Parasitic helminth infections and the control of human allergic and autoimmune disorders

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Abstract

The profile of global health today presents a striking reciprocal distribution between parasitic diseases in many of the world's lower-income countries, and ever-increasing levels of inflammatory disorders such as allergy, autoimmunity and inflammatory bowel diseases in the more affluent societies. Attention is particularly focused on helminth worm parasites, which are associated with protection from allergy and inflammation in both epidemiologic and laboratory settings. One mechanistic explanation of this is that helminths drive the regulatory arm of the immune system, abrogating the ability of the host to expel the parasites, while also dampening reactivity to many bystander specificities. Interest has therefore heightened into whether helminth parasites, or their products, hold therapeutic potential for immunologic disorders of the developed world. In this narrative review, progress across a range of trials is discussed, together with prospects for isolating individual molecular mediators from helminths that may offer defined new therapies for inflammatory conditions.
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Introduction

The health profile of countries across the world reveal many stark contrasts, including a remarkable reciprocity between helminth parasite infections in most low-income tropical countries, and diseases of modernity such as allergy and autoimmunity in the more affluent, developed populations [1]. In the latter, these syndromes are becoming increasingly prevalent, with asthma exceeding 10% of children in many European countries [2], while the incidence of autoimmune diseases such as type 1 diabetes [3] as well as of inflammatory bowel disease (IBD) [4] continues to surge.

Allergic and autoimmune disorders represent exaggerated immunologic responses to harmless antigens such as those from innocuous environmental organisms or from our own body. The question has arisen of whether parasites dampen the immune system of their host to promote their own survival and while doing so also prevent untoward overreactions that generate immunopathology. Thus, in parasite-free environments the modulating effect of parasitic infections may be lost and the immune system more prone to causing disease—a scenario that Velasquez-Manoff has called 'an epidemic of absence' [5].

A vast array of socioeconomic, dietary, environmental and genetic factors must underpin the disparity in disease profiles between different parts of the globe [6]. Hence the question is not whether helminth parasites alone can account for these differences but rather whether their effect on the host immune system makes a significant contribution to muting immunologic diseases; if so, we then will ask if we can identify the pathways driven by helminths and learn from them to develop new therapies to treat the disorders that are becoming increasingly common [7,8].

Helminths and the Immune System

Helminths comprise a diverse set of parasitic and free-living worms with a long evolutionary history; multiple lines have

adopted the parasitic lifestyle and in each case become exquisitely well adapted over evolutionary time to the immune system of their chosen host. Their strategies have been highly successful: for example, even today, over 2 billion people worldwide carry helminth infections [9], and until the 19th century, it is likely that all humans would have been infected for much of their life with one or more helminth species. Some of these parasites, such as the schistosomes that cause bilharzia (schistosomiasis), are highly pathogenic causing visceral inflammation and liver fibrosis even in children, and they also have many more subtle detrimental effects [10]. However, in many other helminth infections, carriers are often asymptomatic, reflecting a form of immunologic tolerance by the host towards the parasite [11]. Indeed, it appears that an early, more vigorous immune response to infection (as seen, for example, in travellers) becomes subdued as chronic infection becomes established in residents who experience continual exposure and as maturing parasites produce eggs or microfilarial larvae for onward transmission.

Helminth-infected patients show both quantitative and qualitative shifts in immune responsiveness that reflect either the parasite manipulating the host immune system or the host reaching an accommodation with the parasite to minimize collateral damage. Parasite antigen-specific T-cell reactivity has been found to be depressed in chronically infected filariasis and schistosomiasis patients, but reactivity could be restored after chemotherapeutic cure of infection [12,13], indicating that the presence of helminths actively suppresses host immunity. The profile of immune reactivity is also markedly shifted by infection, with a skewing of cytokine responses away from inflammatory mediators such as interferon gamma [13] and a more prominent role for the regulatory cytokine interleukin (IL)-10 [14]. As a result, the pro-inflammatory Th1 and Th17 T-cell subsets are muted; significantly, where the Th1/17 population breaks through and dominates the antiparasite response, patients develop more severe immune pathology, such as lymphadenitis and elephantiasis in lymphatic filariasis [15] or granulomatous bladder pathology in *Schistosomiasis haematobium* [16].

In parallel with the anti-inflammatory dampening of Th1/17 responses, the Th2 arm of the host immune response is also modulated, but in a more selective manner. Part of the Th2 response remains intact (with high IL-4 levels, for example), but the profile becomes similar to the modified Th2 observed in allergic patients after allergen desensitization [17]. Most notable is the induction of high levels of the immunoglobulin (Ig) G4 antibody isotype and relatively low levels of IgE [18], mechanistically linked to the ability of IL-10 to promote IgG4 production by B cells [19].

Perhaps most significant change in patients' immune profiles is the greater activity of suppressive lymphocyte subsets, in particular regulatory T cells (Tregs) in helminth infections [20–22]. This subset maintains steady-state homeostasis in the immune system, preventing autoimmunity and other potentially deleterious responses to innocuous antigens from commensal microbes [23]. However, helminth parasites appear to have evolved strategies to exploit this pathway to prevent immune expulsion by the host [24]. Effector T-cell responses are subdued by the regulatory compartment but *in vitro* can be recovered by removal of the Treg subset [21]. In addition, other suppressive populations such as regulatory B cells may also be activated [25,26].

Bystander Effects of Helminth Infections

The consequences of dampened inflammatory immunity and expanded regulatory activity may be seen in several settings; helminth-infected children can be less responsive to microbial vaccines [27]; the presence of helminths can actually favour survival of foreign tissue transplanted into patients [28]; and helminth infections also negatively affect the host's ability to combat a range of other pathogens, such as tuberculosis [29]. At least part of this effect is due to Tregs: patients' *in vitro* T-cell responses to bacillus Calmette-Guérin and malaria antigens that are subdued compared to those of non-helminth-infected subjects are rescued by the depletion of Tregs [30]. Each of these observations speaks to a profound systemic impact of helminth parasites on the functions of the whole host immune system [31].

The most striking off-target epidemiologic effects of helminth infections, however, has been their apparent protection against immunologic disorders familiar to residents of countries with developed economies. As long ago as 1968, Greenwood [32] remarked on the very low incidence of rheumatoid arthritis and other autoimmune disorders in African countries with a high prevalence of parasites. More recently, schistosome-infected school children in Gabon were shown to exhibit lower levels of atopic skin allergic reactivity than uninfected classmates [33]. Notably, the helminth-infected children expressed higher levels of the cytokine IL-10, which is emerging as a major player in regulation of both allergy and parasite immunity. A causal relationship between schistosomes and attenuated allergy was shown when praziquantel chemotherapy to clear parasites resulted in higher levels of atopy, which did not rise in control children provided with a placebo [34]. Many further studies have been accomplished in Asia, Africa and Latin America showing that many (but not all [35]) helminth parasites negatively affect allergic reactivity [36–38], although, importantly, the size of the protective effect is likely to depend on the intensity and duration of infection [39,40]. In addition, the

attenuation observed is primarily at the level of allergic sensitization rather than overt clinical allergy in these settings [41].

Autoimmune diseases are less frequent than allergies, particularly in younger persons, and many environmental, genetic and microbiologic factors are likely to influence the incidence of these disorders. Thus, although autoimmunity is less common in tropical environments, evidence for a causal link between helminth infections and any degree of protection against autoimmunity is relatively scanty. However, a surrogate marker (and potentially a precursor of disease) is the level of circulating anti−nuclear antibodies (ANA) in study subjects. In a Zimbabwean setting, it was found that schistosome-infected people had significantly lower ANA titres than age-matched uninfected cohabitants. Overall, anti-ANA antibody levels were inversely proportional to circulating IL-10 levels, lending more support to a central role for this regulatory cytokine. Moreover, these levels increased after schistosome clearance with praziquantel, strongly implicating that the parasite itself generates the conditions in which autoimmune reactivity is suppressed [42].

Acquired Helminth Infection in Immune Dysfunction

Clinical autoimmune disease may also be attenuated by helminths. A striking study from Argentina followed 12 patients with multiple sclerosis (MS) who had adventitiously acquired various gastrointestinal helminth infections. All remained in remission for over 4 years, in contrast to uninfected MS patients with similar severity scores at the outset of the study and who developed various degrees of relapse and exacerbation [43]. The infected, protected patients showed reduced inflammatory cytokine responses, and enhanced production of IL-10 as well as transforming growth factor (TGF)-β, as well as a greater regulatory B-cell compartment [25]. In a follow-up of the same cases, remission continued into the sixth year, when four patients were provided with anthelmintic treatment to alleviate gastrointestinal symptoms; notably, their MS disease activity resumed while IL-10 and TGF-β levels receded [44].

One case has also been reported of ulcerative colitis, a major form of IBD; a patient self-infected with one of the least pathogenic human helminths, *Trichuris trichiura,* and experienced remission of symptoms. Analysis of biopsy specimens revealed that the inflammatory Th17 subset had subsided, whereas Th2 cells expressing IL-4 and a specialized Th22 subset secreting IL-22 were more frequent [45]. In addition, goblet cell−derived mucus production was much enhanced after infection. Taken

together, this study indicated that helminths quelled gut inflammation both by modulating T cell subsets and by promoting barrier function and tissue repair though IL-22 and the mucus response to type 2 cytokines such as IL-4 and IL-13.

Helminth Therapy of Immunologic Disorders

Such remarkable reports have fuelled interest in helminth therapy, entailing deliberate infection of humans with live helminth parasites [46]. The basic premise is that with a judicious choice of species (selecting those of low pathogenicity) and dose (below the presumed threshold of pathogenesis), the immune system can be effectively subdued or recalibrated, and allergic or autoimmune conditions can thus be reversed in patients. After the first small studies over 10 years ago, no fewer than 28 clinical trials of helminth therapy are now at various stages of progress, although relatively few have been completed and subjected to analysis [47].

The most widely used approach has been with the pig whipworm *Trichuris suis.* Closely related to the human-infective *T. trichiura,* this parasite will develop transiently in the human gut but will naturally be expelled with 6 weeks. Infection of humans is achieved by administration of *T. suis* ova (TSO) collected from pigs under Good Manufacturing Practice in a specialized facility. Initial pilot studies reported a beneficial effect on both forms of IBD, Crohn disease and ulcerative colitis [48−50], with improvement rates of over 70% in groups of 30 to 50 patients. These studies also showed minimal adverse effects, although the study was considered to be too small to evaluate safety concerns about the use of live helminths for human therapy [51].

Subsequently, two larger cohorts of over 200 patients have been recruited for clinical trials of TSO in IBD patients. Unfortunately, both trials were discontinued for lack of efficacy; details have yet to be published, but a recent review cited an unusually high remission rate in the placebo group as causing trial failure [47]. It is to be hoped that the full results will shortly become available so that maximum insight can be gained from these major studies.

In parallel, TSO has been tested across a wide range of immune disorders. One early study that has been fully published treated 49 patients with allergic rhinitis Denmark with eight doses of parasite eggs; however, no change in allergic symptoms was observed compared to a similar number of placebo recipients [52]. Further investigation indicated that the *Trichuris* infection had established and provoked a strong antiparasite response; perhaps surprisingly, in this study it was found that infection did not at all affect the allergen-specific response [53].

TSO has also been used in other settings, including autism, psoriasis and food allergy [47,54], although details of clinical outcomes have yet to emerge. More prominently, TSO treatment for MS has been subject to several studies; in two studies with cohorts of four to five patients provided TSO for 12 to 24 weeks, modest immune and clinical parameters were changed, with some evidence of improvement [55,56]. In a separate trial of ten patients, no overall benefit was found [57]. Subsequent larger trials have yet to be fully published, but one showed a 34% reduction in brain lesions after 5 months of TSO treatment in a study that also reported few adverse effects [58].

In parallel, therapies have also been trialled with the human hookworm parasite *Necator americanus;* while pathogenic at higher intensities as a result of its migratory passage through the lung, and while feeding on blood as an adult worm, low doses have been shown not to provoke symptoms in safety tests [59]. A trial of 32 asthma subjects in the United Kingdom was conducted, half of whom received ten *N. americanus* infective larvae; the infected group showed a small improvement in airway function that did not attain statistical significance, arguing for more extensive studies [60].

Investigators in Australia have also tested *N. americanus* infection in patients with intestinal immunopathologies; in a stand-alone study of nine cases of Crohn disease, with a larger infective dose (25–100 larvae), quantitative improvements in disease indices were found, although no placebo group was available for comparison [61]. In a more extensive randomized double-blinded trial of coeliac disease, in which patients are intolerant of gluten, lower doses (5–10 larvae) were administered, and again, quite subtle health gains were recorded that did not attain statistical significance [62].

Conclusion and Outlook

Both active practitioners and interested observers have made many important comments drawing on our understanding and experience of helminth modulation of host immunity and pathogenesis in the therapeutic setting [47,63–65]. The first point is that much of the impetus for applying helminth therapy to humans has been derived from compelling animal studies (discussed in more detail elsewhere [8,66]), most of which test short-term priming and challenge rather than reversal of long-established reactivity [63]. Secondly, we have little insight into the appropriate dose or duration of infection that is required to exert a significant effect—a concern particularly with human hookworm studies, in which safety considerations limit the parasite dose that can be applied. Thirdly, there will be 'horses for courses,' and an intestinal helminth species is likely to be much more effective in dampening inflammation in its own setting than in more distant locales (such as the central nervous system). Finally, and perhaps most importantly, the human species is highly polymorphic and reacts to helminth infection in a spectral manner. Because parasitism is on balance detrimental, administration of live helminths is itself a balancing act, attempting to maximize any beneficial effects against a deleterious backdrop. Where the fulcrum of that balance sits will very much vary according to the genetic makeup of the individual.

These considerations have led many in the field to place greater emphasis on identifying molecular mediators derived from helminths that may replicate the benefits of the parasite without entailing any of the detriments [67–71]. Indeed, a panoply of candidate molecular therapies are now emerging from detailed studies on helminths (reviewed in [8,72]), some of which are showing impressive *in vivo* efficacy [73–76]. On a platform of individual molecular components, each can be evaluated for their relative efficacy on different indications and applied accordingly; effective immunomodulators can be delivered to the inflamed tissue even when distant from the normal niche of the parasite, at an optimal dose; and even against the background of human genetic diversity, the defined molecules from parasites are much more likely to confer only the benefits, and none of the harm, of their parental organism.

Transparency Declaration

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