

Chapter 17

Helminth Immunoregulation and Multiple Sclerosis Treatment

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Lay Summary Multiple sclerosis (MS) is a disease of the central nervous system (CNS) (brain, spinal cord and optic nerve), characterized by loss of myelin, an insulating cover of fat and proteins surrounding structures of the nervous system. As a consequence of this damage, conduction of nerve impulses is slower and patients present different symptoms, which can lead to irreversible disability. MS is the second cause of disability in young adults after traumatic brain injury. Although its origin remains unknown, there is scientific evidence to support the hypothesis that the individual's own immune system damages myelin, making MS a so-called autoimmune disease. During the last half of the twentieth century, the number of MS cases has increased significantly, probably due to different environmental factors, including decline of infections resulting from better public health practices. Epidemiological studies have demonstrated that patients infected with certain kinds of parasites, particularly those called helminths, present a more benign disease course. Parasites are often long-lived and inhabit hosts with an intact immune system; consequently, it is not surprising that they would acquire modulatory molecules enhancing their survival. Studies of autoimmune diseases in different animal models have corroborated these epidemiological findings. Mice infected with helminths show protection from disease or attenuation of symptoms. These observations have triggered interest in exploring the clinical efficacy of establishing controlled parasite infections in patients with allergic and autoimmune diseases. To date, clinical trials using this approach are based on small sample sizes and oriented to reproduce epidemiological data and confirm observations in animal models. Clearly,

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more prolonged and extensive studies including larger numbers of patients are needed to assess this novel therapeutic strategy. Alternatively, identification of parasite-derived molecules responsible for the modulation of the host immune system would allow the treatment of autoimmune diseases without the risk of potential side effects observed using live parasites. Although positive results have been reported administering parasite products in mouse models of autoimmunity, much remains to be explored before the field can move from experimental animal models to clinical practice.

17.1 Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS, affecting an estimated 2 million people worldwide and representing the second cause of nervous system disability in young adults after traumatic brain injury. The disease affects mainly young adults between 20 and 40 years of age and is approximately 2–3 times more frequent in females than in males. Its symptoms vary both over time and among patients, and their broad spectrum exerts considerable impact on health-related quality of life experienced by patients and their families compared to other chronic, debilitating diseases. MS course is highly variable, but most classically characterized by a relapsing–remitting (RR) pattern in which acute exacerbations are followed by periods of stability (remissions). However, in up to 50 % of patients, the pattern evolves to a secondary progressive course after 10–15 years of disease, characterized by relentless neurological deterioration over a period of several years, something that may occur from the onset (primary progressive course) in a minority of patients (~15 %; [1]).

Although the aetiology of MS remains elusive, several lines of evidence support the hypothesis that autoimmunity plays a major role in disease pathogenesis [2]. Autoimmune diseases are currently considered to result from complex interactions between individual genetic susceptibility and external environmental factors [3, 4]. Based on the findings of several genomewide association studies, the genetic component of MS is believed to result from common allelic variants in several genes acting as cooperative networks [5].

One of the most striking illustrations of the importance of the environment in MS pathogenesis is the particular geographical distribution of the disease. Prevalence rates are greater in high-latitude regions and uncommon near the equator [6]. Additionally, population migration studies indicate that individuals moving from areas of low, to areas of high risk, particularly before the age of 15, show similar incidence to host country populations, suggesting the presence of either a protective factor in the region of origin or, alternatively, a harmful factor in the

adopted region [7]. Space–time cluster analyses performed both in Norway and in Sardinia have shown clustering between 13 and 20, and 1 and 3 years of age, respectively [8, 9]. The hypothesis analysed in these studies suggests that the higher-than-expected disease prevalence in individuals living close to one another during the same time period may have resulted from exposure to putative environmental risk factor(s) prior to disease onset and considers the probable cause to be infection acquired either in adolescence or in early childhood by individuals not protected through previous infection, depending on population-specific susceptibility. Furthermore, serial cross-sectional comparisons of MS epidemiology from various continents provide compelling evidence in favour of a significant rise in MS incidence and prevalence in recent decades [10]. Given the short duration over which these population changes have occurred, genetic factors alone seem an unlikely cause, indicating that MS risk is likely influenced by the environment. Therefore, MS most likely results from the combination of both genetic and environmental factors. Identifying these environmental factors and elucidating how they increase autoimmune disease risk would help develop new MS treatment strategies. Candidates likely to be responsible for the development of MS, alone or in combination, include most notably sunlight–UV exposure/or vitamin D deficiency, and viral infections, and cigarette smoking. Factors may not only influence disease onset at any time in the life of an individual, but also affect relapse rates in patients presenting relapsing–remitting forms of MS (RRMS) [11–14].

17.2 Research Findings

17.2.1 *The Hygiene Hypothesis and the “Old Friends” Hypothesis*

An ongoing debate persists as to whether infections prevent or precipitate autoimmune diseases (see also Chap. 15). Several studies implicate infectious environmental factors present during childhood and young adulthood as strong determinants of MS risk. Microbial infections have also been identified as triggers inducing autoimmunity, resulting in clinical disease manifestations in genetically predisposed individuals. Alternatively, infections might accelerate subclinical autoimmune processes [15, 16].

Conversely, however, certain epidemiological and experimental studies support the hygiene hypothesis, which considers infections protect rather than induce or accelerate autoimmune diseases such as MS [17]. In line with this concept, Leibowitz and coworkers suggested, in 1966, that greater MS prevalence correlated with high levels of sanitation in childhood environments [18]. There is increasing evidence that lack of exposure to organisms that were part of mammalian evolutionary history is leading to disordered regulation of the immune system and hence to increases in several chronic inflammatory disorders [19]. Epidemiological data

have demonstrated an inverse relation between infections, and allergic and autoimmune diseases in the developed world during the last five decades, even after adjusting for improvements in access to medical attention and diagnostic capabilities [17]. The rise observed in autoimmune disease prevalence is too rapid to be considered secondary to genome alterations, implying some critical environmental change must have taken place. Progressive industrial development has pushed human migration from rural areas to cities, exposing the immune system to new environments, and the decreased incidence of many infectious diseases resulting from better public health practices has likely increased autoimmune disease emergence. Organisms changed or depleted from the modern environment and shown to be relevant to immunoregulation include the following: firstly microbiota, commensal organisms on the skin and in the gut; secondly environmental saprophytes like lactobacilli and many actinomycetes species; and finally helminths [19].

The component of the hygiene hypothesis implicated in faulty induction of immunoregulation is explained as the “old friends” hypothesis [19]. This hypothesis excludes childhood diseases as a requisite factor and focuses on organisms that have coevolved with mammals for a very long time, ones that were always present (lactobacilli, a variety of saprophytic mycobacteria and helminths), were tolerated by the immune system and were absent from the pathogen load in developed nations. Thus, induction of appropriate levels of immunoregulation by “old friends” becomes a physiological necessity, in which genes involved in this immunoregulatory setting are located in certain micro-organisms rather than in the mammalian genome. The theory postulates that reduced exposure to “old friends” would therefore not allow ending appropriately inflammatory episodes, leading to a range of chronic inflammatory disorders.

Allergies and autoimmune diseases have increased both their prevalence and incidence with decreasing helminthic infection. Individuals infected by helminths are less likely to suffer allergic sensitization or allergic disorders [19]. Likewise, epidemiological investigations demonstrating an inverse correlation between the global distribution of MS and that of the parasite *Trichuris trichiura*, a common human pathogen, further strengthen the hygiene hypothesis [20]. MS prevalence appears to fall steeply once a critical threshold of *T. trichiura* prevalence (about 10 %) is exceeded in any given population. Thus, the dichotomous distribution of MS and *T. trichiura* infection suggests that helminth infection protects against MS development. Indeed, regions of the world where poor sanitary conditions generate endemic areas of parasitoses show lower prevalence of allergic and autoimmune diseases. Additionally, evidence for a causal effect of parasites on reducing allergies and autoimmune diseases stems from reports that clearance of infection using antihelminthic treatment increases reactivity to skin tests against different allergens, as well as disease activity in MS patients [21, 22]. This protective effect of helminths might depend on parasite load. Elevated numbers of organisms may trigger regulatory circuits, while lower ones may act as immune adjuvants, enhancing allergic sensitization.

Animal models have confirmed the hypothesis that helminths can dampen allergic manifestations and autoimmune disease by driving immune regulation. Many examples exist in both spontaneous and induced models of human autoimmune diseases, where helminth infection or products thereof influence the course of autoimmune pathology [23–26]. One particular animal model, experimental autoimmune encephalomyelitis (EAE), which mimics essential clinical and pathological characteristics of MS, has been used in several studies investigating the impact of helminth infections, or their products, on disease severity and immunological response. In most EAE models, prior infection with helminths, or exposure to non-viable ova, or to parasite-secreted products reduced both incidence and severity of the disease. These observations would indicate the presence of a systemic anti-inflammatory milieu generated by multiple cell types and molecular mediators, influencing autoimmune response [23, 27]. Heterogeneity of immunological response can be attributed to specific helminth species, helminth-derived products, age at which infection was acquired and infection intensity. Helminths are often considered a homogeneous species, but significant differences exist between organisms. Conversely, there is evidence from mouse models to suggest that helminth infections, under certain conditions, can also exacerbate disease [28]. For these reasons, caution is recommended when interpreting data from animal models.

17.2.2 Induction of Immunoregulatory Circuits by Helminths

The immune system is made up of different cell types able to recognize and eliminate pathogens. Type-1 immune responses protect against intracellular pathogens, type-2 responses are directed mainly against parasites, and type-17 cells are important in the control of extracellular bacteria and fungi. However, these different cell populations can also inflict damage to tissues when acting in uncontrolled manner. T helper (Th)-1 and Th-17 cells release proinflammatory cytokines necessary to attack pathogens. However, inappropriate activation is associated with several autoimmune diseases. Likewise, Th-2 cells drive different antiparasite mechanisms, but when overactivated can lead to allergic disorders. Th cells are under the control of regulatory networks, represented mainly by T cells, which produce different inhibitory molecules.

In endemic areas, many if not most helminth-infected individuals are relatively asymptomatic. Manifest disease occurs often in individuals with reduced immunity, more susceptible to infection or presenting very high worm burden. Maintaining a disease-tolerant or asymptomatic state requires adequate balance between regulatory immune mechanisms present both in the host and in the helminth. Chronic helminth infections cause continuous and profound effects on the immune system function [29, 30]. Finely tuned immune regulatory networks governing susceptibility and

resistance to helminths exist, which are both redundant and parallel, in order to exclude parasites while minimizing collateral pathology. Current investigations have shown that peripheral T cells from infected patients are unresponsive to stimulation with parasite antigens, and response to other antigens is also reduced, with the regulatory T cells being one of the most common mechanisms in play [31].

The “old friends” hypothesis suggests helminths are recognized by dendritic cells (DCs), and these in turn mature into regulatory DCs and drive regulatory T cell responses against parasite antigens, leading to the release of regulatory cytokines exerting bystander suppression. Furthermore, regulatory DCs increasingly process self-antigens, further elevating regulatory T cell numbers, specifically triggered by these antigens and downregulating autoimmune response [19].

Induction of alternatively activated macrophages has also been identified as key component of immune regulatory networks functioning during helminth infections [29]. In this case, helminths and their excretory–secretory molecules are endowed with the ability to act through a broad array of cellular mediators to temper host immune responses.

Evidence of these protective mechanisms has been demonstrated in patients suffering from MS [32]. In an observational prospective double-cohort study, we demonstrated that RRMS patients infected with different parasites (*Hymenolepis nana*, *T. trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis* and *Enterobius vermicularis*) showed significantly lower number of exacerbations, minimal changes on disability scores as well as significantly lower radiological activity, compared to uninfected MS individuals. Parasite-driven protection leads to the development of interleukin (IL)-10 and transforming growth factor (TGF)- β secreting cells, as well as CD4+CD25+FoxP3+ regulatory T cells, while simultaneously inhibiting T cell proliferation and suppressing interferon (IFN)- γ and IL-12 production [32]. In addition, helminth infection in MS patients induces regulatory B cells capable of dampening the immune response through IL-10 production [33]. Interestingly, when some patients received antihelminthic drug treatment for worsening of parasite-associated symptoms, a major reduction in parasite egg numbers per gram of faeces was observed, as well as significant increase in clinical and radiological MS activity. Flares were accompanied by substantial increase in IFN- γ - and IL-12-producing cell numbers and a decline in IL-10, TGF- β and regulatory T cells, providing evidence of direct autoimmune response suppression as a result of helminth infection [22]. These observations indicate that helminth therapy can induce protection not only through prevention, since helminths can be present before an autoimmune disease develops, but also after the disease is established. Figure 17.1 illustrates the major mechanisms involved in the control of the autoimmune response and allergic processes during helminth infections. Moreover, it is important to note that immunosuppressive effects mediated by parasite infections end once the parasite has been eliminated, suggesting that immune regulation is a transient process requiring constant induction.

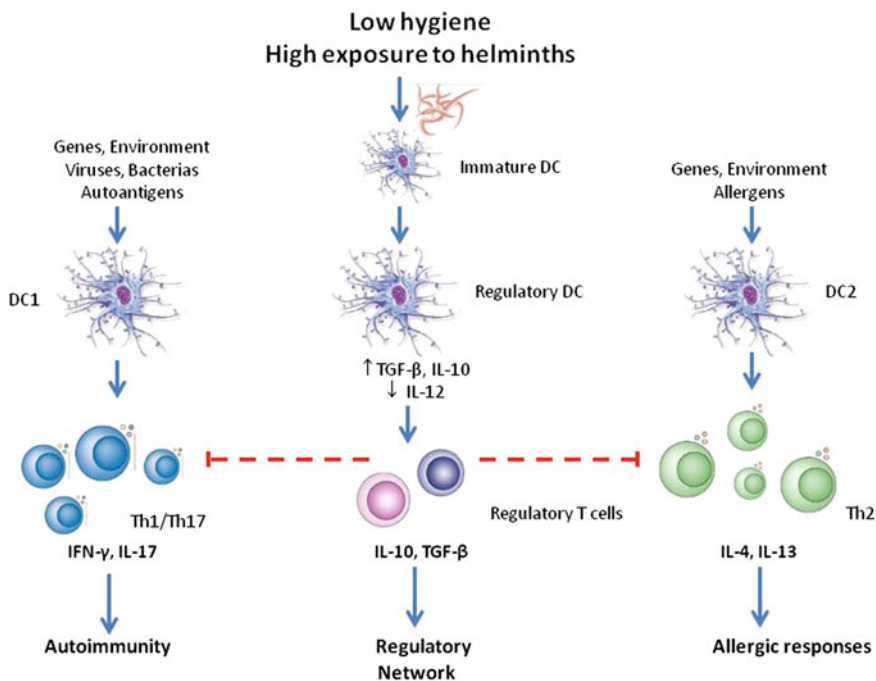


Fig. 17.1 The immune system is educated under different stimuli received by pathogens or the environment. Dendritic cells (DC) can differentiate into different populations according to the type of stimulus they receive and the magnitude of it. Dendritic cells can be stimulated by autoantigens, viruses, bacteria or helminths, inducing the development of Th-1, Th-17, Th-2 or regulatory T cells. Uncontrolled Th-1 or Th-17 activity leads to the development of autoimmunity, whereas an abnormal Th-2 response determines allergic responses. A high parasitic load changes the physiology of the microenvironment, endowing the dendritic cells with the ability to induce regulatory T cells producing IL-10 and TGF- β , generating an anti-inflammatory environment able to inhibit inflammatory responses that affects the development of autoimmunity or allergic reactions. The *dotted lines* represent inhibitory processes

17.3 Implications for Policy and Practice

On the basis of the findings here described, helminth therapy has been used in clinical trials associated with allergic and autoimmune diseases including inflammatory bowel diseases (IBD) and MS [34–36], and several more clinical trials are currently underway in other diseases. It must be pointed out that not all helminth infections can be deemed therapeutically equal, and some might worsen the disease [28, 37]. Therefore, parasite species selection is crucial. In this respect, most current studies use either *Trichura suis* (*T. suis*, pig whipworm) or *Necator americanus* (human hookworm). Using parasites that do not permanently colonize humans (*T. suis*) or organisms that can be administered at low infection intensity and eliminated with antihelminthic drugs (*N. americanus*) decreases the potential for

accidental disease transmission to healthy subjects. In this line, *T. suis* ova (TSO) has recently been approved as an investigational medicinal product (IMP) by both the US Food and Drug Administration and the European Medicines Agency, while *N. americanus* has been granted IMP licence by the Medicines and Healthcare Regulatory Authority in the UK.

Nevertheless, possible caveats should be considered when assessing these trials. Data from animal models demonstrating favourable influence on EAE outcome have preferentially been observed during preimmunization and inductive phases [23, 38], suggesting it may be more difficult to suppress ongoing reactions than prevent their development. Moreover, many trials use asymptomatic infection doses, which are significantly lower than those of natural infections and therefore possibly insufficient to suppress pathology [39].

Initially, encouraging results on the effects of helminth infections in IBD [35, 36] led to trials to establish whether *T. suis* had any effect on MS. The first clinical trial of helminth therapy in MS was the helminth-induced immunomodulation therapy (HINT) study [40]. In this small scale, safety-oriented trial, five newly diagnosed RRMS patients received TSO, administered orally every 2 weeks for 3 months. Mean number of gadolinium (Gd)-enhancing MRI lesions fell from 6.6 at baseline, to 2.0 at the end of treatment and rose again to a mean of 5.8 lesions 2 months after TSO treatment was discontinued. Treatment was associated with relative increases in IL-4 and IL-10 levels in serum, as well as elevation of C-reactive protein and antibodies to *T. suis* excretory/secretory products (IgG1 and IgA), indicating robust systemic immune response to *T. suis* colonization. Peripheral CD4+CD5+FoxP3+ cells increased modestly in 2 of the five study subjects, and TSO was well tolerated. Minor gastrointestinal symptoms observed in 3 of 5 subjects were transient. Although MRI study results seem promising, they should be interpreted with caution due to the small sample size and the short follow-up duration. After reviewing HINT study results, regulatory authorities approved a follow-up clinical trial (HINT 2) with 18 relapsing–remitting MS patients, studied for 20 months using a baseline versus treatment design. Final results of this trial are expected to be published in 2015.

In another study (Trichuris suis ova therapy for relapsing multiple sclerosis—a safety study, TRIMS A) conducted at the Danish Multiple Sclerosis Center of Copenhagen University Hospital, 10 RRMS patients were treated with TSO every 2 weeks for 3 months [41]. The primary outcome measure was MRI activity based on the number of new or enlarging T2 lesions, the number of Gd-enhancing lesions and the volume of T2 lesions. Brain MRI testing was performed every 3 weeks. The investigators concluded that TSO seemed to be safe and well tolerated. However, no clinical, MRI or immunological signals indicating benefit were observed.

Investigators at Charite University in Berlin conducted the first exploratory study in secondary progressive MS patients [42]. Four patients were surveyed during 6 months of therapy with TSO, given orally every 2 weeks. The study focused on T cell modulation as well as on innate immune response. Stimulated peripheral blood mononuclear cells showed slight downregulation of Th-1-associated cytokine patterns, with temporal increase of Th-2-associated cytokines such as IL-4.

A double-blind placebo-controlled phase II trial (*Trichuris suis* ova in recurring–remitting multiple sclerosis and clinically isolated syndrome, TRIOMS) has been initiated by the same investigators [43]. The study will recruit 50 patients with RRMS or clinically isolated syndrome with clinical activity, not undergoing any standard therapy. Patients will receive either TSO every 2 weeks or placebo for a 12-month treatment period and will be followed for an additional 6 months.

Another phase II double-blind placebo-controlled study (worms for immune regulation of multiple sclerosis, WIRMS; NCT01470521) has begun at the University of Nottingham. The study will enrol 72 RRMS and secondary progressive MS patients with superimposed relapse, who will be treated with dermally administered live larvae of *N. americanus* or placebo. Worms will be allowed to remain within host for a full 9 months. Investigators speculate that this period of residence will establish and maintain immunoregulatory mechanisms of sufficient magnitude to translate into the anti-inflammatory effect and consequently generate therapeutic benefit. The cumulative number of new and active lesions on T2-weighted MRI will be the primary outcome measure. Regulatory network induction (regulatory T cell induction, regulatory B cells, Tr1 cells and natural killer cells) will be the secondary outcome measure.

Clearly, at this time, a number of critical issues need to be addressed in further investigations. Questions remain regarding which helminth is most effective, and at what dose, which is the best route of administration or optimal timing for introducing infection in relation to disease onset, whether helminth-derived molecules have the same efficacy as live parasites and what the optimal treatment schedule should be.

Although effects of helminth therapy on vaccine efficacy have not been evaluated, several studies have shown that helminths can influence vaccine efficacy by modulating host immune response, in particular when Th-1-like and cell-dependent responses are required. *S. mansoni* infection was shown to reduce BCG-induced protective response against *Mycobacterium tuberculosis* in mice [44]. Likewise, helminth infections dramatically reduced malaria DNA vaccine immunogenicity [45]. Moreover, epidemiological studies have demonstrated that *Schistosoma* sp. infections decrease the efficacy of vaccines against tetanus and hepatitis B virus [46, 47]. Overall, effects of helminth therapy on vaccine efficacy need to be further investigated.

TSO safety profiles have been extensively studied in IBD patients, even while on concomitant immunosuppressive drugs, without observing any significant side effects. In the HINT 1 study, some patients presented transient diarrhoea and upper abdominal pain 30–50 days after TSO treatment initiation (lasting 3–5 days), symptoms possibly related to an innate inflammatory immune response in the gut induced after initial *T. suis* larvae colonization [40]. These had not been observed in earlier TSO studies in IBD patients, perhaps because they were occurring in the context of moderate gastrointestinal pathology in the study population [48]. Nor did these symptoms interfere with patient daily life activities. An additional concern in helminth therapy is whether helminth colonization may worsen other pathogenic infections (bacterial, parasitic or viral) especially in immunocompromised hosts.

Enhancement of disease and pathology by coinfection of *T. suis* and *Campylobacter jejuni* or *T. Trichiura* has been described. However, this has never been observed in TSO-treated patients [49, 50].

Another helminth studied in clinical trials thus far is the hookworm *N. americanus*. In previous studies of helminth therapy, the most common hookworm-related side effect was localized maculopapular rash at skin entry site, which began within a day or so of infection and typically lasted 2–5 days. In some patients, rash recurred approximately 2–3 weeks after infection for up to 10 days before disappearing. The most troublesome adverse effects were gastrointestinal symptoms, such as diarrhoea and abdominal pain. The other most commonly reported symptoms were malaise and fatigue, which occurred between week six to seven of treatment and have been associated with systemic eosinophilia, rather than with a direct parasite effect. Dose-ranging studies of therapeutic *N. americanus* infection have shown side effects to be dose dependent. Doses higher than 10 larvae correlated with more frequent and severe adverse events than low-dose inocula. All symptoms disappeared completely after subjects were treated with the anti-helminthic drug, mebendazole [48, 51]. It is strongly recommended at this time that live helminths or parasite ova should not be administered outside strictly monitored controlled clinical trials.

17.4 Future Directions

Helminth infections are often long-lived and inhabit immunocompetent hosts; it is therefore not surprising that these organisms may have acquired modulatory molecules attenuating host responses and enhancing their own survival. Understanding host–parasite interactions and identifying different parasite molecules possessing immunomodulatory effects will help combat allergic and autoimmune diseases, without the costly price of infectious side effect. During recent decades, a number of helminth-derived immunomodulatory molecules have been characterized, in terms of both structure and bioactivity [52, 53]. Although this approach might overcome some of the safety concerns regarding the use of live helminths as therapeutic agents, controversies still exist as to whether live infection is a prerequisite for suppression of inflammatory responses in different disease models of autoimmunity.

ES-62, a glycoprotein from the rodent nematode *Acanthonema vitae*, has been widely investigated as an immunomodulatory molecule. Its administration in mice with collagen-induced arthritis resulted in significant reduction in disease severity and slowing down of progression [54]. Likewise, when rDiAg, a product from the filarial parasite *Dirofilaria immitis*, was administered to non-obese diabetic (NOD) mice, it prevented insulinitis and diabetes onset [55]. Furthermore, treatment with soluble products from *T. suis*, *S. mansoni* and *Trichinella spiralis* caused strong reduction in the severity of EAE in mice, significant suppression of pro-inflammatory phenotype in human DCs, as well as subsequent generation of

human Th-1 and Th-17 effector cells [56]. Finally, lacto-N-fucopentaose III (LNFP III), a Lewis X-containing glycan found in *S. mansoni* eggs, suppressed EAE through enhancement of IL-10 and Th-2 cytokines [57]. These few examples of helminth-derived immunomodulatory products illustrate the potential of these molecules to serve as drugs, or templates for drug design. Nevertheless, it would be dangerous to ignore the fact that this regulatory environment could hamper essential and necessary responses to other antigens, vaccinations and life-threatening pathogens. As chronic helminth infections establish and accumulate, suppression may become more generalized and render the host susceptible to secondary infections. At this stage, both beneficial and deleterious consequences of helminth infection need to be clearly identified. Individual species may develop very different infection dynamics over time and/or during peak infection intensity. Moreover, the same species may trigger opposite effects under varying conditions. Finally, if susceptibility to autoimmune diseases is genetically influenced, so too must be the propensity for infections to modulate disease immunopathology, making particular infections protective only in certain genotypes, rather than in the population at large. It is evident that future studies in this area will be required to establish whether certain infections, particularly those produced by helminths during critical periods of infancy, truly exert a protective effect against MS. Clearly, much remains to be explored to move the field from observations in animal models to clinical practice; issues relating to *in vivo* stability and helminth-derived molecule pharmacodynamics, delivery methods, as well as immunogenicity need to be overcome, if new therapeutic modalities are to be developed.

Overall, these observations raise a paradox, namely that deworming populations with helminth-associated morbidity could cause emergence of chronic inflammatory conditions and autoimmune diseases [58]. Therefore, well-designed trials in the context of large-scale deworming programs are warranted, to assess benefits of the intervention, weighed against potential adverse effects such as increased chronic inflammatory disease risk.

Glossary

Actinomycetes	Group of terrestrial or aquatic bacteria
Allergy	Hypersensitivity disorder of the immune system. Symptoms include red eyes, itchiness, runny nose, eczema or asthma attacks
Antibodies	Protein produced by the immune system to recognize or neutralize foreign molecules or micro-organisms
Antigen	Any substance inducing a response of the immune system

Autoimmune disease	Diseases arising as a result of an abnormal immune response by the body, directed against substances and tissues normally present in the body of the host
Clinically isolated syndrome	First episode of a demyelinating disease. It is the step prior to MS development
Commensal organisms	Organisms that obtain benefits from other organisms without producing any damage
Cytokines	Broad and loose category of small proteins that are important in cell signalling. They are released by several cells but particularly by cells of the immune system and affect the behaviour of other cells, or even of the releasing cell itself
Deworming	To give an antihelminthic drug to a person or animal to rid it of intestinal parasites
Demyelinating disease	Disease produced by the loss of myelin
Dendritic cell	Cells that recognize, process and present antigens to T cells, inducing their activation
Experimental autoimmune encephalomyelitis (EAE)	Animal model that mimics essential clinical and pathological characteristics of MS. It can be induced in different species such as rabbit, guinea pigs, rats, mice or monkeys
Gadolinium	Contrast medium used in magnetic resonance imaging studies to highlight abnormalities or disease process. In the brain, a gadolinium-positive lesion means the presence of inflammation
Gut microbiota	Also known as gut flora is a complex group of micro-organism species inhabiting the digestive tract of animals and humans and the largest reservoir of commensal micro-organisms
Helminths	Wormlike organisms living in and feeding on living hosts
Incidence	Measure of the risk of developing some new condition within a given time period
Interferon- γ	A type of cytokine that has most often a pro-inflammatory effect

Interleukins	A group of cytokines produced by white blood cells
Macrophage	Type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes and cancer cells in a process called phagocytosis
Magnetic resonance imaging (MRI)	Also known as nuclear magnetic resonance imaging (NMRI) is a medical imaging technique used in radiology to investigate the anatomy and physiology of the body. MRI scanners use strong magnetic fields and radio waves to form images of the body without exposure to ionizing radiation
Multiple sclerosis	Inflammatory disease in which the insulating covers of nerve cells in the brain, spinal cord and optic nerve are damaged. This damage disrupts the ability of parts of the nervous system to communicate, resulting in a wide range of signs and symptoms
Mycobacteria	Widespread bacteria, typically living in water and food sources. Some, however, including tuberculosis and the leprosy bacteria, appear to be obligate parasites and are not found as free-living members of the genus
Natural killer cell	Type of cytotoxic lymphocytes that induce the death of tumour cells or virally infected cells
Prevalence	Proportion of a population found to have a condition, typically a disease or a risk factor
Saprophytes	Organisms obtaining nutrients from dead organic matter
T helper cell (Th)	Type of T cell that helps the activity of other immune cells by releasing T cell cytokines. These cells help, suppress or regulate immune responses
Transforming growth factor- β	Is a cytokine that controls proliferation, cellular differentiation and other functions in most cells

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