

Involvement of both 'allergic' and 'autoimmune' mechanisms in EAE, MS and other autoimmune diseases

Rosetta Pedotti¹, Jason J. De Voss², Lawrence Steinman² and Stephen J. Galli³

¹Immunology and Muscular Pathology Unit, National Neurological Institute 'C. Besta', Milan, 20133, Italy

²Department of Neurology, Stanford University Medical Center, Stanford, CA 94305, USA

³Department of Pathology, Stanford University Medical Center, Stanford, CA 94305, USA

Allergic and autoimmune diseases have been considered to be at the opposite sides of the spectrum of the immune response. Autoimmune diseases, such as multiple sclerosis (MS), rheumatoid arthritis and type 1 insulin-dependent diabetes mellitus, are considered T helper 1 (Th1)-mediated diseases, and allergic disorders, such as asthma, food allergy or rhinitis, are considered to be Th2-mediated. In this Opinion, we present evidence for the hypothesis that, elements of the immune response classically associated with allergy, importantly contribute to the pathogenesis of autoimmune demyelinating diseases of the central nervous system (CNS), in both the human disease, MS, and its animal model, experimental autoimmune (formerly 'allergic') encephalomyelitis. Autoimmune demyelinating diseases of the CNS, and other autoimmune diseases, can reflect the interplay of both Th1- and Th2-associated mechanisms.

The development and expression of autoimmune disorders can involve an intricate interplay of both cellular and humoral immune responses. Moreover, the naturally occurring human autoimmune disorders could exhibit a heterogeneity in their pathogenesis that reflects a complex interaction of potentially diverse genetically determined and environmental factors that might be difficult to ascertain, let alone to mimic, in mouse or other animal models.

The Th1/Th2 paradigm originally proposed by Mossman and Coffman [1–3] has been enormously helpful to researchers interested in the pathogenesis and treatment of autoimmune diseases, which are debilitating disorders that still cannot be cured and in some cases cannot even be effectively treated. However, the widespread acceptance of the Th1/Th2 paradigm has had the unfortunate unintended consequence of appearing to confine the study of 'Th2-associated responses' to the field of allergists and/or (for asthma) pulmonologists, leaving the 'Th1-associated disorders' to rheumatologists, endocrinologists and neurologists. As recent findings suggest, it is becoming increasingly difficult to draw a sharp line between the effector mechanisms that contribute to allergy and

autoimmunity, or between Th1- and Th2-associated disorders. Indeed, epidemiological findings indicate that Th1- and Th2-associated disorders, both steadily increasing over the past three decades, are not mutually exclusive. Contrary to some initial reports, there is a trend toward an association, in individual patients, between allergies and certain autoimmune disorders, such as diabetes mellitus and rheumatoid arthritis [4–6]. These findings raise the possibility that common mechanisms can contribute to the increases in both autoimmune and allergic diseases [6].

In this Opinion, we will draw on evidence derived from studies of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), to illustrate that effector mechanisms characteristically thought to be those of 'allergic' disorders can be elicited in experimental models of autoimmunity. We will also show that these mechanisms might contribute to the pathology associated with these responses or might confound attempts to use immunological approaches in the treatment of such diseases.

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MS is a chronic inflammatory disease of the central nervous system (CNS), characterized by discrete areas of inflammation and demyelination that can occur in multiple anatomical locations in the CNS and that can wax and wane in severity over time [7]. CD4⁺ T helper cells reactive to myelin, which produce proinflammatory cytokines, such as interferon- γ (IFN- γ), osteopontin (OPN) and tumour necrosis factor- α (TNF- α), are known to have a leading role [8]. In the complex Th1/Th2 paradigm, MS and EAE do not neatly fit into either category, yet they are generally perceived as Th1-mediated diseases [8–10]. Moreover, several experiments support a role for Th1 responses in promoting, and Th2 responses in suppressing, MS and EAE [11]. Nevertheless, adoptive transfer of myelin-reactive Th2 cells to immune-deficient mice can induce EAE [12], and eosinophils, regarded as Th2-associated cells, might contribute to disease development [13]. More recent observations suggest that EAE can result in the elicitation, in the same subjects, of both Th1- and Th2-associated mechanisms [14–17]. In the following

three sections, we will summarize the observations that support our hypothesis that both Th1- and Th2-associated mechanisms can contribute to EAE, MS and other autoimmune diseases.

Anaphylaxis to self-peptides

The observation that anaphylaxis can develop to 'self-peptides' that are also potential targets of autoimmune attack represents perhaps the most dramatic evidence of the clinically significant occurrence of both allergic and autoimmune effector mechanisms in the same subjects. When SJL female mice are immunized with the self-peptide myelin proteolipid protein (PLP) 139–151 in complete Freund's adjuvant (CFA, which contains *Mycobacterium tuberculosis*), T cells specific for PLP139–151, which are naturally circulating in the periphery, undergo activation and clonal expansion and produce proinflammatory Th1 cytokines, such as IFN- γ , interleukin-2 (IL-2) and TNF- α [18]. Ten days after the immunization, a relapsing-remitting form of EAE develops [14]. Surprisingly, when mice with PLP139–151-induced EAE were re-exposed to soluble preparations of PLP139–151 during the recovery-relapsing phase (this was done initially in an attempt to modulate the immune response for therapeutic purposes), the majority of the mice developed anaphylactic shock [14].

Anaphylaxis is the most severe manifestation of allergic reactions [19]. In humans IgE is the antibody isotype most clearly associated with anaphylaxis, however, both IgE and IgG1 can elicit these allergic reactions in mice (Box 1). The anaphylaxis to PLP 139–151 that can be observed in this EAE model might reflect primarily the action of IgG1 antibodies [14]. Notably, in this EAE model [14], anaphylaxis to PLP 139–151 was associated with the development of both antigen-specific IgG1 (associated with Th2 responses), and IgG2a (associated with Th1 responses) [20].

Anaphylaxis could also be induced by re-exposure to soluble preparations of a self-myelin antigen in a chronic-progressive model of EAE, induced in C57BL/6 female mice by immunization with myelin oligodendrocyte glycoprotein (MOG) 35–55 [14,15]. High titers of antigen-specific IgG1 [15,21,22], antigen-specific IgE [22] and of total IgE [15] were detectable in mice immunized in this way six weeks after the induction of EAE, at the time when, in our experiments, we demonstrated that anaphy-

laxis could be elicited [14,15]. Genetic deletion of Fc γ RIII did not eliminate anaphylaxis [15], suggesting a contribution of IgE to anaphylaxis in this model.

The development of anaphylaxis to self-peptide preparations is not restricted to models of EAE, in that this phenomenon has recently been shown to occur in another model of Th1-mediated disease: insulin-dependent (i.e. 'type 1') diabetes mellitus (IDDM) in non-obese diabetic (NOD) mice [16,17]. NOD mice, which spontaneously develop IDDM, can develop fatal anaphylactic reactions on re-exposure to preparations of immunodominant GAD65 (glutamic acid decarboxylase 65) self-peptides [17] (key target antigens in the development of IDDM in humans as well as NOD mice [23]) or to insulin peptides [16], after immunization with these peptides. Both studies implicated a contribution of IgG1 to anaphylaxis in these models but Liu *et al.* [16] showed that, in the insulin-peptide model, that full expression of the response might require the participation of both IgG1 and IgE antibodies.

The mechanisms underlying the development of anaphylaxis to self-peptides remain to be further clarified. It is likely that this response could require the administration of specific self-peptide sequences that are unlikely to occur naturally *in vivo*, and/or the administration of such self-peptides in quantities, and by anatomical routes, that do not occur except as part of an experimental manipulation. Nevertheless, the findings reported indicate that the administration of self-peptides might lead not only to organ-specific or systemic autoimmunity but also to allergy. These observations clearly indicate that great caution should be exercised in the use of self-peptide preparations to modulate immune responses in clinical trials involving subjects with autoimmunity. They also raise the question of whether 'allergy' (as opposed to 'autoimmunity') to self-molecules could occur under more natural conditions.

Mast cells in autoimmune CNS pathology

Mast cells are crucially important effector cells in many forms of anaphylaxis and other immediate hypersensitivity responses [19]. The broad array of mediators, cytokines and chemokines produced by mast cells suggest that these cells might importantly modulate the immune response, as well as directly express effector function [24–27].

The possibility that mast cells might contribute to the pathogenesis of MS has long been a matter of speculation

Box 1. Mechanisms of anaphylaxis

Although anaphylaxis, or clinically similar 'anaphylactoid' reactions, can be elicited by several different mechanisms, the most commonly occurring anaphylactic reactions induced by antigen in humans are thought to be mediated largely (if not solely) by IgE antibodies [19]. The underlying mechanism is the antigen-dependent crosslinking of IgE bound to the high affinity receptor for IgE, Fc ϵ RI, on the plasma membrane of mast cells and basophils, resulting in the aggregation of the receptors and the massive and rapid release of a variety of potent, biologically active mediators by these cells (reviewed in Ref. [27]).

By contrast, in mice, antibody- and antigen-dependent mast-cell activation can be elicited both by IgE and by IgG1 antibodies (reviewed in Refs [19,69]). In normal mice, only mast cells and basophils express

the receptor for IgE (Fc ϵ RI) but additional mouse effector cells, including monocytes and macrophages, can express Fc γ RIII, and thereby bind IgG1 (reviewed in Refs. [19,27,69]). Accordingly, anaphylaxis in the mouse can be elicited by IgE and/or IgG1-dependent mechanisms, through the activation of mast cells and basophils, and, in the case of IgG1-dependent responses, through other effector cells as well [57,69]. Together with histamine, which is one of the main mediators of human and murine anaphylaxis, in mice, platelet-activating factor (PAF) also represents an important mediator of anaphylaxis. Indeed, depending on the conditions of immunization and antigen re-exposure, the role of the IgG1–Fc γ RIII–macrophage–PAF pathway can be more important than that of the IgE–Fc ϵ RI–mast cell–histamine axis [57].

(reviewed in Ref. [26]). The recent work of Secor *et al.* [28] and Robbie-Ryan *et al.* [22], which has demonstrated a mast-cell-dependent contribution to the pathology associated with certain models of EAE in mice [22,28], has helped to reactivate interest in this topic.

In MS, mast cells can be found within and around the plaques, generally clustered around venules and capillaries (reviewed in Ref. [29]). As has been noted by many others [30,31], this anatomical location places mast cells at important interfaces between the general circulation and the brain parenchyma, both in the normal CNS and in the vicinity of the lesions of MS. More recent work has, if anything, increased interest in the possibility that mast cells can contribute to the pathogenesis of MS. For example, gene microarray analysis revealed an elevation in mRNA for components of the FcεRI in chronic MS plaques [32]. This finding was in accord with earlier immunopathological studies showing that, in brains of MS patients, mast cells are activated and express FcεRI, and that their numbers are lower in acute lesions than in chronic active plaques [33].

In EAE, numerous studies have reported a correlation between the number, distribution and/or activation state of brain mast cells and the development and severity of the disease (reviewed in Ref. [34]). A definitive role for mast cells in a model of EAE has been shown by Secor *et al.* by using *c-kit* mutant (*Kit^W/Kit^{W-v}*) mast cell-deficient mice. They showed that in the absence of mast cells, in *Kit^W/Kit^{W-v}* mice, EAE developed later and had a significantly more benign course than in the congenic wild type (*Kit^{+/+}*) mice [28]. Reconstitution of *Kit^W/Kit^{W-v}* mice with mast cells derived from wild-type mice [28] but not from mice genetically lacking either FcγRIII (FcγRIII^{-/-}) or both FcγRIII and FcεRI (FcR γ chain^{-/-}) mice [22], restored the typical EAE susceptibility. It remains to be determined how mast cells influence pathology in this model because the method of mast-cell reconstitution used in these experiments does not result in the appearance of many mast cells in the CNS [26]. Nevertheless, these experiments indicated that the abnormality in the expression of EAE in the *Kit^W/Kit^{W-v}* mice reflected their mast-cell deficiency, not some other consequence(s) of their *c-kit* mutations. Other groups had shown that EAE was also ameliorated in FcγRIII^{-/-} and FcR γ chain^{-/-} mice [15,32,35].

Taken together, these findings suggest that the triggering of FcγRIII and FcεRI by specific antibodies, with the activation of mast cells and probably other effector cells (especially through IgG1), represents one important effector mechanism in these models of EAE. Notably, however, features of EAE, albeit in attenuated form, developed in these models even in the virtual absence of mast cells or in the complete absence of signaling through FcγRIII and FcεRI [15,22,28,32,35]. Thus, these data by no means indicate that the development of pathology in EAE absolutely requires these effector mechanisms. Nevertheless, it seems reasonable to propose that the binding of specific myelin antigens to IgG1, and probably also IgE antibodies, and IgG1- and IgE-dependent mast-cell activation with subsequent mediator release, can contribute to the pathogenesis of EAE, perhaps especially in the

progression phase. However, other mechanisms can also activate mast cells during EAE (reviewed in Ref. [34]). The importance of mast cells in the pathology of MS, and the mechanisms by which mast cells contribute to the pathogenesis of EAE (and MS), remain important topics for further work.

It should be noted that mast cell-reconstituted *Kit^W/Kit^{W-v}* mice have also been used to identify a role for mast cells (and presumably antibody-dependent mast-cell activation) in animal models for other autoimmune diseases, such as bullous pemphigoid [36] and rheumatoid arthritis [37]. In such settings, mast-cell activation is likely to reflect some combination of antibody- (e.g. IgG1 antibody-) and complement-dependent mechanisms.

Taken together, these studies support the idea that antigen- and antibody-dependent mast-cell activation and mediator release (and perhaps mast-cell activation by additional mechanisms) can contribute to the expression of several features of these disorders. The extent to which mast cells might contribute to the pathology (and/or to immunoregulation) in other models of autoimmunity, and in the corresponding human diseases, clearly merits further investigation.

'Allergy mediators' and autoimmune CNS injury

It has been known for over 20 years that the pharmacological inhibition of mast cell-associated mediators can ameliorate EAE [14,15,38–40]. Such mediators include those like histamine, which can be produced by mast cells and basophils, as well as from other sources, including CNS neuronal sources [41,42], and those like the mast cell-associated tryptases, which are produced mainly by mast cells [43,44].

Several potential roles have been proposed for histamine (and serotonin, which can be produced and stored by mouse but not human mast cells) in the development of EAE. Most of this evidence has been derived from pharmacological studies and by reference to the known effects of these mediators on such physiological processes as blood-vessel permeability. Thus, histamine [45,46], together with serotonin [47] and cytokines, such as TNF-α [48,49], can enhance the permeability of the blood–brain barrier and/or upregulate the expression of vascular endothelial cell-associated molecules that promote trafficking of leukocytes through post-capillary venules and into the brain parenchyma [30].

Linthicum and colleagues and Black *et al.* showed that treatment with *Bordetella pertussis* toxin (PTX) increases the sensitivity of the CNS vasculature to histamine, a phenomenon called vasoactive amine sensitization (VAAS), and PTX is needed as an 'adjuvant' to induce EAE in those strains of mice that are not ordinarily very sensitive to histamine [38,50,51]. Linthicum also showed that histamine and serotonin inhibitors can block the effect of PTX and prevent EAE [38]. Nevertheless, treatment with cyproheptadine, an inhibitor of both histamine and serotonin, reduced the pathology associated with EAE in a model induced without PTX [14], suggesting an important role for histamine and/or serotonin even in the absence of PTX.

Bordetella pertussis histamine sensitization (*Bphs*) is the

gene that controls PTX-induced VAAS, and susceptibility to EAE and other autoimmune disease is linked to a 'susceptible' allele for this gene [52–54]. Interestingly, Ma and colleagues reported recently that Bphs is histamine receptor 1 (H1R) [55]. As few as three polymorphisms in the H1R allele distinguish mouse strains susceptible to autoimmune diseases from resistant strains. Although it might at first appear surprising that polymorphisms of a gene encoding for the receptor of a molecule classically associated with allergies and Th2 responses can confer susceptibility or resistance to autoimmune diseases, it should be kept in mind that histamine can also modulate T-helper and B-cell responses. Indeed, depending on the type of histamine receptor engaged, histamine can enhance Th1 responses (through H1R) or reduce both Th1 and Th2 responses (through H2R) [56]. This suggests that histamine, through H1R, could participate in the polarization towards Th1 that occurs during EAE and MS.

Interestingly, by gene microarray analysis, we found relative overexpression of the H1R gene in the chronic

plaques of MS patients [32]. In EAE, H1R and H2R are expressed on mononuclear cells within the inflammatory foci in the brain, although encephalitogenic Th1 cell lines activated against PLP 139–151 expressed more H1R and less H2R compared to Th2 cell lines [15]. Furthermore, EAE is reduced both in H1R deficient mice, in which a suppression of IFN- γ and an upregulation of IL-4 is observed during the course of the disease [55], and in mice treated daily with pyrilamine, a highly specific H1R antagonist [15].

Platelet activating factor (PAF) also represents an important mediator of anaphylaxis in mice [57] (Box 1). PAF can increase vascular permeability in the brain [58–60]. Moreover, PAF has been implicated in MS. The PAF receptor gene is overexpressed in chronic MS lesions [32] and PAF is elevated in the cerebrospinal fluid (CSF) and plasma of patients with the relapsing-remitting form of MS [61]. In a relapsing-remitting model of EAE, the PAF receptor is differentially expressed in the brain and spinal cord during the different phases of the disease and daily treatment with a PAF antagonist ameliorated EAE [15]. In

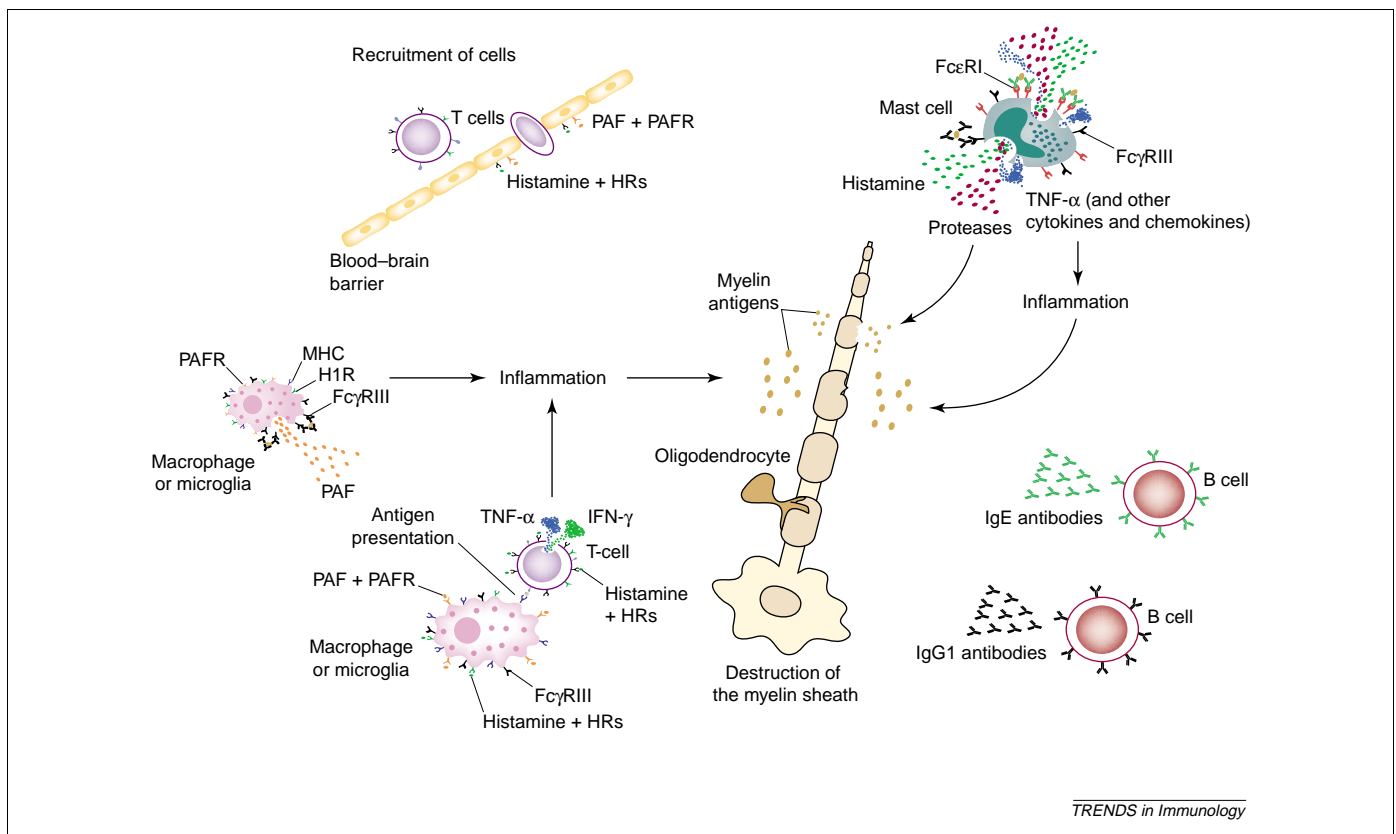


Fig. 1. Immune processes classically associated with Th2 responses that might contribute to the pathology of EAE. T lymphocytes gain access to the CNS by diapedesis through the blood–brain barrier; such T-cell recruitment is a complex multi-step process that can be influenced by several mediators, cytokines and chemokines, including those derived from macrophages, microglia, mast cells and T cells themselves [7,8]. Once within the CNS, T cells, on appropriate activation (e.g. with specific antigen presented in the context of MHC class II) can release inflammatory cytokines, such as TNF- α and IFN- γ . B cells, mast cells, recruited macrophages and resident microglia might also contribute to pathology. Mast cells can be activated by immune complexes involving IgG1 (through Fc γ RIII) or by IgE and antigen (through Fc ϵ RI); mast cells also can be activated by other mechanisms; activated mast cells then can secrete a broad array of mediators, including histamine, TNF- α (and many other cytokines and chemokines) and serine proteases [24–26,69]. Histamine can contribute to the opening of the blood–brain barrier by binding to HRs expressed on endothelial cells [15,45,46] and can also enhance Th1 responses, by binding to H1R expressed on activated Th1 cells [15,56,70]. Immune complexes involving IgG1 antibodies, acting through Fc γ RIII located on macrophages or microglial cells (as well as on mast cells) [57,69], can also cause the release of PAF, that can in turn increase blood–brain barrier permeability [58,59], as well as augment inflammation by many other mechanisms. In addition to promoting myelin sheath destruction through the direct effects of certain secreted mediators, T cells, macrophages, microglia and mast cells can also contribute to the development of a local inflammatory response, in which additional recruited cells and mediators might also contribute to destruction of the myelin sheath. This figure represents an oversimplification of the pathogenesis of EAE because several additional potential effector mechanisms have been implicated in the development and progression of EAE. Abbreviations: CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; HRs, histamine receptors; H1R, histamine receptor 1; IFN- γ , interferon- γ ; PAF, platelet activating factor; PAFR, platelet activating factor receptor; TCR, T-cell receptor; TNF- α , tumour necrosis factor- α .

the case of PAF, cells other than mast cells, such as monocytes and macrophages, could represent the more important sources in EAE and MS.

Mast-cell tryptase represents yet another mast cell-associated mediator that has been implicated in EAE and MS. In humans, tryptase can be expressed in basophils, as well as in mast cells [62], although mast cells appear to represent the quantitatively more important source [63]. Tryptase can enhance vascular permeability [64] and, *in vitro*, can enhance P-selectin expression through endothelial protease-activated receptor 2 [65]. At least one *in vivo* substrate of the mouse mast cell-associated tryptase, mouse mast-cell protease-7 (MMCP-7), is believed to be fibrinogen [66]. Perivascular fibrinogen and fibrin deposits are found in EAE and inflammatory MS lesions [67]. Upregulation of tryptase gene expression was detected in acute MS plaques [32] and tryptase is also elevated in the CSF of patients with MS [68]. In addition, MMCP-7, is significantly upregulated in the acute phase of EAE in the brain and spinal cord; relapsing animals also showed increased expression of MMCP-7 in the spinal cord [15]. Taken together, these data suggest that mast-cell tryptase might participate in the tissue responses associated with both EAE and MS. However, the nature and importance of this role (or roles) remain(s) to be clarified.

Concluding remarks

Immunological effector mechanisms and mediators classically thought to contribute to the expression of Th2-associated responses can also be detected in EAE and MS, classically considered examples of Th1-associated autoimmune disorders. Moreover, several lines of evidence suggest that these 'allergy-associated' mechanisms and mediators could importantly contribute to the pathogenesis or progression of these conditions (Fig. 1). Such blurring or overlap of a distinct division between Th1- and Th2-associated mechanisms also seems to occur in other autoimmune disorders. More widespread appreciation of this point could result in the formulation of new strategies for the therapy of MS and other autoimmune diseases. Although there might be significant differences between the pathogenesis of the human disorders and the mouse 'models' of these conditions and these differences clearly need to be further defined and considered, Th2- or 'allergy-associated' mediators and mechanisms might represent a rich source of new targets for the treatment of autoimmune diseases.

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