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Looking beyond the induction of Th2 responses to explain immunomodulation by helminths

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pim.12194

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Disclosures: None

Abstract

Although helminth infections are characteristically associated with Th2-mediated responses that include the production of the prototypical cytokines IL-4, IL-5, and IL-13 by CD4+ cells, the production of IgE, peripheral blood eosinophilia and mucus production in localized sites, these responses are largely attenuated when helminth infections become less acute. This modulation of the immune response that occurs with chronic helminth infection is often induced by molecules secreted by helminth parasites, by non-Th2 regulatory CD4+ cells, and by non-classical B cells, macrophages and dendritic cells. This review will focus on those parasite- and host-mediated mechanisms underlying the modulated T cell response that occurs as the default in chronic helminth infections.

Parasitic helminths are complex organisms (worms), characterized by their ability to maintain chronic infections in human hosts and are a major health care concern worldwide (often in resource limited countries) infecting more than two billion people. Common helminth infections impose major social, economic, and medical burdens on those regions where these infections are most endemic. Anthelmintic therapy, despite its success under certain circumstances, still suffers from drug distribution logistics, the length of treatment for certain helminths and the potential problem of drug resistance. Therefore, the focus of this review will be on the strategies used by these parasites to establish and maintain infection, processes that likely modulate host immune responses.

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Host-helminth interface

Helminths, in contrast to the single cell protozoa, are large extracellular (the exception being *Trichinella spiralis*) parasites that do not multiply in their vertebrate hosts. Helminths have complex life cycles often with many developmental stages that can be antigenically distinct leading to distinct immune responses that evolve differentially over the course of a helminth infection. In addition, because of differing tissue tropism of the various helminths, responses can be either localized (e.g. intestinal mucosa and draining lymph nodes in intestinal nematode infection or skin/subcutaneous tissue and draining lymph nodes in *O. volvulus* infection) or systemic (e.g. in schistosomiasis, toxocariasis, blood-borne filarial infections). Moreover, because helminths survive in the host for decades chronically producing larvae (or eggs), their *modus operandi* involves host immune modulation such that their own survival (and continued transmission from host to host) is assured.

The prototypical host immune response to all pathogenic helminths of humans (based largely on studies in easily polarized mouse models of infection) is one often characterized as Type-2 (or Th2) and involves: 1) the production of the cytokines IL-4, IL-5, IL-9, IL-10 and IL-13; 2) the induction of antigen-specific IgG1, IgG4 and IgE; and 3) the expanded populations of eosinophils and alternatively activated macrophages/immunoregulatory monocytes (1-3). This Type 2 response occurs primarily at the time of patency (when egg laying or microfilarial release from adult females occurs (1), its initiation requiring interaction with many different cell types, most notably: 1) stromal cells; 2) dendritic cell and macrophage populations; 3) eosinophils; 4) mast cells and basophils; 5) dermal cells; 6) epithelial cells; and 7) innate lymphoid cells (ILCs). These innate responses that promote Type-2 responses are most often very quickly modulated by

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both adaptive and natural regulatory T cells, regulatory monocytes/macrophages (Mregs) and B cells (Breg), eosinophils and likely other, heretofore, unidentified cell populations (Figure 1).

Mechanisms of evasion and immune modulation by helminth parasites

Helminths exert profound regulatory effects on the host with both parasite antigen-specific and more generalized levels of immune modulation. It has been shown that patients with filarial infections, schistosomiasis, or even soil transmitted gastrointestinal helminths (STHs) have markedly diminished responses to parasite antigens (3, 4); in addition, these parasites also can induce attenuated responses to non-helminth antigens (5-8) including those that are delivered as approved vaccines (9-13). The chronicity of many of these helminth parasites is presumed to reflect successful immune evasion strategies that allow these parasites to avoid elimination (14); this immune evasion is often dependent on the modulation of the parasite-specific host responses.

Parasite-dependent mechanisms of evasion and immune-modulation

As parasites enter immunologically privileged sites such as the central nervous system or the eye (e.g. Toxocara spp., *Taenia solium, O. volvulus*) or when, because of the complexities of their life cycle, they enter a host cell that renders them immunologically privileged, as seen in *T. spiralis* infection (15), they are provided a means for remaining hidden from immune attack. Encystation, another mechanism utilized by helminth parasites to avoid immune-mediated attack, occurs in infections such as *Echinococcus* spp. and *T. solium.* Loosely related to this process is a process seen in *O. volvulus* infection in which the adult parasites live within a nodule that is encased in host derived lymphatic endothelial-like cells (16) within which is human extracellular matrix.

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Parasite gene-encoded secreted (or surface exposed) proteins, glycoproteins, glycans, and lipoproteins also appear to play an important role in host immune modulation (17). Perhaps the best studied is a phosphorylcholine (PC)-containing molecule called ES-62 (18) from filarial worms that has been shown to inhibit the proliferation of CD4+ T cells and conventional B cells, decrease IL-4 and IFN-γ production, promote IL-10 production by B1 B cells, and condition APCs to inhibit Th1 responses (19-22). ES-62 has also been shown to exhibit bystander anti-inflammatory activity in animal models of arthritis (23), skin sensitization (24) and lung airway hyper-reactivity (25).

Helminth antigens have a wide array of glycan- and lipid-containing proteins (26, 27) that are structurally related to host-derived glycans and lipids (28). The host-like glycans interact directly with mammalian C-type lectin receptors, galectins, jacalins, and mannose receptors to shape innate and adaptive immune responses (29). Similarly, helminth lipids have also been implicated in immune modulation with schistosome lyso-phosphatidyl serine by conditioning dendritic cells to induce IL-10 secreting Tregs (30).

The schistosome-secreted proteins alpha-1 (also known as IL-4 inducing principle of schistosome eggs or IPSE) and omega-1 (a ribonuclease) - both of which are secreted/excreted by schistosome eggs - have been shown to play a significant role in shaping the CD4+ effector response (31-34).

Helminth parasites also utilize mechanisms involving cytokine mimicry and/or antagonism to alter the host immune response. The first helminth-encoded cytokines were found to be homologs of TGF-β (35, 36), and many helminth genomes encode members of the TGF-β receptor superfamily. All of the filarial helminths produce homologs of macrophage migration

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inhibitory factors (MIF) (37-41) and SOCS-1 (42, 43), molecules known to be anti-inflammatory. *T. muris* was shown to express a homolog of IFN-γ that binds to the IFN-γR in vitro (44).

Helminth parasites have the ability to utilize chemokine- or chemokine receptor-like proteins to modulate host immunity. As more and more helminth genomes are being elucidated and annotated, increasingly more chemokine and chemokine receptor mimics are being discovered (e.g.in the filariae (42) or in *N. americanus* (45)). Specific examples with experimental data underlying this concept of chemokine mimicry include an *Ascaris suum*-expressed neutrophil chemoattractant with chemokine binding properties (46) and an *S. mansoni* chemokine receptor-like protein that binds CXCL8 and CCL3 resulting in an anti-inflammatory effect (47).

Helminths secrete two major classes of protease inhibitors - cystatins and serpins - each with proposed immunomodulatory roles (48-50). Cystatins inhibit cysteine proteases (cathepsins and aspartyl endopeptidases) required for antigen processing and presentation and thereby inhibiting T cell activation. They have also been shown to elicit the regulatory cytokine – IL-10, leading to direct impairment of T cell proliferation. The serpins are serine protease inhibitors that specifically inhibit neutrophil proteinases, cathepsin G and neutrophil elastase.

Other parasite products mediate their effect by blocking effector functions including recruitment and activation of inflammatory cells and by limiting the destructive potential of activated granulocytes or macrophages in the local extracellular milieu. Platelet activating factor (PAF) can be inactivated by a secreted *N. brasiliensis*-derived PAF hydrolase (51). Eotaxin-1 has been shown to be degraded by a hookworm metalloprotease (52). Other modulators, such as helminth-derived or -induced prostaglandins and other arachidonic acid family members are known regulate a variety of cellular functions (53-55). Finally, helminths (known to be

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susceptible to oxidation-mediated killing) express both secreted and membrane associated glutathione peroxidase, glutathione-S-transferase and superoxide dismutase that have the potential for subverting this killing mechanism (56-59).

Host –related factors in immune-mediated modulation

Cells of the innate immune system

In the process of establishing a patent infection, the infectious stages must traverse a set of barriers the cells of which form an innate interface that can serve to modulate/induce certain immune or inflammatory functions (see Figure 1). This section examines these cells in the context of their interaction with parasitic helminths.

Helminths and epithelial/ innate lymphoid cells

Epithelial cells are the first barrier layer that helminth larvae encounter, and the capacity of these cells to interact with helminth parasites through pattern recognition receptors (TLRs, NLRs) and through the production of IL-25, IL-33 and thymic stromal lymphopoietin, (TSLP), considered to be "alarmins" (60), seems be important in driving an early response to these pathogens. In addition, epithelial cells in the intestine, for instance, are in constant contact with the intestinal microflora thereby being well positioned for immunological surveillance in the gastrointestinal tract. Moreover, epithelial cells (throughout the body) have been shown to induce tolerogenic signals to T cells and B cells (61).

Innate lymphoid cells (ILCs) represent a novel family of hematopoietic effectors that serve protective roles in innate immune responses to infectious microorganisms and in

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homeostasis of tissue stromal cells (reviewed in (62, 63)). Among these are the ILC2 cells that are known to produce IL-5, IL-13, IL-9, IL-4, and IL-10. Although they are found in abundance in the skin, in subepithelial portions of the intestine and airways among other sites, whether they play a regulatory role through the secretion of IL-10 remains an unanswered question.

Helminths and dendritic cells

Dendritic cells (DC) are antigen-presenting cells that play an essential role in presenting antigen to T cells to initiate immune responses. The role of DCs in T cell subset differentiation has been well characterized in both murine and human helminth infections (reviewed in (64-66)) and, on balance, helminth-educated DCs clearly promote both Th2 and regulatory responses (67-71). However how helminths (and their secreted/excreted products) alter DC function is less well understood, although helminth products very clearly alter the function and maturation of DC (72, 73) as well as impair in their ability to respond pattern recognition receptor stimulation (7, 69, 74, 75). By whatever mechanism, these helminth-modulated DC fail to respond appropriately to other infectious stimuli (e.g. *Mycobacterium tuberculosis* or *P. falciparum* (7, 76-78).

Helminths and macrophages

Although macrophages can function as effector cells in bacterial and protozoal infections through the production of nitric oxide (among other mediators) their interaction with helminths through the action of IL-4 and IL-13 induce a population of macrophages termed alternatively activated macrophages (AAMs) that are characterized by the expression of arginase, *YM1*, *YM2*, and RELM-α (79-82) These AAMs are known to be important in wound healing. By virtue of

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their expression of regulatory molecules such as IL-10, TGF-β and PDL2 these macrophages may have a predominantly regulatory role in helminth infections.

While helminth infection does induce expression of these AAMs and other regulatory monocyte/macrophage populations in humans ((83-86), the primary functional consequences of having increased frequencies of these cells is interference with full T cell activation (86, 87).

Helminths and eosinophils

Blood and tissue eosinophilia is characteristic of helminth infection and is mediated largely by IL-5. Recruitment of eosinophils to the site of infection occurs very early in experimental helminth infection and occurs by 2-3 weeks following human infection (88, 89). Although much attention has been drawn to eosinophils as effectors in killing helminth parasites, more and more evidence also points to their role in tissue remodeling, metabolic homeostasis, and their ability to act as anti-inflammatory cells through the release of pre-formed cytokines.

Helminths and basophils/mast cells

Basophils are an important component of the immune response to helminth infections (90, 91). Basophils gained prominence because of their potential role in Th2 cell differentiation as the initial source of "innate" IL-4 (92) that was capable of driving a Th2 response in murine models of helminth infection but also of inducing AAMs. However, the preponderance of evidence now suggests that in helminth infection, an adaptive Th2 response (and IgE production) precedes the basophil-induced IL-4 (93-98). Mast cells certainly contribute inflammatory responses directed toward many helminth parasites, but likely play little role in modulating responses to helminth parasites in the tissues (99).

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Cells of the adaptive immune system

Helminths and T cells

As noted in the introductory paragraphs, helminth infections, at the time of patency, are associated with a marked Th2 polarization that is modulated relatively soon thereafter, through the expansion of regulatory cell populations (largely Tregs, but also Mregs and Bregs). The ontogeny of the Th2 response and its effector function is the subject of several other papers in this series and thus will not be discussed further herein.

In mouse models of filarial and schistosome infections parasite survival has been linked to the activity of Tregs. Indeed immunity to infection (when it can be induced) can be enhanced by Treg depletion. Because both natural regulatory T cells (nTregs) and adaptive regulatory Tregs (aTregs) are expanded following helminth infections they will be discussed in turn.

nTregs play an important role in the modulation of T cell responses in infectious diseases, cancer and autoimmune diseases (100-103). Characterized by the surface expression of CD25 and CD127 and by the transcription factor Foxp3, nTregs can suppress T cell responses through a contact-dependent mechanism the nature of which is still not fully understood. Evidence from mouse models and to a lesser degree from human studies argues that nTregs play a role in controlling pathology and immunity during helminth infections. In *H. polygyrus*-infected mice, for example, nTregs are present in greater frequencies, express higher levels of CD103, and are intrinsically more able to suppress T cell responses than Tregs from naïve mice. In murine filarial infections, parasite survival is linked to nTreg activity. Similarly, Treg cells are also instrumental in controlling Th2 responses in chronic *S. mansoni* infection.

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aTregs, in contrast, are known to act through the production of cytokines, particularly IL-10 and TGF-β Evidence for the involvement of regulatory T cells (particularly aTregs) in helminth mediated down modulation of the immune responses has been accumulating. IL-10 and TGF-β both factors associated with regulatory T cells, are elicited in response to helminth infections and in vitro neutralization of IL-10 and TGF-β (to a lesser extent) restores T cell proliferation and cytokine production in filarial infections (lymphatic filariasis and onchocerciasis) and in schistosomiasis (104-109). In addition, T cell clones secreting IL-10 and TGF-β have been isolated from patients with onchocerciasis (110).

Helminths and B cells

Helminths interface with B cells through the T cell dependent induction of antibody production and at the cellular level by inducing B cell activation and cytokine production, IL-10 most prominently (111). Immune regulation by B cells in the context of helminth infections has been best studied in mouse models of and human studies in schistosome infection. In murine schistosome infection it was clearly shown that B cell deficiency leads to enhanced CD4-mediated pathology and that IL-10 producing B cells (Bregs) were important for prevention of pathology (112 , 113]. In humans with *S. haematobium* infections, such IL-10 producing Bregs have also been shown not only to be expanded but also to downregulate the parasite antigen-driven T cell effector cytokine response through the production of IL-10 (114).

Modulation of T cell effector function

The hallmark of most helminth infections is their chronicity (115), a state that requires the dampening of effector responses. The signature of such a dampened immune response in

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helminth infection is a down-regulated parasite-specific effector T cell response (so-called T cell hyporesponsiveness). Effector T cell responses can be modulated through a variety of mechanisms that include at the T cell level: 1) the production of IL-10 (107, 109, 116) and TGF-β (110, 117, 118); 2) increased surface expression of CTLA-4 (119) and PD-1(120); 3) the modulation of the transcription factor Tbet (43); and 4) the induction of anergy (121). Finally, T cells from filarial infected individuals exhibit classical signs of anergy including diminished T cell proliferation to parasite antigens, lack of IL-2 production (122) and increased expression of E3 ubiquitin ligases (121). Similarly, anergic T cells are found in both humans and mice with schistosomiasis and, in the latter case, these T cells express high levels of GRAIL (gene related to anergy in lymphocytes) (123).

Effector T cell function can also be limited by "faulty" signals delivered by antigen presenting cells. Dendritic cells are the first antigen-presenting cells to encounter helminth parasites, and helminth modulation of DC function has been well characterized (72). Filarial parasites induce downregulation of MHC class I and class II as well as cytokines and other genes involved in antigen presentation, thereby rendering DC suboptimal in activation of CD4+ T cells (124). Schistosomes induce similar effects on DC (69) and by Nlrp3-induced IL-β production (125, 126). Finally, soluble products from several pathogenic helminths have been shown to induce apoptosis of DC (127, 128).

The role of helminth infections in modulating the activation status of macrophages has already been alluded to above. However, a heterogeneous population of immature myeloid cells termed myeloid-derived suppressor cells (MDSC) share the ability to suppress immune responses. Several helminth parasites have been associated with the expansion and accumulation of MDSC (129-131).

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Putting it all together

Helminth parasites, be they systemic or localized to the GI tract, are characteristically long-lived and have evolved in such a way that they rarely induce symptomatic infections. Moreover, complete parasite elimination in immunocompetent hosts often is dictated by the lifespan of the particular parasite rather than by the host immune and inflammatory responses, responses that would be deleterious. Therefore, the disease manifestations, which are less often found in these infections, are commonly associated with immune- and not parasite-mediated pathology. The optimal response to helminth infection is one that balances parasite control at levels where the parasite can be tolerated and immune homeostasis can be maintained without significant tissue damage. This immune homeostasis requires the orchestration of myriad factors (both host- and parasite-derived [see Figure 2]) that serve to limit pathology and allow for parasite survival and continued transmission from host to host.

The consequences of the chronicity of many tissue invasive helminth parasites remain relatively unstudied, as do the consequences of the enormous antigenic load provided by the secreted/excreted products of these parasites. How high antigen load and/or chronic antigenic stimulation can have such profound functional effects on cells of both the innate and adaptive arms of the immune system will likely be addressed in the near future. What is clear, however, is that one must expand/shift the paradigm away from helminth-induced Type 2 responses to allow for an understanding of helminth-induced immune modulation.

Figure legends.

Figure 1. Immune responses in helminth infections as a function of time following infection. Infectious stages of helminth parasites initiate infection at barrier sites and activate a variety of different cell types such as innate lymphoid cells (ILCs), macrophages (MAC), dendritic cells

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(DCs), natural killer cells (NK), eosinophils (Eos) and basophils/mast cells (Baso/MC). At this relatively early phase of infection the parasite induces the differentiation of effector Th1, Th17 and Th2 cells, which together with IgE antibody, may lead to attrition of some of the parasites. At the time of patency (when egg laying/microfilarial release occurs) there is a small expansion of Th2 CD4+ cells and a concomitant contraction of Th1 cells. With the evolution of chronic longstanding infection, there is an associated expansion of IL-10- and/or TGF-β-producing regulatory T cells (Tregs). The high levels of IL-10 produced induce the production of IgG4 which together with IL-4, IL-13, and/or TGF-β induce the differentiation of alternatively activated macrophages (AAM) and inhibit the function of a variety of other cells including central memory (TCM) and effector (Teff) T cells.

Figure 2. Schematized understanding of the host response to helminth infection. Shown in blue are the characteristic mechanisms induced by the host responses (purple) or by the helminth infections/products (green) that lead to specific outcomes (red).

Acknowledgements: This work was funded in part by the Division of Intramural Research (DIR), National Institute of Allergy and Infectious Diseases, NIH.

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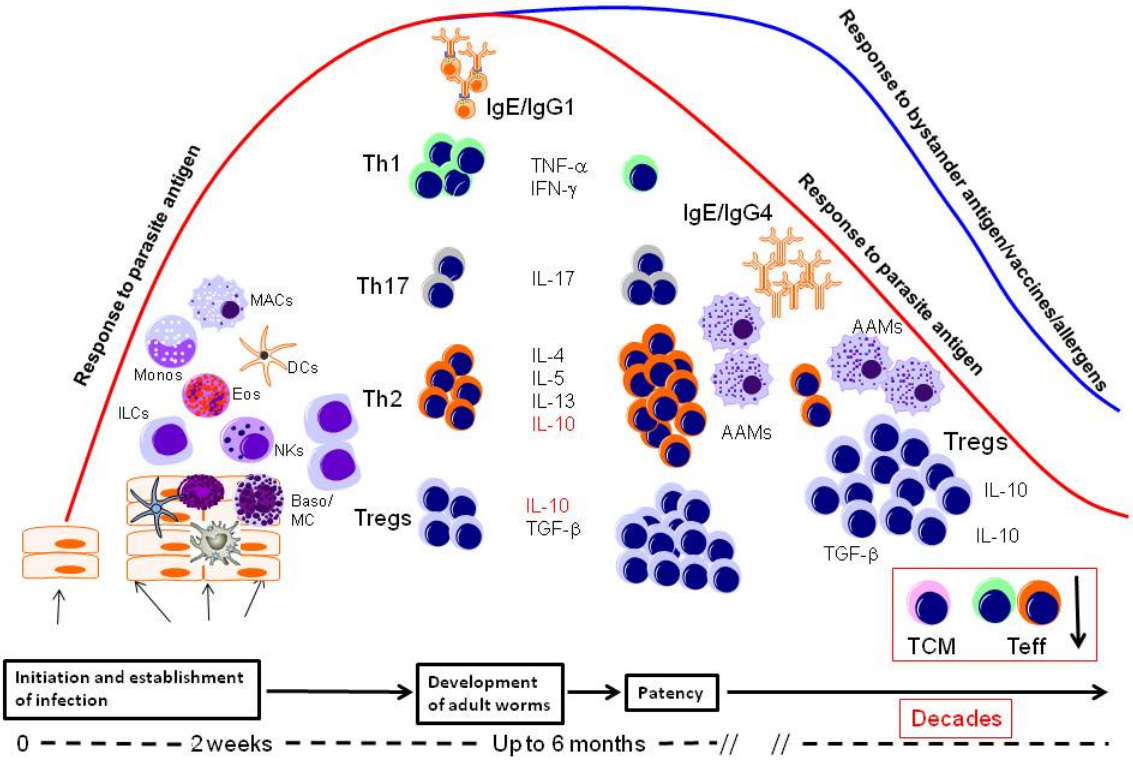

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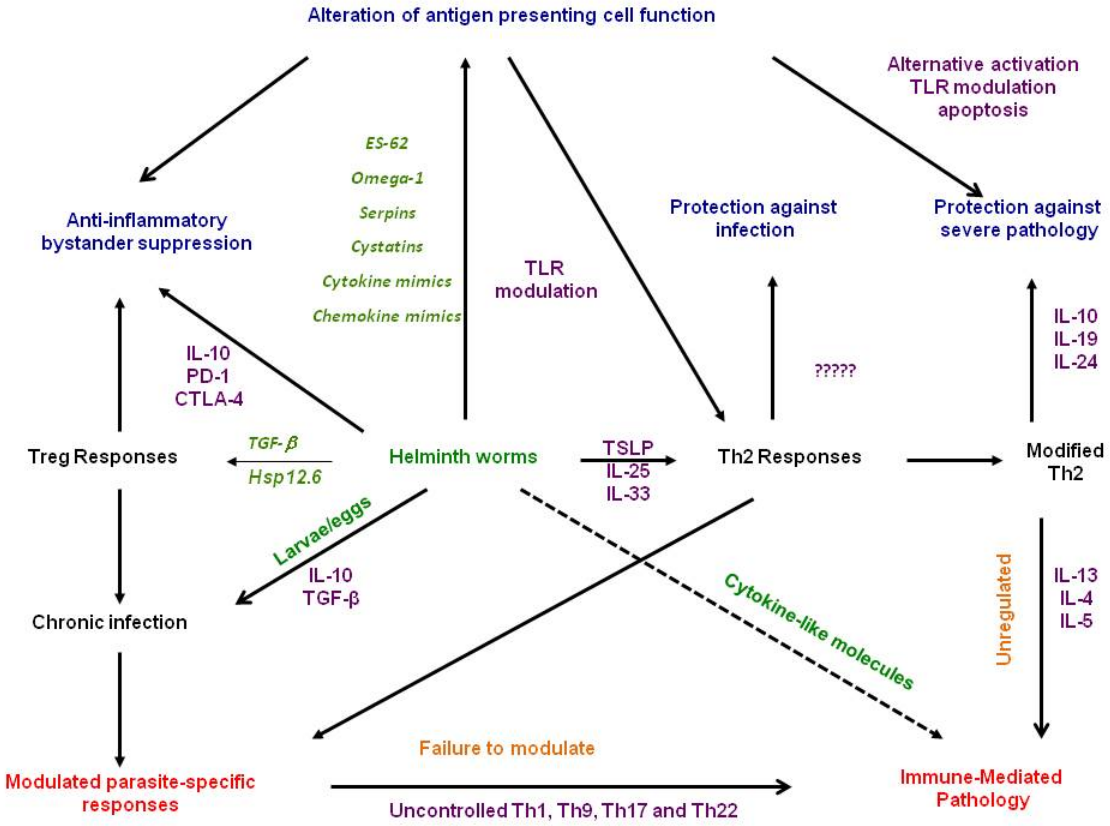

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