Opinion

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Evolutionary Parasitology

The therapeutic helminth?

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By definition, parasites harm their hosts. Yet substantial evidence from animal models of human disease support the hypothesis that infection with helminths can suppress the development of other maladies. Here, the view is presented that assessment of the immunophysiological response to helminths could identify that infection with specific parasites would be therapeutically useful (although many helminths could not fulfil this role) and lead to precise knowledge of the immune events following infection, to identify ways to intervene in disease processes (in the absence of infection *per se*) that can be used to treat, and eventually cure, inflammatory and autoimmune disease.

Examining immunopathological relationships

The mammalian immune system has evolved under selective pressure to combat infective organisms: principally microbes, but also helminth parasites. This is not a unidirectional relationship. As the immune system of the host evolves to detect and, subsequently, inactivate and/or destroy invaders, parasites develop strategies, including mechanisms to escape detection (e.g. antigenic variation) and active manipulation of hosts' immune cells, to circumvent or dampen the host response(s). The ability to interfere with the immune responses of their hosts affords parasites the opportunity to establish, develop, reproduce and complete their life cycles.

Inherent in the well-adapted parasite–host relationship is that the parasite should not kill the host – at least, not until the parasite has successfully reproduced. Extrapolating from this, the supposition arises that, although manipulation of the host's immune system could leave the host vulnerable to other infections, it could also confer a concomitant health benefit by suppressing immunopathological reactions. Intuitively, it is tempting to accept this supposition because it implies that the successful, well-adapted parasite has evolved to help itself by helping its host. But is this really the case? Desowitz [1] cites several examples of 'harmonious parasites' and although some seem anecdotal, they illustrate the concept of a parasitic infection imparting some benefit on the host. This notion has been resurrected in recent years. Here, the thesis is developed that analyses of laboratory-based rodent–helminth model systems and assessment of individuals infected with helminth parasites will reveal novel ways to manipulate the human immune system to treat autoimmune and inflammatory diseases. However, the physician credo 'first do no harm' must be borne in mind. While advocating the medical potential of the 'therapeutic helminth', the potential drawbacks of such a treatment strategy must be considered (e.g. the pathology associated with *Schistosoma* or *Echinococcus* would exclude these species as therapeutic helminths but does not undermine their usefulness in dissecting immune signalling and immunomodulation in animal models).

The host response to infection with helminth parasites

Authoritative reviews on the mammalian response to infection with helminths are available. In brief: although nuances of specific host–parasite interactions exist, several stereotypic immune events characterize the host response to infection with helminths. As metazoans, helminths cannot be phagocytosed, and whereas innate immunity will participate in orchestrated responses that ultimately destroy or eradicate the worm, anti-helminthic responses are considered the remit of adaptive immunity, coordinated by T-helper cell-type 2 (Th2) cytokines and involving B cells and antibody that enable opsinization and complement fixation, activation of eosinophils and mast cells, and, if the parasite resides in a mucosal tissue, goblet cell hyperplasia and increased mucus production.

Three general approaches can be applied to assessing the immunology of host–helminth interactions (Figure 1): analysis of immune reactions in (i) permissive or (ii) non-permissive hosts and (iii) assessment of helminth-derived products on isolated immune cells or in rodent models of disease [2]. These laboratory-based systems are an essential complement to analysis of immunological events (e.g. cytokine profiles) in infected humans.

Emergence of inflammatory and autoimmune disease

During the past 40 years, there has been an exponential increase in the incidence of autoimmune and idiopathic inflammatory disorders such as inflammatory bowel disease (IBD), diabetes and atopic disease in Westernized societies, and a similar pattern is emerging in urbanized areas of developing countries [3]. This increase is too rapid to be driven solely by genetic factors (although there can be a genetic predisposition for developing these diseases), and so, environmental triggers were sought to explain the emergence of these chronic, debilitating disorders. The global distribution of, for example, IBD is virtually the mirror image of that of endemic helminth infections. Thus, epidemiological data support the postulate that infection

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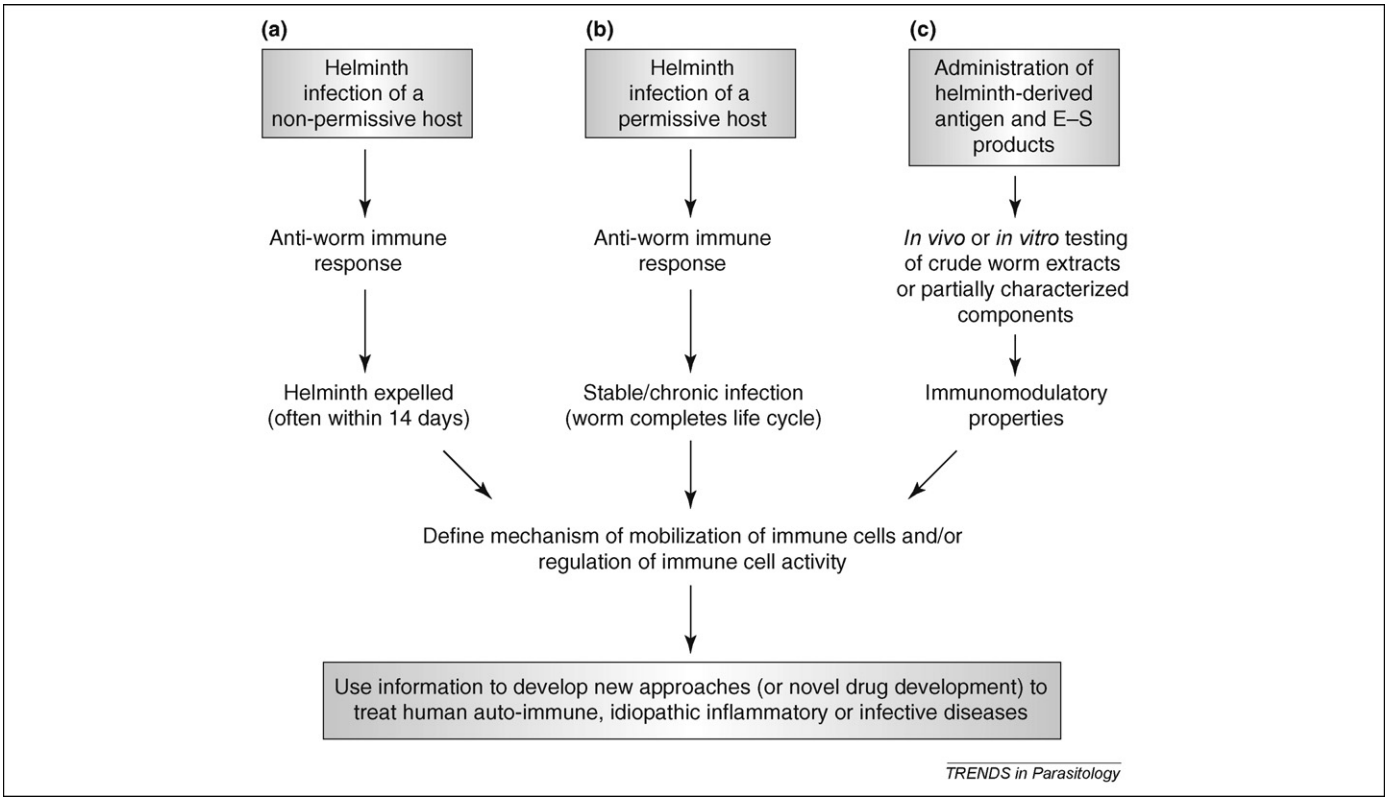

Figure 1. Flow chart illustrating the approaches that can be utilized to assess the immunological consequences of infection with helminth parasites or exposure to excretory–secretory (E–S) products from helminths and how this can be used to develop novel therapies for human disease.

with helminth parasites, whether acute or chronic, might provide some protection against these diseases; the corollary being that increased hygiene, sanitation and de-worming strategies in urbanized societies have left the populations of these areas vulnerable to the onset of inflammatory and autoimmune disease [4] (a similar argument can be made for the reduction in bacterial infection and increases in autoimmunity). Epidemiological data are, at best, correlative, and caution must be exercised when using such data to support a causative relationship [5]. However, epidemiological findings can be the basis for the generation of hypotheses that can subsequently be tested in laboratory or field studies.

Animal models provide proof-of-principle data for a 'therapeutic helminth'

As the intricate workings of the mammalian immune system are defined, several regulatory and 'off' mechanisms have emerged, the role of which is to limit immune responses and return the system to the homeostatic set-point (i.e. termination of inflammation is not simply a consequence of cessation of inflammatory mediator production but a coordinated active process driven by pro-resolution signals and the induction of regulatory cells) [6–8]. Rodent model systems recapitulate many (but not all) aspects of human inflammatory and autoimmune disease and have been immensely useful in defining mechanisms of inflammation, immunopathology and tissue recovery after infection or injury. Knowledge of immunity enables one to predict that the reactions set in motion in response to infection with helminths would prevent concomitant disease driven by an opposing spectrum of immune events. From this theoretical perspective, numerous investigators have shown that infection with a variety of helminths can ameliorate disease in murine model systems (Table 1). Thus, helminth-evoked Th2 events were shown to ameliorate disorders in which Th1 events predominated: an intuitive and readily acceptable position. On occasion, infection was found to worsen disease in the animal models (see below), and a benefit was only noted in, for example, airway hyper-reactivity when male-only (unnatural) *Schistosoma-mansoni*-infected mice were examined; however, this does not negate the value of the identification of an anti-inflammatory macrophage subtype in this study [9]. Also, *S. mansoni*-induced reduction in allergic airway inflammation was found to be time- and burden-dependent, with only chronically or heavily infected mice protected from ovalbumin-evoked allergic reaction [10]. Moreover, mice (and humans – see below) infected with helminth parasites might also be less susceptible to Th2 or allergic-type disease (Table 1), challenging the notion that the benefit of a therapeutic helminth is simply and solely via the induction of Th2 cytokines. Despite some model-specific findings, the view is emerging that the response to helminths, at least in mice, can manifest as a generalized immunosuppression or immunoregulation whereby regulatory T cells, B cells and macrophages predominate [6].

Data from animal studies leave little doubt that one effect of infection with helminth parasites can be the amelioration of other immunopathologies: a health benefit mediated via a variety of effector systems (Table 1). The question arises: can this information be translated into

Table 1. Evidence from animal models in support of a 'therapeutic helminth'

Species	Effect of infection	Mechanism	Refs
Schistosoma mansoni	Inhibition of DSS-induced colitis	Mobilization of an immunosuppressive or immunoregulatory macrophage phenotype	[30]
	Inhibition of TNBS-induced colitis in rats	Modulation of colonic cytokine levels	[31]
	Protection against anaphylaxis	IL-10-producing (IL-4 deficient) B cells	[32]
	Reduction in the severity of EAE in mice	Suppression of IL-12p40 production	[33]
	Prevention of diabetes in the NOD mouse	Generation of Th2 response	[34]
	Chronic, high-density infection alleviates allergic airway inflammation in mice	Generalized suppression of antigen-induced cytokines; increased IL-10 from B cells and $CD4^+$ T cells	[10]
	Suppression of collagen-induced arthritis in mice	Downregulation of Th1 cytokines, IL-1β and NFκB in the paw; increased IL-4 and IL-10	[35]
S. mansoni (male cercariae only)	Protects mice from allergen-induced airway hyper-responsiveness	Reduced IL-5, increased IL-10 and evidence for B-cell involvement	[9]
S. mansoni eggs (given ip)	Inhibition of TNBS-induced colitis in mice	Skewing of cytokines towards Th2; increased colonic IL-10 mRNA	[36]
	Reduction in the severity of EAE in mice	Cytokine skewing from Th1 to Th2	[37]
Hymenolepis diminuta	Inhibition of ion transport abnormalities in the colon of DSS-treated mice	Not determined	[38]
	Blockade of DNBS-induced colitis in mice	Production of IL-10	[28]
Ascaris suum	Chronic infection reduces ragweed-triggered allergic eye disease in mice	Mobilization of $CD4^+CD25^+$ T cells	[39]
Heligosomoides polygyrus	Inhibition of colitis in piroxicam-treated IL-10-deficient mice	Increases in IL-13 and Foxp3 mRNA indicating regulating T cells; IL-10-mediated suppression of IL-17 production	[40]
	Inhibition of TNBS-induced colitis in mice	Skewing of cytokines towards Th2	[41]
	Inhibition of *Helicobacter-felis*-associated gastric atrophy in mice	Reduced expression of Th1-type cytokines (IFNγ, TNFα and IL-1β)	[42]
	Amelioration of spontaneous arthritis (and kidney damage) in MRL/*lpr* mice	Skewing of cytokines towards Th2	[43]
	Suppression of a murine model of asthma	Induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells and IL-10 production	[44]
	Suppression of allergic airway inflammation	Induction of $CD4^+CD25^+Foxp3^+$ regulatory T cells: IL-10 not involved	[45]
	Inhibition of peanut-induced allergic responses n mice	Reduced IL-13 output from T cells: involvement of IL-10	[46]
Litomosoides sigmodontis	Inhibition of allergic airway inflammation and hyper-reactivity in mice	Mobilization of regulatory T cells and TGFβ	[47]
Nippostrongyloides brasiliensis	Amelioration of spontaneous arthritis (and kidney damage) in MRL/*lpr* mice	Skewing of cytokines towards Th2 type	[43]
	Suppression of allergen-induced airway inflammation in mice	Involvement of IL-10	[48]
Trichinella spiralis	Inhibition of DNBS-induced colitis in mice	Skewing of cytokines towards Th2 type and reduced IFNγ production	[49]

Abbreviations: DNBS, dinitrobenzene sulphonic acid; DSS, dextran sodium sulphate; EAE, experimental allergic encephalitis; ip, intra-peritoneal; IL, interleukin; TNBS, trinitrobenzene sulphonic acid.

therapies for specific diseases in humans? For example, delivery of recombinant interleukin (IL)-10 has been postulated as a treatment for IBD [11], yet clinical trials testing this strategy have been largely unsuccessful [12]. The 'lesson' from helminth–rodent model systems is that the temporal and spatial kinetics of IL-10 production could be key for a therapeutic benefit of IL-10; kinetics that might be difficult to recapitulate with a systemic infusion of recombinant cytokine but are a component of the natural host response to infection with enteric helminth parasites. Similarly, infections with helminths have illustrated anti-inflammatory and/or anti-allergic roles for regulatory T and B cells, such that the ability to create analogous events in humans (via actual infection, cell delivery or drug intervention) would be predicted to be of therapeutic value. The challenge is to determine the relative importance of each regulatory cell or molecule (e.g. IL-10 versus transforming growth factor-β) in the immunomodulation and see which, if any, can be adapted as treatment for human disease. Furthermore, mice generate immunological memory to helminths – in non-permissive hosts, secondary infections are rapidly expelled (i.e. within a few days). Consequently, if antigens can be identified that trigger a memory response and mobilization of immunoregulatory events, it should be possible to use these antigens as 'drugs' to treat disease in a previously infected (≡ immunized) individual.

Using helminths to treat human disease

A reduced incidence of atopic, allergic-type disorders has been correlated with natural infection with trematode and nematode parasites (Table 2). Furthermore, a randomized controlled trial of anthelminthics in Gabonese schoolchildren resulted in an increased prevalence of sensitivity to house-dust mite concomitant with the reduction in *Ascaris* and *Trichuris* infections [13]. Reduced atopic disease in *Schistosoma*-infected individuals could be due to increased IL-10 production [14,15], whereas a similar benefit in *Ascaris-lumbricoides*-infected individuals was IL-10 independent [16]. By contrast, a meta-analysis of 30 studies

Table 2. Evidence from investigations in humans in support of a 'therapeutic helminth'

Helminth	Disease in which benefit was observed	Refs
Trichuris suis[a]	IBD[b]: Crohn's disease	[18]
	IBD: ulcerative colitis	[19]
Necator americanus[a]	IBD: Crohn's disease	[21]
	Asthma[c]	[20]
Mixed[d,e]	Multiple sclerosis	[50]
Schistosoma haematobium, Ascarious lumbricoides and/or *Ancylostoma duodenale*[d]	Atopic/allergic disease	[15,51,52]
Theoretical speculation	Cardiovascular disease	[53]

[a]Physician-prescribed infection.
[b]IBD, inflammatory bowel disease.
[c]A dose-ranging safety study based on epidemiological data indicating that hookworm infection producing 50 eggs per gram of faeces might protect against asthma.
[d]Natural infection.
[e]Individual patients were infected with *Hymenolepis nana, Trichuris trichiura, Ascaris lumbricoides, Strongyloides stercolaris* or *Enterobius vermicularis*.

concluded that overall parasitic infections did not protect against asthma and that infection with *A. lumbricoides* was, in fact, associated with an increased risk for developing asthma [17]. Such contrasting opinions are not unusual because factors such as size of the worm burden, chronicity of the infection, concurrent infections and environmental differences affect the outcome of analyses of natural infections in humans. Further in-depth analyses are required before definitive statements can be made on natural infections with helminths in support of (or refuting) their presence causing a reduced susceptibility to autoimmune or inflammatory disorders. But what of the use of a prescribed therapeutic helminth?

Recently, Summers and colleagues conducted two small trials [18,19] in which patients with Crohn's disease or ulcerative colitis consumed viable ova of the porcine whipworm, *Trichuris suis*. This was a bold step. A statistically significant number of patients derived symptomatic relief and/or objective improvement of their disease after treatment (given every 2–3 weeks for 12–24 months). These studies have been followed with dose-finding analyses of *Necator americanus* as a putative treatment for Crohn's disease and asthma [20,21]. Collectively, these are intriguing but preliminary observations and they require confirmation (or refutation) in larger multi-centre, multi-investigator trials. In addition, Summers *et al.* reported neither persistent infection nor side-effects of infection with *T. suis*. However, there are obvious concerns when introducing a foreign species into a new niche (Box 1). A case report documents *T. suis* in the ileocecal region and the presence of a sexually mature male worm after physician-prescribed *T. suis* [22]. This study and commentary on the potential for *T. suis* to invade the human gut [23] raise the omnipresent spectre of clinically significant xenoinfection as a consequence of iatrogenic *T. suis* infection or, indeed, that of any 'therapeutic helminth'.

Box 1. Potential concerns with helminth therapy

- The parasite itself must elicit minimal pathology in the host, negating the use of organisms such as *S. mansoni* (although this does not undermine the value of these parasites in model systems aimed at defining anti-inflammatory, immunosuppressive and immunoregulatory pathways and/or mechanisms).
- Use in immunovulnerable patients, such as infants or the elderly.
- Use in immunocompromised individuals.
- The potential that skewed immunological response to combat helminth parasites could increase susceptibility to bacterial, viral or protozoan pathogens.
- The potential to exaggerate specific diseases, for example, those in which eosinophils participate (e.g. eosinophilic oesophagitis).
- The possibility that aberrant migration of an invasive helminth will elicit problems outside of the organ in which the disease to be treated occurs.
- The potential for worms to establish and reproduce if infection is chronic.
- Long-term monitoring for unpredictable outcomes. (For example, would an increase in $CD4^+$ cells in response to infection with helminths increase the chance of infection with HIV in an individual in a susceptible environment?)

First do no harm

In addition to the concerns raised regarding the use of *T. suis*, adverse effects of infection with helminth parasites in the context of other diseases or infections have been shown in animal models. For instance, we found that infection with *Hymenolepis diminuta* worsens the outcome of oxazolone-induced colitis in mice [24]: an event that might have been driven by additional IL-5 or eosinophil activity. In addition, infection with *Heligosomoides polygrus* increased morbidity and mortality in mice co-infected with the low-grade bacterial pathogen *Citrobacter rodentium* [25,26] (*C. rodentium* is used as a model of enteropathogenic *Escherichia coli*, infection with which is associated with notable infant mortality caused by diarrhoea). Finally, there will undoubtedly be disorders in which infection with parasitic helminths has neither positive nor negative impacts, as we showed recently in the rat model of acetic-acid-induced gastric ulceration [27]. Finally, almost invariably, the animal studies have been acute in nature and, thus, provide no information on any long-term sequelae (either good [i.e. prolonged protection] or bad [e.g. the induction of fibrosis]) of the use of a parasitic helminth as a therapeutic.

Concluding remarks and future perspectives

Data from animal models (and to a lesser extent, human studies) show that infection with helminth parasites can block the induction of or reduce the severity of other diseases. To date, the majority of these studies have used prophylactic strategies (and few have assessed potential concomitant side-effects), and these need to be complemented by data from treatment protocols [28]. The beauty of this approach lies in the fact that as a therapy, the natural response of the host to infection is utilized. By adopting a

more tolerant view of the helminth parasite, the opportunity arises to reveal novel ways to manipulate the human immune system to treat autoimmune and idiopathic inflammatory diseases. The tools required (e.g. immunological assays and model systems) are available, and the tasks that lie ahead can be achieved. Specific helminth species that can be used safely to treat specific human diseases in appropriate individual patients might be identified and, if so, are likely (at least in the foreseeable future) to be used as an adjunct therapy with currently accepted treatments (although a combination of helminth therapy and broad-spectrum immunosuppression would be inadvisable). However, the prospect of xeno-infection notwithstanding, the psychological aspect of knowingly harbouring a live parasite might be insurmountable for some patients. Perhaps of greater medical applicability (and acceptability) will be the elucidation of the immunological mechanism by which infection with helminths ameliorates concomitant disease in animal models – for example, mobilization of regulatory immune cells and mediators or stimulation of anti-inflammatory (e.g. lipoxin) signals. Thus, the continued use of helminth–rodent models and an expansion to non-rodent systems is warranted to facilitate the development of novel therapies without the need for infection *per se*. Targeted immunological manipulation based on the findings from such studies, complemented by use of helminth-derived immunoregulatory molecules [29] (an area with huge untapped potential), should enable considerable advances in the medical management of human idiopathic, inflammatory and autoimmune conditions.

Independent of whether one takes an anthropomorphic stance, believing the helminth helps itself by reducing its hosts' susceptibility to other diseases, or accepts the view that the evolutionary by-product of effective anti-helminth immunity protects against concurrent diseases, a substantial body of evidence indicates that reassessment of host–parasite interactions in the context of a 'therapeutic helminth' will yield innovative approaches to treating human disease.

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