Immunoregulation of CNS autoimmunity by helminth and mycobacterial infections

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Abstract

The 'hygiene hypothesis' has been proposed to explain apparent increases in autoimmune disease and allergy in areas of the world with improved health care and sanitation. This hypothesis proposes that the lack of serious childhood infections impairs development of an appropriately educated immune response. Imbalance of Th1 and Th2 responses and lack of regulatory T-cell populations are two of many proposed potential mechanisms for immune failures such as autoimmunity and allergy. We summarize the literature evidence for the influence of infectious organisms on autoimmunity with focus on helminth and mycobacterial infections. We also demonstrate that Schistosoma mansoni ova pretreatment, Mycobacterium bovis (BCG) infection, and lyophilized Mycobacterium tuberculosis all modify the course of clinical disease in mice induced for experimental autoimmune encephalomyelitis (a mouse model for human multiple sclerosis (MS)). Our data supports the applicability of the hygiene hypothesis to CNS autoimmune disease. © 2002 Published by Elsevier Science B.V.

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1. Introduction

In the natural environment, the human immune repertoire is constantly shaped by environmental exposures to infectious agents, resulting in the generation of memory T-cells capable of responding rapidly to antigenic re-stimulation and establishing a pre-existing immune status. Memory T-cell responses are also continually modulated by ongoing autoimmune triggers and infectious exposures. This paper will review the evidence for the influence of infection by pathogenic microorganisms on autoimmune disease. We will specifically highlight interactions between helminth and mycobacterial infections and the CNS autoimmune diseases, multiple sclerosis, and its mouse model, experimental autoimmune encephalomyelitis (EAE). It is clear that autoimmunity and infectious diseases do not occur in isolation. The outcome of noninfectious diseases is influenced both by the pre-existing immune status of the individual and by exposures to infectious pathogens from the natural environment [1,2].

2. EAE as a model of CNS autoimmunity

EAE is one of best-studied autoimmunity models, characterized by an autoimmune attack on CNS myelin mediated by neural autoantigen specific T helper cells [3]. It is currently the best available model for human multiple sclerosis [4]. In the induction of EAE, autoreactive T-cells are activated in the periphery of mice by antigen presenting cells (APC) that have been activated by exposure to mycobacterium in CFA favors matura-
tion of these Th1 cells. The mechanisms that lead to autoimmunity are still controversial, however in MS and its animal models, the role of autoimmune, functionally polarized Th1 cells has been strongly suggested.

3. Th1 and Th2 subsets of CD4+ helper T-cells

At least two distinctly polarized subsets of antigen-experienced T-cells have been identified. Th1 cells secrete primarily IL-2, IFNγ, and TNF-β and express chemokine receptor CCR5 as well as IL18 receptor. Th2 cells produce IL-4, -5, -6, -10 and IL-13 cytokines and express the G-protein linked receptors CCR3 and CCR4. Th1 cells influence the outcome of exposure to infectious pathogens and regulate autoimmune diseases, whereas Th2 cells are the key effectors in response to allergies and helminthic infections (Fig. 2) [5]. Th1 and Th2 clones also differ in their requirements for antigen presentation. Different antigen presenting cells, depending on their differentiation stage, activation status and the cytokine microenvironment, can preferentially stimulate T-cells to secrete Th1 or Th2 patterns of cytokines. The existence of functionally polarized human T-cell responses based on their profile of cytokine secretion has been established for both CD4+ T helper (Th) and CD8+ T cytotoxic cell subsets (Tc) [6].

The contributing role of different factors inducing T-helper cell differentiation into the polarized Th1 or Th2 pathway has been controversial, however, it has been demonstrated that infectious pathogens play an important role in this process. It is clear that there is a differential cytokine profile evoked by different infectious agents, influenced by the nature and concentration of the peptide ligand, the activity of co-stimulatory molecules, the local microenvironment of secreted hormones, and the context of different host genetic backgrounds. Moreover, polarized Th1-type and Th2-type responses also play different roles in protection, with Th1 effective in the defense against intracellular pathogens and Th2 against intestinal nematodes. These different pathways are responsible for different types of immunopathologic reactions [6,17].

Infectious diseases have well-established effects on Th1/Th2 cytokine profiles. Mycobacterial infections are typically inducers of Th1 cytokines, IFNγ, and lymphotoxin (TNFβ) [7]. Conversely, chronic parasitic infections such as schistosomiasis, and ascariasis induce...
strongly Th2 polarized cytokine environments with predominant IL-4 and IL-5 [8–10]. The cytokine microenvironment also determines the maturation path of activated T-cells with IL-12 and IFNγ favoring Th1, and IL-4 and IL-10 favoring Th2 outcomes [11–16].

Although a highly cross-regulated control of polarized Th1 and Th2 cell types is a well-established paradigm, the exact mechanism of this cross talk is complex and remains under investigation. Cytokines produced by Th1 cells have negative regulatory effects on Th2 cells and vice versa. IFNγ negatively impacts proliferation of Th2 cells [18] and IL-10 inhibits IFNγ and other cytokine secretion by Th1 cells [19,20]. Most of the work describing cross-regulation of T helper subsets has been done in vitro using T-cell clones cultured in the presence of various cytokines and the result is observed. These models do not necessarily illuminate cross-regulatory events that take place in vivo [21]. There is plentiful evidence of cross-regulation in vivo however.

Identification of a dichotomy in T-helper cells (Th1/Th2) helped explain observations of mutually exclusive DTH and antibody responses [22–24].

4. Infections, establishing a preexisting immune status in individuals, can modify the response to subsequent immune stimuli

The argument that development of the immune system is strongly influenced by continuous environmental infectious stimulation and is capable of modifying subsequent immune responses has been supported by many observations. For example, patients infected with Schistosoma mansoni mount a Th2-type response to tetanus toxoid immunization instead of the more common Th1 or Th0 type response [9,25]. Furthermore, Ethiopian immigrants with a high prevalence of helminthic infections have eosinophilia and a propensity to respond to PHA with Th2-type, rather than Th1-type cytokines [26]. Infection of mice with S. mansoni delays clearance of vaccinia virus, an infection best controlled by a strong Th1 response. Mice develop a Th2 type response when infected with the microfilaria, Brugia malayi, or when immunized with soluble filarial extract from this parasite. The ongoing Th2 response to this helminth antigen modulates the Th1 response to non-parasite or microbial antigen [27,28]. Moreover, the murine intestinal nematode, Nippostrongylus brasiliensis stimulates Th2 activity. Rats infected with Nippostrongylus showed delays in kidney graft rejection (a DTH response), most likely by the cross-regulatory suppression of Th1 activity [29]. BCG vaccination cannot induce effective Th1 protection against tuberculosis in worm-infested areas. The efficacy of vaccination appears to be restored by treatment of helminthic infections [30].

We argue that these modified immune responses are not exclusively attributed to a modified Th1/Th2 response, but other factors are likely important in the establishment of a pre-existing immune status.
5. Infectious diseases frequently demonstrate a shift in T helper subset predominance in the natural course of the infection

Measles infection initially induces a Th1 dominated response. Following clearance of the virus, the response shifts to a Th2 dominated response. The generalized immunosuppression following infection may result from viral infection of T and B-lymphocytes, PMNs and circulating monocytes and is responsible for the deaths from secondary infections that follow measles infection in developing countries. The role of B-cells as primary APC’s may be responsible for the shift to a Th2 profile. It has also been theorized that Th2 cells are present from the beginning of the response and they are more long-lived than Th1 cells [31]. Similar shifts from Th1 to Th2 responses have been observed in HIV infection [32] where the shift has been associated with onset of AIDS; in Plasmodium chabaudi chabaudi malaria (the mouse model for human falciparum malaria) where the life cycle of the parasite shifts from extracellular to intra-cellular; and in S. mansoni infection where the shift seems to correlate with the onset of egg laying by mature female worms [8].

Shifts from Th2 to Th1 have been observed less commonly, either occurring naturally or induced for therapeutic reasons. In a Leishmania model, Nabors et al. have been able to induce a therapeutic Th2 to Th1 shift in mice by administration of both Pentostam (a leismanicidal drug) and IL-12. The mechanism is unclear, since normally, Th2 cells become unresponsive to IL-12 early in their differentiation [33].

6. Cross-reactive priming of autoimmune T-cells plays an important role in the induction of autoimmune disease

In spite of the generally accepted importance of autoimmune Th1 cells in the induction of autoimmunity, the exact mechanisms that lead to autoimmunity are still not clear. Infectious pathogens may play an important role in the initiation of autoimmune diseases. Activated, autoreactive T-cells can induce autoimmune disease whereas resting autoreactive T-cells cannot [34]. This has been demonstrated using several animal models of autoimmune disease; adoptive EAE, collagen induced arthritis (CIA) and herpes simplex keratitis (HSK).

Pathogens have been implicated in the activation of normally innocuous, low affinity self-reactive T-cells [35,36]. The potential mechanisms for induction of autoimmunity by infectious agents are reviewed in more detail by Wucherpfennig[37]. Mechanisms by which infections may induce autoimmunity include molecular mimicry, superantigen activation of T-cells expressing targeted β chain alleles (Vβ), enhanced antigen processing by activated APC’s, bystander activation, and activation of lymphocytes by lymphotropic viruses [37]. While infections are generally accepted as factors in induction of autoimmune disease, the focus of this review is on the lack of early exposure to helminth and mycobacterial infections as a risk factor in autoimmune disease.

7. Lack of early exposure to helminth and/or mycobacterial pathogens may be a risk factor for autoimmune disease

Autoimmunity and allergy are both on the rise worldwide, representing major concerns for the healthcare system [38]. In the case of the increase in allergy, arguments have been made that the increase is related to a decrease in childhood infections as a result of improved sanitation and control of many previously endemic pathogens. The hygiene hypothesis suggests that there has been a population shift from T-helper 1 (Th1) to Th2 responses as a result of the cleaner environment [39–42]. One might have predicted a simple shift in the balance from Th1 to Th2 should have been accompanied by a concurrent decrease in autoimmune diseases that are predominately mediated by Th1 cells, i.e. MS, type 1 diabetes mellitus, inflammatory bowel disease (IBD) and others.

In fact, there has been a parallel increase in allergy and autoimmunity, both increasing predominantly in developed countries and in urban areas [38]. This pattern of concurrent increase of Th1 mediated and Th2 mediated diseases, both characterized perhaps by disorder immunoregulation, has led us and others to hypothesize that reduced exposure to both Th1-inducing and Th2-inducing pathogens in childhood can increase susceptibility to both allergy and autoimmunity [43]. In support of the hygiene hypothesis’ applicability to autoimmune disease, there has been a recent report of an inverse relationship between risk of type 1 diabetes mellitus in children and daycare attendance and/or high numbers of contacts in early childhood [44]. Another report from Lithuania suggests that the occurrence of infection in the first 6 months of life correlates with lower incidence of type 1 diabetes and infection incidence at later times shows no correlation with diabetes incidence. The role of infections in the etiology of type 1 diabetes as well as other autoimmune diseases is controversial. Certain enteroviral infections might trigger the beta-cell destruction but insufficient exposure to early infections might increase the risk [45].

Here, we review data that support the link between a relative lack of infectious exposure and increased incidence of CNS and other autoimmune disease, and conversely, the protective effects of infectious agents in autoimmune diseases.
8. Mycobacteria prevent or ameliorate autoimmunity

Andersen et al. reported that a lack of exposure to both mycobacteria (as indicated by a negative tuberculin skin test) and measles (based on parental report at school enrollment) before age seven correlated with higher incidence of multiple sclerosis in adult life. This data was based on a retrospective case matched study including 92 MS patients and 276 age and sex matched controls selected from a reference population (births 1930–1950) of 198,000 school health records from Copenhagen, Denmark reported in 1981 [46]. We have addressed the role of mycobacterial infection in influencing autoimmunity in the CNS by infecting C57BL6 mice with Mycobacterium bovis strain BCG. Our data indicate that while MOG$_{35-55}$ peptide induces EAE in C57BL6 mice with 100% efficiency, BCG infected animals demonstrated a significant protection from this CNS autoimmune disease. When we infect these mice for 6 weeks with M. bovis strain BCG, they are protected from EAE as demonstrated by lower incidence, lower mean clinical scores and later onset (manuscript in preparation). We have also seen a therapeutic effect of intraperitoneally injected, lyophilized M. tuberculosis that is most dramatic when the bacteria are given at 2 days post induction of EAE. There was a significant improvement in clinical EAE when M. tuberculosis was given 4, 7 and 10 days post EAE induction. Thus, this treatment has some efficacy up to the time of onset of symptoms (Fig. 3).

The protective effect of mycobacterial components was reported in a guinea pig model of EAE as early as 25 years ago [47]. It has also been suggested that purified protein derivative (PPD) is the major component of M. tuberculosis implicated in protection from EAE. Recently, a 12-kDa PPD protein was demonstrated to be important in the protective activity of PPD [48,49]. Sequence studies indicated that this 12-kDa protein might belong to the bacterial heat shock protein family. Thus, similarly to hsp65-induced protection in arthritis or diabetes, the mechanism of protection might be based on shared T-cell epitopes with target self-antigen. Furthermore, Lehmann et al. reported that Bordetella pertussis is effective in inducing protection against EAE in SJL and SJLxBalbC F1 mice. According to their study, the mechanisms of the protective effects of Bordetella pertussis and mycobacterium in EAE are not the same. Adoptive transfer experiments indicated that the protection by M. tuberculosis is mediated by T-cells whereas similar transfers of B. pertussis sensitized T-cells are not protective [50]. Interestingly, both of these organisms have been routinely used for their adjuvant effects in the induction of EAE [48,49]. Brenner et al. demonstrated that protection from EAE by B. pertussis toxin immunization is mediated by antibodies. In a fostering experiment, they showed that protection is transferred to newborn rats during lactation. This protection could also be passively transferred by intraperitoneal injection of immune serum to naive adult rats [51].

Mycobacterial exposure has shown protective effects in other, non-CNS autoimmune diseases. Non-obese diabetic mice develop insulin dependent diabetes mellitus with high incidence when not exposed to mycobacteria. M. avium infection induces resistance to diabetes in these mice. The authors report that the resistance induced by mycobacteria seems to be mediated by a Th1 subset consistent with a regulatory (CD45RB low, CD38$^+$) population that triggers anergy or deletion of self-reactive peripheral lymphocytes [52,53]. Adjuvant arthritis (AA) also seems to be prevented or ameliorated by early exposure to mycobacteria. Lewis rats, intraperitoneally infected shortly after birth with BCG develop less severe AA than their uninfected littermates when AA is induced by a standard protocol [54]. We have summarized the evidence for bacterial infection induced protection from autoimmune disease from the literature and from our research in Table 1.
9. Evidence of early helminth exposure in modulation of CNS and other autoimmune diseases

In contrast to bacterial infections, helminth or parasitic infections are known to induce Th2-type immunity [8,55]. The correlation between these types of infections and lower incidence of autoimmune diseases has been suggested previously. For example, MS occurs very rarely in areas with endemic schistosome infections, as opposed to the higher incidence of MS and other autoimmune diseases in areas with more stringent hygienic standards [56,57]. This difference suggests an inverse correlation between higher hygienic standards and the development of Th1 type autoimmune diseases. To address the nature of Th1 and Th2 cross-regulation in a natural immune environment, we asked whether ‘natural Th2 pre-conditioning’ of experimental animals would influence the development of Th1 modulated autoimmune in a CNS autoimmune disease such as EAE.

We induced a Th2 environment in SJL mice by intraperitoneal and subcutaneous S. mansoni ova immunization (manuscript submitted). We observed a significant protection from EAE in S. mansoni ova pre-immunized animals, indicating that parasitic infections can influence the course of a CNS autoimmune disease, and suggesting the importance of an experienced immune system in autoimmunity. As some intestinal helminthic infections induce minimal pathology, infection or treatment with helminth components might offer a new therapeutic option to prevent and/or ameliorate MS.

Individuals with predominant Th2 responses against egg antigens have less severe egg-associated morbidity than those with predominantly Th1 responses, thus a Th2 predisposition in dealing with helminth eggs is selectively advantageous to the human host. From an evolutionary perspective, people living in endemic areas with high prevalence of helminth infections might be positively selected because of their adaptively advantageous Th2 responses. More importantly, many helminth parasites can survive in the host for many years [58]. The long-term exposure to helminth antigens, beginning early in childhood, may have a deep impact on maturation of the host’s immune system. Similar protection from development of insulin dependent diabetes mellitus by infection with S. mansoni or by injections of schistosome eggs has been reported in susceptible non-obese diabetic mice [59].

The inverse relationship between risk of type 1 diabetes mellitus in children and daycare attendance could be due to differences in helminth infestation. Daycare centers and institutions support the transmission of many infections. The report correlating first half year of life infections with lowered incidence of IDDM also supports the application of the hygiene hypothesis to autoimmunity [45]. Neither of these reports is specific concerning what types of infections were encountered at higher incidence in the respective protected populations. We would speculate, however, that increased contact with other young children early in life would increase exposure of a full spectrum of infectious diseases.

Elliott et al. have suggested that lack of exposure to helminth infections in childhood may be a factor in the increasing incidence of Crohn’s disease [60]. Crohn’s disease is an autoimmune disease with detectable organ-specific antibodies against the intestinal goblet cells and acinar cells of the exocrine pancreatic tissue [61]. The autoimmune inflammation causes cramping, diarrhea, and bloating. This autoimmune disease can also be manifested in autoimmune attacks on other target organs such as the eye. According to Mayer et al., an evolution of understanding of the etiology of inflammatory bowel diseases (IBD), ulcerative colitis and Crohn’s disease has occurred in the past 30 years. In the 60s and 70s, IBD was considered to be an autoimmune disease in which there was a directed attack by humoral and cellular elements of the immune system against intestinal tissues. Since that time, there has been growing appreciation that defects in cellular immunity, not auto-reactive in nature, may play a larger role in disease pathogenesis [62].

Another organ specific autoimmune disease, collagen-induced arthritis (CIA), a mouse model for rheumatoid arthritis, is down regulated by infection with Trypanosoma brucei in DA rats. This protective effect was most significant when the rats were infected with live trypanosomes before induction of CIA [63]. Daniel-Ribeiro and Zanini reported that natural and ‘patho-
genic’ autoantibodies are protective against malaria and conversely, infection with malaria may offer protection from autoimmune disease [64,65]. In the same vein, polyclonal immunoglobulins from malaria infected BALB/c mice have shown a therapeutic effect on a lupus-like syndrome in a lupus prone strain (NZBxNZW F1 mice) [66].

Table 2 summarizes evidence for protective effects of parasitic infection in both CNS autoimmunity and several other autoimmune diseases.

In summary, the results of these studies provide evidence in support of the idea that infection with helminths can modulate the development of Th1 diseases by influencing the cytokine environment of immune competent cells. A large block of evidence suggests that long-term infections with helminths in childhood might have deep impact on the maturation of Th1 and Th2 cells. Exposure to helminths and other parasites, such as malaria and trypanosomes, could be an important factor in influencing the development of Th1 cell-mediated autoimmune diseases in adulthood.

10. Mechanisms of immunoregulation by helminth and mycobacterial infections

In the next paragraphs, we summarize several of the mechanisms that have been proposed in the literature illustrating our current understanding with regard to the immunoregulation by helminth and mycobacterial infections. It is probable that multiple mechanisms contribute to different extents to produce the final result. It is also likely that other mechanisms, not understood at this time, might play a role.

The most commonly accepted mechanism for the immunoregulatory effects of infectious agents on CNS autoimmunity is cross talk between Th1 and Th2 subsets [67]. The cross talk described in the Falcone and Bloom study entails a preconditioned Th2 response to KLH antigen resulting in a Th2 microenvironment influencing the maturation of autoreactive T-cells and resultant protection from EAE. This mechanism has been called immune deviation and several investigators have achieved improved results in autoimmune disease models using immune deviation strategies [68,69] (Fig. 4A).

Recent data suggests the importance of other regulatory or suppressor mechanisms on both innate and adaptive elements of the peripheral and CNS immune systems (Fig. 4B). Th2 cytokines, particularly IL-10, have been demonstrated to inhibit macrophage activation with resulting suppression of IL-12 production and Th1 differentiation. TGFβ acts directly on Th1 cells inhibiting their growth and proliferation [70]. Regulatory or suppressor T-cells can play an active role in suppressing other T-cells. When suppressor T-cells exist, transfer of these cells can transfer tolerance. Th1 suppressor T-cells have been described. These cells express CD4 and CD25 (IL-2Rα). Their suppression requires cell-cell contact and antigen specificity. It is independent of soluble factors as demonstrated by the inability of supernatants from these cells to mediate suppression [71]. Cell surface expression of TGFβ on CD4+ CD25+ regulatory T-cells has been described recently [72]. The finding of surface-bound TGFβ provides clarification for seemingly contradictory reports concerning the role or lack of role for soluble factors including TGFβ in suppression.

Possibly, infectious foci play a role in protection from autoimmune disease by sequestration or modification of trafficking of auto-reactive T-cells. We have observed that activated T-cells traffic to granulomas regardless of their antigenic specificity (manuscript in preparation). The autoreactive T-cells needed to trigger CNS disease may potentially be prevented from reaching threshold levels in the CNS by re-directed trafficking to other pre-existing inflammatory sites by strong chemokine gradients and/or shared addressins (Fig. 4C).

Although control of autoimmunity via immune modulation offers a very desirable therapy, we also have to consider the side effects of such a therapy. Genain et al. demonstrated that immune deviation can increase concentrations of pathogenic autoantibodies and in some circumstances exacerbate autoimmune disease in a marmoset EAE model. Marmosets were tolerized by intraperitoneal administration of soluble rMOG and demonstrated early protection from EAE followed by late lethal complications. High levels of MOG specific autoantibodies were demonstrated in the tolerized marmosets. Autoantibody generation (Fig. 4D) was attributed to Th2 cytokine effects on B-cells, induction of the shift from low affinity IgM antibodies to high

Table 2
Parasites with protective effects in autoimmune disease

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<th>Organism</th>
<th>Autoimmune disease</th>
<th>Species</th>
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<tr>
<td>S. mansoni ova</td>
<td>EAE</td>
<td>SIL mice</td>
<td>Qing et al., submitted</td>
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<tr>
<td>T. brucei brucei</td>
<td>CIA</td>
<td>DA rats</td>
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<td>Malaria</td>
<td>Lupus syndrome</td>
<td>NZBxNZW mice</td>
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<td>T. trichuria</td>
<td>IBD</td>
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<tr>
<td>S. mansoni live infection or ova</td>
<td>IDDM</td>
<td>NOD mice</td>
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affinity IgG1 [73]. Since both Th1 T-cells and myelin specific autoantibodies have been implicated in pathology of human MS, both T and B-cells need to be considered in any potential therapeutic regimen.

One common feature of microorganisms recognized by the immune system is the expression of pathogen associated molecular patterns (PAMPs) that are recognized by toll-like receptors (TLRs). These receptors are expressed on cells of the innate immune system [74,75]. The engagement of PAMPs with Toll-like receptors can also trigger the induction of IL-12 [76] and the induction of Th1 T-cell responses [77]. The role of PAMPs and TLRs in the regulation of innate immunity in the CNS can also influence adaptive immunity in the brain. These pathogens can also directly interact with APCs and modulate T-cell functions in this way. APC function can be altered not only by toll-like receptors, but also by other regulatory agents like cytokines. CD4+ T-cells can modify the capacity of APC’s to induce autoimmune cells.

In summary, there are clearly multiple mechanisms providing immunoregulation by helminth and mycobacterial infections. To further understand these processes and how they interact will be crucial for our understanding of the complexity of immunoregulation.

11. Concluding remarks

Immunoregulation of CNS autoimmunity by mycobacterial pathogens has been reported previously [48–50]. Furthermore, it has also been suggested that mycobacterial infections play a beneficial role in allergic reactions [78]. In this paper, we argue the possibility of a more general paradigm of infectious pathogens as regulators of autoimmune reactions in the CNS. We summarize available data from the literature that suggests that not just mycobacteria, but also helminth pathogens are able to modulate CNS autoimmunity. Helminthic pathogens have also been demonstrated to...
play a role in atopic diseases such as allergy [78]. Confounding these observations, it is now indicated that Th1-type autoimmunity can also be influenced by parasites.

Further understanding of the regulatory mechanisms engaged by various classes of infectious pathogens on the immune system will aid our understanding of the extremely complex and enigmatic role they play in induction and prevention of CNS autoimmune diseases. The ultimate goal of this understanding would be to harness the immune regulatory effects of pathogenic organisms or their active components in control of CNS autoimmune diseases such as MS, without inducing the pathology that accompanies chronic infection with these organisms.

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