatory activity of helminths is the characterization of the IMs from helminths that can mimic the desirable anti-inflammatory effects of infection. In this article we have outlined various helminth IM described to-date. In the future, the identification of new helminth-derived IM has the potential to lead to the development of novel therapeutic strategies for the treatment of a range of human immunological and non-immunological disorders.

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