FOCUS: NEUROSCIENCE

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

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†Abbreviations: EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis; CD, cluster of differentiation; CFA, complete Freund’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; 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, cerebrospinal 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.

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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 Freund’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-
responses 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 differentation [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
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), 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 IFN-γ 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-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 IFN-γ 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), phosphoinositide 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 (GM-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 pleiotropic 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 Aicardi-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 pathologies is 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 differen-
tiation by inhibiting T-bet and STAT4 expression [203]. Treg cells regulate im-
une 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 funda-
mental 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 under-
stand why it is ineffective for treating a portion of RRMS patients and other forms 
of MS. IL-10 cannot be targeted for treat-
ment of MS due to the consequences of 
tumor growth. TGF-β is not ideal for thera-
peutic 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, mi-
croglia, 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 ap-
propriately 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, inflamma-
tion, and debris; however, astrocytes and oligodendrocytes are also capable of recog-
nition and responding. Understanding the microenviroment 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 per-
ipheral immune cells, including their activ-
dity during EAE. First, in a resting state, they survey the CNS for signs of trauma or in-
fec tions [205]. Once they encounter antigen from debris, infected cells, and viral or bac-
terial protein, microglia become activated. Classical activation leads to both innate and 
adaptive immune responses. Microglia are highly sensitive to pathogen-associated mo-
 lecular patterns sensed by pattern recogni-
tion receptors such as Toll-like receptors 
(TLDRs) [206] and NOD-like receptors; sim-
ilar 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 mi-
croglia also upregulate proteins necessary 
for antigen presentation, which allow them 
to present antigen to infiltrating T cells. In 
EAE, disease progression depends on the re-
activation of T cells in the CNS, and al-
though microglia are not the only cells that 
are responsible, they certainly are capable of 
it [208,209].

Microglia promote both disease pro-
gression and endogenous repair during EAE. 
Disease progression is mediated by antigen 
presentation to infiltrating T cells, which in-
volves cytokine production by microglia and 
results in more inflammatory cytokine pro-
duction by reactivated T cells [210,211]. For 
example, microglia produce TNF-α, IL-6, 
and IL-1β in response to IFN-γ or TLR stim-
uli [206,212]. Microglia promote an envi-
ronment 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; participate 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.

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