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Vaccine against autoimmune disease: can helminths or their products provide a therapy?

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There is an increasing interest in exploiting the immunomodulatory effects of helminths and their products in treatment of diseases such as allergy, autoimmunity and inflammatory bowel disease. Detailed examination of the ways in which helminth derived products interact with the host immune system and with host physiology has revealed that these may be multifaceted and have almost certainly arisen following co-evolution of helminths and their hosts. Clinical trials have been initiated with encouraging results in the treatment of inflammatory bowel disease and also Multiple Sclerosis. Identification of key pathways that are manipulated by helminths to ameliorate ongoing inflammatory conditions increases the prospect of developing novel therapies for the treatment and possible prevention of a range of debilitating and life threatening conditions.

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Introduction

There has been a dramatic rise in many inflammatory conditions in the developed world over the past 50 years. For instance, the autoimmune disease, Type 1 diabetes (T1D), has been increasing at a rate of 4% per annum in several European countries [1]. This increase is faster than could be accounted for by genetic change and is not due to improved diagnosis. As most autoimmune conditions are influenced not only by genetic background but also by environmental factors there is interest in identifying potential environmental factors that might influence onset of autoimmune pathology. While it is always conceivable that a novel disease initiating agent has emerged and is mediating the increased incidence of autoimmune pathology it is unlikely that one agent could be responsible for the incredible rise in the incidence of allergy,

inflammatory bowel disease and autoimmune conditions such as T1D and Systemic Lupus Erythematosus (SLE). An alternative view is that a major environmental change resulting from improved living conditions and vaccination strategies has been a lack of exposure of our immune systems to infections of historical importance. Our immune systems co-evolved with some of these infections and it is proposed that the lack of interplay between certain infectious agents and our immune system has contributed to the rise in autoimmunity. Brian Greenwood was probably one of the first researchers to highlight this, initially in his observation that parasitic infections in Nigeria might play a role in preventing autoimmune disease [2]. He subsequently demonstrated this experimentally when he showed that malaria infection prevented onset of autoimmunity in SLE prone mice [3]. Studies of Multiple Sclerosis (MS) incidence in Israel in 1966 linked development of this autoimmune pathology with improved sanitation. Some 20 years later in the 'Hygiene Hypothesis' Strachan proposed that decreased exposure to infectious agents may have contributed to the rise in allergic diseases [4]. There are now many experimental observations as well as some epidemiological studies, which provide support for the hypothesis that some infectious agents, particularly helminths, have the ability to influence the hosts' immune system such that there is improved regulation of inflammatory responses. This ability to downregulate inflammation would be in both the host's and the parasite's interest and is the result of millions of years of co-evolution.

The ability of helminths and some other infectious agents to downmodulate inflammatory responses has led to the exploration of the clinical efficacy of controlled infections on disease pathogenesis as well as a search for defined microorganism derived molecules with potential to act as biomodulators for therapeutic use in the treatment of inflammatory disease. Recent data contributing to our understanding of the potential beneficial effects of helminth infections or helminth derived products on autoimmunity will be described in subsequent sections.

Evidence that helminths can modulate inflammatory disease

Epidemiology

SLE prevalence is higher in individuals of African descent in the USA but is vanishingly rare in tropical Africa. In addition to the early studies of Greenwood linking malaria to a reduced incidence of rheumatological disorders, including SLE, in Nigeria such a link has been

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Table 1

Helminth infections preventing animal models of autoimmune diseases

Helminth infections	Disease models	Mechanisms of protection	References
<i>Schistosoma mansoni</i>	T1D, EAE GD, CIA	Induction of Th2 immune-response	[9,11–13]
<i>Trichinella spiralis</i>	T1D	Induction of Th2 immune-response	[15]
<i>Litomosoides sigmodontis</i>	T1D	Induction of Th2 and Treg immune-response	[14,26]
<i>Heligmosomoides polygyrus</i>	T1D, IBD	Induction of Th2 immune-response	[15,16]
<i>Fasciola hepatica</i>	EAE	Suppression of Th1 and Th17 by TGF- β	[17]

Abbreviations: T1D, type 1 diabetes; EAE, experimental autoimmune encephalomyelitis; GD, Graves' disease; CIA, collagen induced arthritis; IBD, inflammatory bowel disease.

proposed as an explanation for the current high incidence of Multiple Sclerosis (MS) and T1D in Sardinia [5]; the lack of malaria in recent times allowing the expression of these genetically predisposed autoimmune pathologies. Genetic selection for increased resistance to malaria for example through expression of a particular Fc γ RIIb polymorphism is associated with increased risk of SLE providing a molecular basis for the increased susceptibility to SLE in certain ethnic groups [6]. Other polymorphisms have been identified that suggest that improved responses to *Plasmodium falciparum* might have played a role in the increased incidence of MS in Sardinia [5,7]. The observation by Correale and Farez that MS patients with helminth infections had a diminished disease progression compared to non-infected MS patients also provided support for the hypothesis that some infectious agents had the ability to downmodulate inflammatory pathology [8].

Experimental observations linking infection with prevention of autoimmunity

Studies in animal models have provided strong evidence for the ability of helminths to modulate the host immune system inducing immune changes that can prevent different models of autoimmune diseases (Table 1). *Schistosoma mansoni* infection in NOD mice was the first study to demonstrate that immuno-modulation by a helminth could prevent autoimmune disease in a well-established spontaneous model of type 1 diabetes (T1D) [9,10]. Soon after more studies demonstrated that experimental *Schistosomiasis* was also able to ameliorate induced murine models of experimental autoimmune encephalomyelitis (EAE), Graves' hyperthyroidism (GH) and collagen induce arthritis (CIA) [11–13]. T1D in NOD mice was also shown to be prevented by other helminth infections: *Trichinella spiralis*, *Litomosoides polygyrus* and *Heligmosomoides polygyrus* [14,15]. The rationale behind these initial studies was that Th2 immunity induced by helminth infection had a good chance of preventing inflammatory autoimmune disease in animal models. However, it soon became obvious that the mechanisms of protection were more complex than skewing the autoreactive Th1/Th17 response to a Th2 response. For example mice lacking IL-10 regulatory mechanisms were shown to be protected from inflammatory bowel disease (IBD) by *H. polygyrus*

infections and disease resolution was not associated by increase in IL-4 or IL-5 but by IL-13, demonstrating the complexity of Th2 responses in helminth infections [16]. Moreover studies using *Fasciola hepatica* infection were shown to prevent EAE in a TGF β -dependent manner [17]. Helminth infections clearly impact many immune cell types including innate and regulatory cell population as well as epithelial cells and the study of their complex interactions and the molecules involved is fundamental for a better understanding of both infections and autoimmunity.

How might infection prevent autoimmunity?

Type 2 immunity to helminths is actively driven by multiple molecular interactions between parasite expressed/secreted products and host immune cells. Helminth products are a complex mix of glycoproteins, proteins, glycolipids, and polysaccharides able to modulate signalling through pathogen recognition receptors (PRR) on host innate cells, inducing major phenotypic and functional changes that drive the secretion of type 2 cytokines and the expansion of regulatory cell populations [18]. Studies in DCs and macrophages have revealed the importance of PRR in helminth manipulation of the host immune system. The binding and recognition of parasite products through toll-like receptors (TLR) and C-type lectin receptors (CLR) induce anti-inflammatory characteristics in innate cells changing their cytokine secretion pattern and surface molecule expression. Dendritic cells (DCs) exposed to helminth infection or antigens are frequently described as tolerogenic-DCs (tDCs), because of their poor capacity to secrete IL-12 and their increased ability to secrete IL-10 [19,20]. Besides inducing Th2 phenotype in T cells, DCs acquiring these characteristics are less likely to prime and sustain autoimmune-inflammatory responses. Type2 cytokines are fundamental in antagonising Th1/Th17 mediated-inflammation but they are not only secreted by Th2 cells; innate cells including NK/T and granulocytes, are also an important source of IL-4, IL-5, IL-13 during helminth infections. Recently, the discovery of innate lymphoid cells (ILCs) has added further complexity to the understanding of type 2 responses to helminths [21•]. Type 2 immunity to helminths also includes the expansion of T regulatory cell populations (Tregs). The

Table 2**Examples of helminth derived immuno-modulators**

Helminth	Unfractionated products	Mechanism of action	Disease model	References
<i>S. mansoni</i>	Eggs	Induction of Th2 cells	T1D, EAE, IBD	[9,39,40]
<i>S. mansoni</i>	SWA	Anti-inflammatory signature of innate immune cells, induction of Th2 and expansion of iNKT cells	T1D	[20]
<i>S. mansoni</i>	SCA	Anti-inflammatory signature of innate immune cells, induction of Th2 and Treg.	T1D	Manuscript in preparation
<i>S. mansoni</i>	SEA	Expansion of alternatively activated macrophages, tolerogenic DCs, Th2 cells and Treg	T1D	[20,27,41,42]
<i>L. sigmodontis</i>	LS Ag	Shift to Th2-type response and Treg increase	T1D	[14]

Abbreviations: T1D, type 1 diabetes; EAE, experimental autoimmune encephalomyelitis; CIA, collagen induced arthritis; IBD, inflammatory bowel disease; Treg, regulatory T cells; DCs, dendritic cells; iNKT cells, invariant NK T cells; SEA, soluble egg antigen; SWA, soluble worm antigen; SCA, soluble cercaria antigen; *L. sigmodontis* antigen, LS Ag.

Table 3**Examples of helminth derived immuno-modulators**

Helminth	Immune-modulatory products	Mechanism of action	Disease model	References
<i>S. mansoni</i>	LNFP III	Anti-inflammatory, drive Th2 responses, B cell IL-10 production.	T1D, EAE and Psoriasis	[43,44]
<i>A. viteae</i>	ES-62	Anti-inflammatory and Th2 responses	CIA	[45]
<i>D. immitis</i>	DiAg	Shift to Th2-type response	T1D	[46]
<i>S. mansoni</i>	IPSE	Eosinophils IL-4 inducing factor	Not tested	[47]
<i>S. mansoni</i>	Omega-1	Th2 and Treg inducing factor	Not tested	[48*,49–51]
<i>T. spiralis</i>	rTsP53	Skews to Th2 response and macrophage alternative activation	colitis	[52]
<i>A. viteae</i>	Avcystatin	Induces IL-10 in macrophages	colitis, asthma	[53,54*]
<i>F. hepatica</i>	FhCL1 and FhGST-si	Inhibition of Th17 responses	Not tested	[55,56]

Abbreviations: T1D, type 1 diabetes; EAE, experimental autoimmune encephalomyelitis; CIA, collagen induced arthritis; Treg, regulatory T cells; LNFP III, lacto-n-fucopentaose III.

term T regulatory cells comprises different T cell subsets capable of 'suppressive' function, these cells include not only CD4⁺ T cells expressing Foxp3 (Foxp3⁺ Tregs) but also CD4⁺ T cells not expressing Foxp3 (Tr1). Both types of Tregs are induced in helminth infections [22,23]. Tregs are critical for the prevention of autoimmunity and for maintenance of immune homeostasis, and the regulation of immune responses to foreign as well as self-antigens [24,25]. In helminth infections Tregs as well as other regulatory cell types (B cells, NKT cells) are induced and control Th1, Th17 and Th2 responses, preventing untimely parasite expulsion but also host tissue damage. Mechanisms of suppression can be soluble factor-mediated (e.g., IL-10 and TGF- β) or cell-contact-mediated via co-stimulatory molecules (e.g., or CTLA-4 and GITR). Helminth products have been shown to upregulate both TGF- β and IL-10 expression in Tregs and these mechanisms have been shown to be important in helminth-mediated prevention of autoimmunity in animal models [14,26,27]. As highlighted above underpinning the changes induced by helminths in the adaptive arms of the immune system are their effects on cells of the innate immune system, the effects on DCs and in

particular the generation of alternative activation in macrophages and expansion and recruitment of eosinophils. Importantly such effects impact not only on the immune system but also on host metabolism as shown by the observation that infection with *Nippostrongylus brasiliensis* causes recruitment of eosinophils into adipose tissue of mice fed a high fat diet and alters macrophages from an inflammatory phenotype to one of alternative activation with concomitant improvement in glucose homeostasis and insulin resistance [28**]. The finding that many of the effects on autoimmunity can be obtained with either crude extracts of parasite derived products, or purified products, has opened up the potential to use these biomodulators therapeutically. The mechanisms by which helminth extracts or defined helminth products have been found to modulate the immune response or inhibit autoimmunity are summarised in Tables 2 and 3, respectively.

Helminths in the clinic

Clinical trials have been carried out to establish the therapeutic potential of helminth-based approaches. These studies have employed either *Trichurus suis* (pig

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whipworm) or *Necator americanus* (human hookworm). Initial studies with *T. suis* focussed on establishing whether individuals suffering from inflammatory bowel disease (IBD) showed amelioration of symptoms following infection with *T. suis* ova [29]. The initial encouraging results on effects of helminth infection on IBD have been substantiated and have lead to trials being initiated to determine whether *T. suis* has any effect on MS [30,31[•]]. There was a suggestion in one of the studies of improved disability score mirroring the observations of Correale and Farez on the beneficial effects of helminth infection on this autoimmune condition [31[•]]. Additionally, as was also shown by Correale and colleagues improvement was not sustained following clearance of the parasite [31[•],32[•]].

Early studies of *N. americanus* focussed on establishing a well-tolerated infectious dose for clinical application. Trials to establish the effect of *N. americanus* infection on asthma and celiac disease have all been initiated [33,34]. While so far there has been little evidence of clinical improvement in the studies carried out in celiac disease volunteers, there was evidence of an altered immune response with diminished Th1 and Th17 responses [35]. Infection with *N. americanus* in healthy individuals is associated with increased production not only of IL-10 and TGF β but also IL-22 and reduced IL-23, which may contribute to a reduced Th17 response and tissue repair [36^{••}]. The lack of effect of this infection on the different clinical situations under study has been attributed to the use of a low dose of infection. It is unclear whether a dose escalation study will be carried out and it is possible that *T. suis* might also prove to be effective in the treatment of celiac disease.

Conclusions

While there are promising clinical outcomes of these interventions using helminths there are several hurdles that would need to be overcome [37^{••}]. Questions remain regarding optimal timing of infection in relation to disease onset with some infections providing optimal prevention of autoimmunity if given before onset of clinical symptoms. Clinical data obtained thus far suggest that it may be essential to have longer lasting infections to maintain clinical improvement. There are also several reasons why it might be better to use a defined product than have a whole infection. Importantly, it should be easier to optimise a dosing schedule and furthermore it would circumvent the concerns that some individuals might feel about acting as host to helminths. However, with regard to the use of defined parasite-derived or indeed any microbially derived immunomodulatory products in the clinic there are also challenges that would need to be overcome. A major concern is the immunogenicity of some of the immunomodulatory parasite derived products. For this reason much emphasis is being placed on identifying the pathways through which they

exert their immunomodulatory effects. By understanding the pathways involved in prevention of autoimmunity it might be possible to develop small molecules with the ability to mimic the effect of helminth vaccination without inducing an immune response. Such an approach is currently being pioneered with ES-62, a molecule with established potency against Th17 mediated autoimmune and allergic pathologies [38]. ES-62 does not prevent the onset of Th1 mediated diabetes in NOD mice (Thomas *et al.*, unpublished observations) highlighting the need to also understand the disease pathogenesis in selecting the immunomodulatory agent of choice.

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