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FOCUS: NEUROSCIENCE

Cytokine Control of Inflammation and Repair in the Pathology of Multiple Sclerosis

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Cytokines are secreted signaling proteins that play an essential role in propagating and regulating immune responses during experimental autoimmune encephalomyelitis (EAE†), the mouse model of the neurodegenerative, autoimmune disease multiple sclerosis (MS). EAE pathology is driven by a myelin-specific T cell response that is activated in the periphery and mediates the destruction of myelin upon T cell infiltration into the central nervous system (CNS). Cytokines provide cell signals both in the immune and CNS compartment, but interestingly, some have detrimental effects in the immune compartment while having beneficial effects in the CNS compartment. The complex nature of these signals will be reviewed.

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†Abbreviations: EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; CD, cluster of differentiation; CFA, complete Freud's adjuvant; PLP, proteolipid protein; RRMS, relapsing remitting multiple sclerosis; APC, antigen presenting cell; CNS, central nervous system; BBB, blood brain barrier; MHCII, major histocompatibility complex class II; Th, T helper cell; Treg, T regulatory cell; IL, interleukin; STAT, signal transducer and activator of transcription; T-bet, Tbox expressed in T cells; IFN, interferon; TNF, tumor necrosis factor; KO, knock out; Jak, janus kinase; tmTNF-α, membrane bound TNF-α; NFκB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; CSF, cerebral spinal fluid; WT, wildtype; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; SLE, systemic multi-organ autoimmune disease; ROR, RAR-related orphan receptor; CCR, CC-chemokine receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; JNK, c-Jun N-terminal kinase; C/EBP, ccaat-enhancing binding protein; PI3K, phosphoinositide 3K; ERK, extracellular signal-regulated kinase; KC, keratinocyte-derived chemokine; G-CSF, granulocyte colony stimulating factor; NK, natural killer; FoxP3, forkhead P3; TGF, transforming growth factor; TLR, toll-like receptors; cKO, conditional knock out; CCL, cc-chemokine ligand; CNTF, ciliary neurotrophic factor; OPC, oligodendrocyte progenitor cell; TG, transgenic; Tx, treatment; cKD, conditional transgenic knock down in a specific cell population by lentiviral vector; rAdV, replication deficient adenovirus; r, recombinant; R, receptor; ab, antibody; act1 (IL-17R), act1 is an accessory protein of the IL-17 receptor complex; i.c., intracerebral administration; PI, post immunization.

Keywords: cytokines, experimental autoimmune encephalomyelitis, multiple sclerosis, neuroinflammation

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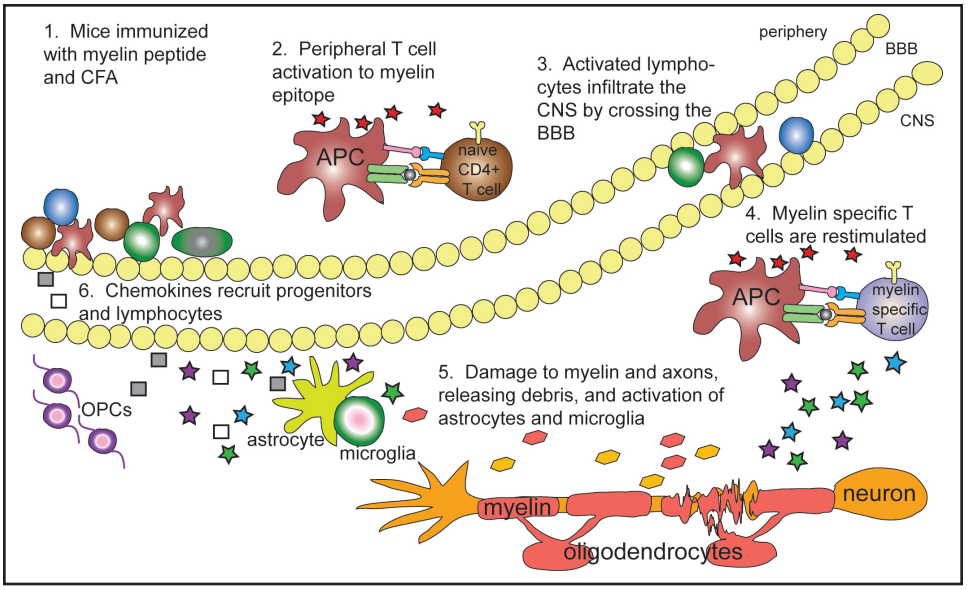

Figure 1. Diagram of EAE pathology. Stars represent cytokines, octagons represent debris, squares represent chemokines, and yellow circles are endothelial cells.

INTRODUCTION

Cytokines are small proteins or glycoproteins secreted by a wide range of cells for intercellular communication. In the context of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS), cytokines are intimately involved in the progression and regulation of disease. EAE is an autoimmune disease driven by myelin-specific cluster of differentiation (CD)4+ T cells that mediate the destruction of myelin and neural axons [1-3]. MS patients with demyelinated lesions experience neurological symptoms such as muscle spasms, cognitive deficits, numbness, blurred vision, and, in some cases, limb paralysis [4,5]. The etiology of MS is unknown, although it is well accepted that there are both genetic and environmental contributions [6]. Currently, treatments for MS address symptoms or broadly suppress the immune system [6], leaving a considerable opportunity for research into the cause and pathology of the disease in order to create a more effective treatment.

The role of cytokines and their respective receptors in MS pathology has been examined through histological studies on post-mortem MS tissue [7,8], murine models of MS such as EAE [9], and transgenic mice [10]. EAE is induced in mice by immunization with myelin peptide and complete Freud's adjuvant (CFA) or the adoptive transfer of CD4+ T cells from myelin peptide/CFA immunized mice into naïve recipients [3,11,12]. A major benefit of EAE is that immunization in different genetically susceptible strains of mice yield distinct disease courses, one of which is similar to the most common courses of MS. For instance, SJL/J mice immunized with peptide from proteolipid protein (PLP139-151)/CFA are susceptible to a relapsing-remitting disease course, which exhibits a disease course similar to relapsing-remitting MS (RRMS). The epitopes that drive MS, however, are unknown. In EAE, myelin-specific T cells are activated by antigen presenting cells (APCs) in the peripheral draining lymph nodes and infiltrate the central nervous system (CNS) by crossing the blood brain barrier (BBB) (Figure 1). Once in the brain or spinal cord, T cells are re-stimulated by APCs, and the resulting inflammation leads to myelin destruction, astrogliosis, and the production of chemotactic cytokines that recruit both progenitors and a secondary wave of leukocytes from the periphery (Figure 1) [6]. Disease progresses by lymphocytes launching re-

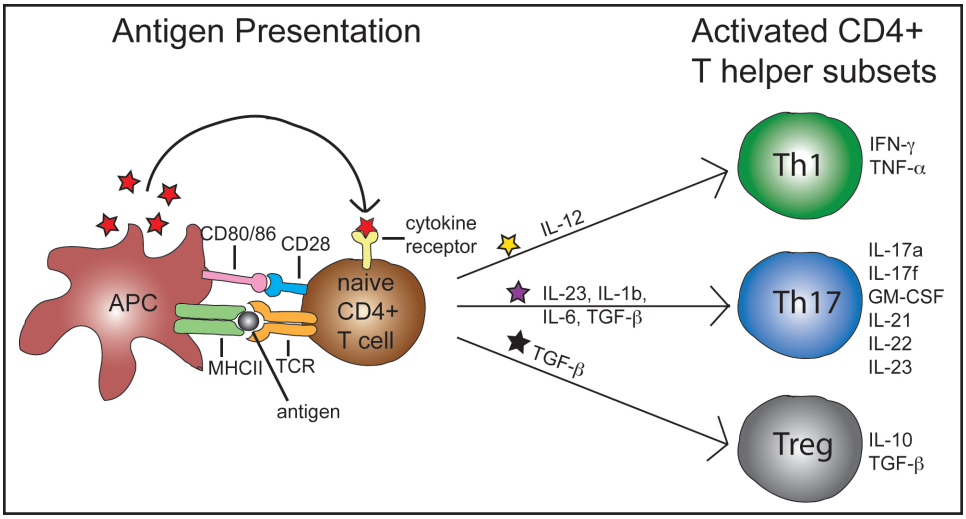

Figure 2. Diagram of cytokines produced by activated antigen presenting cells during antigen presentation to naïve T cells and the cytokines produced by T helper cells after differentiation. Stars represent cytokines.

sponses against new epitopes from the myelin and axon debris released in lesions [13]. Cytokines and chemokines are involved in every aspect of EAE pathology; however, only non-chemotactic cytokines will be reviewed. For a full review of chemokines and their involvement in EAE pathology, please refer to Dogan and Karpus, 2004 [14].

There are multiple pathways in which cytokines are involved in EAE pathology. In the immune compartment, cytokines are involved in modulating APCs for ideal antigen presentation to CD4+ T cells via the upregulation of major histocompatibility complex class II (MHCII), which presents cognate antigenic peptides to MHCII restricted peptide-specific T cell receptors on the surface of CD4+ T cells (Figure 2) [15]. Additionally, cytokines stimulate APCs to upregulate costimulatory molecules required for full T cell activation [15,16]. During T cell priming, APCs also release cytokines that induce differentiation of naïve CD4+ T helper cells into effector or regulatory T cell subsets: T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), or regulatory T cells (Treg) (Figure 2) [16]. Cytokines are also involved in aiding T cell trafficking into the CNS [17-20]. In the CNS compartment, cytokines affect the permeability of the blood brain barrier [21-24], oligodendrocyte progenitor differentiation [25-27], and activation of microglia and astrocytes to participate in disease progression and remyelination [28-31].

Due to the inducible nature of EAE, it can be used in transgenic mice, devoid of the cytokine gene of interest. This type of experimental approach has identified a substantial list of cytokines that are essential for disease induction or progression, as well as highlighting those that are important but surprisingly nonessential (Table 1). Cytokine research has also defined several pathogenic T cell subsets, often reopening the debate over which subsets are most essential in mediating disease. In the present review, cytokines will be examined within the context of these subsets.

CYTOKINES IN THE IMMUNE COMPARTMENT

Th1-Associated Cytokines

The discovery of EAE as a T cell-mediated disease prompted the search and characterization of such T cells. This breakthrough was based on the resistance of mice devoid of T cells to the induction of EAE and the restored susceptibility once CD4+ T cells were reintroduced or adoptively transferred [32]. The first CD4+ T cell subset determined to be

Table 1. Summary of EAE Outcomes in Transgenic and Cytokine Treated Rodents.

Cytokine/ Receptor	Tg/Tx	EAE Outcome	Reference
IL-23p19	KO	Resistant to disease onset	[49]
IL-23p19	KO + IL-23-rAdV	Susceptible	[49]
IL-12/23p40	KO	Resistant to disease onset	[49]
IL-12/23p40	KO + IL-23-rAdV	Delayed onset & attenuated disease	[49]
IL-12p35	KO	Susceptible	[49,50]
IFNγ	anti-IFNγ-ab	Exacerbated disease	[75,76]
IFNγ	KO	Exacerbated disease	[10]
IFNγ	rIFNγ	Resistant to disease onset	[77]
TNFα	KO	Resistant to disease onset	[88]
TNFα	KO + pertussis toxin	Susceptible	[88]
TNFα	anti-TNFα-ab	Delayed onset, prevents transfer disease	[86,87]
TNFR1	KO	Attenuated disease	[89]
TNFR1	anti-TNFR1-ab	Resistant to disease onset	[90]
TNFR2	KO	Exacerbated disease	[89]
TNFR1/TNFR2	KO	Resistant to disease onset	[89]
IL-17a	KO	Susceptible	[142]
IL-17f	KO	Susceptible	[142]
IL-17f	KO + anti-IL-17a-ab	Susceptible	[142]
IL-17a	anti-IL-17a-ab	Mildly reduced disease	[143]
IL-17R	anti-IL-17R-fc-ab	Attenuated disease	[142]
Act1 (IL-17R)	KO	Attenuated disease	[19]
Act1 (IL-17R)	cKO in neuroectoderm	Limited disease progression	[19]
Act1 (IL-17R)	cKO in myeloid lineage or epithelial cells	Susceptible, normal disease	[19]
Act1 (IL-17R)	cKD in astrocytes	Inhibited disease progression	[228]
GM-CSF	KO	Resistant to disease onset	[144]
GM-CSF	KO + rGM-CSF	Susceptible	[144]
GM-CSF	anti-GM-CSF	Attenuated disease	[146]
IL-21	KO	Susceptible	[156,157]
IL-21R	KO	Susceptible	[156,157]
IL-22	KO	Susceptible	[155]
IL-1βR1	KO	Attenuated disease	[106]
IL-1βR1	cKO in epithelial cell	Attenuated disease	[158]
IL-33Rα	KO	Exacerbated disease	[160]
IL-33	anti-IL-33-ab	Delayed onset, attenuated disease	[161]
IL-33	rIL-33	Exacerbated disease	[161]
IFN-β	KO	Exacerbated disease	[174]
IFNAR	cKO in myeloid lineage	Exacerbated disease	[175]
IFNAR	cKO in T cell, B cell, or neuroectodermal cells	Susceptible, normal disease	[175]
IL-10	rIL-10	Prevented disease onset	[190]
IL-10	rIL-10 i.c.	Delayed onset and attenuated disease	[192]
IL-10	IL-10-rAdV i.c.	Prevented (tx at day 10 PI) and attenuated (tx at day -2)	[192]

pathogenic in EAE was the Th1 subset [11,33-35]. Th1 activation is characterized by the requirement for the inductive interleukin (IL)-12 cytokine [36], expression of transcription factors signal transducer and activator of transcription (STAT)4 and T-box expressed in T cells (T-bet) [37,38], and the production of interferon (IFN)-γ and tumor necrosis factor (TNF)-α [33]. Th1 cells are important for protection against intracellular pathogens, but they are also pathogenic in EAE [39-41]. Not only is the adoptive trans-

fer of CD4+ Th1 cells sufficient to induce disease in naïve mice, but knock out (KO) mice of the transcription factors necessary for the differentiation of Th1 cells, STAT4 and T-bet, were found to be resistant to EAE [11,34,35,39,42,43].

IL-12 is a disulfide-linked heterodimer molecule composed of p35 (IL12A) and p40 (IL12B) subunits [44]. It is produced by APCs and stimulates pleiotropic biological activities in natural killer (NK) cells, CD4+ and CD8+ T cells [44]. In the presence of antigen presentation to a T cell, APCs produce IL-12 to induce a Th1 phenotype [36]. IL-12 signals through the STAT4 pathway to express the inducible subunit of the IL-12 heteromeric receptor, IL-12Rβ2, providing a positive feedback loop in Th1 differentiation [45,46]. Together with the constitutively expressed receptor subunit IL-12Rβ1, the receptor can bind IL-12, allowing for the tyrosine phosphorylation of IL-12Rβ2 and providing binding sites for the janus kinase (Jak)2 [47]. This pathway leads to the phosphorylation of the transcription factor STAT4, which translocates to the nucleus and binds to the IFN-γ promoter [48]. This feedback loop promotes a strong Th1 differentiation pathway, and thus, it was no surprise that IL-12p40 KO mice were found to be resistant to EAE [49,50]. However, the IL-12p40 subunit is shared with IL-23, where it dimerizes with IL-23p19 to signal through the IL-23R that consists of the IL-23R and IL-12Rβ1 subunits [44,51]. The more definitive study to determine whether IL-12 was actually essential for EAE disease induction compared disease courses in IL-12p35 KO, IL-23p19 KO, and the shared IL-12/23p40 KO mice [49,50]. The p19 KO and p40 KO mice were found to be resistant to EAE induction, while the p35 KO mice were found to be susceptible, revealing that IL-12 is not essential for disease induction (Table 1). These data suggest that although Th1 cells are sufficient to induce EAE, they are not the only effector population of CD4+ T cells in EAE.

The type-II interferon, IFN-γ, is a non-covalent homodimer cytokine that is classically involved in immunity against viruses, bacteria, and tumors as it is known to be secreted by NK cells, NK T cells, CD4+ T cells, CD8+ T cells, and professional APCs [52-57]. It signals through the IFN-γ receptor, consisting of two subunits, IFN-γR1 and IFN-γR2 [58]. Once bound to its receptor, IFN-γ induces signaling through the JAK1&2/STAT1 pathway, resulting in the promotion or blocking of specific genes [59-66]. Notably, IFN-γ enhances APC function by promoting the upregulation of molecules important for antigen presentation such as MHCII and co-stimulatory molecules such as CD80 and CD86 [67-70].

IFN-γ is produced by Th1 cells, including myelin specific T cells [71,72]. IFN-γ levels correlate with disease severity in EAE, suggesting that it is pathogenic [73,74]. Despite the sufficiency of Th1 cells to induce disease, treatment of EAE with anti-IFN-γ antibody and mice with disrupted IFN-γ gene expression exhibited more severe EAE disease (Table 1) [10,75,76]. Additionally, treatment with recombinant IFN-γ attenuated disease (Table 1) [77]. Collectively, these data suggest that the pathway controlling Th1 differentiation contributes to disease, yet their production of IFN-γ is not essential. This discovery led to research focused on other mechanisms of encephalogenicity by myelin specific CD4+ T cells.

TNF-α is a 17 kDa transmembrane or soluble protein that is capable of signaling as a homotrimer while it is membrane bound (tmTNF-α) or in a soluble form once it is proteolytically cleaved by metalloprotease TNF-α converting enzyme [78]. Although activated macrophages and T cells are a major source of TNF-α, several other cell types, including brain resident cells, are capable of producing it as part of the acute phase response to bacterial products, injury, and IL-1 [78,79]. TNF-α signals through two receptors; TNFR1 is widely expressed and binds both membrane bound and soluble forms of TNF-α, whereas TNFR2 is mainly expressed on lymphocytes and binds to membrane bound ligands [80,81]. TNF-α signaling mediates cell death cascades through activating one or more of the three

classic pathways: nuclear factor (NF)κB, mitogen activated protein kinase (MAPK), and caspases [82,83]. Apoptosis is an important part of the inflammatory response to clear infected cells or tumors, making TNF-α a critical and well-researched cytokine.

In MS, TNF-α is found at high levels in patients' cerebral spinal fluid (CSF) and active lesions [84,85]. TNF-α can be produced by lymphocytes and activated glia (astrocytes and microglia) [78,79]. TNF-α is classically a proinflammatory cytokine, thus it was no surprise that TNF-α deficient mice and wildtype (WT) mice treated with blocking antibodies for TNF-α were found to be resistant to EAE induction or had delayed onset (Table 1) [86-88]. However, a divergent role for TNF-α was discovered with single and double receptor KO mice. Single TNFR1 and double TNFR1/TNFR2 KO mice experienced milder disease or were found to be resistant to EAE, whereas TNFR2 KO mice exhibited significantly enhanced disease (Table 1) [89,90]. These data suggest that tmTNF-α signaling with TNFR2 has a protective role [91]. It is this protective role that may explain why a significant number of MS patients treated with anti-TNF-α in a clinical trial experienced exacerbated disease [92,93]. Moreover, patients with other autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) who were treated with anti-TNF-α agents experienced demyelinating lesions, suggesting that TNF-α is also important for myelin maintenance [94-99].

The research into the EAE pathological contributions of IL-12, IFN-γ, and TNF-α revealed several important conclusions. Even if a T cell population is pathogenic, its encephalogenicity may not be dependent on the main cytokines that they produce. Also, therapeutically targeting a cytokine and its respective receptors may yield different effects. Most importantly, therapeutically targeting a cytokine in mice may not translate to an effective treatment in humans. The failure of the anti-TNF-α agents to effectively treat MS and the drug's ability to cause demyelinating lesions in non-neurodegenerative, autoimmune disease patients was shocking. Caution should be applied when targeting cytokines with pleiotropic effects. It may be safer to target specific receptors if cytokine pathways are targeted at all. IFN-γ and TNF-α levels are currently excellent read outs for whether or not tested drugs are effective at ridding the CNS of Th1 mediated inflammation. Although the research into IFN-γ and TNF-α and their role in EAE did not yield an effective treatment for MS, it did reveal that there is another pathogenic T cell subset involved in EAE pathology.

Th17-Associated Cytokines

Th17 cells are a subset of CD4+ T helper cells that are involved in protection against TLR2-mediated bacterial and fungal infections, but primarily integral in autoimmune pathology such as RA, IBD, psoriasis, systemic multi-organ autoimmune disease (SLE/lupus), and MS [49,100-104]. Originally, Th1 cells were believed to be the most important cells driving MS pathology, but the EAE susceptibility of IFNγ KO mice [10] led to the search for another mechanism of disease. The importance of Th17 cells in EAE was identified by the study previously described, i.e., where IL-23p19 KOs were found to be resistant to EAE but IL-12p35 KOs were not [49,104]. This was important because IL-23 is the cytokine that APCs produce to induce a Th17 phenotype from naïve CD4+ cells during antigen presentation. Furthermore, the adoptive transfer of myelin-specific Th17 cells into naïve mice was sufficient to induce EAE [104]. However, the lone transfer of Th1 cells is also sufficient to induce disease, thus both T cell subsets contribute to disease, the balance of which is still being researched heavily.

Th17 cell differentiation can be induced by IL-23, IL-1β, IL-6, and transforming growth factor (TGF)-β [105,106], promoted by transcription factors RAR-related orphan receptor (ROR)γt and STAT3 [107-109], and maintained by IL-23 (Figure 2) [110]. Th17 cells are also defined by their C-C chemokine receptor (CCR)6 expression, and their entrance into the CNS is dependent

upon that receptor [111]. Th17 cells are classically known by their production of IL-17a and IL-17f; however, they are also capable of producing IL-21, IL-22, IL-23, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Figure 2) [112]. Th17 differentiation can be inhibited by cytokines produced by other T helper subsets such as IFN-γ [113].

IL-23 is heterodimeric protein made up of two subunits, p19 and p40, the latter being the subunit shared with IL-12 [114]. IL-23 signals through the IL-23 receptor, which is a combination of the IL-23R and IL-12Rβ1 subunits [115]. IL-23 also activates the transcription factor STAT3 for promoting Th17 development, maintenance, and IL-17a production [116,117].

As previously discussed, IL-23 is important for Th17 differentiation and the induction of EAE [49,104]. The encephalogenicity of Th17 cells is dependent upon IL-23 signaling during antigen presentation, but not the TGF-β and IL-6 exposure previously described *in vitro* [118]. IL-23 receptor signaling is also required for Th17 accumulation in the CNS [118,119]. Although it is not an effector cytokine, IL-23 is an essential cytokine driving EAE by promoting and maintaining Th17 cells and mediating their growth in the CNS.

IL-17 is a 35kDa secreted glycoprotein that signals as a homodimer or heterodimer [120,121]. There are six members in the IL-17 family, IL-17a-f, and their unique protein structure bears no resemblance to other cytokines [122]. IL-17f shares roughly 50 percent homology with IL-17a, whereas B-E shares less than 30 percent homology with it. IL-17a and IL-17f signal through the IL-17 receptor complex, IL-17R, which includes a heterotrimer of IL-17RA and IL-17RC [123-125]. Human IL-17a and IL-17f have the same binding affinity for IL-17RC, but IL-17a has a much higher affinity for IL-17RA [120,122]. The IL-17R complex signals through multiple pathways, including NFkB, MAPKs, JAK/STAT, c-Jun N-terminal kinases (JNKs), Ccaat-enhancer-binding-proteins (C/EBPs), phosphoinoitide 3-kinase (PI3K), and extracellular signal-regulated kinases (ERKs) [122,126-128]. These pathways mediate the expression of IL-6, keratinocyte-derived chemokine (KC), granulocyte colony-stimulating factor (G-CSF), and other chemokines [129,130]. In synergy with TNF-α, IL-17 signaling is also capable of stabilizing the mRNA of several TNF-α induced genes [130].

Th17 cells are not the only source of IL-17; γδT cells, CD8+ T cells, natural killer (NK) cells, induced NK cells, neutrophils, and macrophages are also known to produce IL-17 [131-135]. IL-17 is well-known for recruiting neutrophils due to their high expression of IL-17R and potent acute phase responses [136,137]. In MS, IL-17 is present in active plaques and CSF of patients with active disease [138-140]. However, the IL-17a KO, IL-17f KO, and IL-17f KO mice treated with IL-17a neutralizing antibodies were all found to be susceptible to EAE (Table 1) [141,142]. Antibody-mediated neutralization of IL-17a in wildtype (WT) mice only mildly reduced disease severity [143]. Although the Th17 subset is named after their production of IL-17a and f, IL-17 is not the essential effector cytokine produced by IL-23 induced Th17 cells, leading to a widespread search for an effector cytokine of Th17 cells.

GM-CSF is an IL-23-driven Th17 cytokine [144-146]. It is a protein that signals through the heterodimer GM-CSF receptor, CD119, made up of alpha and beta subunits [147-149]. GM-CSF activates myeloid lineage cells such as granulocytes, macrophages, epithelial cells, microglia, and monocytes to rapidly proliferate via JAK2/STAT5 and MAP kinase signaling pathways [150]. This mitogenic activity is an essential step in activating APCs during a wide variety of immune responses.

In EAE, GM-CSF is necessary for disease as GM-CSF KOs were found to be resistant to disease induction (Table 1) [144]. Disease can be rescued by the administration of GM-CSF post myelin immunization (Table 1) [144]. Due to the variety of cells GM-CSF can stimulate, it was important to determine the cell in which signaling was necessary for disease. A bone marrow chimera study determined that myeloid

cells, but not microglia, are key responders [146]. This corresponds with earlier observations that GM-CSF administration stimulated CD11b+ Ly6C hi monocytes into the circulation [151]. GM-CSF is an IL-23 driven Th17 effector cytokine in EAE, but more research is needed in determining whether this is a worthwhile therapeutic target.

IL-21 and IL-22 were initial candidates for essential effector cytokines in EAE because Th17 and γδT cells produce them [152,153], and the gene for the IL-22 receptor is associated with MS risk [154]. However, the transgenic KO mice for IL-21, IL-21 receptor, and IL-22 were all found to be susceptible to EAE induction (Table 1) [155-157]. Moreover, Th17 development and recruitment to the CNS was normal in IL-21 and IL-21 receptor KOs [157]. These data suggest that IL-21 and IL-22 are not effector cytokines driving EAE.

IL-1β is a protein produced by activated macrophages to mediate plieotropic effects that range from proliferation to apoptosis. Due to this dynamic signaling, IL-1β plays multiple pathogenic roles in EAE. The importance of IL-1β is highlighted by the significant reduction in disease severity during EAE in IL-1β receptor KO mice (Table 1) [106]. IL-1β is involved in Th17 differentiation, T cell trafficking, and CNS tissue damage [106,158,159].

Th17 cells can be induced *in vitro* in a number of ways; however, IL-23 remains the most important for driving effective Th17 mediated disease [104]. In combination with IL-23, IL-1β promotes differentiation of pathogenic Th17 cells as well as γδ T cells [106,153]. IL-1β may play a role in lymphocyte trafficking into the CNS because the conditional KO (cKO) of the IL-1 receptor in epithelial cells exhibited decreased disease severity, adhesion molecule expression, and CD45+ cell infiltration (Table 1) [158]. There is also evidence that suggests that IL-1β causes disruption in inhibitory connections in the cerebellum during EAE and MS [159]. IL-1β is a cytokine common to many immune responses, but contributes several key pathogenic steps in EAE.

IL-33, an IL-1 family cytokine, is emerging as another potential cytokine important to disease progression. There are elevated levels of IL-33 in the spinal cord during EAE [160,161]; however, the results from EAE experiments in IL-33 receptor KO mice and wildtype mice with neutralizing antibodies against IL-33 provide conflicting conclusions (Table 1). More research will determine whether IL-33 is inflammatory or regulatory in EAE pathology.

Compared to the Th1 story, the Th17-associated cytokines are still being heavily studied for both pathogenic contributions and therapeutic targeting. Similar to IFN-γ and Th1 cells, IL-17 was found to be nonessential to Th17 cell encephalogenicity. However, there are more cytokines associated with inducing or being produced by Th17 cells that may be important. This exciting area of research is being studied in the CNS compartment as well.

Regulatory Cytokines

IFN-β is a type I interferon, a class of cytokines that are produced by host cells in response to virus, bacteria, parasite, or tumor recognition [162]. In autoimmune diseases such as SLE and Aicadi-Goutieres Syndrome, type I IFNs are associated with driving disease progression; however, in MS, IFN-β has a potent anti-inflammatory effect and has been used to treat RRMS for nearly two decades [163-165]. For 80 percent of RRMS patients, IFN-β treatment extends remission periods and decreases the frequency and severity of relapses, but only recently have researchers begun to understand why the other 20 percent are unresponsive [166]. There is evidence that IFN-β suppresses Th17 cells in multiple ways [113,167-171], but is ineffective in regulating Th1-mediated inflammation [167], suggesting that RRMS patients who are unresponsive to IFN-β treatment have more of a Th1-mediated pathology than Th17. However, there is also evidence that supports the exact opposite conclusion [172,173]. The balance between Th1- and Th17-mediated MS has been the aim of several studies in the last few years; however, there is still a large amount of research yet to be done to end the debate.

The effectiveness of IFN-β treatment in RRMS is mirrored by its ability to suppress EAE, as well as the exacerbated disease observed in IFN-β KO mice (Table 1) [174]. To determine which cell type was the most important responder to IFN-β mediating disease regulation, cell type-specific KO mice of the type I interferon receptor IFNAR were examined for EAE severity [175]. Disease severity was increased in myeloid lineage specific KO of IFNAR but not in the T cell, B cell, or neuroectodermal specific KO mice, which strongly suggests that immunoregulation by IFN-β is mediated by myeloid-derived APCs such as dendritic cells and macrophages [175].

Tregs are forkhead box P3 (Foxp3)+ CD4+ CD25+ T cells that either naturally develop in the thymus or can be induced in the periphery. They are maintained by the presence of TGF-β during antigen presentation and suppress Th1 and Th17 cells through IL-10 and TGF-β expression (Figure 2). Tregs are a necessary part of any immune response because as soon as pathogens are cleared and immunity is acquired, they limit the inflammation in order to protect host tissue from bystander damage. In autoimmunity, Tregs can be ineffective in controlling host-specific T cell responses, allowing chronic damage to the host.

IL-10 is a powerful anti-inflammatory cytokine. IL-10 signals as a homodimer by binding with the heterodimeric IL-10 receptor to suppress expression of inflammatory cytokines, adhesion molecules, and proteins essential for antigen presentation [176]. Regulatory immune cells such as Tregs and regulatory B cells exert their control through IL-10 production; however, multiple cell types are capable of producing it in response to danger signals such as endotoxins, catecholamines, and TNF-α [177-180].

Relevant to EAE pathology, IL-10 is best known for its ability to inhibit the gene expression of Th1 induced cytokines [181,182] in T cells, macrophages, and monocytes [183]. Additionally, IL-10 significantly reduces APC activation states by reducing their expression of proteins necessary for antigen presentation such as MHCII, costimulatory molecules, and adhesion molecules [184,185]. T and B cells are also affected by IL-10. Th1 cell proliferation is limited by IL-10, but surprisingly Th17 and cytotoxic CD8+ T cells are unaffected [186,187]. Conversely, IL-10 promotes immunity by enhancing B cells proliferation and differentiation into plasma cells [188,189]. As far as EAE pathology was concerned, IL-10 had considerable interest in its therapeutic potential. As expected, IL-10 administration prevented and attenuated EAE (Table 1) [190-192]. Unfortunately, IL-10 administration also inhibits immune-mediated tumor regulation, promoting cancerous tumor growth [182]. In fact, tumor cells often overexpress IL-10 as a mechanism of evading the immune system [193,194]. Thus, IL-10 is an important regulatory cytokine that the immune system uses to control local inflammation, but it is a difficult target to therapeutically capitalize on because it is capable of creating an equally undesirable imbalance in the immune system.

TGF- β1 is a secreted protein that signals as a homodimer to control cell growth and differentiation. TGF-β signals through a TGF-β receptor made up of a homo or heterodimer of TGF-β receptor types 1, 2, or 3. Upon ligand binding to a type 2 receptor dimer, a type 1 receptor dimer is recruited to make up a heterotetrameric receptor complex [195]. TGF-β classically signals through the SMAD pathway [195,196] to inhibit cell growth.

The role of TGF-β in EAE pathology has been controversial in the context of skewing naïve T cells into Th17 or Treg differentiation by APCs. In the presence of IL-6 and antigen presentation, TGF-β can induce IL-17 producing T cells *in vitro* [104,197,198]. However, data suggests that these cells are not pathogenic in EAE, but instead IL-23-induced Th17 cells drive disease [118]. Conflicting studies have led the field to consider the plasticity of Th17 and Treg cells during immune responses and MS pathology, but more research is needed.

The role for TGF-β as an effector cytokine of Tregs is less controversial. Not only do Tregs produce TGF-β, but TGF-β

signaling is necessary for natural Treg survival [199]. TGF-β can be produced by other cells types, but Treg cells are the essential source for maintaining self tolerance [200,201,202]. TGF-β suppresses Th1 differentiation by inhibiting T-bet and STAT4 expression [203]. Treg cells regulate immune responses and maintain self-tolerance through IL-10 and TGF-β production. In MS, this balance between inflammation and regulation is uneven.

Regulatory cytokines are sought after for therapeutic reasons due to their fundamental ability to suppress immune responses. Fortunately IFN-β is currently used to treat the majority of RRMS patients; however, more research is being done to understand why it is ineffective for treating a portion of RRMS patients and other forms of MS. IL-10 cannot be targeted for treatment of MS due to the consequences of tumor growth. TGF-β is not ideal for therapeutic targeting because it may be involved in skewing T cells to a Th17 phenotype in the presence of IL-6. Thus, other than IFN-β, there have not been any other regulatory cytokines safe for treating MS.

CYTOKINES IN THE CNS COMPARTMENT

Once lymphocytes cross the BBB (a process reviewed by Alvarez et al., 2011, [204]) and infiltrate the CNS, they encounter brain resident cells: neurons, astrocytes, microglia, oligodendrocytes, and progenitors. Neurons actively communicate to facilitate the main functions of the brain. As the most abundant cell type in the CNS, astrocytes are stationed everywhere in order to regulate homeostasis. Microglia, distinct for their myeloid origin, constantly survey the CNS for infections and tissue damage and then appropriately respond to clear them. The dense lipid bilayer processes of oligodendrocytes, known as myelin, are responsible for wrapping the long axons of neurons to insulate fast, electrical signaling. Microglia are the primary responders to pathogens, inflammation, and debris; however, astrocytes and oligodendrocytes are also capable of recognition and responding. Understanding the microenvironment of the brain is necessary for studying the immune responses within it; therefore, cytokine-mediated effects will be discussed by cell type.

Microglia have many similarities to peripheral immune cells, including their activity during EAE. First, in a resting state, they survey the CNS for signs of trauma or infections [205]. Once they encounter antigen from debris, infected cells, and viral or bacterial protein, microglia become activated. Classical activation leads to both innate and adaptive immune responses. Microglia are highly sensitive to pathogen-associated molecular patterns sensed by pattern recognition receptors such as Toll-like receptors (TLRs) [206] and NOD-like receptors; similar to macrophages, this recognition induces proliferation and launches the upregulation of proinflammatory cytokines, chemokines, antimicrobial peptides, reactive oxygen species, and nitric oxide [207]. Microglia also are capable of phagocytosing debris and infected cells. Classically activated microglia also upregulate proteins necessary for antigen presentation, which allow them to present antigen to infiltrating T cells. In EAE, disease progression depends on the reactivation of T cells in the CNS, and although microglia are not the only cells that are responsible, they certainly are capable of it [208,209].

Microglia promote both disease progression and endogenous repair during EAE. Disease progression is mediated by antigen presentation to infiltrating T cells, which involves cytokine production by microglia and results in more inflammatory cytokine production by reactivated T cells [210,211]. For example, microglia produce TNF-α, IL-6, and IL-1β in response to IFN-γ or TLR stimuli [206,212]. Microglia promote an environment conducive to remyelination [213], the process of oligodendrocyte progenitor cells (OPCs) differentiating into mature, myelinating cells following a demyelinating insult. For instance, the production of TNF-α and IL-1β can have beneficial effects in the CNS. Mice lacking the TNF or IL-1β gene experienced a delay in remyelination,

suggesting that they are involved in the reparative process [214]. The protective phenotype of IL-4 conditioned microglia promotes OPC proliferation and expression of insulin-like growth factor, a trophic factor for neural tissue [215]. Along with infiltrating macrophages, microglia also promote oligodendrocyte regeneration by phagocytosing myelin debris and apoptotic cells, but this can be blocked by TNF-α [216-218]. Cellular debris is inhibitory to remyelination, making the phagocytosing activity of microglia essential for recovery [219].

Astrocytes are no longer considered "support" cells; they are directors in the CNS as they have an indispensable role in nearly every cellular process. As reviewed by Wang and Bordey (2008), astrocytes are involved in development by controlling neural maturation, synaptogenesis, and angiogenesis; maintain homeostasis by buffering extracellular potassium and neurotransmitter concentrations; communicate with other astrocytes and possibly neurons by calcium signaling; regulate synaptic plasticity; participates in BBB regulation; and in response to inflammation or tissue injury, protect neurons by physically containing it and alerting both microglia and progenitors [220,221]. These dynamic cells are very involved in cellular processes in the CNS; however, their responses to inflammatory cytokines are their most important role during EAE.

In response to cytokines, astrocytes balance both disease progression and promote repair [222]. Astrocytes promote disease progression by expressing chemokines that attract more lymphocytes from the periphery and secondary to microglia, reactivate T cells by presenting antigen [221]. IFN-γ induces the upregulation of MHCII and costimulatory factors in astrocytes, which can be inhibited by TNF-α, IL-1α, and TGF-β [223-225]. IFN-γ stimulated astrocytes are capable of inducing Th1 differentiation and proliferation from naïve T cells and sufficiently re-stimulate T cells before adoptive transfer into naïve mice to induce EAE [70,223,226]. Myelin-specific T cell proliferation induced by IFN-γ-stimulated astrocytes can be blocked by antibodies against IL-12/23 p40, suggesting that astrocytes can promote Th1 and Th17 subsets [227].

Whether or not astrocytes actively prime T cells *in vivo* is unknown; however, there is strong evidence that their response to IL-17 signaling is necessary for disease progression [19]. A neuroectodermal cKO of act1, an integral adapter protein in the IL-17R signaling complex, experienced normal disease induction but limited progression and secondary infiltration of leukocytes, whereas the cKO in the myeloid compartment exhibited normal disease (Table 1) [19]. Supporting this data, a knock down of IL-17R specifically in astrocytes inhibited disease progression (Table 1) [228]. Due to the ability of astrocytes to upregulate a variety of chemokines depending on the stimulus [221], it is possible that they play an active role in recruiting DCs and myelin specific T cells in a subset-specific way. Th17 cells can be defined by their expression of CCR6, a receptor for the C-C chemokine ligand (CCL)20, and astrocytes stimulated with IL-1β and TNFα express CCL20 [17,111]. These data suggest that it is possible that astrocytes are important for Th17 recruitment during later stages in EAE. Stimulus-specific chemokine expression is a hallmark of astrocytic immune responses, which may be manipulated in different ways by the microenvironment of each form of MS.

Additionally, inflammation induces astrocytes into a protective phenotype that promotes cell survival and repair. Activated astrocytes form a physical barrier known as astrogliosis in order to contain inflammation and prevent further tissue destruction [229]. Astrocytes can also control microglial responses by either activating them with G-CSF and GM-CSF or suppressing them with TGF-β and IL-10 [230-233]. Even though IL-6 mediates chronic inflammation in the periphery, it has a neuroprotective effect on astrocytes. IL-6 stimulates astrocytes to produce neurotrophins such as neurotrophin-3, neurotrophin-4, and nerve growth factor, which support neuronal and oligodendroglial survival [234]. The frequency of IL-6 producing astrocytes is also correlated with oligoden-

drocyte preservation near inactive MS lesions [235]. Astrocytic production of IL-6 can also mediate neuronal survival during glutamate toxicity by stimulating the upregulation of Adenosine A(1) receptors [236]. IL-1β also induces a protective response in astrocytes. It can activate astrocytes to restore the BBB following CNS insult [237], making it more difficult for leukocytes to infiltrate. Astrocytic upregulation of the neuronal and glial trophic factor, ciliary neurotrophic factor (CNTF) following CNS injury is dependent on IL-1β signaling [238]. Not only does CNTF provide a survival signal to neurons and oligodendrocytes, it also promotes adult OPC differentiation *in vitro* [239,240]. Overall, astrocytes can have both a detrimental and protective effect during EAE, depending on the microenvironment in which they are exposed. At first, it seems counterproductive, but astrocytes are really multitasking to control a dire situation.

Oligodendrocytes are necessary for optimal neuronal signaling. The processes of oligodendrocytes wrap tightly around segments of axons; often one oligodendrocyte ensheaths multiple axons instead of multiple segments on just one axon. Myelin insulates axons for optimal speeds of conduction by lowering the capacitance across the membrane and increasing the electrical resistance. Action potentials propagate due to ions flowing across the membrane at the nodes between myelin segments, forcing the current to hop from one node to the next, down the axon. Without this, or if part of the myelin is damaged during MS, neuronal signaling can become erroneous and leaves the denuded axon vulnerable to damage itself.

Although the main purpose of oligodendrocytes is myelination, they are responsive to cytokine signaling. In MS, OPCs are also extensively studied for their response to inflammation because they are necessary for remyelinating lesions. Most direct effects have been assessed on primary rat OPC cultures and brain slice cultures, but *in vivo*, remyelination as a process can be assessed in transgenic mice after a demyelinating insult. Remyelination is an endogenous process that involves the migration of progenitors to the lesion, proliferation, maturation, and wrapping of an axon. Cytokines often enhance one step while simultaneously inhibiting another, making it very complicated to strategically enhance remyelination altogether. For instance, TGF-β and IL-1β each individually inhibit OPC proliferation but enhance survival and differentiation [27,241]. For IFN-γ, differential effects may be concentration dependent as high levels lead to demyelination, but low levels are associated with protecting mature oligodendrocytes [242-245]. TNF-α is quite destructive along the entire lineage; it inhibits OPC proliferation and differentiation while also inducing apoptosis in mature oligodendrocytes [26,246,247]. Conversely, IL-6 enhances OPC differentiation and survival even in the presence of glutamate excitotoxicity [248,249]. Surprisingly, IFN-β has no effect on the proliferation, differentiation and survival of an OPC cell line [250], suggesting that the beneficial effects of IFN-β administration in EAE and MS are solely in the immune compartment. This one-sided effect seems to be unique to IFN-β because most of the cytokines that are pro-inflammatory in the immune compartment stimulate multiple protective or reparative effects in the CNS compartment.

SUMMARY

In summary, cytokines produced by cells mediating both the innate and adaptive immune responses, as well as cytokines produced by CNS-resident cells, orchestrate a variety of inflammatory and protective responses in the pathophysiology of MS. A more complete understanding of these responses and how they can be controlled should lead to more effective therapies for MS.

REFERENCES

1. Holda JH, Swanborg RH. Autoimmune effector cells. II. Transfer of experimental allergic encephalomyelitis with a subset of T lymphocytes. Eur J Immunol. 1982;12(5):453-5.
2. Lisak RP, Behan PO. Experimental autoimmune demyelinating diseases: experimental allergic encephalomyelitis and experimental allergic neuritis. Biomedicine. 1975;22(2):81-7.
3. Lebar R, Voisin GA. [Use of water-soluble adjuvant fraction from "Mycobacterium

smegmatis" with encephalitogenic basic protein to induce autoimmune experimental allergic encephalomyelitis in guinea pigs (author's transl)]. Ann Immunol (Paris). 1974;125(6):911-6.
4. Schwyzer RU, Henzi H. Reflections on the pathogenesis of optic (retrobulbar) neuritis in multiple sclerosis. Med Hypotheses. 1988;27(3):167-79.
5. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Philos Trans R Soc Lond B Biol Sci. 1999;354(1390):1649-73.
6. Miller E. Multiple sclerosis. Adv Exp Med Biol. 2012;724:222-38.
7. Kreth HW, Dunker R, Rodt H, Meyermann R. Immunohistochemical identification of T-lymphocytes in the central nervous system of patients with multiple sclerosis and subacute sclerosing panencephalitis. J Neuroimmunol. 1982;2(2):177-83.
8. Hauser SL, Bhan AK, Gilles F, Kemp M, Kerr C, Weiner HL. Immunohistochemical analysis of the cellular infiltrate in multiple sclerosis lesions. Ann Neurol. 1986;19(6):578-87.
9. Eng LF, Ghirnikar RS, Lee YL. Inflammation in EAE: role of chemokine/cytokine expression by resident and infiltrating cells. Neurochem Res. 1996;21(4):511-25.
10. Ferber IA, Brocke S, Taylor-Edwards C, Ridgway W, Dinisco C, Steinman L, et al. Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). J Immunol. 1996;156(1):5-7.
11. Pettinelli CB, McFarlin DE. Adoptive transfer of experimental allergic encephalomyelitis in SJL/J mice after in vitro activation of lymph node cells by myelin basic protein: requirement for Lyt 1+ 2- T lymphocytes. J Immunol. 1981;127(4):1420-3.
12. Lublin FD. Relapsing experimental allergic encephalomyelitis. An autoimmune model of multiple sclerosis. Springer Semin Immunopathol. 1985;8(3):197-208.
13. McRae BL, Vanderlugt CL, Dal Canto MC, Miller SD. Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis. J Exp Med. 1995;182(1):75-85.
14. Dogan RN, Karpus WJ. Chemokines and chemokine receptors in autoimmune encephalomyelitis as a model for central nervous system inflammatory disease regulation. Front Biosci. 2004;9:1500-5.
15. Nakahara T, Urabe K, Fukagawa S, Uchi H, Inaba K, Furue M, et al. Engagement of human monocyte-derived dendritic cells into interleukin (IL)-12 producers by IL-1beta + interferon (IFN)-gamma. Clin Exp Immunol. 2005;139(3):476-82.
16. Petermann F, Korn T. Cytokines and effector T cell subsets causing autoimmune CNS disease. FEBS Lett. 2011;585(23):3747-57.
17. Ambrosini E, Columba-Cabezas S, Serafini B, Muscella A, Aloisi F. Astrocytes are the major intracerebral source of macrophage inflammatory protein-3alpha/CCL20 in relapsing experimental autoimmune encephalomyelitis and in vitro. Glia. 2003;41(3):290-300.
18. Skundric DS, Huston K, Shaw M, Tse HY, Raine CS. Experimental allergic encephalomyelitis. T cell trafficking to the central nervous system in a resistant Thy-1 congenic mouse strain. Lab Invest. 1994;71(5):671-9.
19. Kang Z, Altuntas CZ, Gulen MF, Liu C, Giltiay N, Qin H, et al. Astrocyte-restricted ablation of interleukin-17-induced Act1-mediated signaling ameliorates autoimmune encephalomyelitis. Immunity. 2010;32(3):414-25.
20. Kroenke MA, Carlson TJ, Andjelkovic AV, Segal BM. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. J Exp Med. 2008;205(7):1535-41.
21. Huppert J, Closhen D, Croxford A, White R, Kulig P, Pietrowski E, et al. Cellular mechanisms of IL-17-induced blood-brain barrier disruption. Faseb J. 2010;24(4):1023-34.
22. Jiang H, Williams GJ, Dhib-Jalbut S. The effect of interferon beta-1b on cytokine-induced adhesion molecule expression. Neurochem Int. 1997;30(4-5):449-53.
23. Yu C, Argyropoulos G, Zhang Y, Kastin AJ, Hsuchou H, Pan W. Neuroinflammation activates Mdr1b efflux transport through NFkappaB: promoter analysis in BBB endothelia. Cell Physiol Biochem. 2008;22(5-6):745-56.
24. Pan W, Banks WA, Kennedy MK, Gutierrez EG, Kastin AJ. Differential permeability of the BBB in acute EAE: enhanced transport of TNT-alpha. Am J Physiol. 1996;271(4 Pt 1):E636-42.
25. Balabanov R, Strand K, Goswami R, McMahon E, Begolka W, Miller SD, et al. Interferon-gamma-oligodendrocyte interactions in the regulation of experimental autoimmune encephalomyelitis. J Neurosci. 2007;27(8):2013-24.
26. Pang Y, Cai Z, Rhodes PG. Effect of tumor necrosis factor-alpha on developing optic nerve oligodendrocytes in culture. J Neurosci Res. 2005;80(2):226-34.
27. Vela JM, Molina-Holgado E, Arevalo-Martin A, Almazan G, Guaza C. Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. Mol Cell Neurosci. 2002;20(3):489-502.
28. Meeuwsen S, Persoon-Deen C, Bsibsi M, Ravid R, Noort JM. Cytokine, chemokine and growth factor gene profiling of cultured human astrocytes after exposure to proinflammatory stimuli. Glia. 2003;43(3):243-53.
29. Liberto CM, Albrecht PJ, Herx LM, Yong VW, Levison SW. Pro-regenerative proper-

ties of cytokine-activated astrocytes. J Neurochem. 2004;89(5):1092-100.
30. Merrill JE, Zimmerman RP. Natural and induced cytotoxicity of oligodendrocytes by microglia is inhibitable by TGF beta. Glia. 1991;4(3):327-31.
31. Merrill JE. Effects of interleukin-1 and tumor necrosis factor-alpha on astrocytes, microglia, oligodendrocytes, and glial precursors in vitro. Dev Neurosci. 1991;13(3):130-7.
32. Lafaille JJ, Keere FV, Hsu AL, Baron JL, Haas W, Raine CS, et al. Myelin basic protein-specific T helper 2 (Th2) cells cause experimental autoimmune encephalomyelitis in immunodeficient hosts rather than protect them from the disease. J Exp Med. 1997;186(2):307-12.
33. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 1986;136(7):2348-57.
34. Waldburger KE, Hastings RC, Schaub RG, Goldman SJ, Leonard JP. Adoptive transfer of experimental allergic encephalomyelitis after in vitro treatment with recombinant murine interleukin-12. Preferential expansion of interferon-gamma-producing cells and increased expression of macrophage-associated inducible nitric oxide synthase as immunomodulatory mechanisms. Am J Pathol. 1996;148(2):375-82.
35. Yura M, Takahashi I, Serada M, Koshio T, Nakagami K, Yuki Y, et al. Role of MOG-stimulated Th1 type "light up" (GFP+) CD4+ T cells for the development of experimental autoimmune encephalomyelitis (EAE). J Autoimmun. 2001;17(1):17-25.
36. Trinchieri G. Interleukin-12 and its role in the generation of TH1 cells. Immunol Today. 1993;14(7):335-8.
37. Jacobson NG, Szabo SJ, Weber-Nordt RM, Zhong Z, Schreiber RD, Darnell JE, Jr., et al. Interleukin 12 signaling in T helper type 1 (Th1) cells involves tyrosine phosphorylation of signal transducer and activator of transcription (Stat)3 and Stat4. J Exp Med. 1995;181(5):1755-62.
38. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000;100(6):655-69.
39. Domingues HS, Mues M, Lassmann H, Wekerle H, Krishnamoorthy G. Functional and pathogenic differences of Th1 and Th17 cells in experimental autoimmune encephalomyelitis. PLoS One. 2010;5(11):e15531.
40. Thomas SM, Garrity LF, Brandt CR, Schobert CS, Feng GS, Taylor MW, et al. IFN-gamma-mediated antimicrobial response. Indoleamine 2,3-dioxygenase-deficient mutant host cells no longer inhibit intracellular Chlamydia spp. or Toxoplasma growth. J Immunol. 1993;150(12):5529-34.
41. Nash TW, Libby DM, Horwitz MA. IFN-gamma-activated human alveolar macrophages inhibit the intracellular multiplication of Legionella pneumophila. J Immunol. 1988;140(11):3978-81.
42. Lovett-Racke AE, Rocchini AE, Choy J, Northrop SC, Hussain RZ, Ratts RB, et al. Silencing T-bet defines a critical role in the differentiation of autoreactive T lymphocytes. Immunity. 2004;21(5):719-31.
43. Chitnis T, Najafian N, Benou C, Salama AD, Grusby MJ, Sayegh MH, et al. Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis. J Clin Invest. 2001;108(5):739-47.
44. Schoenhaut DS, Chua AO, Wolitzky AG, Quinn PM, Dwyer CM, McComas W, et al. Cloning and expression of murine IL-12. J Immunol. 1992;148(11):3433-40.
45. Wu C, Wang X, Gadina M, O'Shea JJ, Presky DH, Magram J. IL-12 receptor beta 2 (IL-12R beta 2)-deficient mice are defective in IL-12-mediated signaling despite the presence of high affinity IL-12 binding sites. J Immunol. 2000;165(11):6221-8.
46. Morinobu A, Gadina M, Strober W, Visconti R, Fornace A, Montagna C, et al. STAT4 serine phosphorylation is critical for IL-12-induced IFN-gamma production but not for cell proliferation. Proc Natl Acad Sci USA. 2002;99(19):12281-6.
47. Yamamoto K, Shibata F, Miura O, Kamiyama R, Hirosawa S, Miyasaka N. Physical interaction between interleukin-12 receptor beta 2 subunit and Jak2 tyrosine kinase: Jak2 associates with cytoplasmic membrane-proximal region of interleukin-12 receptor beta 2 via amino-terminus. Biochem Biophys Res Commun. 1999;257(2):400-4.
48. Park WR, Nakahira M, Sugimoto N, Bian Y, Yashiro-Ohtani Y, Zhou XY, et al. A mechanism underlying STAT4-mediated up-regulation of IFN-gamma induction inTCR-triggered T cells. Int Immunol. 2004;16(2):295-302.
49. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature. 2003;421(6924):744-8.
50. Gran B, Zhang GX, Yu S, Li J, Chen XH, Ventura ES, 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. J Immunol. 2002;169(12):7104-10.
51. Chua AO, Wilkinson VL, Presky DH, Gubler U. Cloning and characterization of a mouse IL-12 receptor-beta component. J Immunol. 1995;155(9):4286-94.
52. Marcucci F, Waller M, Kirchner H, Krammer P. Production of immune interferon by murine T-cell clones from long-term cultures. Nature. 1981;291(5810):79-81.

53. Fleischmann WR, Jr., Schwarz LA, Fleischmann CM. Requirement for IFN gamma in potentiation of interferon's antiviral and anticellular activities: identity of mouse and human systems. J Interferon Res. 1984;4(2):265-74.
54. Dunn PL, North RJ. Early gamma interferon production by natural killer cells is important in defense against murine listeriosis. Infect Immun. 1991;59(9):2892-900.
55. Simon D, Kozlowski E, Simon H. Natural killer T cells expressing IFN-gamma and IL-4 in lesional skin of atopic eczema. Allergy. 2009;64(11):1681-4.
56. Sridhar S, Begom S, Bermingham A, Ziegler T, Roberts KL, Barclay WS, et al. Predominance of heterosubtypic IFN-gamma-only-secreting effector memory T cells in pandemic H1N1 naive adults. Eur J Immunol. 2012;42:2913-24.
57. Fricke I, Mitchell D, Mittelstadt J, Lehan N, Heine H, Goldmann T, et al. Mycobacteria induce IFN-gamma production in human dendritic cells via triggering of TLR2. J Immunol. 2006;176(9):5173-82.
58. Walter MR, Windsor WT, Nagabhushan TL, Lundell DJ, Lunn CA, Zauodny PJ, et al. Crystal structure of a complex between interferon-gamma and its soluble high-affinity receptor. Nature. 1995;376(6537):230-5.
59. Briscoe J, Guschin D, Rogers NC, Watling D, Muller M, Horn F, et al. JAKs, STATs and signal transduction in response to the interferons and other cytokines. Philos Trans R Soc Lond B Biol Sci. 1996;351(1336):167-71.
60. Greenlund AC, Farrar MA, Viviano BL, Schreiber RD. Ligand-induced IFN gamma receptor tyrosine phosphorylation couples the receptor to its signal transduction system. EMBO J. 1994;13(7):1591-600.
61. Igarashi K, Garotta G, Ozmen L, Ziemiecki A, Wilks AF, Harpur AG, et al. Interferon-gamma induces tyrosine phosphorylation of interferon-gamma receptor and regulated association of protein tyrosine kinases, Jak1 and Jak2, with its receptor. J Biol Chem. 1994;269(20):14333-6.
62. Schindler C, Shuai K, Prezioso VR, Darnell JE, Jr. Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. Science. 1992;257(5071):809-13.
63. Sekimoto T, Imamoto N, Nakajima K, Hirano T, Yoneda Y. Extracellular signal-dependent nuclear import of Stat1 is mediated by nuclear pore-targeting complex formation with NPI-1, but not Rch1. EMBO J. 1997;16(23):7067-77.
64. Darnell JE, Jr., Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science. 1994;264(5164):1415-21.
65. Decker T, Meinke A. Jaks, Stats and the immune system. Immunobiology. 1997;198(1-3):99-111.
66. Silvennoinen O, Ihle JN, Schlessinger J, Levy DE. Interferon-induced nuclear signalling by Jak protein tyrosine kinases. Nature. 1993;366(6455):583-5.
67. Watanabe Y, Jacob CO. Regulation of MHC class II antigen expression. Opposing effects of tumor necrosis factor-alpha on IFN-gamma-induced HLA-DR and Ia expression depends on the maturation and differentiation stage of the cell. J Immunol. 1991;146(3):899-905.
68. Celada A, Maki RA. IFN-gamma induces the expression of the genes for MHC class II I-A beta and tumor necrosis factor through a protein kinase C-independent pathway. J Immunol. 1991;146(1):114-20.
69. Pechhold K, Patterson NB, Craighead N, Lee KP, June CH, Harlan DM. Inflammatory cytokines IFN-gamma plus TNF-alpha induce regulated expression of CD80 (B7-1) but not CD86 (B7-2) on murine fibroblasts. J Immunol. 1997;158(10):4921-9.
70. Tan L, Gordon KB, Mueller JP, Matis LA, Miller SD. Presentation of proteolipid protein epitopes and B7-1-dependent activation of encephalitogenic T cells by IFN-gamma-activated SJL/J astrocytes. J Immunol. 1998;160(9):4271-9.
71. Renno T, Zeine R, Girard JM, Gillani S, Dodelet V, Owens T. Selective enrichment of Th1 CD45RBlow CD4+ T cells in autoimmune infiltrates in experimental allergic encephalomyelitis. Int Immunol. 1994;6(3):347-54.
72. Kuchroo VK, Das MP, Brown JA, Ranger AM, Zamvil SS, Sobel RA, et al. B7-1 and B7-2 costimulatory molecules activate differentially the Th1/Th2 developmental pathways: application to autoimmune disease therapy. Cell. 1995;80(5):707-18.
73. Kennedy MK, Torrance DS, Picha KS, Mohler KM. Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. J Immunol. 1992;149(7):2496-505.
74. Begolka WS, Vanderlugt CL, Rahbe SM, Miller SD. Differential expression of inflammatory cytokines parallels progression of central nervous system pathology in two clinically distinct models of multiple sclerosis. J Immunol. 1998;161(8):4437-46.
75. Heremans H, Dillen C, Groenen M, Martens E, Billiau A. Chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice: enhancement by monoclonal antibodies against interferon-gamma. Eur J Immunol. 1996;26(10):2393-8.
76. Lublin FD, Knobler RL, Kalman B, Goldhaber M, Marini J, Perrault M, et al. Monoclonal anti-gamma interferon antibodies enhance experimental allergic encephalomyelitis. Autoimmunity. 1993;16(4):267-74.
77. Voorthuis JA, Uitdehaag BM, De Groot CJ, Goede PH, van der Meide PH, Dijkstra CD. Suppression of experimental allergic en-

cephalomyelitis by intraventricular administration of interferon-gamma in Lewis rats. Clin Exp Immunol. 1990;81(2):183-8.
78. Beutler B, Cerami A. The biology of cachectin/TNF—a primary mediator of the host response. Annu Rev Immunol. 1989;7:625-55.
79. McCoy MK, Tansey MG. TNF signaling inhibition in the CNS: implications for normal brain function and neurodegenerative disease. J Neuroinflammation. 2008;5:45.
80. Grell M, Douni E, Wajant H, Lohden M, Clauss M, Maxeiner B, et al. The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor. Cell. 1995;83(5):793-802.
81. Grell M, Wajant H, Zimmermann G, Scheurich P. The type 1 receptor (CD120a) is the high-affinity receptor for soluble tumor necrosis factor. Proc Natl Acad Sci USA. 1998;95(2):570-5.
82. Darnay BG, Aggarwal BB. Early events in TNF signaling: a story of associations and dissociations. J Leukoc Biol. 1997;61(5):559-66.
83. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol. 2006;69(1):195-206.
84. Hofman FM, Hinton DR, Johnson K, Merrill JE. Tumor necrosis factor identified in multiple sclerosis brain. J Exp Med. 1989;170(2):607-12.
85. Sharief MK, Hentges R. Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis. N Engl J Med. 1991;325(7):467-72.
86. Ruddle NH, Bergman CM, McGrath KM, Lingenheld EG, Grunnet ML, Padula SJ, et al. An antibody to lymphotoxin and tumor necrosis factor prevents transfer of experimental allergic encephalomyelitis. J Exp Med. 1990;172(4):1193-200.
87. Selmaj K, Raine CS, Cross AH. Anti-tumor necrosis factor therapy abrogates autoimmune demyelination. Ann Neurol. 1991;30(5):694-700.
88. Kassiotis G, Kranidioti K, Kollias G. Defective CD4T cell priming and resistance to experimental autoimmune encephalomyelitis in TNF-deficient mice due to innate immune hypo-responsiveness. J Neuroimmunol. 2001;119(2):239-47.
89. Suvannavejh GC, Lee HO, Padilla J, Dal Canto MC, Barrett TA, Miller SD. Divergent roles for p55 and p75 tumor necrosis factor receptors in the pathogenesis of MOG(35-55)-induced experimental autoimmune encephalomyelitis. Cell Immunol. 2000;205(1):24-33.
90. Korner H, Lemckert FA, Chaudhri G, Etteldorf S, Sedgwick JD. Tumor necrosis factor blockade in actively induced experimental autoimmune encephalomyelitis prevents clinical disease despite activated T cell infiltration to the central nervous system. Eur J Immunol. 1997;27(8):1973-81.
91. Caminero A, Comabella M, Montalban X. Tumor necrosis factor alpha (TNF-alpha), anti-TNF-alpha and demyelination revisited: an ongoing story. J Neuroimmunol. 2011;234(1-2):1-6.
92. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. Neurology. 1996;47(6):1531-4.
93. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology. 1999;53(3):457-65.
94. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001;44(12):2862-9.
95. Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF therapy. Neurology. 2001;57(10):1885-8.
96. Enayati PJ, Papadakis KA. Association of anti-tumor necrosis factor therapy with the development of multiple sclerosis. J Clin Gastroenterol. 2005;39(4):303-6.
97. Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology. 2005;129(3):819-26.
98. Tanno M, Nakamura I, Kobayashi S, Kurihara K, Ito K. New-onset demyelination induced by infliximab therapy in two rheumatoid arthritis patients. Clin Rheumatol. 2006;25(6):929-33.
99. Winkelmann A, Patejdl R, Wagner S, Benecke R, Zettl UK. Cerebral MRI lesions and anti-tumor necrosis factor-alpha therapy. J Neurol. 2008;255(Suppl 6):109-14.
100. Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LA, et al. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum. 2004;50(2):650-9.
101. Lubberts E, Joosten LA, van de Loo FA, Schwarzenberger P, Kolls J, van den Berg WB. Overexpression of IL-17 in the knee joint of collagen type II immunized mice promotes collagen arthritis and aggravates joint destruction. Inflamm Res. 2002;51(2):102-4.
102. Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. Inflamm Bowel Dis. 2006;12(5):382-8.

103.Doreau A, Belot A, Bastid J, Riche B, Trescol-Biemont MC, Ranchin B, et al. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. Nat Immunol. 2009;10(7):778-85.
104.Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005;201(2):233-40.
105.Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol. 2007;8(9):942-9.
106.Sutton C, Brereton C, Keogh B, Mills KH, Lavelle EC. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. J Exp Med. 2006;203(7):1685-91.
107.Huang Z, Xie H, Wang R, Sun Z. Retinoid-related orphan receptor gamma t is a potential therapeutic target for controlling inflammatory autoimmunity. Expert Opin Ther Targets. 2007;11(6):737-43.
108.Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell. 2006;126(6):1121-33.
109.Wei L, Laurence A, Elias KM, O'Shea JJ. IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. J Biol Chem. 2007;282(48):34605-10.
110.Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem. 2003;278(3):1910-4.
111.Reboldi A, Coisne C, Baumjohann D, Benvenuto F, Bottinelli D, Lira S, et al. C-C chemokine receptor 6-regulated entry of TH-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. Nat Immunol. 2009;10(5):514-23.
112.Maddur MS, Miossec P, Kaveri SV, Bayry J. Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. Am J Pathol. 2012;181(1):8-18.
113.Durelli L, Conti L, Clerico M, Boselli D, Contessa G, Ripellino P, et al. T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-beta. Ann Neurol. 2009;65(5):499-509.
114.Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000;13(5):715-25.
115.Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. J Immunol. 2002;168(11):5699-708.
116.Cho ML, Kang JW, Moon YM, Nam HJ, Jhun JY, Heo SB, et al. STAT3 and NF-kappaB signal pathway is required for IL-23-mediated IL-17 production in spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice. J Immunol. 2006;176(9):5652-61.
117.Harris TJ, Grosso JF, Yen HR, Xin H, Kortylewski M, Albesiano E, et al. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. J Immunol. 2007;179(7):4313-7.
118.McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, et al. TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. Nat Immunol. 2007;8(12):1390-7.
119.Gyulveszi G, Haak S, Becher B. IL-23-driven encephalo-tropism and Th17 polarization during CNS-inflammation in vivo. Eur J Immunol. 2009;39(7):1864-9.
120.Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, et al. Human IL-17: a novel cytokine derived from T cells. J Immunol. 1995;155(12):5483-6.
121.Kennedy J, Rossi DL, Zurawski SM, Vega F, Jr., Kastelein RA, Wagner JL, et al. Mouse IL-17: a cytokine preferentially expressed by alpha beta TCR + CD4-CD8-T cells. J Interferon Cytokine Res. 1996;16(8):611-7.
122.Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol. 2009;9(8):556-67.
123.Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, et al. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. J Immunol. 2006;177(1):36-9.
124.Wright JF, Bennett F, Li B, Brooks J, Luxenberg DP, Whitters MJ, et al. The human IL-17F/IL-17A heterodimeric cytokine signals through the IL-17RA/IL-17RC receptor complex. J Immunol. 2008;181(4):2799-805.
125.Chang SH, Dong C. IL-17F: regulation, signaling and function in inflammation. Cytokine. 2009;46(1):7-11.
126.Qian Y, Liu C, Hartupee J, Altuntas CZ, Gulen MF, Jane-Wit D, et al. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. Nat Immunol. 2007;8(3):247-56.
127.Chang SH, Park H, Dong C. Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. J Biol Chem. 2006;281(47):35603-7.
128.Novatchkova M, Leibbrandt A, Werzowa J, Neubuser A, Eisenhaber F. The STIR-domain superfamily in signal transduction, development and immunity. Trends Biochem Sci. 2003;28(5):226-9.

129.Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology. 2010;129(3):311-21.
130.Hartupee J, Liu C, Novotny M, Li X, Hamilton T. IL-17 enhances chemokine gene expression through mRNA stabilization. J Immunol. 2007;179(6):4135-41.
131.Kasten KR, Prakash PS, Unsinger J, Goetzman HS, England LG, Cave CM, et al. Interleukin-7 (IL-7) treatment accelerates neutrophil recruitment through gamma delta T-cell IL-17 production in a murine model of sepsis. Infect Immun. 2010;78(11):4714-22.
132.Li L, Huang L, Vergis AL, Ye H, Bajwa A, Narayan V, et al. IL-17 produced by neutrophils regulates IFN-gamma-mediated neutrophil migration in mouse kidney ischemia-reperfusion injury. J Clin Invest. 2010;120(1):331-42.
133.van de Veerdonk FL, Marijnissen RJ, Kullberg BJ, Koenen HJ, Cheng SC, Joosten I, et al. The macrophage mannose receptor induces IL-17 in response to Candida albicans. Cell Host Microbe. 2009;5(4):329-40.
134.Passos ST, Silver JS, O'Hara AC, Sehy D, Stumhofer JS, Hunter CA. IL-6 promotes NK cell production of IL-17 during toxoplasmosis. J Immunol. 2010;184(4):1776-83.
135.Vanbervliet B, Akdis M, Vocanson M, Rozieres A, Benetiere J, Rouzaire P, et al. Histamine receptor H1 signaling on dendritic cells plays a key role in the IFN-gamma/IL-17 balance in T cell-mediated skin inflammation. J Allergy Clin Immunol. 2011;127(4):943-53 e1-10.
136.Witowski J, Pawlaczyk K, Breborowicz A, Scheuren A, Kuzlan-Pawlaczyk M, Wisniewska J, et al. IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GRO alpha chemokine from mesothelial cells. J Immunol. 2000;165(10):5814-21.
137.Laan M, Cui ZH, Hoshino H, Lotvall J, Sjostrand M, Gruenert DC, et al. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. J Immunol. 1999;162(4):2347-52.
138.Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. Nat Med. 2002;8(5):500-8.
139.Matusevicius D, Kivisakk P, He B, Kostulas N, Ozenci V, Fredrikson S, et al. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. Mult Scler. 1999;5(2):101-4.
140.Hedegaard CJ, Krakauer M, Bendtzen K, Lund H, Sellebjerg F, Nielsen CH. T helper cell type 1 (Th1), Th2 and Th17 responses to myelin basic protein and disease activity in multiple sclerosis. Immunology. 2008;125(2):161-9.
141.Komiyama Y, Nakae S, Matsuki T, Nambu A, Ishigame H, Kakuta S, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. J Immunol. 2006;177(1):566-73.
142.Haak S, Croxford AL, Kreymborg K, Heppner FL, Pouly S, Becher B, et al. IL-17A and IL-17F do not contribute vitally to autoimmune neuro-inflammation in mice. J Clin Invest. 2009;119(1):61-9.
143.Hofstetter HH, Ibrahim SM, Koczan D, Kruse N, Weishaupt A, Toyka KV, et al. Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. Cell Immunol. 2005;237(2):123-30.
144.McQualter JL, Darwiche R, Ewing C, Onuki M, Kay TW, Hamilton JA, et al. Granulocyte macrophage colony-stimulating factor: a new putative therapeutic target in multiple sclerosis. J Exp Med. 2001;194(7):873-82.
145.El-Behi M, Ciric B, Dai H, Yan Y, Cullimore M, Safavi F, et al. The encephalitogenicity of T(H)17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. Nat Immunol. 2011;12(6):568-75.
146.Codarri L, Gyulveszi G, Tosevski V, Hesske L, Fontana A, Magnenat L, et al. RORgammat drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. Nat Immunol. 2011;12(6):560-7.
147.DiPersio JF, Golde DW, Gasson JD. GM-CSF: receptor structure and transmembrane signaling. Int J Cell Cloning. 1990;8(Suppl 1):63-74; discussion, 75.
148.Griffin JD, Cannistra SA, Sullivan R, Demetri GD, Ernst TJ, Kanakura Y. The biology of GM-CSF: regulation of production and interaction with its receptor. Int J Cell Cloning. 1990;8(Suppl 1):35-44; discussion, 45.
149.Walker F, Burgess AW. Internalisation and recycling of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor on a murine myelomonocytic leukemia. J Cell Physiol. 1987;130(2):255-61.
150.Liva SM, Kahn MA, Dopp JM, de Vellis J. Signal transduction pathways induced by GM-CSF in microglia: significance in the control of proliferation. Glia. 1999;26(4):344-52.
151.King IL, Dickendesher TL, Segal BM. Circulating Ly-6C+ myeloid precursors migrate to the CNS and play a pathogenic role during autoimmune demyelinating disease. Blood. 2009;113(14):3190-7.
152.Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 2007;448(7152):480-3.
153.Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. Immunity. 2009;31(2):331-41.
154.Beyeen AD, Adzemovic MZ, Ockinger J, Stridh P, Becanovic K, Laaksonen H, et al.

IL-22RA2 associates with multiple sclerosis and macrophage effector mechanisms in experimental neuroinflammation. J Immunol. 2010;185(11):6883-90.
155. Kreymborg K, Etzensperger R, Dumoutier L, Haak S, Rebollo A, Buch T, et al. IL-22 is expressed by Th17 cells in an IL-23-dependent fashion, but not required for the development of autoimmune encephalomyelitis. J Immunol. 2007;179(12):8098-104.
156. Coquet JM, Chakravarti S, Smyth MJ, Godfrey DI. Cutting edge: IL-21 is not essential for Th17 differentiation or experimental autoimmune encephalomyelitis. J Immunol. 2008;180(11):7097-101.
157. Sonderegger I, Kisielow J, Meier R, King C, Kopf M. IL-21 and IL-21R are not required for development of Th17 cells and autoimmunity in vivo. Eur J Immunol. 2008;38(7):1833-8.
158. Li Q, Powell N, Zhang H, Belevych N, Ching S, Chen Q, et al. Endothelial IL-1R1 is a critical mediator of EAE pathogenesis. Brain Behav Immun. 2011;25(1):160-7.
159. Mandolesi G, Grasselli G, Musella A, Gentile A, Musumeci G, Sepman H, et al. GABAergic signaling and connectivity on Purkinje cells are impaired in experimental autoimmune encephalomyelitis. Neurobiol Dis. 2012;46(2):414-24.
160. Jiang HR, Milovanovic M, Allan D, Niedbala W, Besnard AG, Fukada SY, et al. IL-33 attenuates EAE by suppressing IL-17 and IFN-gamma production and inducing alternatively activated macrophages. Eur J Immunol. 2012;42(7):1804-14.
161. Li M, Li Y, Liu X, Gao X, Wang Y. IL-33 blockade suppresses the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. J Neuroimmunol. 2012;247(1-2):25-31.
162. Paolicelli D, Direnzo V, Trojano M. Review of interferon beta-1b in the treatment of early and relapsing multiple sclerosis. Biologics. 2009;3:369-76.
163. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology. 1993;43(4):662-7.
164. Prinz M, Knobeloch KP. Type I interferons as ambiguous modulators of chronic inflammation in the central nervous system. Front Immunol. 2012;3:67.
165. Jacobs L, Rudick R, Simon J. Extended observations on MS patients treated with IM interferon-beta1a (Avonex): implications for modern MS trials and therapeutics. J Neuroimmunol. 2000;107(2):167-73.
166. Schwid SR, Panitch HS. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis. Clin Ther. 2007;29(9):2031-48.
167. Ramgolam VS, Sha Y, Jin J, Zhang X, Markovic-Plese S. IFN-beta inhibits human Th17 cell differentiation. J Immunol. 2009;183(8):5418-27.
168. Sweeney CM, Lonergan R, Basdeo SA, Kinsella K, Dungan LS, Higgins SC, et al. IL-27 mediates the response to IFN-beta therapy in multiple sclerosis patients by inhibiting Th17 cells. Brain Behav Immun. 2011;25(6):1170-81.
169. Prinz M, Kalinke U. New lessons about old molecules: how type I interferons shape Th1/Th17-mediated autoimmunity in the CNS. Trends Mol Med. 2010;16(8):379-86.
170. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005;6(11):1123-32.
171. Kurtuncu M, Tuzun E, Turkoglu R, Petek-Balci B, Icoz S, Pehlivan M, et al. Effect of short-term interferon-beta treatment on cytokines in multiple sclerosis: Significant modulation of IL-17 and IL-23. Cytokine. 2012;59(2):400-2.
172. Axtell RC, de Jong BA, Boniface K, van der Voort LF, Bhat R, De Sarno P, et al. T helper type 1 and 17 cells determine efficacy of interferon-beta in multiple sclerosis and experimental encephalomyelitis. Nat Med. 2010;16(4):406-12.
173. Axtell RC, Raman C, Steinman L. Type I Interferons: Beneficial in Th1 and Detrimental in Th17 Autoimmunity. Clin Rev Allergy Immunol. 2012 Jan 10. Epub ahead of print.
174. Teige I, Treschow A, Teige A, Mattsson R, Navikas V, Leanderson T, et al. IFN-beta gene deletion leads to augmented and chronic demyelinating experimental autoimmune encephalomyelitis. J Immunol. 2003;170(9):4776-84.
175. Prinz M, Schmidt H, Mildner A, Knobeloch KP, Hanisch UK, Raasch J, et al. Distinct and nonredundant in vivo functions of IFNAR on myeloid cells limit autoimmunity in the central nervous system. Immunity. 2008;28(5):675-86.
176. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001;19:683-765.
177. Platzer C, Meisel C, Vogt K, Platzer M, Volk HD. Up-regulation of monocytic IL-10 by tumor necrosis factor-alpha and cAMP elevating drugs. Int Immunol. 1995;7(4):517-23.
178. Platzer C, Fritsch E, Elsner T, Lehmann MH, Volk HD, Prosch S. Cyclic adenosine monophosphate-responsive elements are involved in the transcriptional activation of the human IL-10 gene in monocytic cells. Eur J Immunol. 1999;29(10):3098-104.

179.Platzer C, Docke W, Volk H, Prosch S. Catecholamines trigger IL-10 release in acute systemic stress reaction by direct stimulation of its promoter/enhancer activity in monocytic cells. J Neuroimmunol. 2000;105(1):31-8.
180.Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy—review of a new approach. Pharmacol Rev. 2003;55(2):241-69.
181.Ito S, Ansari P, Sakatsume M, Dickensheets H, Vazquez N, Donnelly RP, et al. Interleukin-10 inhibits expression of both interferon alpha- and interferon gamma-induced genes by suppressing tyrosine phosphorylation of STAT1. Blood. 1999;93(5):1456-63.
182.Matsuda M, Salazar F, Petersson M, Masucci G, Hansson J, Pisa P, et al. Interleukin 10 pretreatment protects target cells from tumor- and allo-specific cytotoxic T cells and downregulates HLA class I expression. J Exp Med. 1994;180(6):2371-6.
183.Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. J Immunol. 1991;147(11):3815-22.
184.Willems F, Marchant A, Delville JP, Gerard C, Delvaux A, Velu T, et al. Interleukin-10 inhibits B7 and intercellular adhesion molecule-1 expression on human monocytes. Eur J Immunol. 1994;24(4):1007-9.
185.de Waal Malefyt R, Abrams J, Bennett B, Figdor CG, de Vries JE. Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. J Exp Med. 1991;174(5):1209-20.
186.Groux H, Bigler M, de Vries JE, Roncarolo MG. Interleukin-10 induces a long-term antigen-specific anergic state in human CD4+ T cells. J Exp Med. 1996;184(1):19-29.
187.Groux H, Bigler M, de Vries JE, Roncarolo MG. Inhibitory and stimulatory effects of IL-10 on human CD8+ T cells. J Immunol. 1998;160(7):3188-93.
188.Levy Y, Brouet JC. Interleukin-10 prevents spontaneous death of germinal center B cells by induction of the bcl-2 protein. J Clin Invest. 1994;93(1):424-8.
189.Rousset F, Peyrol S, Garcia E, Vezzio N, Andujar M, Grimaud JA, et al. Long-term cultured CD40-activated B lymphocytes differentiate into plasma cells in response to IL-10 but not IL-4. Int Immunol. 1995;7(8):1243-53.
190.Rott O, Fleischer B, Cash E. Interleukin-10 prevents experimental allergic encephalomyelitis in rats. Eur J Immunol. 1994;24(6):1434-40.
191.Croxford JL, Feldmann M, Chernajovsky Y, Baker D. Different therapeutic outcomes in experimental allergic encephalomyelitis dependent upon the mode of delivery of IL-10: a comparison of the effects of protein, adenoviral or retroviral IL-10 delivery into the central nervous system. J Immunol. 2001;166(6):4124-30.
192.Cua DJ, Hutchins B, LaFace DM, Stohlman SA, Coffman RL. Central nervous system expression of IL-10 inhibits autoimmune encephalomyelitis. J Immunol. 2001;166(1):602-8.
193.Yue FY, Dummer R, Geertsen R, Hofbauer G, Laine E, Manolio S, et al. Interleukin-10 is a growth factor for human melanoma cells and down-regulates HLA class-I, HLA class-II and ICAM-1 molecules. Int J Cancer. 1997;71(4):630-7.
194.Kim J, Modlin RL, Moy RL, Dubinett SM, McHugh T, Nickoloff BJ, et al. IL-10 production in cutaneous basal and squamous cell carcinomas. A mechanism for evading the local T cell immune response. J Immunol. 1995;155(4):2240-7.
195.Wrana JL. Phosphoserine-dependent regulation of protein-protein interactions in the Smad pathway. Structure. 2002;10(1):5-7.
196.ten Dijke P, Hill CS. New insights into TGF-beta-Smad signalling. Trends Biochem Sci. 2004;29(5):265-73.
197.Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature. 2006;441(7090):231-4.
198.Veldhoen M, Stockinger B. TGFbeta1, a "Jack of all trades:" the link with pro-inflammatory IL-17-producing T cells. Trends Immunol. 2006;27(8):358-61.
199.Karpus WJ, Swanborg RH. Protection against experimental autoimmune encephalomyelitis requires both CD4+ T suppressor cells and myelin basic protein-primed B cells. J Neuroimmunol. 1991;33(2):173-7.
200.Li MO, Wan YY, Flavell RA. T cell-produced transforming growth factor-beta1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. Immunity. 2007;26(5):579-91.
201.Pesu M, Watford WT, Wei L, Xu L, Fuss I, Strober W, et al. T-cell-expressed proprotein convertase furin is essential for maintenance of peripheral immune tolerance. Nature. 2008;455(7210):246-50.
202.Gutcher I, Donkor MK, Ma Q, Rudensky AY, Flavell RA, Li MO. Autocrine transforming growth factor-beta1 promotes in vivo Th17 cell differentiation. Immunity. 2011;34(3):396-408.
203.Lin JT, Martin SL, Xia L, Gorham JD. TGF-beta 1 uses distinct mechanisms to inhibit IFN-gamma expression in CD4+ T cells at priming and at recall: differential involvement of Stat4 and T-bet. J Immunol. 2005;174(10):5950-8.
204.Alvarez JI, Cayrol R, Prat A. Disruption of central nervous system barriers in multiple sclerosis. Biochim Biophys Acta. 2011;1812(2):252-64.
205.Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005;308(5726):1314-8.
206.Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive im-

mune responses through multiple TLRs. J Immunol. 2004;173(6):3916-24.
207.Saijo K, Glass CK. Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol. 2011;11(11):775-87.
208.Aloisi F, Ria F, Penna G, Adorini L. Microglia are more efficient than astrocytes in antigen processing and in Th1 but not Th2 cell activation. J Immunol. 1998;160(10):4671-80.
209.Olson JK, Girvin AM, Miller SD. Direct activation of innate and antigen-presenting functions of microglia following infection with Theiler's virus. J Virol. 2001;75(20):9780-9.
210.Aloisi F. Immune function of microglia. Glia. 2001;36(2):165-79.
211.Katz-Levy Y, Neville KL, Girvin AM, Vanderlugt CL, Pope JG, Tan LJ, et al. Endogenous presentation of self myelin epitopes by CNS-resident APCs in Theiler's virus-infected mice. J Clin Invest. 1999;104(5):599-610.
212.Kielian T, Mayes P, Kielian M. Characterization of microglial responses to Staphylococcus aureus: effects on cytokine, costimulatory molecule, and Toll-like receptor expression. J Neuroimmunol. 2002;130(1-2):86-99.
213.Napoli I, Neumann H. Protective effects of microglia in multiple sclerosis. Exp Neurol. 2010;225(1):24-8.
214.Arnett HA, Mason J, Marino M, Suzuki K, Matsushima GK, Ting JP. TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. Nat Neurosci. 2001;4(11):1116-22.
215.Butovsky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, et al. Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. Mol Cell Neurosci. 2006;31(1):149-60.
216.Stoll G, Jander S. The role of microglia and macrophages in the pathophysiology of the CNS. Prog Neurobiol. 1999;58(3):233-47.
217.Bruck W, Bruck Y, Friede RL. TNF-alpha suppresses CR3-mediated myelin removal by macrophages. J Neuroimmunol. 1992;38(1-2):9-17.
218.Bauer J, Sminia T, Wouterlood FG, Dijkstra CD. Phagocytic activity of macrophages and microglial cells during the course of acute and chronic relapsing experimental autoimmune encephalomyelitis. J Neurosci Res. 1994;38(4):365-75.
219.Franklin RJ, Kotter MR. The biology of CNS remyelination: the key to therapeutic advances. J Neurol. 2008;255(Suppl 1):19-25.
220.Wang DD, Bordey A. The astrocyte odyssey. Prog Neurobiol. 2008;86(4):342-67.
221.Chastain EM, Duncan DS, Rodgers JM, Miller SD. The role of antigen presenting cells in multiple sclerosis. Biochim Biophys Acta. 2011;1812(2):265-74.
222.Nair A, Frederick TJ, Miller SD. Astrocytes in multiple sclerosis: a product of their environment. Cell Mol Life Sci. 2008;65(17):2702-20.
223.Cornet A, Bettelli E, Oukka M, Cambouris C, Avellana-Adalid V, Kosmatopoulos K, et al. Role of astrocytes in antigen presentation and naive T-cell activation. J Neuroimmunol. 2000;106(1-2):69-77.
224.Zeinstra E, Wilczak N, Streefland C, De Keyser J. Astrocytes in chronic active multiple sclerosis plaques express MHC class II molecules. Neuroreport. 2000;11(1):89-91.
225.Gresser O, Hein A, Riese S, Regnier-Vigouroux A. Tumor necrosis factor alpha and interleukin-1 alpha inhibit through different pathways interferon-gamma-induced antigen presentation, processing and MHC class II surface expression on astrocytes, but not on microglia. Cell Tissue Res. 2000;300(3):373-82.
226.Soos JM, Ashley TA, Morrow J, Patarroyo JC, Szente BE, Zamvil SS. Differential expression of B7 co-stimulatory molecules by astrocytes correlates with T cell activation and cytokine production. Int Immunol. 1999;11(7):1169-79.
227.Constantinescu CS, Tani M, Ransohoff RM, Wysocka M, Hilliard B, Fujioka T, et al. Astrocytes as antigen-presenting cells: expression of IL-12/IL-23. J Neurochem. 2005;95(2):331-40.
228.Yan Y, Ding X, Li K, Ciric B, Wu S, Xu H, et al. CNS-specific therapy for ongoing EAE by silencing IL-17 pathway in astrocytes. Mol Ther. 2012;20(7):1338-48.
229.Buffo A, Rolando C, Ceruti S. Astrocytes in the damaged brain: Molecular and cellular insights into their reactive response and healing potential. Biochem Pharmacol. 2010;79(2):77-89.
230.Fischer HG, Bielinsky AK. Antigen presentation function of brain-derived dendriform cells depends on astrocyte help. Int Immunol. 1999;11(8):1265-74.
231.Hailer NP, Heppner FL, Haas D, Nitsch R. Astrocytic factors deactivate antigen presenting cells that invade the central nervous system. Brain Pathol. 1998;8(3):459-74.
232.Aloisi F, De Simone R, Columba-Cabezas S, Penna G, Adorini L. Functional maturation of adult mouse resting microglia into an APC is promoted by granulocyte-macrophage colony-stimulating factor and interaction with Th1 cells. J Immunol. 2000;164(4):1705-12.
233.Aloisi F, Ria F, Adorini L. Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. Immunol Today. 2000;21(3):141-7.
234.Marz P, Heese K, Dimitriades-Schmutz B, Rose-John S, Otten U. Role of interleukin-6 and soluble IL-6 receptor in region-specific induction of astrocytic differentiation and neurotrophin expression. Glia. 1999;26(3):191-200.
235.Schonrock LM, Gawlowski G, Bruck W. Interleukin-6 expression in human multiple sclerosis lesions. Neurosci Lett. 2000;294(1):45-8.
236.Biber K, Lubrich B, Fiebich BL, Boddeke HW, van Calker D. Interleukin-6 enhances

expression of adenosine A(1) receptor mRNA and signaling in cultured rat cortical astrocytes and brain slices. Neuropsychopharmacology. 2001;24(1):86-96.
237.Herx LM, Yong VW. Interleukin-1 beta is required for the early evolution of reactive astrogliosis following CNS lesion. J Neuropathol Exp Neurol. 2001;60(10):961-71.
238.Herx LM, Rivest S, Yong VW. Central nervous system-initiated inflammation and neurotrophism in trauma: IL-1 beta is required for the production of ciliary neurotrophic factor. J Immunol. 2000;165(4):2232-9.
239.Stankoff B, Aigrot MS, Noel F, Wattilliaux A, Zalc B, Lubetzki C. Ciliary neurotrophic factor (CNTF) enhances myelin formation: a novel role for CNTF and CNTF-related molecules. J Neurosci. 2002;22(21):9221-7.
240.Talbott JF, Cao Q, Bertram J, Nkansah M, Benton RL, Lavik E, et al. CNTF promotes the survival and differentiation of adult spinal cord-derived oligodendrocyte precursor cells in vitro but fails to promote remyelination in vivo. Exp Neurol. 2007;204(1):485-9.
241.McKinnon RD, Piras G, Ida JA, Jr., Dubois-Dalcq M. A role for TGF-beta in oligodendrocyte differentiation. J Cell Biol. 1993;121(6):1397-407.
242.Corbin JG, Kelly D, Rath EM, Baerwald KD, Suzuki K, Popko B. Targeted CNS expression of interferon-gamma in transgenic mice leads to hypomyelination, reactive gliosis, and abnormal cerebellar development. Mol Cell Neurosci. 1996;7(5):354-70.
243.Lin W, Harding HP, Ron D, Popko B. Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. J Cell Biol. 2005;169(4):603-12.
244.Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B. Interferon-gamma inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. Brain. 2006;129(Pt 5):1306-18.
245.Lin W, Bailey SL, Ho H, Harding HP, Ron D, Miller SD, et al. The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. J Clin Invest. 2007;117(2):448-56.
246.Su Z, Yuan Y, Chen J, Zhu Y, Qiu Y, Zhu F, et al. Reactive astrocytes inhibit the survival and differentiation of oligodendrocyte precursor cells by secreted TNF-alpha. J Neurotrauma. 2011;28(6):1089-100.
247.Hovelmeyer N, Hao Z, Kranidioti K, Kassiotis G, Buch T, Frommer F, et al. Apoptosis of oligodendrocytes via Fas and TNF-R1 is a key event in the induction of experimental autoimmune encephalomyelitis. J Immunol. 2005;175(9):5875-84.
248.Pizzi M, Sarnico I, Boroni F, Benarese M, Dreano M, Garotta G, et al. Prevention of neuron and oligodendrocyte degeneration by interleukin-6 (IL-6) and IL-6 receptor/IL-6 fusion protein in organotypic hippocampal slices. Mol Cell Neurosci. 2004;25(2):301-11.
249.Valerio A, Ferrario M, Dreano M, Garotta G, Spano P, Pizzi M. Soluble interleukin-6 (IL-6) receptor/IL-6 fusion protein enhances in vitro differentiation of purified rat oligodendroglial lineage cells. Mol Cell Neurosci. 2002;21(4):602-15.
250.Halfpenny CA, Scolding NJ. Immune-modifying agents do not impair the survival, migration or proliferation of oligodendrocyte progenitors (CG-4) in vitro. J Neuroimmunol. 2003;139(1-2):9-16.