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Review article

Parasites–allergy paradox: Disease mediators or therapeutic modulators

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ABSTRACT

The noticeable phenomenon of an increased frequency of immune-inflammatory disorders, in the industrialized world, has led to the implication of parasitic infections in the pathophysiology of these diseases. Most of the studies investigated the infection connection to allergy have centered on helminthes. Parasitic helminthes are a group of metazoans that are evolutionary diverse, yet converge to evolve common modes of immunomodulation. Helminth immunoregulation is mainly mediated by a regulatory response including Treg and Breg cells with alternatively-activated macrophages. There is increasing evidence for a causal relationship between helminth infection and allergic hyporesponsiveness, however, conflicting data are still generating. The helminth immunoregulation seems to be species-specific and phase-specific. It depends on the stage of the clinical disease which correlates with a corresponding parasitic stage (egg, larva or mature adult). Here, we review the cellular and molecular mechanisms utilized by helminthes to manipulate the immune system and the consequent bystander immunomodulatory responses toward environmental allergens. We especially focus on parasitic species and molecules involved in the modulation of allergic disorders and summarize the experimental and clinical trials using them as therapeutic agents. We also discuss the potentials and obstacles, for helminthes and/or their derived molecules, to emerge as novel therapeutic modalities.

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1. Introduction

The accumulated information investigating the association of parasitic infections with allergic disorders, is mostly conflicting. Genetic, environmental, life cycle-phase-specific and niche-specific factors intensify the complexity of the association. This relationship has not only an epidemiological perspective but interesting immunological and clinical aspects as well. There is an obvious similarity between the inflammation caused by the allergic immune responses to many environmental allergens and that developed in response to some helminth antigens [1]. Immune responses to both are characterized by a predominant T helper type 2 (Th2) activation with consequent upregulation of IL-4, IL-5 and IL-13. This is usually accompanied by tissue eosinophilia, over-secretion of mucus and upregulation of IgE antibody [2,3]. Most of the studies investigated the infection connection to allergy have centered on helminths [4] noted that their data have mostly offered a solid evidence for a protective contribution of helminth infections.

Parasitic helminthes are a group of metazoans with a long but diverse evolutionary history. The helminthes that infect humans fit in two taxonomic phyla, platyhelminths (flatworms) and nematodes (roundworms). Platyhelminths consist of the trematodes or flukes (leaf-like worms) and the cestodes (tapeworms). Nematodes include the majority of helminthes that are prevalent in humans. These parasites that have independently evolved, to attain different invasion methods and different host niches, exhibit a striking convergence of their modes of immunomodulation [5]. In their way to evade host immune mechanisms to establish their existence in safe niches, parasites adopt immunosuppressive pathways that might also repress bystander reactions to allergens and self-antigens [6].

What was considered as a general immunosuppression induced by helminthes, is currently acknowledged as an immunomodulation, a conserved phenomenon across species, classes to phyla [7]. Helminth immunomodulation has two predominant characteristics; first is the induction of a Th2 response with a specific cytokine paradigm comprising IL-4, IL-5 and IL-13 together with IgE antibody and recruitment of eosinophils and mastocytes; secondly, is the activation of a regulatory response that include anti-inflammatory cytokines namely IL-10 and TGF-β together with regulatory T-(Treg) and B-(Breg) cells and alternatively-activated macrophages [8].

A comprehensive analysis of the parasite biology and the predominant immune responses, in both allergy and helminth exposure, is a prerequisite for better understanding of this multifaceted relationship. This review explores the epidemiology, biology and immunology of the complex relationship between allergy and parasitic infection. The paper also tackles the discrepancies in this relationship and discusses the explanations for these in the literature. It also provides an insight on the protective pathways against allergic disorders conferred by parasites with distinct emphasis on helminth infections. It is also concerned with the therapeutic potentials of live-helminth infection as well as helminth-derived molecules and summarizes related clinical and experimental trials in the literature.

1.1. Parasites, allergic disorders and the "hygiene hypothesis"

During the twentieth century, there were an unusually noticeable phenomenon of an increased frequency of several inflammatory diseases in the developed part of the world. These included allergic diseases and autoimmune disorders such as diabetes, multiple sclerosis (MS), rheumatoid arthritis (RA), allergic diseases and inflammatory bowel disease (IBD) [9,10]. The genetic background was not an enough answer to the compelling question of why such increases have been so rapid. Environmental factors and different susceptibility to triggering agents such as microbial infections were suggested to explain the phenomenon. Thus a classic model of gene–environment interaction, was proposed to justify the recent nature of these increases. The model suggested a major underlying ground for environmental factors with genetic factors just determine who is susceptible to clinical disease due to these ecological limiting factors [11]. "Hygiene hypothesis," was first suggested by Strachan, who realized a negative association between hay fever and the number of older siblings in a meta-analysis study included around 17,000 children [12]. This hypothesis was later extended to include autoimmune disorders [13]. Many studies have indicated high rate of autoinflammatory disorders, expressed by increased prevalence of autoimmune diseases and allergies in developed countries [14,15]. It is believed that the growing rate of urbanization, in the industrialized countries, have created an urban environment depleted from many organisms co-evolved with mammals, and impose a co-evolutionary pressure that is ultimately was able to set up a "normal" of immune programming to combat infectious agents. Higher quality of life and refined standards of living in the developed world led to a decrease in the infections burden. The limited exposure to microbial infections especially during childhood may have led to failure of the immune system to program itself to face these infections. This eventually result in an off-balanced, dysregulated immune responses [16]. The occurrence as well as the severity of allergic disorders are not limited to environmental factors encountered during childhood and adulthood [17,18]. There is compelling proof that the vulnerability to allergy and the qualitative divergence of immune reactions in response to homologous and heterologous antigens might be concluded during the uterine life or soon after. Prenatal programming according to maternal signals has been

reported to influence the immune system maturation of the offsprings [19,20]. Established helminth infection during pregnancy has been suggested to distinctly alter the allergic phenotype of born children stretching from protection to exacerbation [21]. Children born and grow in a rural areas, exposed to a diverse spectrum of infectious agents, develop asthma less frequently than those from urban districts [22]. Additionally, children born to mothers exposed to farm animals and consumed raw milk, during pregnancy, have lesser chance to get allergic disorders [18]. Children born to mothers infected with schistosomes and treated with praziquantel while pregnant, demonstrated a higher frequency of eczema, indicating allergy-preventing effects of maternal schistosomiasis [23].

One example that illustrates the hygiene hypothesis is malaria's prevalence, which is in reverse correlation to autoimmune diseases in Sardinia. Compelling proofs link the disappearance of malaria, due to human's eradication program, with the increased frequency of multiple sclerosis (MS) [24,25]. MS is extremely rare in regions with a 10% or more prevalence of *T. trichiura* and shows a sharp rise in regions with lower prevalence [26]. Moreover, the positive association of infections to autoimmune diseases was also established in the Finland's part of Karelian region with an extremely high incidence of autoimmunty and allergic disorders, while their prevalence in the Russian's side, with higher incidence of infections, is far lower [27,28]. All these reports are entirely correlative, circumstantial evidence without a direct proof of a link. However, it has been shown that MS patients, who later acquired helminthic infections, developed a remarkably reduced disease progression. The reduced disease activity was marked by higher levels of circulating Treg cells that release IL-10 and TGF-β in reply to a certain myelin peptide [29]. A regulatory B cells population that secretes IL-10 was also upregulated in these patients. Relapses have reported to occur rapidly on helminth eradication [30].

2. Immunomodulation by parasites

Many microbes are implicated as possible immunomodulators especially those that have a long co-evolutionary association with humans and are transmitted mainly by fecal–oral route or soil transmitted [12] Most of the attention was centered on the role of helminth infections in tipping the balance to retain regulated immune responses and reverse their deleterious consequences to counteract allergies [31,32].

Helminths are masters of immune modulation; a possible requirement to establish chronic infections. In order to combat the efforts of the host to expel them and to create an environment that is permissive for long-term parasitism, it is essential for parasites to modulate host immune responses that endanger their existence. This is in part achieved by enhancing certain immune cell populations especially regulatory T (Treg) [33], TGF-β and IL-10-producing B cells [34,35], and enhance also the immune-dampening properties of helminth-derived antigens [36]. Owing to the resultant immunosuppressive effects that extend to bystander antigens, such as allergens, helminthes have a significant contribute to the low prevalence of allergic diseases in helminth endemic areas [37].

From a viewpoint of translational biology, clarification of immune reactions in response to helminth infection might be useful in mitigating bystander inflammatory reactions. An accumulated literature has indicated that helminth infections confer, at least, a partial protection against a diverse spectrum of auto-inflammatory diseases. This protective action has been mediated through either a direct immunomodulatory effect exerted by the excretory/secretory (ES) antigens of the parasite or via the transfer of anti-helminth immune molecules to a host [38].

Helminth infections have been reported to reduce the susceptibility to autoimmune and/or allergic disorders. A negative association was recognized between autoimmune liver diseases and infestation with *Strongyloides stercoralis* [39]. Infection with helminthes, especially *Schistosoma sp.*, conferred a hyporesponsive effect on the atopic reaction in skin prick tests [40,41]. Moreover, the protective effects of helminth infections have been also demonstrated in a *S. mansoni*-worm-only infection in animal models of airway hypersensitivity [42]. While helminth infection confers an anti-allergic effect, de-worming could lead to enhanced sensitization. Eradication of certain helminths was enough to boost atopic skin sensitization in Venezuela [43], in Gabon [44], and in Vietnam [45].

2.1. Modulation of innate immune cells

Processing of an antigen and its presentation to T cells, by antigen presenting cells, typically dendritic cell (DC), is the first reaction of the immune system to an infectious agent. This response is marked by an upregulation of surface ligands expression that, in turn, with some soluble mediators activate T cells that are specific to this specific antigen [5]. This interaction might determine the immune response quality directing it to either Th1 or Th2 paradigm [46], or alternatively toward a Treg regulatory pathway [47].

Parasite antigens could manipulate this process, inhibiting the proinflammatory Th1/17 response or directing DC phenotype toward an anergic or tolerogenic pattern. DCs, cultured with soluble egg antigen (SEA) of *S. mansoni*, are able to initiate IL-4-independent Th2 response without the process of classical ligand expression [48]. Likewise, *Nippostronglyus brasiliensis* adult [49] or larval [50] ES antigens provoke a Th2 response independent from IL-4-, IL-5- or B cell [51]. Transfer of DCs, sensitized with these antigens, was able to induce the same response in vivo [52]. Dendritic cells, sensitized with *Fasciola hepatica* ES antigens, can induce in vitro T cells differentiation toward a Th2 phenotype [53]. Thus an array of antigens from different parasites to consume a common alternative pathway of IL-4-independent activation of macrophages and DC to provoke an anti-inflammatory Th2 immune response [54,55].

Basophils are essential innate effector cells, which have a role in the defense against helminths and a proinflammatory action during allergic inflammation. Basophils are also effective modulator of Th2 response during helminthic infection and allergen sensitization [56]. Some studies

[57,58] suggest that basophils might act, in these situation as APC inducing Th2 responses in the absence of DCs. Basophils are able of cross-linking surface-bound IgE to secrete IL-4 in a significant manner as a consequence of a dominant Th2 paradigm initiated in response to circulating parasitic antigen-specific IgE complex. Some helminthic antigens could activate basophil responses to mediate parasite and/or host survival. Schistosomes are able to induce basophil production of IL-4 without prior IgE response to schistosome antigens [5]. However, basophils develop an IL-10-dependent hyporesponsive pattern to parasitic antigens, in certain chronic infections like *S. mansoni* or *Litomosoides sigmodontis*, a finding helps elucidate the possible mechanisms by which helminths might suppress allergy and may reveal how helminths modulate other disorders [59].

Concerning eosinophils, similar paradoxical responses were observed. Although still considered as tissue-damage and pathology promoters, eosinophils also have immunoregulatory functions that may influence the outcome of infection [60]. Following helminth infection there is a remarkable rise of eosinophil counts in the blood that soon migrates to the infection site where degranulation occurs. Peak eosinophilia levels coincide with larval migration and gradually decrease when larvae develop into mature adults [61]. Eosinophils seem to communicate with virtually all immune cells and are involved in a wide range of anti-helminthic actions. They have a direct killing effect on *Strongyloides stercoralis* [62] and have an effect on *Nocardia brasiliensis* expulsion [63]. Eosinophils are also implicated in tissue damage during some filarial infection such as *Onchocerca volvulus* [64,65], *Wuchereria bancrofti* [66] and are active components in granuloma formation pathognomonic of schistosome infection [67]. On the other hand, helminthes have a manipulative ability exerting their trickery in attracting eosinophils through chemotactic molecules to secure their endurance, or through evasion pathways exploited to avoid eosinophil-mediated anti-helminth toxicity [60].

While several helminth ES antigens induce eosinophilia, helminth infections, in murine models of asthma, result in reduced eosinophils. Some parasitic products directly suppress eosinophil responses such as *H. polygyrus* ES (HES) antigens that suppress eosinophilia in allergen-sensitized animal models [68]. *N. americanus* ES products, having neutrophil chemotactic actions, may suppress the recruitment of eosinophils, that are possibly damaging, while promoting that of ineffectual neutrophils [69,70].

2.2. Modulation of adaptive immune response

The allergic reaction is a complex process influenced by numerous effectors and marked by a Th2-type hyperresponsiveness to allergens that may result in severe inflammation in certain target tissues including the lung in patients with asthma [71]. A significant pro-inflammatory role of the Th17 [72] and Th9 has been also reported [73] and a similar Th1 role was mainly linked to severe asthma [74]. Throughout the allergic response, certain cytokines such as tumor necrosis factor alpha (TNFA-α) and IL-13, that significantly modulate the anti-helminth immune responses [75,76], are additionally stimulated, aggravating the inflammatory actions, of the IgE-mast cell-mediated on the bronchial epithelium and smooth muscle [77]. Similar roles have been also expressed by IL-17A [78]. The Th2 cells, activated by helminthes, may also combat allergic responses possibly by inducing regulatory T cells which in turn, suppress both Th1 and Th2 arms of immunity [79].

Several studies have tackled the immunomodulatory effects of parasitic antigens on adaptive immune reactions coordinated by CD4+ T cells. These modulatory pathways have been mostly studied in animal murine models. A helminth that was deeply studied in murine models of IBD, is the intestinal nematode; *Heligmosomoide polygyrus*. It exercises immunoregulatory effects through three main mechanisms; modulation of intestinal DCs maturation [80]; direct induction of Treg proliferation [81] and modulation of the intestinal microbiome [82]; other pathways might include stimulation of reg B cells [83], modulation of the Treg/Th17 ratio in the intestine [84] and induction of regulatory macrophages [85].

Altering DC reactive patterns is a main indirect immunomodulatory pathway adopted by parasites. *T. spiralis* and *E. multilocularis* ES antigens, in vitro, induce a switch of DCs toward provoking Th2 and Foxp3+ Treg responses [86–88]. Likewise, DCs co-cultured with ω-1 *S. mansoni* SEA, initiate Foxp3+ Treg response, by stimulation of TGF-β and retinoic acid-activating enzymes [89]. HES antigen-sensitized DCs result in a T cells suppressive phenotype inhibiting IFN-γ and IL-4 while upregulating IL-10 [90]. HES products can directly activate Foxp3 expression in naïve T cells without prior DCs sensitization [81]. Excretory/secretory antigens of *Teladorsagia circumcincta*, a related nematode, induce a similar regulatory response. Distinctly, *Spirometra mansoni* ES antigens have been reported to, in vitro, boost the Tregs suppressive action [91].

2.3. Helminths as disease stimulators

While most studies indicate a protective downregulatory effect of helminth infection on allergic disorders, a general rule cannot be concluded. A great deal of caution should be considered not to overstretch the generated data in order to get general conclusions ignoring many fundamental variables that are assumed to shape the association of helminth infection to allergic disorders. Some studies have reported a link between *Ascaris* infection and higher incidence of asthma [92], indicating an influencing role of the helminth species. However, the role model for a helminth provokating allergy, is anisakiasis which was reported to provoke asthma, urticaria, and anaphylaxis [93]. In addition, allergy related to the migration of *Strongyloides spp.* is commonly noticed in endemic regions [94]. Moreover, *Toxocara spp.*, for which man is not a natural host, has been also reported to induce allergic disorders [95].

The timing as well as the course of infection are probably influence the helminth/allergy relationship. Offspring from schistosome-infected mothers that were mated in the chronic phase of infection with dominant maternal TH2 immune phase, were more prone and developed

aggravated allergic airway inflammation [21]. Early and/or long-lasting infections protect against allergies, while late and/or short-lived infections aggravate allergic symptoms [31]. Interestingly, low-intensity helminth infections are likely exacerbate allergic disorders in contrast to heavy infection [96]. Moreover, travelers to endemic regions who happen to get schistosomiasis, develop severe allergic lung symptoms [97]. The helminth ability to modulate host immune responses may be in part controlled by host genetics. Genetically susceptible individuals are more at risk of developing allergy in response to helminth infection [98].

Experimental infections, of murine models, confirm this paradoxical helminth/allergy relationship. Experimental infection with *Hymenolepis diminuta*, a cestode, of mice with oxazolone-induced colitis, led to a substantial increase in the pathology [99]. Likewise, infection with *Taenia crassiceps* has led to cardiomyopathy [100] and amplification of liver pathology caused by carbon tetrachloride [101]. Furthermore, mice infected with the latter parasite were more at risk to infection with *Leishmania major* and *L. mexicana* [102]. In the same context, concurrent *H. polygyrus* infection has been reported to enhance the colonic inflammation induced by a bacterial infection with *Citrobacter rodentium* [103].

3. Helminth therapy

The principle that helminths could be therapeutic via induction of immunoregulation has initiated enormous research efforts to explore the molecular pathways involved to come out with an array of therapeutic molecules instead of using the parasites themselves in therapeutic regimens.

3.1. Live-infection therapy

The immunosuppression of human pathology during parasitic infections has been comprehensively studied [104,105], and helminth therapy is unofficially available [5]. Currently, clinical trials (phase III) are underway for a new drug called "*Trichuris Suis* Ova (TSO)" utilizing *T. suis* egg as therapeutic agent [106].

Hypothetically, helminth therapy is reasonably straightforward. Simply, identify a candidate group of patients and a suitable helminth species, execute required quality control and studies for dose-ranging, then infect and let the natural course of host-parasite interaction proceeds. Undoubtedly, the choice of therapeutic helminth is of extreme significance. The use of a human parasite is not advised or a great caution must be taken if to be utilized [38]. Several helminth species, that are likely suitable for controlled therapeutic clinical trials on humans, have been identified. Generally, they are either natural human parasites that are known to exhibit insignificant virulence or animal parasitic species that are unable to accomplish their life cycles in humans; nevertheless, they are can stimulate an immune response similar to that evoked by their close relatives of human parasites [107].

Several reports have stated negative associations between intensity of worm load, and allergic sensitization to common allergens [108–110]. More notably, the risk of allergic airway spasm was reduced in people with hookworm infection; *N. americanus* [111]. Patients with hydatid disease, produced by the larva of a dog cestode; *Ecchinococcus granulosus*, normally show a prevalent Th2 paradigm and IgE elevation [112]. Normally Th2 response and IgE are responsible of higher risk of asthmatic responses [96]; thus, infection with *E. granulosus* might enhance the airway allergic response. Nevertheless, no reports indicate a higher risk of allergic disease in *E. granulosus*-endemic areas. Recently, *E. granulosus* infection markedly mitigates allergic airway inflammation probably by upregulating IL-10 and reducing IL-5 and IL-17A [113]. While schistosomiasis is predominantly associated with a Th2 response [114], schistosome infections improve the clinical picture of atopic disorders in humans [35]. Moreover, residents in endemic regions of schistosomiasis had asthma less frequent than those inhabiting schistosomes-free zones [115]. Pin-worm infection was reported to have a protective effect against asthma and allergic rhinitis in young children resulting in a milder clinical presentations of asthma [40]. Similarly, de-worming of children in Vietnam, Venezuela or Gabon [32,43,44] for 12 months or more, all result in increased skin sensitization and enhancement of prick test reactions.

The therapeutic immunoregulatory effect of helminths is first founded for allergic disorders [116]. Clinical trials have mostly been carried out using the *Trichuris suis*, a pig whipworm, that infrequently infects humans, and *Necator americanus*, a hookworm that naturally parasitizes humans [107]. In the early 2000s, *Trichuris suis* was suggested to be a safe and effective therapeutic candidate for inflammatory bowel disease (IBD) [117]. A single dose of *T. suis* ova was used to treat Crohn's disease patients. Up to 7500 ova per dose was well tolerated and did not result in side effects even with long-term treatment [118]. Further use of *T. suis* eggs showed encouraging therapeutic effects on MS [119] and or on some food allergies [105].

Hypothetical suggestions were also made for possible use of *T. suis* ova in autism spectrum disorders therapy [120]. Furthermore, the effect of therapy with helminths on type I diabetes or rheumatoid disease has also been investigated [121,122].

However, the transformation of helminth therapy into standard medical practice confronts serious challenges. Genuine practical and ethical matters might represent serious obstacles to live infection therapy. First, live parasite resources would not cover the expected increasing demands; the frequency of parasitic infections is declining while there is a steep rise of allergic disorders. Secondly, many ambiguous factors determine the outcome of infection [123]. Genetic and environmental factors enforce an individual or community level of outcome prediction, therefore, expectation of a single pattern, of parasitic disease outcome, is not practical. Live helminth treatment has another disadvantage of being largely given on random basis with no defined doses or well-known mechanisms of action [5]. Most reports are based on a small number of patients and can be considered only preliminary. The reported data have been relatively recent and thereby the deleterious outcomes of long-term or repeated helminthic infections are basically unpredictable [38]. Therefore, the

characterization of parasite-derived molecules as novel immunomodulators for therapeutic purposes, are urgently needed [5].

3.2. Helminth-derived molecules therapy

Molecular characterization of host pathways possibly consumed by parasites as well as parasitic motifs that are involved in mitigating immunopathology, must initially be distinguished. Naturally extracted helminths products or synthetic analogs that exhibit immunomodulatory actions can be considered for novel therapeutic approaches. Non-living parasite-derived molecules might be the future therapeutic candidates of many chronic inflammatory disorders.

Helminths are metazoans with multicellular nature. Therefore, they could represent an unlimited source of many immunomodulatory molecules. Molecular immunomodulatory helminth products belong to diverse biochemical classes; carbohydrates, proteins, and lipids, have been characterized. A broad range of parasite-derived molecules of several parasite species has been tested. The nature of these molecules range from whole parasite extracts, through fractionated parasitic products, and secretory materials, to recombinant proteins and synthetic glycans [34]. Lacto-Nfucopentaose III (LNFP III), oligosaccharide from schistosome ova, was showed to induce IL-10 production and stimulate macrophages [124]. A schsitosome-egg-derived chemokine-binding protein (CBP) demonstrated the ability to impede the neutrophil recruitment to inflammatory sites [125]. An antioxidant protein (Peroxiredoxin) from *S. mansoni* [126] and *F. hepatica* [127], alternatively stimulate macrophages. Peroxiredoxin is also engaged in the induction of Th2 responses. Another significant molecule, that is also derived from schistosome ova, is the IL-4-inducing principle of *S. mansoni* eggs (IPSE) that is able to induce basophil production of IL-4 via an IgE-dependent and antigen-independent pathway [128].

These therapeutic classes have been screened at different levels of testing from in vitro testing of a single molecule on an individual immune cell type through to complex animal models of immune-inflammatory diseases [5]. Some helminth-induced immune byproducts, especially the cytokines, could have protective respiratory and anti-allergic effects, and may therefore become useful as therapeutic modalities for many allergic disorders. Interestingly, it was identified that in helminth-infected mothers, the transfer of maternally derived IFN-γ during the acute phase of infection to the fetus rather than helminth antigens is essential for the progeny's protective immune phenotype [21]. With further study, identification of additional helminth-induced immune substances could open the way to novel approaches for immune manipulation. Nevertheless, the potential, of helminth-derived molecules, as a basis of novel medications has not been yet accomplished. This probably indicates the complexity of extracting refined molecules, of therapeutic quality, from little crude parasitic material that is practically available. Technical issues, concerning the purification of certain molecules such as lipids and glycans, are also potential obstacles. However, the progress in protein purification, sequencing and transcriptomics indicates that helminth-derived immunoregulatory molecules might emerge as a promising array of medications [38].

4. Conclusion

The anti-parasite immune responses, while usually fail to eradicate helminths, yet, they might benefit the host by suppressing deleterious allergic reactions. Several studies demonstrate a protective action of helminth infection against allergic diseases, however, a causal association between helminth infections and allergy remains to be proven. The helminth-mediated immunomodulation of allergy is probably mediated by a regulatory response that includes anti-inflammatory cytokines, alternatively-activated macrophages as well as regulatory Treg and Breg cells. The timing of infection might have a determining effect on the development of allergic responses. Early exposures, in utero or soon after, to helminthes could favorably program the immune system to express efficient anti-allergic responses. The therapeutic effect of live helminth infections seems to be not only species-specific but also phase-specific depending on the clinical stage of the disease (acute or chronic) which correlates with a corresponding life-cycle stage of the parasite (egg, larva or mature adult). Eggs of *T. suis* and larvae of *N. americanus* are the most used parasitic stages in human clinical trials. However, live-infection therapy faces real practical and ethical obstacles to evolve as a standard therapeutic modality. Future research should focus on comprehensive characterization of helminth-derived molecules that have a potential therapeutic utility.

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Cooper PJ. Intestinal worms and human allergy. Parasite Immunol 2004;26:455–67.
[2] Holgate ST. The epidemic of allergy and asthma. Nature 1999;402:B2–4.
[3] Maizels RM, Yazdanbakhsh M. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nat Rev Immunol 2003;3:733–44.
[4] Smits HH, Hartgers FC, Yazdanbakhsh M. Helminth infections: protection from atopic disorders. Curr Allergy Asthma Rep 2005;5:42–50.
[5] McSorley HJ, Hewitson JP, Maizels RM. Immunomodulation by helminth parasites. Defining mechanisms and mediators. Int J Parasitol 2013;43:301–10.
[6] Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. Nat Rev Immunol 2011;11:375–88.
[7] Harnett W. Secretory products of helminth parasites as immunomodulators. Mol Biochem Parasitol 2014;195:130–6.
[8] Hepworth MR, Grencis RK, Artis D. Regulation of immunity and inflammation following intestinal helminth infection in parasitic nematodes: molecular biology, biochemistry and immunology. Oxfordshire, UK: CABI; 2013. p. 106–29.
[9] Abdel-Nasser AM, Rasker JJ, Valkenburg HA. Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis. Semin Arthritis Rheum 1997;27:123–40.
[10] Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911–20.
[11] Rook GAW. Hygiene hypothesis and autoimmune diseases. Clin Rev Allerg Immunol 2012;42:5–15.

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[12] Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259–60.
[13] Zaccone P, Fehervari Z, Phillips JM, Dunne DW, Cooke A. Parasitic worms and inflammatory diseases. Parasite Immunol 2006;28:515–23.
[14] Moroni L, Bianchi I, Lleo A. Geoepidemiology, gender and autoimmune disease. Autoimmun Rev 2012;11:A386–92.
[15] Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clin Exp Immunol 2010;160:1–9.
[16] van Panhuis WG, Grefenstette J, Jung SY, Chok NS, Cross A, Eng H, et al. Contagious diseases in the United States from 1888 to the present. N Engl J Med 2013;369:2152–8.
[17] Rowe J, Kusel M, Holt BJ, Suriyaarachchi D, Serralha M, Hollams E, et al. Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. J Allergy Clin Immunol 2007;119:1164–73.
[18] Ege MJ, Strachan DP, Cookson WO, Moffatt MF, Gut I, Lathrop M, et al. Gene-environment interaction for childhood asthma and exposure to farming in Central Europe. J Allergy Clin Immunol 2011;127:138–44.
[19] Conrad ML, Ferstl R, Teich R, Brand S, Blumer N, Yildirim AO, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe *Acinetobacter lwoffii F78*. J Exp Med 2009;206:2869–77.
[20] Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. PLoS ONE 2010;5:e10134.
[21] Straubinger K, Paul S, da Costa OP, Ritter M, Buch T, Busch DH, et al. Maternal immune response to helminth infection during pregnancy determines offspring susceptibility to allergic airway inflammation. J Allergy Clin Immunol 2014;134(6):1271–9.
[22] Schaub B, Liu J, Hoppler S, Schleich I, Huehn J, Olek S, et al. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol 2009;123:774–82.e5.
[23] Mpairwe H, Webb EL, Muhangi L, Ndibazza J, Akishule D, Nampijja M, et al. Anthelminthic treatment during pregnancy is associated with increased risk of infantile eczema: randomised-controlled trial results. Pediatr Allergy Immunol 2011;22:305–12.
[24] Bitti PP, Murgia BS, Ticca A, Ferrai R, Musu L, Piras ML, et al. Association between the ancestral haplotype HLA A30B18DR3 and multiple sclerosis in central Sardinia. Genet Epidemiol 2001;20:271–83.
[25] Sotgiu S, Angius A, Embry A, Rosati G, Musumeci S. Hygiene hypothesis: innate immunity, malaria and multiple sclerosis. Med Hypotheses 2008;70:819–25.
[26] Fleming JO, Cook TD. Multiple sclerosis and the hygiene hypothesis. Neurology 2006;67:2085–6.
[27] Kondrashova A, Seiskari T, Ilonen J, Knip M, Hyoty H. The 'hygiene hypothesis' and the sharp gradient in the incidence of autoimmune and allergic diseases between Russian Karelia and Finland. APMIS 2013;121:478–93.
[28] Seiskari T, Kondrashova A, Viskari H, Kaila M, Haapala AM, Aittoniemi J, et al. Allergic sensitization and microbial load—a comparison between Finland and Russian Karelia. Clin Exp Immunol 2007;148:47–52.
[29] Correale J, Farez M. Association between parasite infection and immune responses in multiple sclerosis. Ann Neurol 2007;61:97–108.
[30] Correale J, Farez MF. The impact of parasite infections on the course of multiple sclerosis. J Neuroimmunol 2011;233:6–11.
[31] Cooper PJ, Barreto ML, Rodrigues LC. Human allergy and geohelminth infections: a review of the literature and a proposed conceptual model to guide the investigation of possible causal associations. Br Med Bull 2006;7:9–80, 203–218.
[32] Flohr C, Tuyen LN, Quinnell RJ, Lewis S, Minh TT, Campbell J, et al. Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. Clin Exp Allergy 2010;40:131–42.
[33] Layland LE, Mages J, Loddenkemper C, Hoerauf A, Wagner H, Lang R, et al. Pronounced phenotype in activated regulatory T cells during a chronic helminth infection. J Immunol 2010;184:713–24.
[34] McSorley HJ, Maizels RM. Helminth infections and host immune regulation. Clin Microbiol Rev 2012;25:585–608.
[35] Mangan NE, Fallon RE, Smith P, van Rooijen N, McKenzie AN, Fallon PG. Helminth infection protects mice from anaphylaxis via IL-10-producing B cells. J Immunol 2004;173:6346–56.
[36] Pearce EJ. Priming of the immune response by schistosome eggs. Parasite Immunol 2005;27:265–70.
[37] Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733–43.
[38] Hernandez JLR, Leung G, McKay DM. Cestode regulation of inflammation and inflammatory diseases. Int J Parasitol 2013;43:233–43.
[39] Aoyama H, Hirata T, Sakugawa H, Watanabe T, Miyagi S, Maeshiro T, et al. An inverse relationship between autoimmune liver diseases and *Strongyloides stercoralis* infection. Am J Trop Med Hyg 2007;76(5):972–6.
[40] Medeiros Jr M, Figueiredo JP, Almeida MC, Matos MA, Araújo MI, Cruz AA, et al. *Schistosoma mansoni* infection is associated with a reduced course of asthma. J Allergy Clin Immunol 2003;111:947–51.
[41] Rujeni N, Figueiredo JP, Almeida MC, Matos MA, Araújo MI, Cruz AA, et al. Atopy is inversely related to schistosome infection intensity: a comparative study in Zimbabwean villages with distinct levels of *Schistosoma haematobium* infection. Int Arch Allergy Immunol 2012;158:288–98.
[42] Mangan NE, van Rooijen N, McKenzie AN, Fallon PG. Helminth-modified pulmonary immune response protects mice from allergen-induced airway hyperresponsiveness. J Immunol 2006;176(1):138–47.
[43] Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol 1993;92:404–11.
[44] van den Biggelaar AH, Rodrigues LC, van Ree R, van der Zee JS, Hoeksma-Kruize YC, Souverijn JH, et al. Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. J Infect Dis 2004;189:892–900.
[45] Flohr C, Tuyen LN, Lewis S, Quinnell R, Minh TT, Liem HT, et al. Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: a cross-sectional study. J Allergy Clin Immunol 2006;118:1305–11.
[46] Moser M, Murphy KM. Dendritic cell regulation of TH1–TH2 development. Nat Immunol 2000;1:199–205.
[47] Yamazaki S, Inaba K, Tarbell KV, Steinman RM. Dendritic cells expand antigen-specific Foxp3+ CD25+ CD4+ regulatory T cells including suppressors of alloreactivity. Immunol Rev 2006;212:314–29.
[48] Jankovic D, Kullberg MC, Caspar P, Sher A. Parasite-induced Th2 polarization is associated with down-regulated dendritic cell responsiveness to Th1 stimuli and a transient delay in T lymphocyte cycling. J Immunol 2004;173:2419–27.
[49] Holland MJ, Harcus YM, Riches PL, Maizels RM. Proteins secreted by the parasitic nematode *Nippostrongylus brasiliensis* act as adjuvants for Th2 responses. Eur J Immunol 2000;30:1977–87.
[50] Marsland BJ, Camberis M, Le Gros G. Secretory products from infective worms of *Nippostrongylus brasiliensis* induce a rapid allergic airway inflammatory response. Immunol Cell Biol 2005;83:40–7.
[51] Holland MJ, Harcus YM, Balic A, Maizels RM. Th2 induction by *Nippostrongylus* secreted antigens in mice deficient in B cells, eosinophils or MHC Class I-related receptors. Immunol Lett 2005;96:93–101.
[52] Balic A, Harcus Y, Holland MJ, Maizels RM. Selective maturation of dendritic cells by *Nippostrongylus brasiliensis*-secreted proteins drives Th2 immune responses. Eur J Immunol 2004;34:3047–59.
[53] Falcon C, Carranza F, Martinez FF, Knubel CP, Masih DT, Motran CC, et al. Excretory–secretory products (ESP) from *Fasciola hepatica* induce tolerogenic properties in myeloid dendritic cells. Vet Immunol Immunopathol 2010;137:36–46.
[54] Atochina O, Da'dara AA, Walker M, Harn DA. The immunomodulatory glycan LNFPIII initiates alternative activation of murine macrophages in vivo. Immunology 2008;125:111–21.
[55] Bhargava P, Li C, Stanya KJ, Jacobi D, Dai L, Liu S, et al. Immunomodulatory glycan LNFPIII alleviates hepatosteatosis and insulin resistance through direct and indirect control of metabolic pathways. Nat Med 2012;18:1665–72.
[56] Nakanishi K. Basophils as APC in Th2 response in allergic inflammation and parasite infection. Curr Opin Immunol 2010;22:814–20.
[57] Sokol CL, Chu NQ, Yu S, Nish SA, Laufer TM, Medzhitov R. Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. Nat Immunol 2009;10:713–20.
[58] Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomin PR, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote Th2 cytokine-dependent immunity. Nat Immunol 2009;10:697–705.

[59] Larson D, Hubner MP, Torrero MN, Morris CP, Brankin A, Swierczewski BE, et al. Chronic helminth infection reduces basophil responsiveness in an IL-10-dependent manner. J Immunol 2012;188:4188–99.
[60] Gentil K, Hoerauf A, Layland LE. Eosinophil-mediated responses toward helminthes. Chapter 10.2. In: Lee JJ, Rosenberg HF, editors. Eosinophils in health and disease. Academic Press; 2012.
[61] Pearce EJ, MacDonald AS. The immunobiology of schistosomiasis. Nat Rev Immunol 2002;2:499e511.
[62] Rotman HL, Yutanawiboonchai W, Brigandi RA, Leon O, Gleich GJ, Nolan TJ, et al. Strongyloides stercoralis: eosinophil-dependent immune-mediated killing of third stage larvae in BALB/cByJ mice. Exp Parasitol 1996;82:267e78.
[63] Dixon H, Blanchard C, Deschoolmeester ML, Yuill NC, Christie JW, Rothenberg ME, et al. The role of Th2 cytokines, chemokines and parasite products in eosinophil recruitment to the gastrointestinal mucosa during helminth infection. Eur J Immunol 2006;36: 175363.
[64] Folkard SG, Hogarth PJ, Taylor MJ, Bianco AE. Eosinophils are the major effector cells of immunity to microfilariae in a mouse model of onchocerciasis. Parasitology 1996;112(Pt 3):323e9.
[65] Abraham D, Leon O, Schnyder-Candrian S, Wang CC, Galioto AM, Kerepesi LA, et al. Immunoglobulin E and eosinophil-dependent protective immunity to larval *Onchocerca volvulus* in mice immunized with irradiated larvae. Infect Immun 2004;72:810e7.
[66] Babayan SA, Read AF, Lawrence RA, Bain O, Allen JE. Filarial parasites develop faster and reproduce earlier in response to host immune effectors that determine filarial life expectancy. PLoS Biol 2010;8:e1000525.
[67] Swartz JM, Dyer KD, Cheever AW, Ramalingam T, Pesnicak L, Domachowske JB, et al. *Schistosoma mansoni* infection in eosinophil lineage-ablated mice. Blood 2006;108:24207.
[68] McSorley HJ, O'Gorman MT, Blair N, Sutherland TE, Filbey KJ, Maizels RM. Suppression of type 2 immunity and allergic airway inflammation by secreted products of the helminth *Heligmosomoides polygyrus*. Eur J Immunol 2012;42:2667–82.
[69] Asojo OA, Goud G, Dhar K, Loukas A, Zhan B, Deumic V, et al. X-ray structure of Na-ASP-2, a pathogenesis-related-1 protein from the nematode parasite, *Necator americanus*, and a vaccine antigen for human hookworm infection. J Mol Biol 2005;346:801–14.
[70] Bower MA, Constant SL, Mendez S. *Necator americanus*: the Na-ASP-2 protein secreted by the infective larvae induces neutrophil recruitment in vivo and in vitro. Exp Parasitol 2008;118:569–75.
[71] Caraballo L. Ascaris and allergy. In: Ascaris: the neglected parasite. Elsevier Inc.; 2013, http://dx.doi.org/10.1016/B978-0-12-396978-1.00002-1.
[72] Souwer Y, Szegedi K, Kapsenberg ML, de Jong EC. IL-17 and IL-22 in atopic allergic disease. Curr Opin Immunol 2010;22:821e6.
[73] Holgate ST. Innate and adaptive immune responses in asthma. Nat Med 2012;18:673e83.
[74] Poon AH, Eidelman DH, Martin JG, Laprise C, Hamid Q. Pathogenesis of severe asthma. Clin Exp Allergy 2012;42:625e37.
[75] Bancroft AJ, McKenzie AN, Grencis RK. A critical role for IL-13 in resistance to intestinal nematode infection. J Immunol 1998;160:345361.
[76] Hayes KS, Bancroft AJ, Grencis RK. The role of TNF-alpha in *Trichuris muris* infection II: global enhancement of ongoing Th1 or Th2 responses. Parasite Immunol 2007;29:583e94.
[77] Nakae S, Ho LH, Yu M, Monteforte R, Iikura M, Suto H, et al. Mast cell-derived TNF contributes to airway hyperreactivity, inflammation, and TH2 cytokine production in an asthma model in mice. J Allergy Clin Immunol 2007;120:48e55.
[78] Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, et al. IL-17A produced by alphabeta T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. Nat Med 2012;18:547e54.
[79] Wilson MS, Taylor MD, Balic A, Finney CA, Lamb JR, Maizels RM. Suppression of allergic airway inflammation by helminth-induced regulatory T cells. J Exp Med 2005;202:1199–212.
[80] Hang L, Setiawan T, Blum AM, Urban J, Stoyanoff K, Arihiro S, et al. Heligmosomoides polygyrus infection can inhibit colitis through direct interaction with innate immunity. J Immunol 2010;185:3184–9.
[81] Grainger JR, Smith KA, Hewitson JP, McSorley HJ, Harcus Y, Filbey KJ, et al. Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-beta pathway. J Exp Med 2010;207:2331–41.
[82] Walk ST, Blum AM, Ewing SA, Weinstock JV, Young VB. Alteration of the murine gut microbiota during infection with the parasitic helminth *Heligmosomoides polygyrus*. Inflamm Bowel Dis 2010;16:1841–9.
[83] Correale J, Farez M, Razzitte G. Helminth infections associated with multiple sclerosis induce regulatory B cells. Ann Neurol 2008;64:187–99.
[84] Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol 2009;9:313–23.
[85] Schnoeller C, Rausch S, Pillai S, Avagyan A, Wittig BM, Loddenkemper C, et al. A helminth immunomodulator reduces allergic and inflammatory responses by induction of IL-10-producing macrophages. J Immunol 2008;180:4265–72.
[86] Gruden-Movsesijan A, Ilic N, Colic M, Majstorovic I, Vasilev S, Radovic I, et al. The impact of *Trichinella spiralis* excretory–secretory products on dendritic cells. Comp Immunol Microbiol Infect Dis 2011;34:429–39.
[87] Aranzamendi C, Fransen F, Langelaar M, Franssen F, van der Ley P, van Putten JP, et al. *Trichinella spiralis*-secreted products modulate DC functionality and expand regulatory T cells in vitro. Parasite Immunol 2012;34:210–23.
[88] Nono JK, Pletinckx K, Lutz MB, Brehm K. Excretory/secretory-products of *Echinococcus multilocularis* larvae induce apoptosis and tolerogenic properties in dendritic cells in vitro. PLoS Negl Trop Dis 2012;6:e1516.
[89] Zaccone P, Burton OT, Gibbs SE, Miller N, Jones FM, Schramm G, et al. The *S. mansoni* glycoprotein omega-1 induces Foxp3 expression in NOD mouse CD4(+) T cells. Eur J Immunol 2011;41:2709–18.
[90] Segura M, Su Z, Piccirillo C, Stevenson MM. Impairment of dendritic cell function by excretory–secretory products: a potential mechanism for nematode-induced immunosuppression. Eur J Immunol 2007;37:1887–904.
[91] Kim HR, Lee SM, Won JW, Lim W, Moon BI, Yang HJ, et al. Functional changes in regulatory T cells during an experimental infection with sparganum (plerocercoid of *Spirometra mansoni*). Immunology 2012;138:57–67.
[92] Palmer LJ, Celedon JC, Weiss ST, Wang B, Fang Z, Xu X. *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. Am J Respir Crit Care Med 2002;165:1489–93.
[93] Audicana MT, Kennedy MW. Anisakis simplex: from obscure infectious worm to inducer of immune hypersensitivity. Clin Microbiol Rev 2008;21(2):360–79.
[94] Leighton PM, MacSween HM. *Strongyloides stercoralis*. The cause of an urticarial-like eruption of 65 years' duration. Arch Intern Med 1990;150(8):1747–8.
[95] Gonzalez-Quintela A, Gude F, Campos J, Garea MT, Romero PA, Rey J, et al. Toxocara infection seroprevalence and its relationship with atopic features in a general adult population. Int Arch Allergy Immunol 2006;139:317–24.
[96] Smits HH, Everts B, Hartgers FC, Yazdanbakhsh M. Chronic helminth infections protect against allergic diseases by active regulatory processes. Curr Allergy Asthma Rep 2010;10(1):3–12.
[97] Smits HH, Yazdanbakhsh M. Chronic helminth infections modulate allergen-specific immune responses: protection against development of allergic disorders? Ann Med 2007;39:428–39.
[98] Moller M, Gravenor MB, Roberts SE, Sun D, Gao P, Hopkin JM. Genetic haplotypes of Th-2 immune signalling link allergy to enhanced protection to parasitic worms. Hum Mol Genet 2007;16:1828–36.
[99] Hunter MM, Wang A, McKay DM. Helminth infection enhances disease in a murine TH2 model of colitis. Gastroenterology 2007;132:1320–30.
[100] D'Souza M, Garza MA, Xie M, Weinstock J, Xiang Q, F Robinson P. Substance P is associated with heart enlargement and apoptosis in murine dilated cardiomyopathy induced by *Taenia crassiceps* infection. J Parasitol 2007;93:1121–7.
[101] Lopez-Navarrete G, Ramos-Martinez E, Suarez-Alvarez K, Guirre-Garcia J, Ledezma-Soto Y, Leon-Cabrera S, et al. Th2-associated alternative Kupffer cell activation promotes liver fibrosis without inducing local inflammation. Int J Biol Sci 2011;7:1273–86.
[102] Rodrigues M, Terrazas LI, Marguez R, Bojalil R. Susceptibility of *Trypanosoma cruzi* is modified by previous non-related infection. Parasite Immunol 1999;21:177–85.
[103] Chen CC, Louie S, McCormick B, Walker WA, Shi HN. Concurrent infection with an intestinal helminth parasite impairs host resistance to enteric *Citrobacter rodentium* and enhances Citrobacter-induced colitis in mice. Infect Immun 2005;73:5468–81.
[104] Fleming JO. Helminths and multiple sclerosis: will old friends give us new treatments for MS? J Neuroimmunol 2011;233:3–5.

[105] Jouvin MH, Kinet JP. *Trichuris suis* ova: testing a helminth-based therapy as an extension of the hygiene hypothesis. J Allergy Clin Immunol 2012;130:3–10.
[106] Lukes J, Kuchta R, Scholz T, Pomajbikova K. (Self-) infections with parasites: re-interpretations for the present. Trends Parasitol 2014;30:377–85.
[107] Weinstock JV, Elliott DE. Translatability of helminth therapy in inflammatory bowel diseases. Int J Parasitol 2013;43:245–51.
[108] Araujo MI, Lopes AA, Medeiros M, Cruz AA, Sousa-Atta L, Solé D, et al. Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. Int Arch Allergy Immunol 2000;123:145–8.
[109] Nyan OA, Walraven GE, Banya WA, Milligan P, Van Der Sande M, Ceesay SM, et al. Atopy, intestinal helminth infection and total serum IgE in rural and urban adult Gambian communities. Clin Exp Allergy 2001;31:1672–8.
[110] Cooper PJ, Chico ME, Rodrigues LC, Ordonez M, Strachan D, Griffin GE, et al. Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol 2003;111:995–1000.
[111] Scrivener S, Yemaneberhan H, Zebenigus M, Tilahun D, Girma S, Ali S, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case–control study. Lancet 2001;358:1493–9.
[112] Chandrasekhar S, Parija SC. Serum antibody & Th2 cytokine profiles in patients with cystic echinococcosis. Indian J Med Res 2009;130(6):731–5.
[113] Wang H, Li J, Pu H, Hasan B, Ma J, Jones MK, et al. *Echinococcus granulosus* infection reduces airway inflammation of mice likely through enhancing IL-10 and down-regulation of IL-5 and IL-17A. Parasit Vectors 2014;7(1):522–34.
[114] Fallon PG. Immunopathology of schistosomiasis: a cautionary tale of mice and men. Immunol Today 2000;21(1):29–35.
[115] Araujo MI, Hoppe BS, Medeiros Jr M, Carvalho EM. *Schistosoma mansoni* infection modulates the immune response against allergic and autoimmune diseases. Mem Inst Oswaldo Cruz 2004;99:27–32.
[116] Yazdanbakhsh M, Wahyuni S. The role of helminth infections in protection from atopic disorders. Curr Opin Allergy Clin Immunol 2005;5:386–91.
[117] Bashi T, Bizzaro G, Shor DB, Blank M, Shoenfeld Y. The mechanisms behind helminth's immunomodulation in autoimmunity. Autoimmun Rev 2015;14:98–104.
[118] Sandborn WJ, Elliott DE, Weinstock J, Summers RW, Landry-Wheeler A, Silver N, et al. Randomised clinical trial: the safety and tolerability of *Trichuris suis* ova in patients with Crohn's disease. Aliment Pharmacol Ther 2013;38:255–63.
[119] Fleming JO. Helminth therapy and multiple sclerosis. Int J Parasitol 2013;43:259–74.
[120] Siniscalco D, Antonucci N. Possible use of *Trichuris suis* ova in autism spectrum disorders therapy. Med Hypotheses 2013;81:1–4.
[121] Zaccone P, Cooke A. Helminth mediated modulation of Type 1 diabetes (T1D). Int J Parasitol 2013;43:311–8.
[122] Shor DB, Harel M, Eliakim R, Shoenfeld Y. The hygiene theory harnessing helminths and their ova to treat autoimmunity. Clin Rev Allergy Immunol 2013;45:211–6.
[123] Quinnell RJ. Genetics of susceptibility to human helminth infection. Int J Parasitol 2003;33:1219–31.
[124] Lundy SK, Lukacs NW. Chronic schistosome infection leads to modulation of granuloma formation and systemic immune suppression. Front Immunol 2013;4:39, http://dx.doi.org/10.3389/fimmu.2013.00039.
[125] Smith P, Fallon RE, Mangan NE, Walsh CM, Saraiva M, Sayers JR, et al. *Schistosoma mansoni* secretes a chemokine binding protein with antiinflammatory activity. J Exp Med 2005;202(10):1319–25.
[126] Sayed AA, Williams DL. Biochemical characterization of 2-Cys peroxiredoxins from *Schistosoma mansoni*. J Biol Chem 2004;279(25):26159–66.
[127] Sekiya M, Mulcahy G, Irwin JA, Stack CM, Donnelly SM, Xu W, et al. Biochemical characterisation of the recombinant peroxiredoxin (FhePrx) of the liver fluke, *Fasciola hepatica*. FEBS Lett 2006;580(21):5016–22.
[128] Schramm G, Mohrs K, Wodrich M, Doenhoff MJ, Pearce EJ, Haas H, et al. Cutting edge: IPSE/alpha-1, a glycoprotein from *Schistosoma mansoni* eggs, induces IgE-dependent, antigen-independent IL-4 production by murine basophils in vivo. J Immunol 2007;178(10):6023–7.

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