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Role of Th17 cells in the pathogenesis of CNS inflammatory demyelination

Abdolmohamad Rostami and **Bogoljub Ciric**
Department of Neurology, Thomas Jefferson University, Philadelphia, PA

Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). The etiology of MS is not well understood, but it is believed that myelin-specific $CD4^+$ T cells play a central role in initiating and orchestrating CNS inflammation. In this scenario, $CD4^+$ T cells, activated in the periphery, infiltrate the CNS, where, by secreting cytokines and chemokines, they start an inflammatory cascade. Given the central role of $CD4^+$ T cells in CNS autoimmunity, they have been studied extensively, principally by using experimental autoimmune encephalomyelitis (EAE), an animal model of MS. In the late 1980s, $CD4^+$ T cells, based on their cytokine production, were divided into two helper lineages, Th1 and Th2 cells. It was postulated that Th1 cells, which produce IFN-γ, mediate inflammation of the CNS in MS/EAE, while Th2 cells, which produce IL-4, have a beneficial effect in disease, because of their antagonistic effect on Th1 cells. The Th1/Th2 paradigm remained the prevailing view of MS/EAE pathogenesis until 2005, when a new lineage, Th17, was discovered. In a relatively short period of time it became apparent that Th17 cells, named after their hallmark cytokine, IL-17A, play a crucial role in many inflammatory diseases, including EAE, and likely in MS as well. The Th17 paradigm developed rapidly, initiating the debate whether Th1 cells contribute to EAE/MS pathogenesis at all, or if they might even have a protective role due to their antagonistic effects on Th17 cells. Numerous findings support the view that Th17 cells play an essential role in autoimmune CNS inflammation, perhaps mainly in the initial phases of disease. Th1 cells likely contribute to pathogenesis, with their role possibly more pronounced later in disease. Hence, the current view on the role of Th cells in MS/EAE pathogenesis can be called the Th17/Th1 paradigm. It is certain that Th17 cells will continue to be the focus of intense investigation aimed at elucidating the pathogenesis of CNS autoimmunity.

Keywords

multiple sclerosis; EAE; Th1; Th9; Th17; Treg; γδ T cell; IL-23; GM-CSF; IL-27

Corresponding author: A.M. Rostami, MD, PhD, Department of Neurology, Thomas Jefferson University, Health Professions Academic Building, 901 Walnut Street, Suite 400, Philadelphia, PA 19107, Tel: 215 955 8100, Fax: 215 955 1390, A.M.Rostami@jefferson.edu.

Conflict of interest
The authors declare no conflict of interest.

Introduction

Multiple sclerosis (MS) is a disease that affects the central nervous system (CNS), including the brain, spinal cord and optic nerves (1). MS is characterized by overall reduction in CNS volume, and by accumulation of immune cells mainly in the white matter of various CNS areas, although substantial number of plaques can be found in the grey matter, leading to formation of localized inflammatory foci (2). Inflammatory processes in these foci cause damage to myelin and destruction of oligodendrocytes, injury to axons and their loss, and transient impairment or permanent loss of neurologic function, resulting in disabilities of various types and severity.

The etiology of MS remains elusive, but it is clear that both genetic and environmental factors, perhaps infections, play a role in its development (3). Given that in MS the immune system damages the CNS, MS is considered to be an autoimmune disease. It is believed that $CD4^+$ T cells specific for CNS antigens, most likely myelin components, play a pivotal role in initiation and perpetuation of MS. The prevailing view of MS pathogenesis has been largely formed by analogy to experimental autoimmune encephalomyelitis (EAE), an animal model of MS (4-6). In this model, myelin-specific $CD4^+$ T cells that have developed in peripheral lymphoid organs infiltrate the CNS, where they encounter their cognate antigens presented by local antigen presenting cells (APC). This interaction with APCs leads to re-activation of myelin-specific $CD4^+$ T cells, which in turn activate APCs by cell-cell contact and by secreted pro-inflammatory products, such as cytokines and chemokines. Secretion of pro-inflammatory mediators attracts various immune cells into the CNS, where they are activated and start secreting mediators that damage surrounding CNS tissue, leading to formation of lesions and eventually to neurologic deficits (7).

Th1/Th2 paradigm of MS/EAE

Given that in the prevailing view $CD4^+$ T cells play a central role in CNS autoimmunity, a great deal of MS research has been focused on these cells. In the late 1980s, Mosman et al. (8, 9) postulated that $CD4^+$ T cells can be divided into two helper T cell (Th) types, Th1 and Th2. Th1 cells are characterized by IFN-γ production and have a principal role in defense against intracellular pathogens, whereas Th2 cells produce IL-4 and are mainly responsible for clearance of extracellular parasites.

Analyses of immune responses that develop after immunization with myelin antigens for EAE induction revealed that they are dominated by IFN-γ^+ Th1 cells and that these cells are the most abundant among $CD4^+$ T cells found in the CNS of animals with EAE (10, 11). Furthermore, Th1, but not Th2 myelin-specific cells, were capable of inducing EAE when adoptively transferred into recipient mice (12, 13). These findings led to the conclusion that Th1 cells mediate EAE, and likely, by extension, also MS (14). This conclusion was supported by data showing abundant IFN-γ in CNS lesions of animals with EAE (15) and in active lesions of MS patients (16). At that time IFN-γ was regarded as an exclusively pro-inflammatory cytokine (17), as its numerous immunoregulatory functions were yet to be discovered. The view that Th1 cells mediate CNS inflammation by secreting IFN-γ, which activates other immune cells (i.e. monocytes, macrophages, neutrophils) (18) and drives them to damage CNS tissue, was supported by findings that, when administered to MS patients, IFN-γ exacerbated disease (19).

Additional supporting data for the Th1 paradigm came from STAT4-deficient mice, which were also resistant to EAE (20). STAT4 is a transcription factor necessary for IL-12 signaling downstream of its receptor (21). In addition, T-bet, a master transcription factor necessary for development of Th1 lineage, proved to be necessary for EAE development, as T-$bet^{-/-}$ mice are resistant to EAE (22).

Taken together, the aforementioned findings converged to strongly support a critical role of IL-12/Th1/IFN-γ axis in EAE/MS pathogenesis. However, it is now known that neither IFN-γ nor IL-12 is necessary for EAE development, and that both of them have a suppressive net effect on disease (23-26). The most important findings supporting the limited role of IFN-γ in disease came from the use of knock-out animal models and neutralization of IFN-γ with antibodies. Several groups demonstrated that treatment with anti-IFN-γ antibodies exacerbated EAE in various strains of mice (27-29). Observations in IFN-$\gamma^{-/-}$ and IFN-$\gamma R^{-/-}$ mice confirmed that IFN-γ limits EAE (24, 25, 30-32). In the following section we review the paradigm shift from IL-12/Th1 cells to IL-23/Th17 cells in the pathogenesis of EAE.

IL-12 in EAE

One of the most convincing lines of evidence supporting the Th1 paradigm came from studies on IL-12. This heterodimeric cytokine comprising IL-12p40 and IL-12p35 subunits is produced by activated APCs; it promotes development of Th1 cells and in particular their IFN-γ expression (33, 34). Blockade of IL-12 by neutralizing anti-IL-12p40 antibodies or genetic deficiency in this molecule conferred resistance to EAE induction (35)(36-40). This was thought to result from impairment in development of anti-myelin Th1 responses and greatly reduced IFN-γ production in the absence of IL-12 bioactivity (41). Experiments based on treatment with rIL-12 yielded less consistent data on the role of IL-12 in EAE pathogenesis than those with knockout mice. rIL-12 exhibited opposite effects on EAE depending on the disease phase when treatment was initiated (41-47). Most studies agree that treatment with rIL-12 during the priming phase, before disease onset, suppresses EAE, while treatment initiated after clinical disease has already manifested, or during the chronic/remitting phase, exacerbates disease.

Our laboratory has shown that, in addition to immune system cells, CNS resident cells, both astrocytes and microglia, can produce the IL-12p40 subunit when exposed to inflammatory stimuli (LPS) (48). These cells also secreted TNF and IL-6, suggesting that CNS cells can contribute locally to exacerbation of CNS inflammation in EAE/MS by promoting anti-CNS Th1 responses via production of IL-12 and other pro-inflammatory mediators as well.

(PL/J x SJL/J)F1 mice immunized with myelin basic protein (MBP) develop relapsing-remitting EAE. We have shown that IL-12 administration induces relapses and enhances their severity and frequency (Figure 1). In agreement with these disease-promoting effects of IL-12, neutralization of IL-12 with anti-IL-12p40 Ab blocked relapses (Figure 1). This was true in the case of both spontaneous relapses and staphylococcal enterotoxin-induced relapses (49).

Lack of CD40L-CD40 interaction, as in CD40-deficient mice, results in resistance to EAE. Administration of rIL-12 overcomes resistance to EAE in the absence of CD40L-CD40 interaction (46). Anti-IL-12p40 Ab prevented the reversal induced by exogenous IL-12 and protected mice from EAE. These results demonstrated that IL-12 is sufficient to overcome the CD40L blockade and suggested that induction of IL-12 by CD40L-CD40 interaction is essential for induction of EAE.

Measurement of IFN-γ and IL-4 production by MBP-stimulated lymphocytes from EAE-susceptible SJL/J and EAE-resistant BALB/c mice showed that lymphocytes of SJL/J mice produced IFN-γ and no IL-4, while lymphocytes of BALB/c mice had the opposite pattern of cytokine production (50). Neutralization of IL-12 with anti-IL-12p40 Ab protected SJL/J mice from EAE, whereas BALB/c mice that were treated with neutralizing anti-IL-4 Ab developed EAE. These findings confirmed the crucial role of IL-12 in EAE susceptibility and showed that IL-4 is important for conveying resistance in strains resistant to EAE.

Given that IL-12 is a heterodimeric cytokine, composed of covalently bound p40 and p35 subunits forming IL-12p70, it would be expected that deficiency in either of the subunits results in the same phenotype, as IL-12p70 cannot be formed. However, p40-deficient mice were resistant to EAE, while p35-deficient mice were fully susceptible (23) (Figure 2). Typical inflammation and demyelination were observed in spinal cords of p35-deficient mice, whereas p40-deficient mice had normal spinal cords. p35-deficient mice developed somewhat weaker anti-MOG_{35-55} Th1 responses, with lower production of IFN-γ compared to WT mice. In contrast, p40-deficient mice developed stronger Th2 responses to MOG_{35-55}. Microglia, CNS-infiltrating macrophages, and $CD4^+$ T cells of p35-deficient and WT mice produced TNF, while those same cells from p40-deficient mice did not. These data suggested that a heterodimeric cytokine containing p40, other than IL-12p70, and perhaps IL-23 (p40p19 heterodimer), which had been recently cloned at that time, might play an important role in EAE.

The IL-12 receptor consists of IL-12Rβ1 and IL-12Rβ2 subunits expressed by Th1 cells (51-53). If IL-12 plays a crucial role in EAE development it would be expected that lack of its receptor would result in resistance to disease. To determine the role of IL-12Rβ1 in the development of EAE we used mice deficient in this receptor subunit. IL-12Rβ1$^{-/-}$ mice were completely resistant to EAE induction and exhibited Th2 skewed responses against the immunogen, MOG_{35-55} (54). In a co-culture of purified $CD4^+$ T cells and APCs of MOG-immunized mice IL-12Rβ1$^{-/-}$ APCs drove $CD4^+$ T cells of both WT and IL-12Rβ1$^{-/-}$ mice toward Th2 lineage, whereas WT APCs induced Th1 lineage. In turn, IL-12Rβ1$^{-/-}$ $CD4^+$ T cells suppressed production of IFN-γ and TNF by WT APCs. Furthermore, decreased levels of IL-12p40, p35, and IL-23p19 mRNA were found in IL-12Rβ1$^{-/-}$ APCs. IL-18 production and IL-18Rα expression were also significantly decreased in immunized IL-12Rβ1$^{-/-}$ mice. We concluded that signaling involving IL-12Rβ1 drives development of encephalitogenic Th1 responses. We now know that IL-12Rβ1 is a subunit of not only IL-12R but also of IL-23R (55) and that the lack of IL-12Rβ1 in IL-12Rβ1$^{-/-}$ mice simultaneously prevented signaling of both IL-12 and IL-23. Hence, resistance of IL-12Rβ1$^{-/-}$ mice to EAE should be attributed to the lack of IL-23 signaling and defective Th17 development rather than to the lack of IL-12 signaling and impaired Th1 responses.

Contrary to expectations and findings in IL-12Rβ1-deficient mice, IL-12Rβ2-deficient mice were more susceptible to EAE, as characterized by earlier disease onset, more severe disease, and greater demyelination and CNS inflammation compared to WT mice (26) (Figure 3). IL-12Rβ2-deficient mice had significantly greater proliferation in response to MOG_{35-55} and increased production of TNF, GM-CSF, IL-17, IL-18/IL-18Rα, and NO. Furthermore, expression of IL-23p19 mRNA in spleen cells of immunized IL-12Rβ2-deficient mice was higher than in WT mice. These findings demonstrated that IL-12 is not required for EAE development.

Permanent lack of IL-12 signaling caused by genetic deficiency in either IL-12p35 or IL-12Rβ2 unequivocally demonstrated that IL-12 is not required for development of EAE (23, 26, 40, 56, 57). Most researchers have found that mice deficient in IL-12 signaling develop more severe disease compared to WT controls, demonstrating the suppressive role of IL-12 in EAE pathogenesis. Deficiency in IL-12 signaling affected IFN-γ production to a variable extent in different studies, and it remains unclear to what extent more severe EAE in IL-12-deficient mice is caused by reduced IFN-γ production versus IFN-γ-independent effects of IL-12.

These surprising findings starkly contradicted the Th1 paradigm, and remained unexplained until the discovery of IL-23 in 2000 (58) and Th17 cells in 2005. Even though major Th1 cytokines play a suppressive role in EAE, it is still believed that Th1 cells, in concert with

Th17 cells, contribute to disease development and are thus a part of the Th1/Th17 paradigm that is currently the dominant view of EAE/MS pathogenesis.

IL-23 and Th17 cells in EAE/MS

IL-23 is a covalent heterodimer of IL-12p40 and IL-23p19 (58). Hence, the IL-12p40 subunit is shared between IL-12 and IL-23. Both IL-12 and IL-23 are produced by the same cell types, mainly APCs, and the relative ratio of secretion between IL-12 and IL-23 depends on the nature of stimuli that activated APCs (59, 60). In 2003, Cua et al. showed that IL-23, and not IL-12, plays an essential role in autoimmune inflammation of the CNS (57). They also proposed that IL-23 exerts its pro-encephalitogenic effect by acting on a subset of memory Th1 cells. Langrish et al. have shown that IL-23 drives development of highly encephalitogenic Th cells characterized by IL-17A production (61).

In 2005, two groups simultaneously described a new IL-17A-producing Th lineage that has been named Th17 (62, 63). This seminal discovery marked a new era in autoimmunity research, as Th17 cells proved to be a major factor in a number of autoimmune diseases, including EAE. It became clear that IL-23 promotes development of Th17 cells and stimulates their IL-17A production in a manner analogous to the role of IL-12 in development of Th1 cells and IFN-γ production. The Th1 paradigm (IL-12/Th1/IFN-γ axis) of CNS autoimmunity was rapidly replaced by the Th17 paradigm (IL-23/Th17/IL-17A axis). In this new view of the pathogenesis of CNS autoimmune inflammation, immunization with myelin antigen induces development of Th17 cells in the presence of IL-23. These myelin-specific Th17 cells traffic into the CNS, where they secrete IL-17A, which through chemokine induction attracts various immune cells, and in particular myeloid cells, into the CNS, initiating and perpetuating the inflammatory cascade. However, subsequent studies have shown that IL-17A plays a contributing, but non-essential, role in EAE, as in most studies lack of IL-17A bioactivity led to mitigated disease course and improved recovery, but did not confer resistance to disease (64-70).

GM-CSF, a crucial mediator of Th cell encephalitogenicity

Given that Th17 cells appear to play a crucial role in EAE, while neither their signature cytokine, IL-17A, nor IL-17F, IL-22 or IL-22, is required for EAE development, a search for a mediator produced by Th17 cells that endows them with encephalitogenic capacity led us to hypothesize that GM-CSF plays such a role.

GM-CSF (also known as CSF2), was initially defined by its ability to generate both granulocyte and macrophage colonies from precursor cells (71). GM-CSF can be produced by either bone-marrow-derived cells, such as T cells (72-74) and monocytes/macrophages (75), or by resident tissue cell types, including renal parenchymal cells (76), fibroblasts (77), endothelial cells (78), chondrocytes (76, 79, 80) and smooth muscle cells (81). The GM-CSF receptor (CSF2R) is a heterodimer composed of a specific ligand-binding subunit (CSF2Rα) and a common signal-transduction subunit (CSF2Rβ) (82-84), which is shared with the receptors for IL-3 and IL-5 (85-87). In addition to leukocytes, non-hematopoietic cell types (i.e. keratinocytes, smooth muscle cells, endothelial cells, epithelial cells and neurons) can also express the CSF2R and respond to GM-CSF stimulation (88-95).

Functions of GM-CSFs can be grouped into the following categories: increased cell survival and/or proliferation, differentiation, and activation (96-99). In addition to its effects on haematopoietic precursor cells, GM-CSF can promote the survival and activation of macrophages, neutrophils, basophils and eosinophils, as well as dendritic-cell maturation. Systemic administration of GM-CSF, or when its levels are increased by inflammation or infection, leads to the mobilization of monocytes and other myeloid populations from bone

marrow to blood, and it primes monocytes for an increased *in vitro* response to other stimuli (97, 98, 100). GM-CSF can also mobilize precursors from other lineages, such as endothelial cells (101). Overall, GM-CSF can be viewed as a major regulator involved in the control of granulocyte and macrophage lineage populations at all stages of maturation.

In virtually all animal models of inflammation and autoimmunity that have been tested, GM-CSF depletion resulted in suppression of disease, which is consistent with its pro-inflammatory functions. GM-CSF has well established roles in the following diseases [reviewed in Ref. (102)]: arthritis (103, 104), autoimmune CNS inflammation (105), nephritis (76, 106), lung diseases (96, 97, 107-109), atherosclerosis and vascular injury (110, 111), cancer [reviewed in Ref. (112)], obesity (113) and type 1 diabetes mellitus (114).

In the context of CNS autoimmunity, we have shown that encephalitogenicity of both Th1 and Th17 cells depends on their GM-CSF production (73), as Th cells deficient in GM-CSF cannot induce EAE (Figure 4). Codarri et al. made a similar observation, and in addition found that RORγt is required for production of GM-CSF by Th cells (74). However, in our studies RORγt-deficient cells, of both Th1 and Th17 lineage, produced large quantities of GM-CSF in vitro, contradicting their findings (73). The reason for this discrepancy is unclear.

We found that IL-23 stimulates expression of GM-CSF by Th17 cells, whereas TGF-β1 suppresses it. This finding could explain the dichotomy in pathogenicity of Th17 cells, where Th17 cells stimulated with IL-23 are highly pathogenic, while TGF-β-treated Th17 cells are non-pathogenic (115). In addition, we were able to define a positive feedback loop in which IL-23 produced by APCs induces GM-CSF production by Th17 cells, which in turn stimulates IL-23 production by APCs (73). IL-1β1 is another APC-derived cytokine, in addition to IL-23, that significantly upregulates expression of GM-CSF by Th cells, making them highly pathogenic (73, 74).

IL-27, a potent regulator of Th cells

IL-27 has emerged as a potent regulator of immune responses, and in particular those mediated by Th17 cells. IL-27 can be produced by a number of cell types, but its main source appears to be activated APCs. IL-27 comprises two non-covalently bound subunits, Epstein Barr Virus-Induced gene 3 (EBI-3) and p28 (116). IL-27 signals via its heterodimeric receptor, which consists of the IL-6 receptor subunit gp130 and WSX-1 (also known as TCCR) (117, 118). By activating the Th1-driving transcription factor, T-bet, IL-27 induces IL-12Rβ2 and IFN-γ expression in naïve $CD4^+$ T cells, thereby priming these cells for maturation into effector cells of Th1 lineage (119). IL-27 directly suppresses the development of Th17 cells (69, 120, 121) by inhibiting RORγt expression (122). IL-27 signaling activates STAT1, 3, 4 and 5; however, inhibition of Th17 development by IL-27 is mediated by STAT1 and STAT3 (69). In addition to Th17 cells, IL-27 inhibits Th2 cell development as well as Th2 cytokine production from polarized Th2 cells by down-regulation of GATA-3 and up-regulation of T-bet expression simultaneously (123). IL-27 also inhibits development of Treg cells by a STAT3-dependent mechanism (124) as well as suppresses antigen presentation functions of dendritic cells (125).

IL-27 appears to play mainly a suppressive role in cell-mediated autoimmunity, as demonstrated by its inhibitory effect on a range of animal models; however, there are studies to suggest it may also contribute to pathogenesis in some cases (61, 120, 126-129). IL-27R (WSX-1) deficient mice developed more severe EAE than WT mice, suggesting an anti-inflammatory effect of IL-27, most likely through inhibition of highly encephalitogenic Th17 cells (120).

We have shown that IL-27 strongly suppresses development of Th17 cells, while inducing differentiation of IFN-γ^{+}IL-10^{+} regulatory Tr1 cells (61). Exogenous IL-27 can suppress EAE development (Figure 5), but it has limited efficacy in ameliorating ongoing disease (61). This has been corroborated by another group that used exogenous IL-27 to suppress EAE (126).

Interestingly, IL-27 has a potent regulatory effect on GM-CSF production, but only in the case of Th1 cells, while committed Th17 cells are resistant to suppression of their GM-CSF production by IL-27 (130). This finding is in agreement with our observation that committed Th17 cells exhibit little susceptibility to modulation by IL-27 (131).

Th9 cells and IL-9 in CNS autoimmunity

The momentous changes in our understanding of autoimmunity that began in 2005 with the discovery of Th17 lineage continued with the description of a novel Th9 lineage in 2008 (132, 133), named after its hallmark cytokine, IL-9. In addition to IL-9, Th9 cells can also produce relatively large quantities of IL-10, albeit with different kinetics than IL-9 (134). Th9 cells do not produce cytokines associated with other Th lineages, such as IL-4, IL-17 and IFN-γ (134-136). However, IL-9 is not exclusively produced by Th9 cells, as it can be produced by Th2, Th17 and Treg cells, as well as non-T cells (137-139).

IL-9 was discovered in the late 1980's (140, 141) but its involvement in autoimmune CNS inflammation was described only recently when two groups published largely contradictory findings. Elyaman et al. showed that IL-$9R^{-/-}$ mice immunized with MOG_{35-55} have earlier onset and significantly more severe EAE than IL-$9^{+/+}$ mice (142). IL-9 stimulated suppressive function of Tregs *in vitro*, which provided a mechanistic explanation for more severe EAE, as the lack of IL-9 signaling in IL-$9R^{-/-}$ mice could have resulted in weaker suppressive Treg function, allowing for more robust encephalitogenic responses and consequently exaggerated EAE. The same group subsequently showed that anti-IL-9 Ab treatment has no effect in EAE, at least when mice are treated with the antibody before disease onset (143). In contrast, Nowak et al. found that IL-9 has a pro-inflammatory role in EAE (144). Using approaches with neutralizing anti-IL-9 Ab, adoptive EAE, and passive EAE in IL-$9R^{-/-}$ mice, they showed that deficiency in IL-9 signaling delays disease onset and reduces its severity. The authors found that milder EAE in IL-$9R^{-/-}$ mice correlates with reduced numbers of Th17 cells and IL-6^{+} macrophages in the CNS, and decreased numbers of mast cells in the lymph nodes. It remains unclear why these two studies had contradictory findings.

Studies that followed, including ours, also found that neutralization of IL-9 with Ab (145) and lack of IL-9 signaling (in IL-$9^{-/-}$ mice) (146) attenuate EAE. Subsequently, several other studies have shown that IL-9 plays a pro-inflammatory role in EAE. Anti-IL-9 Ab treatment of IFN-$\gamma^{-/-}$ mice dramatically reduced disease severity and led to complete recovery in otherwise lethal EAE (147). The same group has also shown that adoptive transfer of 2D2 cells polarized into Th9 lineage induces EAE in recipient mice. In a study published by Zhou et al. neutralization of IL-9 with Ab also reduced EAE severity (148). Taken together, several groups, using various approaches, have shown that IL-9 significantly contributes to EAE pathogenesis, while one group concluded that IL-9 either suppresses or has no effect in EAE.

Thus far, most studies on the role of IL-9 in EAE have focused on its effects on immune cells (Tregs, mast cells, Th17 cells), but tissue cells also express IL-9R and can contribute to the effects of IL-9 in disease development or resolution. Most CNS cell types express IL-9R, including astrocytes, oligodendrocytes, microglia and oligodendrocyte progenitors, while neurons do not express the receptor [(148) and our unpublished data]. Zhou et al. have

shown that IL-9 acts on astrocytes and induces production of CCL20 during EAE, which in turn attracts CCR6-expressing immune cells, such as Th17 cells, in the CNS, potentiating its inflammation (148). The importance of this pro-inflammatory mechanism is corroborated by findings that in a melanoma mouse model IL-9 inhibited tumor growth by inducing expression of CCL20 in lung epithelial cells, and promoting the recruitment of $CCR6^+$ DCs and $CCR6^+CD8^+$ T cells (149).

To test the encephalitogenic potential of Th9 cells, Jager et al. polarized MOG-specific $CD4^+$ T cells (2D2 cells) into Th9 lineage and injected them into naïve recipient mice. The Th9 cells induced EAE with similar kinetics and severity as Th1- and Th17-polarized 2D2 cells (150). However, each of the Th lineages mediated development of different lesion patterns, which indicates that different mechanisms dominate their pathogenic action. Interestingly, half of transferred Th9 cells isolated from the CNS at the peak of EAE produced IFN-γ, and smaller quantities of IL-9, IL-10, IL-4 and IL-17, demonstrating the high degree of Th9 lineage plasticity, similar to Th17 cells. The propensity of Th9 cells, at least when they develop *in vitro* and are then transferred into mice, to switch to Th1 lineage and start producing IFN-γ has also been demonstrated in the mouse model of ocular inflammation (151).

Overall, it has been clearly demonstrated that *in vitro* differentiated myelin-specific Th9 cells can be encephalitogenic in adoptive EAE, with potency similar to Th1 and Th17 cells. However, it remains unknown whether substantial myelin-specific Th9 responses develop after immunization with myelin antigens, and whether, if such responses develop, they are of sufficient magnitude to significantly impact EAE. This is similar to Th1 responses, as Th1 cells are encephalitogenic in adoptive EAE, but it is unclear to what extent they contribute to passive EAE induced by immunization. However, in contrast to Th9 responses, it is apparent that immunization with myelin antigens elicits strong Th1 responses, and it is therefore likely that Th1 responses contribute to EAE development. Nevertheless, there is evidence that a large proportion of myelin-specific Th1 cells are ex-Th17 cells (152), suggesting that classic Th1 cells potentially play only a minor role in EAE.

Despite some contradictory findings, the prevailing view is that IL-9 plays a pro-inflammatory role in EAE. However, it remains to be determined to what extent IL-9 is important for encephalitogenicity of Th9 cells, given that hallmark cytokines of Th1 and Th17 cells, IFN-γ and IL-17A, respectively, are not necessary for their encephalitogenicity, which might also be the case with Th9 cells and IL-9. Furthermore, given that IL-9 can be produced by Th17 cells, which are the predominant Th lineage in the CNS of animals with EAE and in acute CNS plaques of MS patients (153), it is possible that the major IL-9 source in the CNS are Th17 and not Th9 cells.

The role of Th9 cells in MS has not been investigated, and there is also a dearth of data on IL-9 in MS. One study has shown that cerebrospinal fluid of MS patients contains increased IL-9 levels (154). We found by immunostaining that a large proportion of $CD4^+$ T cells in CNS lesions of MS patients express IL-9 (unpublished data), indicating that IL-9 may play an important role in MS pathogenesis; this, in combination with findings in EAE, warrants further studies on IL-9 in the context of autoimmune CNS inflammation.

Regulatory T cells in CNS autoimmunity

Regulatory $CD4^+$ T cells (Tregs) have a suppressive effect on immune responses by limiting activation, proliferation, survival, and pro-inflammatory function of various immune cells including Th cells (155). It should be mentioned that other types of immune cells, including $CD8^+$ T cells, B cells and myeloid cells, can also acquire regulatory functions similar to Tregs (156-158). The overall function of Tregs is to maintain immune homeostasis by

preventing autoimmunity and by dampening or quenching anti-microbial immune responses that can harm the organism if they become exaggerated, or are unnecessary after infection has been cleared (159). Thus far, several types of Tregs have been described, differing in their developmental origin, phenotypic characteristics and mechanisms of achieving their regulatory function (155). Forkhead box protein 3 (FoxP3) is a master transcription factor that confers regulatory function to some, but not all, types of Tregs (160). Major types of Tregs are: natural Tregs (nTregs), which are $FoxP3^+$ and develop in the thymus; inducible Tregs (iTregs), which are also $FoxP3^+$ and develop in the periphery from naïve $CD4^+$ T cells; IL-10-secreting Tr1 cells, which develop in the periphery and are $FoxP3^-$; TGF-β-secreting Th3 cells; and $FoxP3^-$ IL-35-secreting iT(R)35 cells (161). In addition to FoxP3, various types of Tregs can express CD25, cytotoxic T-lymphocyte antigen 4 (CTLA4) and glucocorticoid-induced TNF receptor-related protein (GITR), but neither of these markers is exclusively expressed only by Tregs (162).

The role of Tregs in modulating autoimmune CNS inflammation has been extensively studied in EAE. One of the first observations that Tregs regulate EAE was published in 1993. The authors describe that mice recovering from EAE have a population of regulatory $CD4^+$ T cells specific for a peptide of TCR that dominates $CD4^+$ T cell response to myelin peptide (MBP_{1-11}) used to induce EAE. These TCR peptide-specific Tregs suppressed responses directed against MBP_{1-11} peptide *in vivo* and protected mice against MBP-induced EAE (163). In 1994, Tonegawa's group demonstrated that lymphocytes prevent spontaneous EAE in MBP TCR transgenic mice and raised the possibility that regulatory T cells might be responsible for the protective effect (164), an interpretation that was confirmed in a subsequent study (165). The capacity of Tregs to suppress EAE was confirmed in a study in which transfer of $CD4^+CD25^+$ T cells conferred significant protection against clinical EAE (166). Reddy et al. have shown that susceptibility to EAE is inversely correlated with natural frequency of $CD4^+CD25^+$ T cells (Tregs) specific for immunizing myelin peptide, and that depletion of Tregs renders susceptible a mouse strain that is normally resistant to EAE (167). IL-$6^{-/-}$ mice, which do not develop Th17 cells, have a peripheral repertoire dominated by Treg cells and are resistant to EAE induction. However, depletion of Tregs enables development of Th17 cells through the TGF-β/IL-21 pathway and renders IL-$6^{-/-}$ mice susceptible to EAE induction (168). Stephens et al. have shown that Treg cells raise the threshold for triggering autoreactive responses, thereby reducing the risk of autoimmune disease (169). Depletion of Tregs with anti-CD25 Ab in SJL mice immunized for EAE induction resulted in enhanced disease severity and increased mortality, while the transfer of Tregs from naïve mice reduced disease severity. However, transfer of Tregs from IL-10-deficient mice failed to suppress EAE, indicating that Tregs control EAE, at least partially, through an IL-10-dependent mechanism (170). Montero et al. also found that depletion of $CD25^+$ Tregs enhances EAE in C57BL/6 mice and increases MOG_{35-55}-specifc IFN-γ production by T cells (171). The majority of Tregs in the CNS of mice with EAE accumulate in the recovery phase of disease, with up to a third of $CD4^+$ T cells in the CNS being Tregs (172-174). Depletion of Tregs precludes recovery from EAE, indicating that these cells play an important role in this process (174). However, investigators have not always been able to directly demonstrate their suppressive capacity, as Tregs failed to control CNS-derived effector T cells (173). In contrast, Tregs from the CNS of mice in the recovery phase suppressed IFN-γ, but not IL-17 production *in vitro* (175). It appears that, in contrast with peripheral lymphoid organs, the inflammatory environment in the CNS of animals with EAE stimulates rapid proliferation of Tregs (173, 175). An interesting observation made by Liu et al. is that neurons can induce conversion of myelin-specific autoaggressive effector Th cells into $CD4^+CD25^+TGF\text{-}\beta^+CTLA\text{-}4^+FoxP3^+$ Tregs that are suppressive both in vitro and in vivo and are capable of inhibiting progression of EAE (172). Astrocytes can induce Tregs capable of suppressing autoreactive T-cell proliferation *in vitro* and EAE upon adoptive transfer (176). Collison et al. made an

interesting observation in the study by directly comparing potency of nTregs and iT(R)35 cells (161). Adoptive transfer of 1×10^6 nTregs into mice before inducing EAE resulted in milder disease compared to controls. Mice that received iT(R)35 were completely protected from EAE, demonstrating their superior regulatory efficacy, at least in this disease. At the same time Ebi3-deficient (IL-35-deficient) iT(R)35 is entirely dependent on their IL-35 production.

Potential involvement of Tregs in pathogenesis of MS has been revealed by a finding that these cells obtained from blood of patients with RRMS have reduced suppressive capacity compared to those of healthy controls (177-181). A couple of studies found association between functional impairment of Tregs from MS patients and their lower levels of FoxP3 expression (47, 182-184). Interestingly, in more advanced stages of disease, in secondary progressive MS, Tregs had normal suppressive function and normal levels of FoxP3 expression. Furthermore, the defect in function of Tregs in RRMS patients can be corrected by therapy with IFN-γ (185, 186) and copolymer-I (187).

Most studies on the role of regulatory T cells in autoimmune CNS inflammation have focused on classic $CD4^+CD25^+FoxP3^+$ Tregs, perhaps because they were the first type of Tregs to be clearly defined, and because in mice, unlike in humans, expression of FoxP3 correlates quite well with the suppressive function of T cells. Generation of FoxP3 reporter mice, which enabled less ambiguous identification of Tregs, and experiments with live Tregs provided opportunities for rapid advancement in the field. However, $CD4^+$ T cells with regulatory function are diverse, just like various Th lineages. They differ in their phenotype (i.e. FoxP3 expression), mechanism of suppression (i.e. soluble mediators vs. cell surface molecules), phenotypic stability/plasticity and capacity to suppress inflammation.

The role of gamma delta (γδ) T cells in CNS autoimmunity

γδ T cells express on their surface TCR comprising γ and δ chains instead of the conventional α and β chains. They represent minority (up to 5%) of lymphocytes in the blood and in secondary lymphoid tissues, but are highly enriched in the skin and mucosa where they can constitute up to 50% of the T cells (188). Selection of γδ T cells in the adult thymus seems to be independent of ligand recognition by γδ TCR, and development of γδ T cells is not affected in the absence of MHC class I and II (189-191). γδ T cells have the capacity to directly respond to microbial products and to cytokines, without prior engagement of their TCR, which is reminiscent of innate immune cells. γδ T cells seem to have a more prominent role early in immune responses, when they produce large quantities of various cytokines, such as IFN-γ, TNF, IL-10, IL-17A and GM-CSF (192-197).

Studies on the role of γδ T cells in EAE have yielded contradictory results, depending on the EAE model and approaches that have been utilized. In one study, where EAE was induced in B10.PL mice by immunization with spinal cord homogenate, depletion of γδ T cells with antibody against γδ TCR resulted in earlier disease onset and disease relapse, in this otherwise monophasic model (198). Mice depleted of γδ T cell had a markedly stronger Ag-specific proliferative response of splenocytes on days 7 and 14 p.i. These findings suggest that γδ T cells play a protective role in EAE. Studies in mice on the same background (B10.PL) genetically deficient in γδ T cells yielded similar results. These mice developed a chronic disease course rather than monophasic. The presence of γδ T cells was needed to promote IFN-γ production by $CD4^+$ and $CD8^+$ T cells in the CNS before EAE onset, whereas lack of γδ T cells had no effect on IFN-γ production in spleen and lymph nodes (199). The same authors subsequently demonstrated that chronicity of EAE in γδ T cell-deficient mice was due to both increased proliferation of encephalitogenic T cells and reduction in their apoptosis. The regulatory function of γδ T cells was dependent on their

expression of Fas ligand. Hence, the authors concluded that γδ T cells regulate EAE through Fas/Fas ligand-dependent induction of apoptosis of encephalitogenic T cells (200). In contrast to B10.PL mice, transfer of γδ T cells into C57BL/6 mice deficient for these cells did not have an effect on adoptive EAE in these mice, indicating that γδ T cells do not play a significant role in this model (201). C57BL/6 mice transgenic for MBP-specific TCR on background develop spontaneous EAE when they are simultaneously $RAG^{-/-}$, whereas RAG-sufficient mice do not. Crossing of MBP TCR-specific mice with γδ T cell deficient mice did not lead to development of spontaneous EAE, indicating that these cells do not play an important role in this model (165).

In contrast to the above-described protective role or lack of significant role in EAE, a number of studies described a pathogenic role for γδ T cells in EAE. Depletion of γδ T cells with antibody in SJL mice with EAE resulted in disease amelioration, suggesting that γδ T cells contribute to disease pathogenesis (202). Application of anti- γδ T cell Ab resulted in reduction of IL-1, IL-6, TNF, lymphotoxin, and IFN-γ levels in the CNS during EAE onset. The levels of these cytokines eventually normalized, except for IFN-γ. The authors concluded that γδ T cells contribute to the pathogenesis of EAE by augmenting production of proinflammatory cytokines by cells that enter the CNS (203). Furthermore, γδ T cell-deficient C57BL/6 mice developed much reduced disease, both after immunization with MOG_{35-55} and after adoptive transfer of MOG_{35-55}-specifc T cell line (204).

A subset of γδ T cells expresses IL-23R, RORγt and produce sIL-17, IL-21, and IL-22 upon exposure to IL-1β and IL-23, without activation through their TCR. γδ T cells stimulated with IL-1β and IL-23 promoted IL-17 production by $CD4^+$ T cells and increased susceptibility to EAE (205). $IL\text{-}17^+IFN\text{-}\gamma^-$ and $IL\text{-}17^+IFN\text{-}\gamma^+$ γδ T cells were found in relatively high frequency in the CNS of mice with EAE, especially at disease onset. These findings suggested that γδ T cells are an important source of IL-17 in the CNS in early EAE. IL-1β- and IL-23-activated γδ T cells promoted IL-17 production by αβ T cells, either by directly acting on the $CD4^+$ T cells and/or by promoting cytokine production from DCs. Petermann et al. extended the above findings by discovering that $IL\text{-}23R^+$ γδ T cells antagonize Treg cell-mediated suppression of αβ T cells (206). In addition, IL-23-stimulated γδ T cells created a cytokine milieu, independently of IL-6 and IL-21, that directly inhibited conversion of αβ T cells into $Foxp3^+$ Treg cells. Secreted products of IL-23-activated γδ T cells suppressed generation and function of Treg, shifting the balance between Treg cells and conventional αβ T cells in favor of effector Th cells. It remains to be determined which soluble factor(s) produced by $IL\text{-}23R^+$ γδ T cells inhibit Treg cell development and function or enable αβ T cells to resist Treg cell suppression.

Conclusions

For the past seven years Th17 cells have been the focus of intense research in immunology and especially in autoimmunity. Progress in understanding their biology and function has been rapid, and much has been discovered in a short period of time. Views on the pathogenesis of most autoimmune diseases have radically changed and paradigms that dominated research and therapeutic approaches since the 1980s have been replaced with new ones that include Th17 cells.

The discovery of Th17 cells was mainly based on findings in EAE, and subsequent progress in understanding their biology and function was largely driven by the use of this disease model. Soon after their discovery, Th17 cells took center stage in MS research, and they remain central in both basic and translational MS research. It has been demonstrated beyond any doubt that Th17 cells play a crucial role in EAE. However, pathways and mechanisms underlying their encephalitogenicity are still being discovered. Given that IL-17A plays a

limited role in EAE, and that GM-CSF is also produced by Th1 cells, it is unclear which mechanism(s) employed by Th17 cells makes them uniquely encephalitogenic.

One question that has received a great deal of attention is the relative contribution of Th1 and Th17 cells to the pathogenesis of EAE and MS. Th1 cells can transfer EAE in adoptive models, which demonstrates that they can be encephalitogenic on their own, but it appears that they have no capacity to induce active EAE without the involvement of Th17 cells. Th17 cells are necessary for EAE development, but it is not clear if their contribution is sufficient or if that of Th1 cells is also required. This question became perhaps less relevant after the discovery that a great number of Th17 cells change their phenotype and transition into Th1 cells (ex-Th17 cells) during the course of EAE(152) (Figure 6). Thus, in this case the distinction between lineages has been blurred, and insistence on a division of roles that Th1 and Th17 lineages play in EAE can be immaterial, given that the same cells can have both phenotypes. An interesting question about encephalitogenicity that has not been addressed are potential differences between classic Th1 and ex-Th17 cells.

The role of Th17 cells in MS has been largely inferred from animal studies, similar to the role of Th1 cells and other types of immune cells. It is believed that Th17 cells, along with Th1 cells, play a role in MS pathogenesis, which, if not crucial, is at least significant. A majority of $CD4^+$ T cells in acute MS lesions produce IL-17A, and hence can be classified as Th17 cells (153). Certain types of MS, such as opticospinal MS, have a dominant signature of Th17-driven pathology, including a large proportion of granulocytes among CNS-infiltrating cells (207). Possibly, in different types of MS, or in different disease phases, either Th1 or Th17 cells are the main drivers of pathological processes. This might also be the case in the evolution of individual CNS lesions, with one Th lineage initiating pathology and another perpetuating it. Given the view that Th17 cells likely play an important role in MS, they have become a major focus for development of new therapeutic strategies. Thus far, no therapeutic approach that specifically targets Th17 cells or their products (i.e. IL-17A) has been clinically tested and proven useful. Nonetheless, it is certain that Th17 cells will continue to be of intense interest for therapeutic targeting in MS, and as our knowledge of these cells deepens, new approaches will be developed, hopefully with great benefit to MS patients.

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Abbreviations

IL	interleukin
IFN	interferon
MOG	myelin oligodendrocyte glycoprotein
MS	multiple sclerosis
CNS	central nervous system
EAE	experimental allergic encephalomyelitis
APC	antigen presenting cells

MBP	myelin basic protein
TNF	tumor necrosis factor
GM-CSF	granulocyte colony-stimulating factor
NO	nitric oxide
WT	wild-type
Tregs	regulatory T cells

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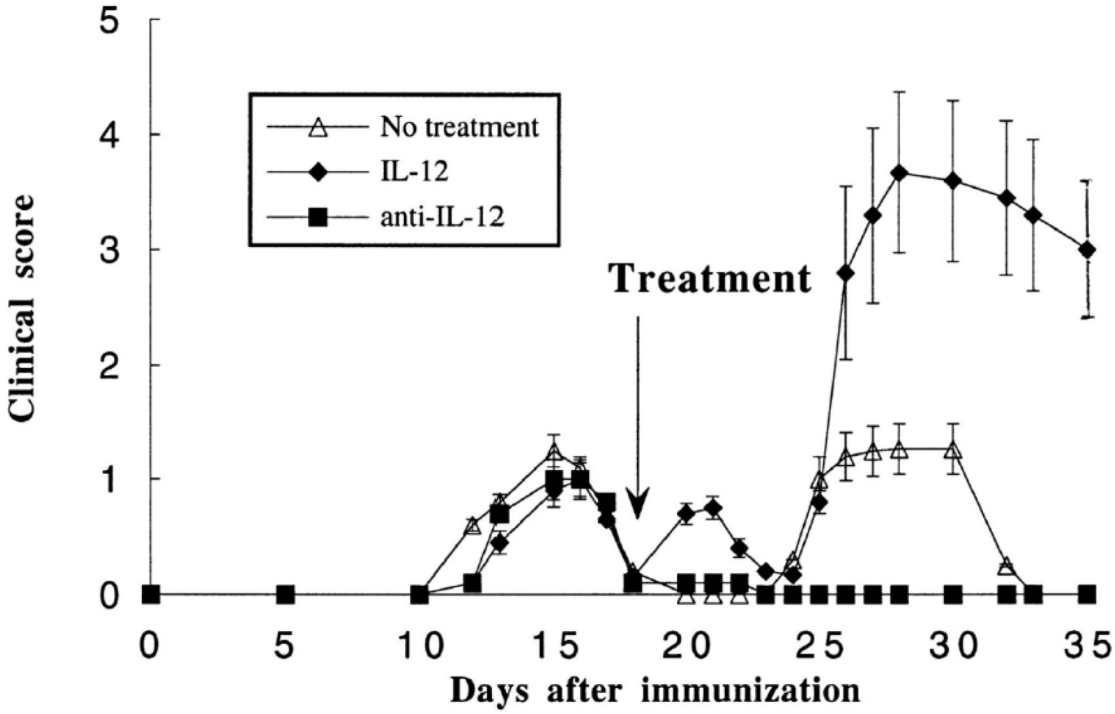

Figure 1.

Effect of IL-12 and of neutralizing anti-IL-12p40 mAb on the course of relapsing EAE. After recovery from the initial attack of EAE, mice were treated as indicated by the arrow. IL-12 treatment induced immediate relapses and worsening later relapses. Anti-IL-12p40 Ab prevented spontaneous relapses. Results are shown as mean × SD of clinical scores. The course of EAE in mice treated with control rat IgG overlaps completely with that of mice receiving no treatment and is not shown. (Figure first published in *Journal of Immunology*, 161:5097-5104, 1998, Constantinescu C et al., Antibodies against interleukin-12 prevent superantigen-induced and spontaneous relapses of experimental autoimmune encephalomyelitis. Copyright 1998. The American Association of Immunologists, Inc.)

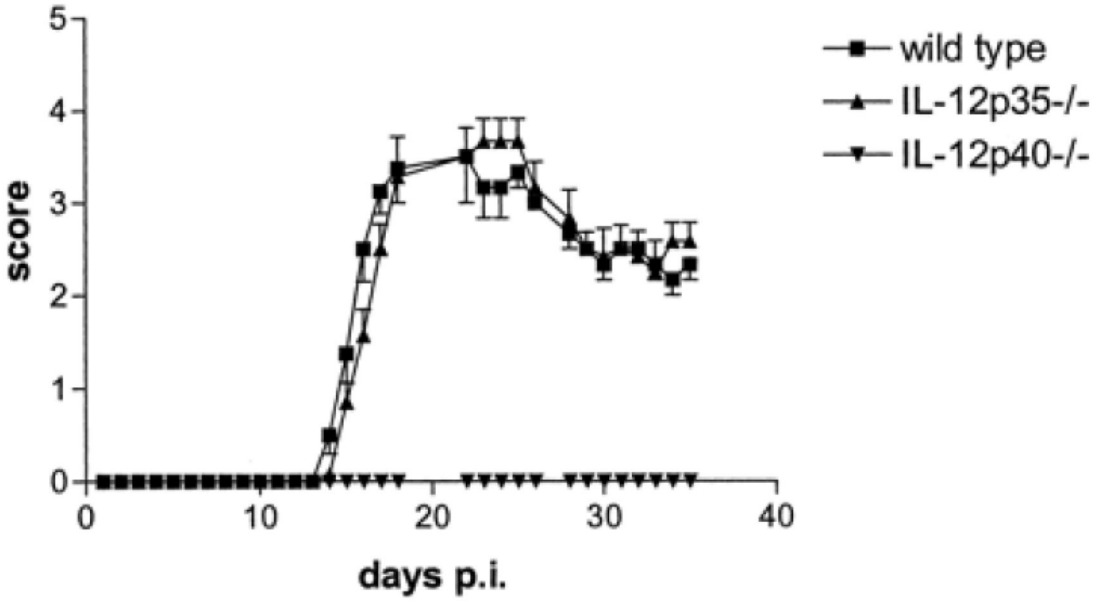

Figure 2.

IL-12p35$^{-/-}$ are susceptible to EAE, while IL-12p40$^{-/-}$ mice are resistant. Female WT, IL-12p35$^{-/-}$, and IL-12p40$^{-/-}$ mice were immunized with MOG_{35-55} in CFA. Data represent the mean clinical scores × SEM. The overall clinical score was not significantly different between WT and IL-12p35$^{-/-}$ mice. (Figure first published in the *Journal of Immunology*, 169: 7104-7110, 2002, Gran B. et al., IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: Evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination. Copyright 2002. The American Association of Immunologists, Inc.)

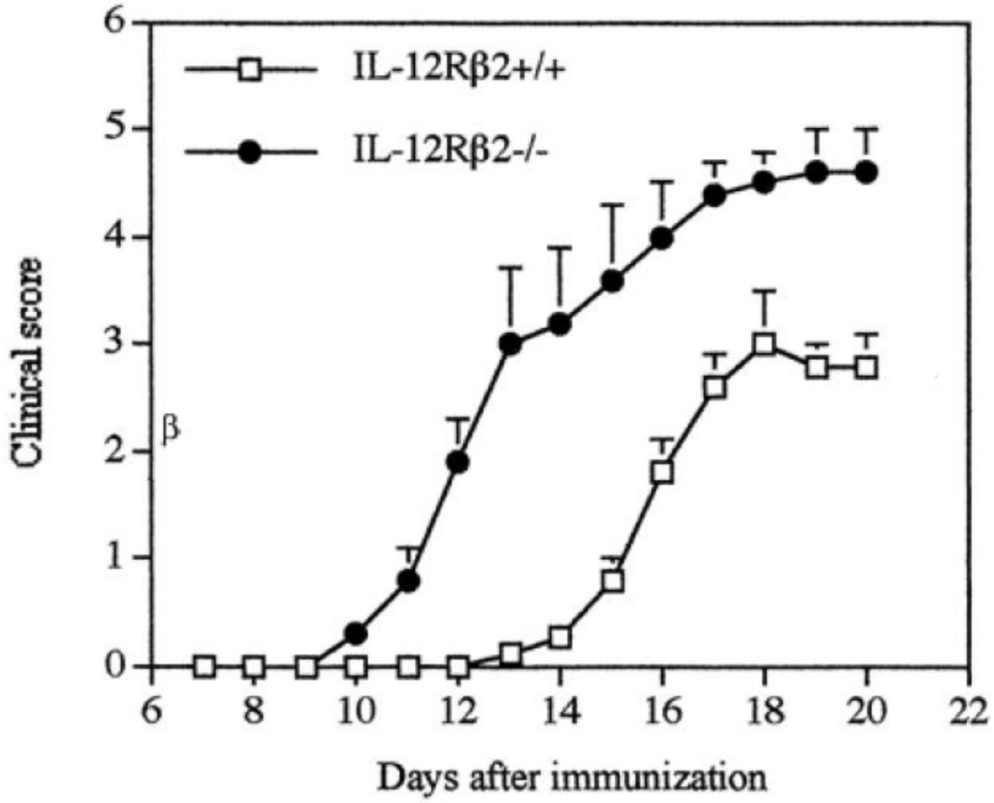

Figure 3.

IL-12Rβ2$^{-/-}$ mice develop severe EAE. Female WT and IL-12Rβ2$^{-/-}$ mice were immunized with MOG_{35-55} peptide in CFA. Data represent mean clinical score × SD. The overall clinical score was significantly different between WT and IL-12Rβ2$^{-/-}$ mice ($p < 0.001$). (Figure first published in *Journal of Immunology*, 2003, 170(4):2153-60, Zhang G-X et al., Induction of experimental autoimmune encephalomyelitis in IL-12 receptor-beta2-deficient mice: IL-12 responsiveness is not required in the pathogenesis of inflammatory demyelination in the central nervous system. Copyright 2003. The American Association of Immunologists, Inc.)

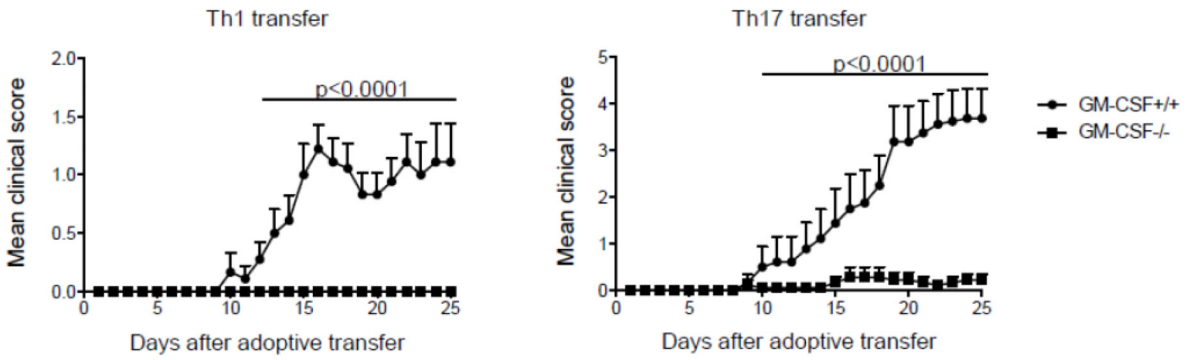

Figure 4.

GM-CSF production by Th1 and Th17 cells is required for their encephalitogenicity. WT or $Csf2^{-/-}$ $MBP_{(Ac1-11)}$ TCR-transgenic splenocytes were activated with $MBP_{(Ac1-11)}$ in the presence of IL-12 (Th1 conditions) or TGF-β plus IL-6, anti-IFN-γ and anti-IL-4 (Th17 conditions), then allowed to 'rest' for 2 days in the presence of IL-2; they were then reactivated for 72 h with $MBP_{(Ac1-11)}$ in the presence of IL-12 (Th1 conditions) or IL-23 (Th17 conditions). Clinical scores of mice that received 5×10^6 $MBP_{(Ac1-11)}$-specific WT or $Csf2^{-/-}$ Th1 or Th17 cells are shown. (Figure first published in: *Nature Immunology*, 2011 Jun;12(6):568-75. El-Behi M, et al., The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF.)

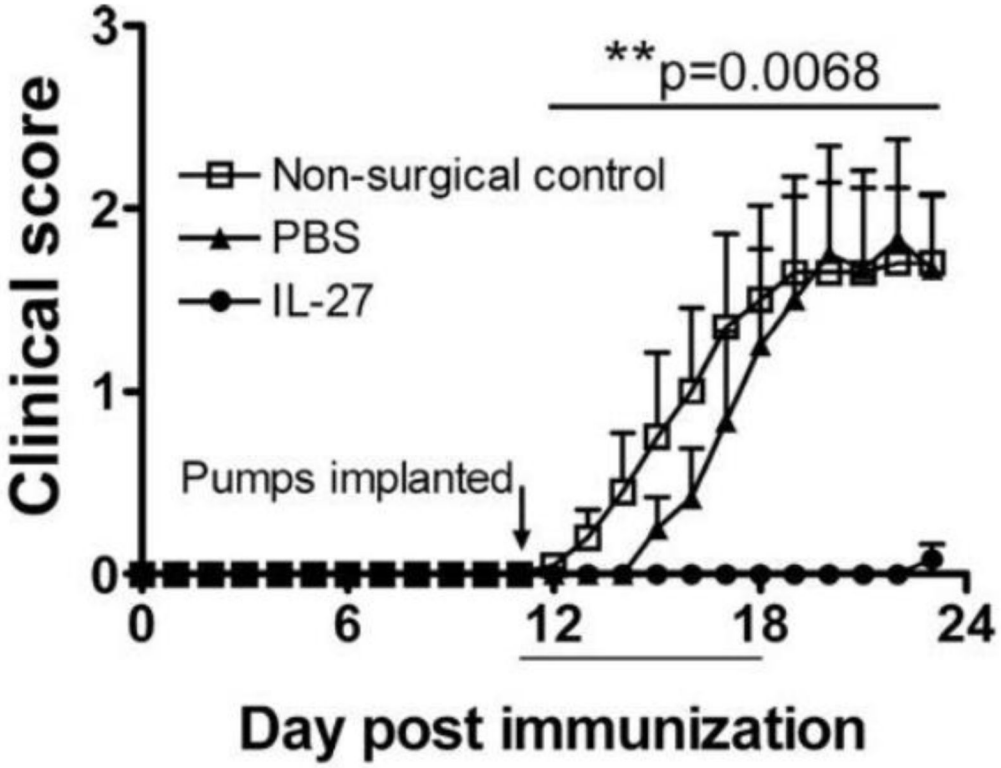

Figure 5.

Exogenous IL-27 suppresses actively induced EAE. EAE was induced in C57BL/6 mice with MOG_{35-55} and osmotic pumps (7-day delivery capacity) containing either rmIL-27 or PBS were implanted s.c. on day 11. Mice that did not undergo surgery were also assessed. (Figure first published in *Journal of Immunology* 179:3268-75, 2007, Fitzgerald DC et al., Suppressive effect of IL-27 on encephalitogenic Th17 cells and the effector phase of experimental autoimmune encephalomyelitis (EAE). Copyright 2007. The American Association of Immunologists, Inc.)

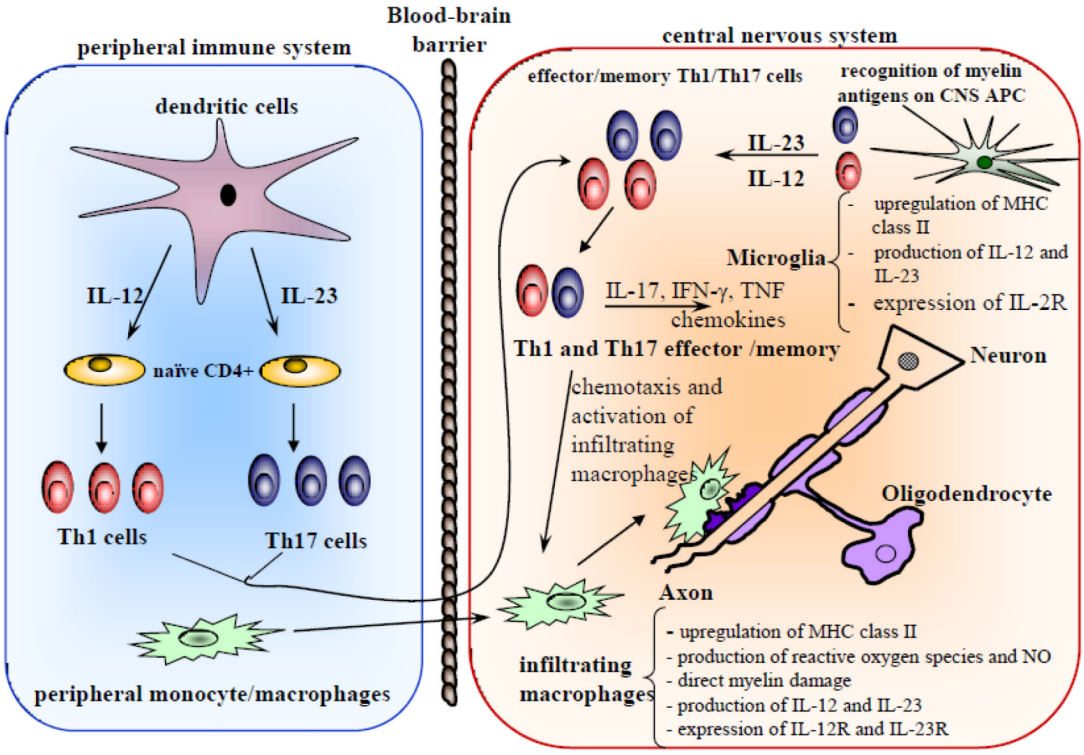

Figure 6.

Th1/Th17 paradigm of CNS inflammatory demyelination. In the peripheral immune system, IL-12 and IL-23, produced by dendritic cells, induces the differentiation of Th1 and Th17 cells, respectively. IL-12 is not strictly required and may actually play an immunoregulatory role in development of EAE, as mice that do not produce, or cannot respond to, IL-12 develop severe EAE. Activated Th1 and Th17 cells migrate into the CNS across the blood-brain barrier. In the CNS, myelin-reactive Th cells interact with resident microglia and are reactivated upon recognition of myelin antigens. Activated effector Th cells produce cytokines and chemokines that lead to an inflammatory pathological cascade in the CNS and damage to the myelin sheath and neuronal axons. (Figure first published in *Drug News & Perspectives* 19(2):77-83, 2006, Touil T et al., Pathophysiology of Interleukin-23 in experimental autoimmune encephalomyelitis. Copyright © 2006 Prous Science, S.A.U. or its licensors. All rights reserved.)