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Review

The mechanisms behind helminth's immunomodulation in autoimmunity

Tomer Bashi [a], Giorgia Bizzaro [a], Dana Ben-Ami Shor [a,b], Miri Blank [a], Yehuda Shoenfeld [a,c,*]

[a] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, affiliated to Sackler Faculty of Medicine, Tel Aviv, Israel
[b] Department of Gastroenterology, Sheba Medical Center, Tel Hashomer, affiliated to Sackler Faculty of Medicine, Tel Aviv, Israel
[c] Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel Aviv University, Tel Aviv, Israel

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ABSTRACT

The incidence of autoimmune diseases has risen throughout the last half a century, mostly in the industrialized world. Helminths and their derivatives were found to have a protective role in autoimmunity and inflammatory conditions, as they manipulate the immune network, attenuating the host's cellular and humoral responses. Indeed, various helminth species used in several human and animal models were shown to limit inflammatory activity in a variety of diseases including inflammatory bowel disease, multiple sclerosis, type 1 diabetes, and rheumatoid arthritis. Our review will focus on the main mechanisms by which helminths and their secreted molecules modulate the host's immune system. The main pathways induce a shift from Th1 to Th2 phenotype, accelerate T regulatory and B regulatory phenotypes, and attenuate the levels of the inflammatory cytokines, leading to a tolerable scenario.

Contents

1. Introduction

For the past several decades, Western industrialized countries were facing a high rate of autoinflammatory disorders, expressed by increased prevalence of autoimmune diseases and allergies [1,2]. As industrialized countries' lifestyle led to a decrease in the infections burden, the limited exposure to microorganisms such as helminths and microbes in childhood may have eventually led to an off-balanced immune system [3]. This theory, known as "hygiene hypothesis," was first proposed by Strachan, who observed an inverse correlation between hay fever and the number of older siblings while following more than 17000 British children born in 1958 [4–6]. One example that illustrates the hygiene hypothesis is malaria's prevalence, which is in reverse correlation to autoimmune diseases in Sardinia. Several epidemiological and immunogenetic evidences link the disappearance of malaria due to human's eradication program with the increase of multiple sclerosis (MS) in Sardinia as well as to the high genetic susceptibility of HLA DR3 within the island [7,8]. Moreover, the contribution of helminths and infections to the development of autoimmune diseases is also demonstrated in the Karelian region. Finland's Karelian maintains one of the highest prevalence of autoimmune and allergic diseases, while Russian's Karelian prevalence is far lower. The fact that the Russian section is rife with

* Corresponding author at: Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan 52621 Israel. Tel.: +972 35308070; fax: +972 5352855.
E-mail address: shoenfeld@post.tau.ac.il (Y. Shoenfeld).

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infections and the Finnish part is dramatically cleaner has high impact on the prevalence difference [9,10]. In addition to the eradication of worms in the Western world, it has been mentioned that helminth's eradication increases atopic skin sensitization in Venezuela [11], in Gabon [12], and in Vietnam [13].

Helminths' aim is to flourish and survive in the host as much as possible. Their purpose is to live along with the host rather than to kill him; therefore, they try to induce a tolerable scenario. It is achieved by several methods such as switching the immune reaction from Th1 to Th2, changing the secreted cytokines, and increasing the amount of T regulatory cells (Tregs). Moreover, many helminth parasites are known to release biologically active excretory–secretory (ES) antigens that directly modulate host immune function [14]. Evidence that helminths play like immunomodulators was given by splenic T cells, taken from helminth-infected rats and transferred into helminth-naïve rats, which ameliorate experimental autoimmune encephalitis (EAE—the most frequently studied animal model of MS [15]) and in some cases protected those animals from developing the disease [16]. Yet it is important to keep in mind that the immunomodulation is affected by several key elements such as the burden of the infection and the host's immune system. In most of the cases, helminths will induce tolerance, but in some scenarios, they may cause an inflammatory response. Affliction spectrum ranges from low pathology/tolerance, along with high parasite burden, to chronic disease/inflammation, along with low parasite burden [17].

2. Helminth therapy trials

The hygiene theory had led to human therapy trials with helminths and helminths' ova.

In the early 2000s, *Trichuris suis* (pig whipworm) was suggested to be safe and possibly effective in the treatment of inflammatory bowel disease (IBD). The pig is the natural host for *T. suis*, which can colonize humans as well, but only for a short period of time [18]. It was demonstrated among 36 Crohn's disease (CD) patients that a single dose of *T. suis* ova (TSO)—up to 7500 ova was well tolerated and did not result in short- or long-term treatment-related side effects [19]. Summers *et al.* studied four patients with active CD and three with ulcerative colitis (UC). In an initial treatment and observation period, a single dose of 2500 live TSO was given orally, and patients were followed every 2 weeks for 12 weeks. Later, safety and efficacy assessment was carried out with repetitive doses, and two patients with CD and two with UC were administrated with 2500 ova at 3-week intervals. Patients with UC experienced a reduction of the Clinical Colitis Activity Index to 57% of baseline. According to the IBD Quality of Life Index, six of seven patients (86%) achieved remission. In some patients who received a single dose, the benefit was temporary, but it could be prolonged with maintenance therapy every 3 weeks [20]. Next, Summers *et al.* conducted a proceeding TSO study, which included twenty nine patients with active CD. Each patient ingested 2500 live TSO every three weeks for 24 weeks. Disease activity was monitored by Crohn's Disease Activity Index (CDAI). The results were impressive: at week 24, 23/29 patients (79.3%) responded and 21/29 (72.4%) remitted [21]. Another randomized, double-blind, placebo-controlled trial included 54 patients with active colitis, defined by CDAI. Patients received orally 2500 TSO or placebo at 2-week intervals for 12 weeks. The primary efficacy variable was improvement of the Disease Activity Index. After 12 weeks of therapy, improvement according to the intent-to-treat principle occurred in 13 of 30 patients (43.3%) with ova treatment compared to 4 of 24 patients (16.7%) given placebo. Improvement was also found with the Simple Index that was significant by week 6 [22,23]. It is important to mention one case report regarding iatrogenic infection by *T. suis* in a 16-year-old adolescent with CD who was treated with TSO. He received 5 oral doses of 2500 TSO off protocol. When admitted to the hospital, pathologic evaluation showed several round helminthic forms directly beneath attenuated ileocecal mucosal epithelium. It was found that the helminths from the TSO had developed in his intestine [24].

Furthermore, TSO have been used as a preliminary therapy course also in MS, a Th1/Th17-associated autoimmune disease. A slight downregulation of the Th1-associated cytokine pattern was shown, especially relevant in interleukin (IL) 2, with a temporary increase of Th2-associated cytokines such as IL-4 [25,26]. In addition, the mean number of new gadolinium-enhancing magnetic resonance imaging (MRI) lesions dropped from 6.6 at baseline to 2.0 at the end of TSO administration. Two months after TSO was discontinued, the mean number of new gadolinium-enhancing MRI lesions rose to 5.8, and no significant adverse effects were observed [26].

In order to prove the beneficial effect of helminths on MS patients, Correale *et al.* conducted a study of twelve patients (8 female and 4 male) with clinical diagnosis of MS, which were assessed in a prospective double-cohort study. The 12 MS patients were infected with several helminth species (*Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Enterobius vermicularis*). Each patient was infected with one species. A control group containing healthy subjects was also infected with helminths, and another 12 uninfected MS patients in remission matched for age, sex, and disease duration served as disease control subjects. It was shown that parasite-infected MS patients had a significantly lower number of exacerbations, minimal variation in disability scores, as well as fewer MRI changes when compared with uninfected MS patients [27,28].

The success of the hygiene theory and the ova treatment served as motivation to understand the mechanisms involved in the helminths' immunomodulation capabilities.

3. Th1 to Th2 switch

T cells undertake the primary role in modulating the outcome of many autoimmune diseases. Naïve T cells can differentiate into helper (Th) and regulatory (Tregs). There are five main subsets of T helper cells: Th1, Th2, Th9, Th17, and Th22 cells [29]. Th1 cells produce proinflammatory cytokines: tumor necrosis factor alpha (TNFα), interferon gamma (IFN-γ), and IL-12. In addition, Th1 cells mediate proinflammatory responses during an autoimmune disease, for example, by increasing IgG2a, IgG2b, and IgG3 antibody subclasses [30]. Th2 cells secrete anti-inflammatory cytokines, IL-4, IL-5, IL-10, and IL-13, and participate in prevention or remission of Th1-mediated autoimmune diseases [31]. Most humans infected with helminths have reduced production of IFN-γ and increased production of IL-4/IL-10 which, together with elevated IgG4 levels, suggest a predominant Th2 phenotype conducive to both parasite survival and host health [32].

Rheumatoid arthritis (RA) is associated with a Th1 response and a general rise in pro-inflammatory cytokines, such as IL-6, IFN-γ, and TNF-α [33]. Early studies showed that the rodent filarial nematode *Acanthocheilonema vitae* secretes ES-62, an immunomodulatory glycoprotein surrounded by phosphorylcholine (PC) moiety attached to the protein by N-type glycans [34]. ES-62 induced a shift from Th1 to Th2 response and attenuated the RA-like disease in collagen induced arthritis (CIA) model in mice. ES-62 elevated the production of IL-10 anti-inflammatory cytokine and reduced levels of IFN-γ and IL-12 pro-inflammatory cytokines. Serum collagen-specific IgG2a, but not IgG1, levels were also significantly reduced in recipients of multiple ES-62 doses [34].

The ligation of pathogen products to Toll-like receptors (TLR) leads to induction of cytokine production by macrophages and dendritic cells (DC). The TLR are thought to recognize specific molecular motifs of the host as well as of pathogen origin, including pathogen-associated molecular patterns (PAMP). The TLR signals are transuded *via* adaptor molecules such as MyD88. This results in the activation of various signaling pathways, including the mitogen-activated protein kinase (MAPK) cascades and nuclear factor (NF)-κB pathway. When TLR4 binds its lipopolysaccharide (LPS) ligand, recruitment of MyD88 leads to the activation of mitogen-activated protein kinase kinase kinase (MAPKKK). The following phosphorylation leads to activation of MAPK cascades and the NF-

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κB inhibitory protein kinase (IκBK) signalsome. The MAPK can then translocate to the nucleus and activate transcription factors, such as Ets-like protein (Elk), activator protein-1 (AP-1), and activating transcription factor 2 (ATF)-2. IκBK phosphorylates IκB, inducing its ubiquitinylation and degradation. Degradation of IκB results in the release of active p50/p65 components of NF-κB, which then translocates to the nucleus and transactivates immunomodulatory genes, such as IL-12. ES-62 inhibits IL-12 production by suppressing the MAPK cascade and NF-κB activation and by inducing ERK, which exerts a negative feedback regulatory signal on IL-12 production. In addition, ES-62 suppresses p38 activation, which is required for the upregulation of IL-12 subunits, p40 and p35 [35–37]. Moreover, in the presence of ES-62, cultures of human RA patients' synovial fluid showed reduced levels of TNF-α and IFN-γ secretion, and their peripheral blood smears exhibited mononuclear cells with low IFN-γ secretion [33,38].

MS is an inflammatory, demyelinating, neurodegenerative disorder of the central nervous system (CNS) of unknown etiology [39]. It was established that *Trichinella spiralis* infection creates an environment unsuitable for the development of EAE [16]. The infection was found to inhibit IL-17 and lower IFN-γ production, together with simultaneous activation of Th2 response acting through cytokines IL-4, IL-10, and tumor growth factor beta (TGF-β) [16].

Type 1 diabetes mellitus (T1DM) is considered a Th1-mediated autoimmune disease, influenced by both genetic and environmental factors. The pathogenicity is attributed to cytotoxic T lymphocytes [40]. The autoantibodies associated with the disease are directed at various islet cell components, which eventually lead to the destruction of the pancreatic insulin-secreting β cells [41].

Four- to 6-week-old non-obese diabetic (NOD) mice, T1DM model, were infected with gastrointestinal helminths *Trichinella spiralis* and *Heligmosomoides polygyrus*. Th2 response was elicited, as shown by increased IL-4 and IgE levels [42]. This was in contrast to the Th1 response that usually accompanied the development of diabetes in NOD mice. This result suggested that the helminth-induced Th2 response might have protected the mice from the effects of Th1-mediated β cell destruction. NOD mice infected with *H. polygyrus* remained free of diabetes over the entire experimental time course (36 to 37 weeks) [42]. Furthermore, *H. polygyrus* infection in mice was found to increase the frequency of $CD4^+$/GFP^+ Th2 cells in lymphoid organs including drainage of mesenteric lymph nodes, the spleen, peripheral blood lymphocytes, and Peyer's patches. These cells were also accumulated in non-lymphoid "hot spots" in the liver, the lung airways, and the peritoneal cavity. Peritoneal Th2 cells were distinguished by an exceptionally low apoptotic potential and high expression of the intestinal homing receptor α4β7 integrin. $CD4^+$/GFP^+Th2 cells from these peripheral sites were fully functional as indicated by rapid IL-4 production upon polyclonal or Ag-specific restimulation [43].

Moreover, the onset of diabetes was prevented by *Litomosoides sigmodontis* filarial worms in infected NOD mice. 6-week-old female NOD mice were infected with either L3-stage larvae, adult female worms, or adult male worms. Glucose levels were monitored over time. The onset of diabetes (glucose levels >230 mg/dl) was prevented in all mice tested until the end of the experiment at 25 weeks of age. Protection against diabetes was associated with a Th2 shift, as IL-4 and IL-5 release from α-CD3/α-CD28-stimulated splenocytes was greater in *L. sigmodontis*-infected mice than in uninfected mice [44]. A following study tested whether infection with *L. sigmodontis* prevents diabetes onset in IL-4–deficient NOD mice and whether depletion or absence of Tregs, IL-10, or TGF-β alters helminth-mediated protection. It was supported that *L. sigmodontis*-mediated protection is dependent on the induction of neither Th2 switch nor IL-4 yet requires TGF-β [45]. In addition to *L. sigmodontis*, also *Schistosoma mansoni* has been shown to prevent T1DM [46]. *S. mansoni* ova prevented the development of the disease in 4- to 6-week-old NOD mice, whereas the non-infected mice developed diabetes at 70% incidence by 27 weeks of age [46].

The live ova of *S. mansoni*, actively secrete the glycoprotein Omega-1 ($\omega - 1$), which has been shown *in vitro* to manipulate human monocyte-derived DC to induce a Th2 response [47], thus regulating host immune response and aiding in the parasite's survival as well as migration [48]. In addition, $\omega - 1$ alone directly elicited human DC to induce Th2 development from naïve $CD4^+$ T cells and further inhibited the release of IL-12 along with induction of IL-4 production, therefore reducing the differentiation of Th1 cells [47,49]. Furthermore, prophylactic use of *S. mansoni* worm soluble products homogenate and α-galactosyl ceramide (α-GalCer) had been carried out in a Graves' mice model [50]. α-GalCer is one of many glycoconjugates expressed by *S. mansoni* worms and live ova [51]. It was indicated that both *S. mansoni* products and α-GalCer protected from Graves' disease, mainly by suppressing a Th1 type anti-TSH receptor immune response at the time of antigen priming. This occurred by raising the anti-inflammatory cytokine IL-10 levels [50]. α-GalCer is controversial since it stimulates natural killer T (NKT) cells to rapidly produce both Th1 and Th2 cytokines. However, at a later point in time and with repeated doses, α-GalCer promotes the development of a Th2 immune response, thus protecting against various autoimmune diseases, such as diabetes as illustrated in NOD mice [46].

4. Th17 response

During inflammatory conditions, part of the immune system response involves Th17 cell differentiation [52]. Th17 lymphocytes secrete IL-17, a pro-inflammatory cytokine found at high levels in autoimmune diseases, such as IBD [53] and MS [54], and in asthma [55]. For example, IL-17 expression was augmented in inflamed mucosa of patients with UC or CD [53,56] and in mice with experimental colitis induced by trinitrobenzenesulphonic acid (TNBS) [57]. Moreover, in EAE and reactive airway disease mice, IL-17 expression was also up-regulated. Proceeding experiments using IL-17-/- murine model demonstrated resistance to the diseases [58,59].

Elliott *et al.* first reported an association between helminth infection and IL-17 downregulation [60]. IL-17 production was strongly inhibited in *H. polygyrus* infected mice. IL-17 mRNA expression was decreased by 16-fold in mesenteric lymph node cells in comparison to its levels in helminth-naive mice. An increase was noticed in the levels of IL-4 and IL-10, which seem to inhibit IL-17 release. However, IL-10 by itself is not able to downregulate IL-17 expression; indeed, IL-17 production was not enhanced by blocking IL-10 signaling. Conversely, IL-4 blockade restored IL-17 production, although not completely [60]. Moreover, *Taenia crassiceps*-infected mice were found to produce less IL-17, with significantly reduced EAE severity symptoms in 50% of the animals [61]. Also *Trichinella pseudospiralis* infection was shown to ameliorate EAE, suppressing the Th17 response and reducing the inflammatory infiltrates in the CNS [62].

Another feature of Th17 is its ability to secrete IL-22, member of the IL-10 cytokine family [63]. In addition, IL-22 is secreted by innate lymphocytes (lymphoid tissue-inducer cells, γδ T cells, and NKT cells [64]) and by Th22, a different lymphocyte subset [65]. IL-22 appears to have a pathogenic role in autoimmune arthritis. Indeed, IL-22 deficient mice are less susceptible to develop CIA [66]. Harnett *et al.* recently studied the influence of ES-62 on IL-22 production in CIA mice [67]. It was suggested by them that IL-22 has dual pro- and anti-inflammatory roles. In the initial step of the disease, systemic IL-17 and IL-22 responses increased pro-inflammatory activity while later IL-22 exerts anti-inflammatory action, via downregulation of IL-17. ES-62 administration ameliorated disease symptoms as well as increased IL-22 levels, which correlated inversely with articular scores and joint inflammation. Furthermore, ES-62-mediated protection against CIA could be blocked by administration of neutralizing anti–IL-22 antibodies. The trigger that switches IL-22 from a pro- to an anti-inflammatory cytokine in CIA is not known. However, they suggested that this occurs around the time of onset of joint pathology [67].

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Interestingly, in a UC patient with low levels of IL-22 were measured in the colon [68]. When infected with *Trichuris trichiura,* the UC symptoms were ameliorated as well as levels of IL-22 were significantly increased in his mucosa. This also supports the beneficial role of IL-22 as promoter of wound healing, proliferation, and antiapoptotic pathways in intestinal epithelial cells [64].

5. T regulatory cells

Helminths' tolerant phenotype is characterized by the production of anti-inflammatory cytokines, mainly, TGF-β and IL-10, and by an increased number of Foxp3$^+$T regulatory cells [69]. TGF-β and IL-10 lead to reduced levels of Th2 cytokines, ablated Th1 cytokines, and decreased IgG4 production by B cells. Moreover, T-cell proliferation against the parasite is suppressed. Therefore, the parasite survives productively in the host, with minimal collateral damage [17,69].

In murine models, helminth infections elicit both "natural" and "adaptive" Foxp3$^+$Tregs responses, which dampen Th2 immunity [70]. Following the infection, a rapid expansion of total Foxp3$^+$ is observed, suggesting the stimulation of natural Tregs [70]. Subsequently, adaptive Foxp3$^+$Tregs are generated [71].

Helminth molecules can especially promote a regulatory phenotype in naïve T cells. For example, *Teladorsagia circumcincta* secretes products capable of directly inducing Foxp3$^+$Tregs [72]. The related gastrointestinal nematode *H. polygyus* ES antigens have also shown to induce *de-novo* expression of Foxp3$^+$Tregs [72,73]. Moreover, *H. polygyrus* activates colonic Tregs and enhances their capability to prevent colitis. It seems that IL-10, produced by Foxp3$^+$ Treg cells, is critically important for protection from colitis [74]. Further support to the beneficial effect of helminths was indicated after treatment with *S. mansoni* soluble worm proteins in TNBS-induced colitis in mice. The infection caused an upregulation of Tregs cytokines in the colon, with an improvement of the disease [75]. Moreover, ES products have also significantly affected Tregs. Mice treated with ES products from *T. spiralis* adult worms ameliorated the severity of DSS-induced colitis, with increased regulatory cytokines IL-10, TGF-β, and Tregs in the spleens, mesenteric lymph nodes, and colons of treated mice [76]. The ES product secreted by *A. vitae*, ES-62, is able to polarize the T-cell response indirectly by modulating the maturation and function of DC and macrophages, which are required for priming and activation of CD4$^+$ T-cells [77]. Moreover, ES-62 induces CTLA-4-expressing Tregs, which are refractory to antigen and can suppress T-cell activation, leading to T-cell hypo-responsiveness [78].

Upregulation of the Tregs population is also illustrated in other autoimmune disease models of mice infected with helminths, exhibiting a protective role. In a mice model of CIA, *Fasciola hepatica* influenced CpG-activated DC to promote Tregs development and diminished the severity and incidence of the disease [79].

Furthermore, EAE in dark agouti rats successfully ameliorated after *T. spiralis* ES muscle larvae (ES L1) products treatment. Prior to the induction of EAE, unconventional CD4$^+$CD25$^-$Foxp3$^+$Tregs were identified in significantly increased proportion both in the periphery and CNS.ES L1-stimulated DC produced significantly less IL-12p70, as well as lower release of IFN-γ and IL-17 by spinal cord infiltrating cell while IL-4, IL-10 and TGF-βlevels were significantly increased [80].

As already mentioned, *L. sigmodontis* filarial worms managed to prevent the onset of diabetes in infected NOD mice. Multicolor flow cytometry studies demonstrated that the protection against diabetes was associated with significantly increased numbers of splenic CD4$^+$CD25$^+$Foxp3$^+$Tregs [44]. Likewise, *in vitro*, $\omega - 1$ has been shown to convert naïve CD4$^+$ T cells of NOD mice into Foxp3$^+$Treg cells [49].

The generation of Foxp3$^+$ cells in response to *S. mansoni* soluble egg antigen (SEA) is TGF-β-dependent, supported by reduced Foxp3$^+$ expression after TGF-β neutralization [81]. SEA is able to induce TGF-β as well as upregulate integrin β8, which is necessary for the dissociation of TGF-β from the inactive complex with latency-associated peptide [81]. Moreover, SEA modulates intracellular pathways leading to increased production of IL-10 and Tregs development [82]. It is important to mention that SEA-mediated signaling is MyD88-dependent, indicated by abrogated cytokine production when MyD88 gene expression is silenced [82]. Conversion of naïve T cells into Treg cells can be induced by a parasite-derived TGF-β mimic, as shown by Grainger *et al. H. polygyrus* ES induced SMAD 2/3 phopsphorylation and stimulated the activation of the host TGF-β signaling pathway, leading to Foxp3$^+$ expression [72]. The blockage of TGF-β in draining lymph node cells, indeed showed reduction of Tregs percentage and inhibition of IL-10 production [79]. Moreover, up-regulation of TGF-β production was found in experimental colitis mice, treated with *T. spiralis* antigens prior to disease induction, leading to symptom improvement [83]. More evidence of the role of TGF-β in inducing Tregs expression is shown by blocking Smad7. Smad7 is a key intracellular antagonist of TGF-β-mediated signaling, which is strongly expressed in intestinal T cells mediating IBD. Blocking its activity in these cells results in a T-cell population with strong regulatory function [84]. Furthermore, Smad7 was not detected in TGF-β-producing cells during parasite infections, allowing the development of Tregs population [27].

6. B10 cells and dendritic cells

B cells are generally considered to be up-regulators of the immune response due to their capability to produce antibodies, including autoantibodies [85]. However, certain B cells can also downregulate the immune response by producing regulatory cytokines and directly interacting with pathogenic T cells. These types of B cells are defined as B regulatory cells (Bregs) [85]. Helminths' protective role also involves the development of Bregs, having suppressive effect on the progression of immune-mediated diseases such as experimental arthritis, EAE and experimental colitis [86–88]. IL-10 secretion is essential for B-cell-induced regulation. Indeed, B cells isolated from IL-10 knockout mice failed to mediate this protective function [86]. Moreover, MS patients' B cells exhibited relative deficiency in their IL-10 producing capacity [89]. Interestingly, it was found that B cells isolated from helminth-infected MS patients produced greater levels of IL-10, likely through the ICOS-B7RP-1 pathway [90]. B cells of helminth-infected subjects produced IL-10, in contrast to intracellular parasite infected-patients [90]. *Paracoccidioides brasiliensis*-infected patients expressed Th2 immune response. However, they showed B cells IL-10 production levels similar to those observed in uninfected MS patients. This result indicates that increased production of IL-10 in helminth-infected patients is not determined by the Th2 profile [91].

Naïve B2 cells are particularly capable to produce IL-10 and induce Foxp3$^+$ expression on CD4$^+$ T cells, promoting their differentiation into Tregs [27]. In addition, IL-10 producing B cells, isolated from helminth-infected MS patients, expressed MHC-I molecule CD1d able to activate NKT cells, thus preventing autoimmune responses in several animal models [92]. Moreover, neurotrophic factors (NTFs), such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), involved in the growth and development of neurons, were produced at greater amounts [90]. The mechanism by which B cells release NTFs, after helminth infection, is vague. One hypothesis is that helminth-derived molecules bind to TrkA or p75NTR receptors present in B cells, triggering the production of NTFs [90]. Alternatively, ligation of CD40 receptor, homologous to NGF receptors, may induce increased production of NGF [93].

B-cell signaling is further modulated by ES products, such as ES-62. It induces the tyrosine phosphatase SHP-1, which dephosphorylates immunoreceptor tyrosine-based activator motifs, preventing recruitment of the Ras/Erk MAPK cascade [94,95]. First, ES-62 is able to recruit GAP and the nuclear Pac-1, leading to blockage of ERK signaling [96]. Second, ES-62 negatively modulates the activation of the MAPK subfamilies, p38 and JNK [97]. Finally, PC-antigens like ES-62 induce IL-10 production

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Table 1
Immunomodulation of autoimmune diseases by helminths.

Mechanism	Diseases	Helminths	References
Th1 to Th2 shift	RA	*Acanthocheilonema vitae*	[33–37,77]
	MS	*Trichinella spiralis*	[16,80]
	GD	*Schistosoma mansoni*	[50]
	T1DM	*Trichinella spiralis*	[42]
		Heligmosomoides polygyrus	[42,43]
		Litomosoides sigmodontis	[44]
		Schistosoma mansoni	[47–49,81]
Th17 downregulation	MS	*Trichinella spiralis*	[16,80]
		Taenia crassiceps	[61]
		Trichinella pseudospiralis	[62]
	IBD	*Heligmosomoides polygyrus*	[60]
Th22 upregulation	RA	*Acanthocheilonema vitae*	[67]
	IBD	*Trichuris trichiura*	[68]
Tregs expansion	RA	*Fasciola hepatica*	[79]
	MS	*Trichinella spiralis*	[80]
		Schistosoma mansoni	[82]
	T1DM	*Litomosoides sigmodontis*	[44,45]
		Schistosoma mansoni	[49,81]
	IBD	*Heligmosomoides polygyrus*	[74]
		Trichinella spiralis	[76,83]
		Schistosoma mansoni	[75]
B10 cells expansion	RA	*Acanthocheilonema vitae*	[94,95,98]
	MS	*Schistosoma mansoni*	[82]
		cp	[99]

RA—rheumatoid arthritis; MS—multiple sclerosis; GD—Graves' disease; T1DM—type 1 diabetes mellitus; IBD—inflammatory bowel disease.

in B1 cells, which support the blocking of IgG2a response, but favor IgG1 production [98].

Other helminth-derived components, such as glycoprotein and lipids, are also involved in human DC activation, modulating anti-inflammatory responses. For example, $\omega - 1$ and helminth cystatins from *A. vitae*, *Brugia malayi*, *Nippostrongylus brasiliensis*, and *Onchocerca volvulus* were able to induce TLR2 expression on both B cells and DC [99]. As mentioned earlier, helminths influence TLR domains expressed on immune cells, including DC and B cells. Helminth parasites may alter TLR function and level of expression [82]. Indeed, surface expression of TLR2 on both B cells and DC is significantly higher in helminth-infected MS patients with respect to the controls [82]. Both TLR2-activated DC and B cells significantly inhibited $CD4^+$ T-cell proliferation along with IFN-γ and IL-17 production. Moreover, TLR2 can be ligated by SEA, inducing intracellular pathways, which result in IL-10 production by both DC and B cells [82].

ES products derived from *H. polygyrus* inhibited murine bone marrow-DC cytokine and chemokine production as well as downregulated co-stimulatory molecule expression (CD40, CD86, and MHC-II), induced by TLR ligation [73]. Moreover, *H. polygyrus* products have been shown to modulate DC function, rendering them capable of driving the $CD4^+$ T cells into the Tregs phenotype [73]. Further illustration is given by *F. hepatica* tegumental coat antigen, suppressing DC maturation. The antigen inhibits cytokine secretion (IL-6, TNF-α, IL-10, and IL-12) and costimulatory molecules production (CD40, CD80, and CD86) [100].

7. Conclusion

Different helminths were proven to secrete molecules able to enhance tolerance in our immune system. Helminth products were seen to act on T cells, B cells, and DC. The main mechanism by which helminth molecules modulate the immune system is by Th1 to Th2 shift, along with reduced production of IFN-ã and IL-12, increased production of IL-4/IL-10, and elevated IgG4 levels. Moreover, the tolerant phenotype is emphasized by the inhibition of Th17 production and increase of Tregs differentiation from naïve T cells, accompanied with IL-10 and TGF-â secretion. In addition to the development of Tregs, the protective role of helminths is also driven by Bregs. Bregs have a suppressive effect on the progression of immune-mediated diseases, by secreting IL-10 (Table 1 and Fig. 1 summarize the main mechanisms).

In conclusion, several molecular mechanisms are triggered by helminth treatment, leading to a tolerant scenario. Therefore, many researchers harness the helminths, their ova, and their antigens in order to develop novel therapeutic compounds to treat autoimmune diseases. Q2

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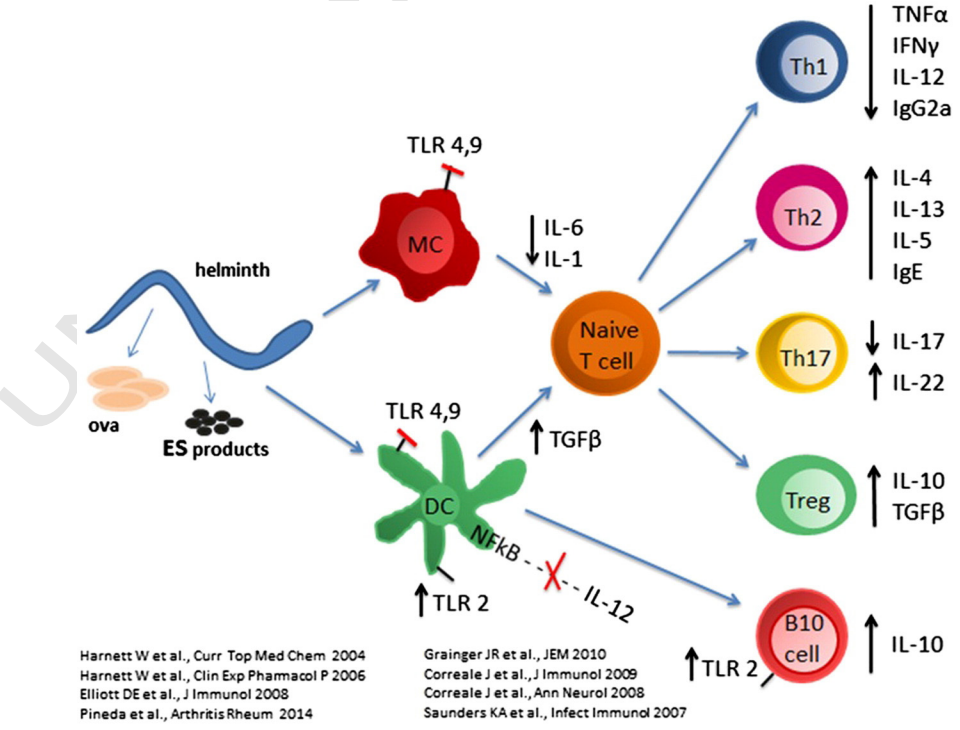

Fig. 1. Mechanism of immunomodulation by helminths.

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