

Role of Th1 and Th2 cells in autoimmune demyelinating disease

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Abstract

Evidence is accumulating that Th1 cells play an important role in the development of multiple sclerosis (MS) and experimental allergic encephalomyelitis (EAE), whereas Th2 cells contribute to recovery from disease. A major determinant in the development of Th1 and Th2 cells is the type of antigen-presenting cell (APC) involved and its functional characteristics, e.g., the production of interleukin-12. Therefore, modulation of APC might interfere with the development of Th1 type responses and as such be beneficial for MS and EAE. The potential of cytokines, in particular interleukin-10, and glucocorticoids to exert a selective effect on APC, and as a consequence to affect the Th1-Th2 balance in EAE, is discussed.

Key words

- Multiple sclerosis
- Experimental allergic encephalomyelitis
- Cytokines
- Glucocorticoids
- Th1 cells
- Antigen-presenting cells

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Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), characterized by degradation of the myelin sheath and loss of oligodendrocytes, resulting in impaired nerve conduction. Progression of the disease, which in some of the patients is characterized by exacerbations and remissions, results in the development of disability. Destruction of the myelin sheath is most likely based on the recognition of myelin-specific antigens by CD4⁺ T helper (Th) lymphocytes and the subsequent activation of macrophages (1). Myelin damage is caused by the combined action of various cytokines, proteases, nitric oxide, and reactive oxygen intermediates secreted by macrophages and T cells that have infiltrated the CNS. Similar mechanisms play a role in experimental allergic encephalomyelitis (EAE), which is widely used as an animal

model for MS. This autoimmune model can be induced in laboratory animals by immunization with myelin proteins and transferred to naive syngeneic recipients by CD4⁺ T cells.

Th1 cells in EAE and MS

Since the recognition that mouse CD4⁺ Th cells can be classified into at least two subsets, each secreting a unique profile of regulatory cytokines (2), much attention has been paid to the role of these subsets in infectious diseases, allergy and autoimmunity (3). Various cell-mediated autoimmune diseases appear to be characterized by a bias towards a Th1 type of response (4). In EAE much evidence has been obtained in support of the concept that Th1 cells play a role in the development of disease and that Th2 cells are involved in the recovery phase (5,6). CD4⁺ T cells producing interferon- γ (IFN- γ)

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(i.e., Th1 cells) are detectable in brain tissue early in the development of disease (7). The effector cells that are capable of transferring disease appear to be IFN- γ - and tumor necrosis factor- β (TNF- β)-producing Th1 cells with specificity for myelin basic protein or proteolipid protein-related peptides (8-11); Th2 cells are ineffective. Th1 cells are also supposed to play a dominant role in Theiler's murine encephalomyelitis virus-induced demyelinating disease (12). Th1 cells may contribute in two ways to the development and progression of disease: 1) as IFN- γ -producing cells that activate macrophages in the degradation of the myelin sheath and 2) by directly damaging the myelin sheath and oligodendrocytes through the secretion of TNF- α and TNF- β (13). An active role for TNF was substantiated by demonstrating that the encephalitogenicity of T cell clones in EAE correlated with their ability to secrete this cytokine (9) and the observation that induction of disease could be inhibited by anti-TNF antibodies (14).

Also in MS, much evidence has been obtained for a role of TNF and IFN- γ in the pathogenesis of the disease. First of all, IFN- γ - and TNF-producing cells have been demonstrated in brain tissue (15,16). Moreover, lymphocytes isolated from cerebrospinal fluid (CSF) or peripheral blood secrete IFN- γ when stimulated with myelin-derived peptides (17,18). In a prospective study, high levels of TNF- α were found in the CSF of the majority of patients with chronic progressive MS and in none of those with stable MS (19). The data suggested that the level of TNF- α in CSF correlates with the severity and progression of the disease. Using a whole-blood mitogen stimulation assay, it was found that an increased production of IFN- γ and TNF precedes exacerbations in MS (20). In a longitudinal study of 34 relapsing-remitting MS patients the capacity to produce TNF- α was predictive of the occurrence of all new relapses in all patients (21). Recently, it has been demonstrated by the polymerase-chain

reaction using peripheral blood mononuclear cells that TNF- α and IFN- γ are upregulated prior to exacerbation of disease (22). The relevance of these observations for MS is further illustrated by the fact that treatment of MS patients with IFN- γ resulted in exacerbation of the disease (23).

Evidence for a downregulatory role of Th2 cells in EAE and MS

The development and function of Th1 cells is under the control of Th2 cells or related cytokines (2). Likewise, Th2 cells may control the development and activity of encephalitogenic Th1 cells in EAE. Indeed, on the basis of mRNA expression in brain tissue, it can be concluded that recovery from disease is accompanied by an upregulation of cytokines which may be derived from Th2 cells (24,25). Moreover, the inhibition of the development of EAE appeared to be associated with the induction of Th2 cells (26). Further *in vivo* support for a role of Th2 cells in downregulation of the disease is the observation that inhibition of disease by tolerance induction is accompanied by an upregulation of interleukin (IL)-4 (27). This suggests that antigen presentation in the gut primes for the induction of a suppressive Th2 response and/or a transient anergy of Th1 cells (5). In MS, recovery from disease was accompanied by an upregulation of IL-10 and transforming growth factor- β (TGF- β ; Ref. 21).

Modulation of the Th1-Th2 balance in EAE

The development of Th1 cells or Th2 cells from a so-called naive precursor cell is highly determined by antigen-presenting cells (APC) and the microenvironment of a developing immune response. Cytokines play an important role in this process: IL-4 is a strong inducer of Th2 responses (28), whereas IFN- γ and TGF- β favor Th1 type responses

(29). However, one of the most important cytokines in this process is most likely IL-12 which primes for Th1 cells (30,31). By modulating IL-12 production in APC with IL-10 (32) a change from a Th1 to a Th2 type response can be achieved (33).

In EAE several attempts have been made to inhibit disease by interference at the cytokine level, resulting in controversial observations. In vivo neutralization of IFN- γ employing specific antibodies caused exacerbations in one study (34) and rendered otherwise resistant mice susceptible to EAE in a second study (35), suggesting that IFN- γ might play a beneficial role in a certain phase of disease activity. Furthermore, the possibility that IFN- γ does not necessarily play a pathogenic role in the development of EAE is supported by the recent finding that IFN- γ knockout mice backcrossed with an EAE-sensitive genetic background remained sensitive to disease induction (36). On the other hand, it was recently demonstrated that IL-12 exacerbated disease, whereas anti-IL-12 prevented disease development (37) which again supports a pathogenic role of Th1 cells.

A typical Th2 cytokine such as IL-4 was found to inhibit EAE in an adoptive transfer model with primed T cells (38) without affecting the extent of the inflammatory response within the CNS. IL-4 treatment was accompanied by an increased Th2 response without the downregulation of Th1 cells.

Our own studies showed that IL-4 had no effect on EAE, actively induced by immunization with the synthetic peptide PLP₁₃₉₋₁₅₁ of proteolipid protein (39). In contrast, IL-10 inhibited the development of disease. In an attempt to establish synergy between IL-4 and IL-10, we observed that IL-4 even abolished the inhibitory effect of IL-10. It was observed that IL-10 treatment shifted the primary antibody response to the encephalitogenic peptide from IgG2a to IgG1, which was suggestive of a shift from a Th1 response to a Th2 response. However, we

obtained no evidence for such a Th1 \rightarrow Th2 shift on the basis of in vitro assessment of cytokine profiles. IL-10 inhibited EAE without showing much effect on IFN- γ production; by contrast, IL-4 significantly inhibited IFN- γ production without having an effect on EAE. Since IL-10 was recently found to inhibit TNF- α -induced relapses of EAE, a possible mechanism of action of IL-10 in EAE might have been the downregulation of TNF receptors (40).

Although little is known about its precise mechanism of action, IFN- β has been recently approved in several countries for the treatment of relapsing-remitting MS, since it causes a 30% decrease in disease progression in these patients (41). IFN- β is also effective in EAE (42). Suggested mechanisms of action of this cytokine are the inhibition of IFN- γ (43) and downregulation of MHC class II antigens on APC (44). Alternatively, the fact that IFN- β inhibits the production of TNF in vitro and stimulates the production of IL-10 suggests that the latter might be an intermediate (45).

Possible role of HPA-axis

The development of autoimmunity may be related to the functioning of the hypothalamus-pituitary-adrenal (HPA) axis. In vivo evidence has been obtained by showing that streptococcal cell wall-induced arthritis develops in Lewis rats due to a defective production of corticotropin releasing hormone and - as a consequence - an impaired corticosterone response (46,47). Otherwise resistant F344 rats become sensitive to arthritis induction after treatment with the glucocorticoid (GC) receptor antagonist RU486. Independently and in a similar fashion, it was demonstrated that the development and activity of EAE in rats is under the control of the HPA axis (48,49). Possibly, the HPA axis might play a role as a natural regulator of Th1 activity and autoimmunity. Accordingly, corticosterone was found to be selec-

tive in suppressing murine Th1 cells but not Th2 cells both *in vitro* and *in vivo* (50,51). Using rat CD4⁺ T cells it was demonstrated that the synthetic GC dexamethasone (DEX) favors the development of Th2 cells (52). Such a selective effect might be due to the fact that Th2 cells are resistant to GC in view of their capacity to secrete IL-4 (53). Alternatively, the activation stage of the cells might play a major role since we demonstrated that human CD4⁺ T cells can be rendered resistant to the suppressive effect of DEX by using anti-CD28 as a co-stimulus (54). We further substantiated this possibility by demonstrating that human naive CD4⁺ T cells are more sensitive to DEX than memory CD4⁺ T cells (55). Likewise, it has been shown recently that the effects of GC on IL-4 and IFN- γ production by human CD4⁺ T cells are dependent on the activation stage of these cells (56).

In a recent study employing whole blood cultures we demonstrated that IL-12 (p40)

and TNF- α production is 10 to 100 times more sensitive to the suppressive effect of DEX than the production of IL-10 (Visser J, Methorst D, de Kloet ER and Nagelkerken L, unpublished data). Moreover, these effects are likely to be mediated by different intracellular receptors. This supports the possibility that GC can modulate the Th1-Th2 balance by modulating the characteristics of antigen-presenting cells, including IL-12. Accordingly, the microenvironment may determine the development of Th1 versus Th2 cells. In MS and EAE, local processes occurring within the central nervous system may exert a selective effect on Th1 or Th2 cells. Therefore, it will be of importance to increase the depth of our insight into the functional characteristics of antigen-presenting cells within the CNS, i.e., microglia, astrocytes and endothelial cells. Such cells might well be the prime target of therapy with cytokines in demyelinating disease.

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