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The Hygiene Theory Harnessing Helminths and Their Ova to Treat Autoimmunity

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Abstract The incidence of autoimmune diseases is increasing in Western countries, possibly due to the improved sanitary conditions and reduced exposure to infections in childhood (the hygiene hypothesis). There is an ongoing debate whether infection prevents or precipitates autoimmune diseases. Various helminths species used in several animal models were shown to limit inflammatory activity in a variety of diseases including inflammatory bowel disease, multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus. At present the scientific data is based mostly on experimental animal models; however, there is an increasing body of evidence in a number of clinical trials being conducted. Herein we review several clinical trials evaluating the anti-inflammatory effects of helminths and assessing their association with different autoimmune diseases, including inflammatory bowel disease, multiple sclerosis, and autoimmune liver diseases. We also describe the common pathways by which helminths induce immune modulation and the key changes observed in the host immune system following exposure to helminths. These common pathways include the inhibition of IFN-γ and IL-17 production, promotion of IL-4, IL-10 and TGF-β release, induction of CD4(+) T cell FoxP3$^+$ expression, and generation of regulatory macrophages, dendritic cells, and B cells. Helminths products are becoming significant candidates for anti-inflammatory agents in this context. However, further research is needed for synthetic analogues of helminths' potent products that mimic the parasite-mediated immunomodulation effect.

Keywords Helminth · Hygiene · Autoimmune · Type 1 diabetes · Inflammatory bowel disease · Multiple sclerosis · Autoimmune liver diseases

Introduction

Improvement in hygiene and reduced exposure to childhood infections have been suggested as a major cause for the increase in autoimmunity [1, 2]. On the other hand, infections may participate in the induction of autoimmunity by influencing the maturation of the immune system from the innate to the adaptive phases [3–6]. So there is an ongoing debate whether infection prevents or precipitates autoimmune diseases. It has been proposed that certain helminthic infections modulate the experimental induction or spontaneous onset of autoimmune diseases such as type 1 diabetes (T1D) [7–9], inflammatory bowel disease (IBD) [10–12], and multiple sclerosis (MS) [13–20].

Studies show that helminthic infections can modulate mammalian immune response in various pathways, including inhibition of interferon (IFN)-γ and interleukin (IL)-17 production, promotion of IL-4, IL-10 and TGF-β release, induction of CD4(+) T cell FoxP3$^+$ expression, and generating regulatory macrophages, dendritic cells, and B cells [21].

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Yet, the mechanisms by which helminths affect autoimmune diseases remain to be fully clarified. The main question is whether the helminths' capability of immune modulation can be applied for therapeutic purposes. The area of worm-based therapies is of great relevance nowadays, and big efforts are applied worldwide to develop new experimental therapies and explore their role in autoimmunity.

Hygiene Hypothesis

During the last several decades, Western countries are being confronted with an increased incidence of many immune disorders, including autoimmune and allergic diseases, inflammatory bowel diseases, and some lymphocyte malignancies. Clean food and water are our standard of life, and epidemiological evidence indicates of a strong correlation between improved sanitation and an increase in allergic disorders. This concept is known as the *hygiene hypothesis* proposed by Strachan [1]. He proposed that there is an inverse association between the occurrence of hay fever and the number of siblings in a family. According to this theory, atopic disorders result from reduced exposure to microorganisms in childhood. The concept began with allergic disorders, but extended fast, and currently relates also to autoimmunity, neuroinflammatory disorders, atherosclerosis, and some cancers. Observations such as in type 1 diabetes and in asthma have raised the theory that "prevention" of childhood infections may predispose to autoimmune or allergic responses [2, 22, 23]. In the 1990s, Weinstock et al. first proposed the "inflammatory bowel disease hygiene hypothesis", which states that raising children in extremely hygienic environments negatively affects immune development, which predisposes them to IBD later in life [24].

Clinical Experimental Therapy in Humans

Inflammatory Bowel Disease

The impressive results of helminths therapy in murine models of IBD [2, 3, 23, 25–29] led to the notion of a trial of such therapy in humans. However, treatment with parasitic helminths require meticulous investigation of the immunologic basis of the condition, as *Hymenolepis diminuta* infection, for example, can be favorable in some models of colitis but can exacerbate oxazolone-induced colitis [30].

Two reports using helminths to treat IBD in humans, published by Summers et al. [10, 11], suggest that helminthic exposure has a beneficiary effect on Crohn's disease (CD) and ulcerative colitis (UC). In these studies UC and CD patients were treated with live *Trichuris suis* ova (TSO), resulting in significant clinical improvement in nearly 80 % of patients in the open-label study in CD [10] and more modest effects in the double blind clinical study in UC [11]. The UC study included 54 patients with active colitis who received either the pig whipworm TSO or placebo at 2-week intervals for 12 weeks. Ova therapy was safe and effective. Clinical improvement occurred in 13/30 patients treated with ova compared with 4/24 patients given placebo [11]. In the CD study, 29 patients with active CD ingested live TSO every 3 weeks for 24 weeks. At week 24, 23/29 patients responded and 21/29 patients remitted. Although neither study addressed the mechanisms in which TSO infection improved clinical IBD, both assumed it was via modulation of the immune response from Th1 to Th2, a helminths-mediated induction of regulatory T cells and alteration of cytokine profile, namely IL-10 and TGF-β, as shown in murine models [25, 27–29, 31]. Future studies are needed to further explore the exact immune mechanisms responsible for the protective effect in humans.

Treatment of CD and UC patients with TSO appeared safe and effective in the short-term basis, and no adverse events were reported [10, 11]. To date in all clinical trials conducted, adverse events associated with TSO treatment were rare, suggesting relative safety even in immune-compromised hosts. Moreover, it has been suggested that the helminth-treated group can be treated with antihelminthic therapy after completion of trials [32]. Further clinical trials utilizing TSO in IBD patients are anticipated.

The hematophagous hookworm, *Necator americanus*, is proposed as an alternative to TSO, as it is easier to use due to longer-lasting effects. A small study tested whether CD patients tolerate *N. americanus* infection. Inoculation proved safe, even in immune-suppressed patients [33]. Mortimer et al. showed that infection with ten *N. americanus* administered by a skin patch on the arm is well tolerated and is a potentially proper dose for therapeutic trials [34].

Multiple Sclerosis

There are a limited number of studies on the effect of helminths infection on MS patients. Most studies were designed as to investigate the clinical and immunological characteristics of MS patients infested with parasites, rather than intentionally exposing these patients to helminths. One such study is a prospective study from Argentina [35, 36] describing 12 MS patients diagnosed with different gastrointestinal parasitic infections with *Hymenolepis nanan*, *Trichiuris trichura*, *Ascaris lumbricoides*, *Strongyloides stercoralis* and *Enterobius vermicularis*. After 63 months of follow-up, four patients received antiparasite treatment. Helminthic infection control was associated with significant deterioration in both clinical and radiological MS manifestations, accompanied by significant increase in IFN-γ and

IL-12-producing cells and decrease in TGF-β and IL-10-secreting cells, and fewer $CD4^+CD25^+FoxP3^+$ Treg cells.

The same group [37] evaluated B cell function of 12 MS patients that were infected by helminths and compared with that of regular MS patients, patients with parasitic infections and no chronic disease, and healthy controls. Helminths infections in MS patients resulted in a B cell population producing high levels of IL-10 and reduced inflammation mediation, in part, by the ICOS-B7RP-1 pathway. The detected IL-10-producing B cell phenotype expressed high levels of CD1d and was similar to the one observed in mature naive B2 cells [CD11b(−), CD5(−), CD27(−), and IgD(+)]. Moreover, B cells isolated from helminth-infected MS patients produced greater amounts of brain-derived neurotrophic factor and nerve growth factor compared with controls, raising the possibility that these cells may exert a neuro-protective effect on the central nervous system. Thus, helminths infection may affect disease progression through immunomodulation as well as immune-mediated neuro-protection.

Autoimmune Liver Disease

Primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC) are chronic liver diseases that likely have an autoimmune basis in their pathogenesis. As with other autoimmune diseases, environmental and genetic factors may play a principal role in their development. A case-control study suggested an inverse relationship between autoimmune liver diseases such as PBC, AIH, and PSC and *S. stercoralis* infection, the most common human helminth. The frequency of *S. stercoralis* infection in the autoimmune liver diseases group (1.0 %) was significantly lower than that found in the control group (7.0 %; P=0.0063) [38].

Hypothesis for Immune Modulation by Helminths

The Th1/Th2 Balance Theory

Most helminths organisms stimulate the host to selectively produce Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) while blocking Th1 cytokine responses (IL-12 and IFN-γ) [39]. This usually leads to increased immunoglobulin E (IgE), mast cell, and eosinophil responses. Initially, the imbalance between Th1 and Th2 was thought to explain all the epidemiology underlying the hygiene hypothesis in general and the helminths' therapeutic effect in specific. However, some facts stand out against this theory. First, individuals infected by helminths are less likely to have allergic disorders, despite the enhanced Th2 response. Second, defects in the IL-12 or IFN-γ (Th1 pathways) do not increase the incidence or severity of allergic disorders, suggesting that Th1 is not a regulator of Th2 response [40]. Third, IFN-γ and other Th1 cytokines are prevalent in disorders such as asthma [41] and atopic dermatitis [42]. Hence, the other mechanisms presented below may be involved.

Suppression of T Helper Type 1/17

Disorders with disproportionate immune responses had been traditionally classified as "Th1 diseases" or "Th2 diseases" according to the Th1/Th2 paradigm; however, another classification of "Th17 disease" is now recognized [43, 44]. Whereas most atopic immune disorders can be classified as Th2 diseases, the classification of autoimmune diseases is far more complex. For example, EAE as a model of MS was long thought to be a Th1 disease; however, recent studies in human as well as in mice revealed that MS is dependent on the IL-23/IL-17 axis (i.e., Th17 response) rather than an IL-12/IFN-γ axis (i.e., Th1 response) [45]. As for IBD the pathogenic roles of both Th1 and Th17 responses in TNBS-induced colitis are still debatable [46, 47]. Regarding T1D the diabetes observed in non-obese diabetic (NOD) mice has been classified as a Th1 disease, yet recent reports confirmed that Th17 cells could also cause diabetes [48].

There is increasing data suggesting an inverse association between helminth infection and both T helper types 1/17 (Th1/17) based inflammatory disorders such as MS, T1D, IBD, and RA [28, 49–51] (Fig. 1). *Trichinella pseudospiralis* infection in EAE mice resulted in suppression of Th17 and Th1 responses, decreased expression of inflammatory cytokines IL-17, IL-6, IL-1β, IFN-γ, and TNF-α in the spinal cord, as well as with reduction in the inflammatory infiltrates in the CNS [50]. A different study showed that *Schistosoma mansoni*-infected mice became resistant to collagen induced arthritis (CIA), coupled with downregulation of both Th1 and Th17 responses of splenocytes [51]. Another study demonstrated the suppression of TNBS-induced colitis by schistosomal antigens accompanied by downregulation of IL-17 gene expression in the colon and mesenteric lymph node [28].

Treg Cells Modulation with Increased Production of IL-10 and TGF-β and $FoxP3^+$ Induction

There is expanding data suggesting that Treg cells produced during parasitic infections can alter the course of autoimmunity. The presence of the parasite appears to induce the production of various Treg cells subsets that recognize autoantigens and inhibit the autoimmune process. Animal models as well as clinical trials suggest a role of Treg cells in the therapeutic effects of helminths. One example is a study in helminths-infected MS patients that showed increased production of specific Treg cells that responded to the myelin basic protein by releasing regulatory cytokines IL-10 and transforming growth factor-β as well as the induction of $CD25^+CD4^+$ $FoxP3^+$. This immune modulation correlated with fewer disease exacerbations and fewer brain lesions

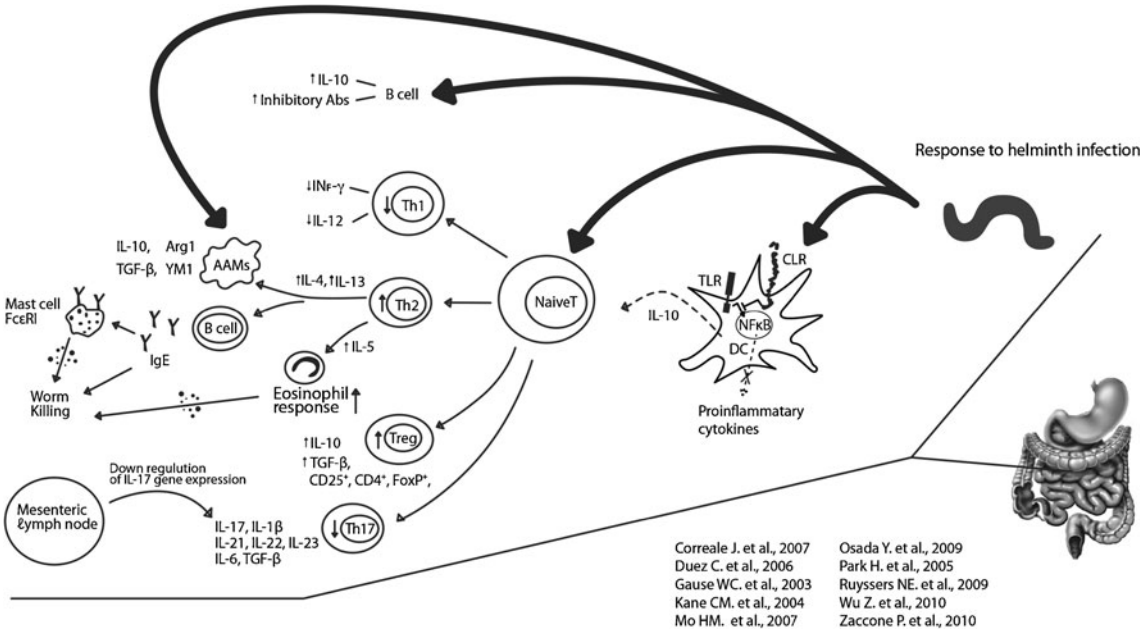

Fig. 1 The immune response to helminths. Following exposure to helminths, key changes are observed in the innate immune system, including modification of DCs. TLRs and CLRs broadly expressed on DCs are the main target for parasites [54]. Helminthic products induce IL-10 production by DCs and have a direct anti-inflammatory effect on DCs by controlling TLR ligand-induced DC maturation [55]. Most helminths stimulate the host to selectively produce Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) while blocking Th1 cytokine responses (IL-12 and IFN-γ) [39]. This usually leads to strong IgE, mast cell, and eosinophil responses and alternatively activated macrophages stimulation. There is an inverse association between helminth infection and both T helper types 1/17 [28, 49–51], which results in lower expression of inflammatory cytokines IL-17, IL-6, IL-1β, IFN-γ, and TNF-α, as well as downregulation of IL-17 gene expression in the colon and mesenteric lymph node [28]. Helminths induce the production of various Treg cells subsets that recognize auto-antigens and, following that, release regulatory cytokines IL-10 and TGF-β together with induction of $CD25^{+}CD4^{+}$ $FoxP3^{+}$ [35, 53]

[35]. Exposure to *Schistosoma japonicum* ova induces the development of Treg cells, limits Th1 responsiveness, and increases Th2 cytokines production in mice, clinically preventing colitis [52]. Expansion and activation of Tregs also was shown to contribute to the prevention of diabetes in NOD mice following in vivo exposure with *S. mansoni* eggs [53].

Dendritic Cell Activation

Following exposure to helminths, key changes are observed in the innate immune system of the host, including modification of dendritic cells (DCs). DCs are essential in directing immune response towards tolerating or activating a pathway. Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) which are broadly expressed on DCs are the main targets for parasites [54]. Studies have shown that *S. mansoni* products induce IL-10 production by the DCs and have a direct anti-inflammatory effect on the DCs by controlling TLR ligand-induced DC maturation [55].

Future Perspectives

Current management of autoimmune diseases relies generally on a nonselective inhibition of the immune system by giving nonselective immunosuppressants such as corticosteroids, cyclophosphamide, methotrexate, anti-TNF, and monoclonal antibodies. This nonselective immune suppression often results in severe infections and malignancies. The helminthic therapy holds expectations for a native therapy, which will modify the immune system with less adverse effects. However, one main concern regarding the treatment with live parasites is the development of helminthic infection, especially when patients are being treated in combination with immunosuppressant. The research for synthetic analogues of helminths' potent products that mimic the parasite-mediated immunomodulation effect could resolve this problem.

Summary

Helminths and their products are considered to possess therapeutic capability to control or even prevent immune-mediated diseases. Thus, helminthic therapy is becoming of major interest, and many researchers are enthusiastic to explore its role in autoimmunity. As shown in the presented review, helminthic infection induce immunomodulation in numerous pathways, including inhibition of IFN-γ and IL-17 production; induction of IL-4, IL-10, and TGF-β release; CD4(+) T cell $FoxP3^{+}$ expression; and generation of regulatory DCs, macrophages,

and B cells. Currently, most of the scientific data is based on experimental animal models; however, there is an increasing body of evidence in a number of clinical trials being conducted. So far the role of helminthic therapy has been investigated in inflammatory bowel disease, multiple sclerosis, type 1 diabetes [7, 9, 22, 53], rheumatoid arthritis [5, 51, 56], and autoimmune liver disease. Other autoimmune diseases that seem to be good candidates based on their etiologies necessitate further study include Sjogren's syndrome, psoriatic arthritis, and vitiligo. As experience in human patients is limited, further investigation is warranted in order to evaluate the clinical significance of the helminths' protective effect, and several large studies are under way. Moreover, additional research is needed in applying helminths products or their synthetic analogues.

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