Published in final edited form as:

Cell Mol Life Sci. 2008 September ; 65(17): 2702–2720. doi:10.1007/s00018-008-8059-5.

Astrocytes in Multiple Sclerosis: A Product of their Environment

Aji Nair^{*}, Terra J. Frederick^{*}, and Stephen D. Miller

Department of Microbiology-Immunology and Interdepartmental Immunobiology Center,
Northwestern University Feinberg School of Medicine, 303 E. Chicago Avenue, Chicago, IL
60611

Abstract

It has long been thought that astrocytes, like other glial cells, simply provide a support mechanism for neuronal function in the healthy and inflamed central nervous system (CNS). However, recent evidence suggests that astrocytes play an active and dual role in CNS inflammatory diseases such as multiple sclerosis (MS). Astrocytes not only have the ability to enhance immune responses and inhibit myelin repair, but they can also be protective and limit CNS inflammation while supporting oligodendrocyte and axonal regeneration. The particular impact of these cells on the pathogenesis and repair of an inflammatory demyelinating process is dependent upon a number of factors, including the stage of the disease, the type and microenvironment of the lesion, and the interactions with other cell types and factors that influence their activation. In this review, we summarize recent data supporting the idea that astrocytes play a complex role in the regulation of CNS autoimmunity.

Keywords

animal models; astrocyte; chemokines; cytokines; demyelination; multiple sclerosis;
neuroinflammation; remyelination

Initiated by the breakdown of the blood-brain barrier (BBB), multiple sclerosis (MS) has classically been considered a T cell-mediated autoimmune disorder of the central nervous system (CNS), characterized by inflammatory cell infiltration and myelin destruction [1]. Focal demyelinated lesions in the white matter are the traditional hallmarks of MS. However recent evidence suggests more widespread damage to the brain and spinal cord, particularly during the progressive phase of disease. Such global injury includes axonal damage, diffuse damage to areas of white matter distant from inflammatory lesions, and demyelination of deep and cortical gray matter [2]. Clinical deficits in MS range from relapsing-remitting to chronic-progressive patterns of expression. Spontaneous remyelination occurs early in relapsing-remitting disease, which restores neurophysiological function in animal models of MS, and likely represents a remission period in human MS [3]. However, recurrent inflammatory attacks and the failure of myelin repair during later progressive phases of disease ultimately lead to permanent debilitation [3]. It is well understood that oligodendrocyte progenitor cells (OPCs) are responsible for remyelinating lesions in the CNS [4], and thus the failure of myelin repair has been attributed to deficiencies in the generation of mature oligodendrocytes or their ability to myelinate, and/or to neurodegeneration and axons that are unreceptive to myelination [5].

Address Correspondence to: Stephen D. Miller, Ph.D., Judy Gugenheim Research Professor, Department of Microbiology-Immunology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, IL 60611, 312-503-7674, FAX: 312-503-1154, s-d-miller@northwestern.edu.

^{*}These two authors contributed equally to this review.

CD4⁺ T cells play an important role in the induction of disease and MS lesion pathogenesis through the secretion of proinflammatory (T_H1 and T_H17) cytokines, and the ensuing activation of other inflammatory cells in the CNS [2,6]. Contributing to CNS tissue damage, CD8⁺ T cells are frequently found in chronic MS plaques and are associated with axonal damage [7]. Extensive microglial, macrophage and dendritic cell activation amplify the destructive inflammatory environment by damaging myelin further, secreting cytokines, and presenting antigen to T cells [8]. Ongoing research also suggests an involvement of B cells in the development of acute lesions, potentially by the secretion of antibodies, the regulation of T cells, and/or presentation of antigens [9].

General Functions of Astrocytes

In 1871, Camillo Golgi identified a novel cell type in the CNS characterized by long, numerous, star-like projections. These cells eventually became known as astrocytes and have been implicated in a variety of essential functions within the CNS. Astrocytes are the most abundant cell type in the mammalian CNS and constitute approximately 90% of the human brain [10]. The ratio of astrocytes per neuron increases drastically among species with increasing brain complexity and size suggesting an evolutionary advantage in animals with a greater number of astrocytes [11]. There are two types of astrocytes in mammals: protoplasmic and fibrous. Protoplasmic astrocytes are found in the gray matter and extend numerous ramified branches that contact neuronal surfaces and blood vessels [12]. Conversely, fibrous astrocytes occupy areas adjacent to axon bundles in white matter tracts with process longer and thinner than protoplasmic astrocytes [13]. While there are obvious morphological and structural differences between protoplasmic and fibrous astrocytes, both classes of cells appear to exhibit similar functions.

Aside from their unique morphology, astrocytes are distinguished by their expression of the intermediate filament GFAP. Upon activation, astrocytes upregulate their expression of GFAP in a process termed gliosis. Reactive gliosis has been used as a marker of pathology in a variety of CNS disease states including multiple sclerosis and Alzheimer's disease [14]. While the precise function of GFAP is unknown, transgenic and knockout mice shed some light on the role of GFAP in CNS pathology. Mice deficient in GFAP display abnormal astrocyte morphology and a structurally and functionally impaired BBB [15]. GFAP^{-/-} mice also exhibit neurological deficits such as altered long-term potentiation [16], poor CNS vascularization [15], and are hypersensitive to traumatic injury [17]. Alternatively, mice that over-express GFAP display a phenotype similar to Alexander's Disease, a deadly neurodegenerative disorder characterized by hypomyelination [18]. Despite the above studies, there is still some controversy as to whether GFAP affects astrocytic function, as GFAP expression is not limited to astrocytes. It has been found in a variety of cells including OPCs [19], non-myelinating Schwann cells [20], pancreatic cells [21], and cells of the enteric nervous system [22].

One major limitation of examining astrocyte activation is the paucity of activation markers. While a majority of studies quantify astrocyte activation by up-regulation of GFAP, other less specific astrocyte markers have also been examined. For example, S100 β is often used as a complement to GFAP as a marker of neurotoxicity despite the fact that it is also expressed in Schwann cells, adipocytes, and chondrocytes [23]. Glutamate transporters GLT-1 and GLAST are also expressed by astrocytes but show varied levels depending on location within the CNS [24]. Finally, the extracellular matrix protein SC1 has been associated with astrocytes in rat CNS [25]. Unfortunately, SC1 expression has not been examined in humans or other species and thus cannot be considered a reliable marker for astrocytes.

Astrocytes as Support Cells

The word “glia” originates from the Greek word meaning “glue” and astrocytes have long been regarded as the glue that holds the CNS together. One of the major functions of astrocytes is the support of neural transmission. Astrocytes provide functional support to neurons by maintaining local ion and pH homeostasis, storing CNS glycogen, and clearing neuronal waste [11,26]. In addition to these functions, astrocytes are able to actively alter synaptic transmission. For instance, astrocytes mediate uptake of neurotransmitters like glutamate thereby decreasing the amount of transmitter in the synaptic cleft [27]. Following injury, astrocytes upregulate expression of glutamate transporters and glutamine synthetase, which allow them to sequester glutamate and convert it to glutamine, thus limiting neuronal and oligodendrocyte damage [28]. Astrocytes also release neuromodulatory factors into the extracellular space, further contributing to modulation of neurotransmission [29]. In addition, recent evidence indicates the presence of astrocyte-neuron gap junctions allowing for bidirectional modulation of synaptic activity [30].

Astrocytes also play a critical role in maintaining survival of neurons and other glia. In the naive adult rat spinal cord, astrocytes express brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) indicating that astrocytes promote neuronal survival in the absence of injury or trauma [31]. Upon injury, however, astrocytes increase production of BDNF and nerve growth factor (NGF) [32], ultimately promoting survival and neurogenesis [33]. Oligodendrocytes also benefit from astrocyte-mediated growth factor production. Astrocyte-conditioned media promoted the survival of OPCs *in vitro* through the actions of platelet-derived growth factor (PDGF) and leukemia inhibitory factor (LIF) [34]. Other astrocyte-derived growth factors that support OPC survival include NT-3, insulin-like growth factor-1 (IGF-I), and ciliary neurotrophic factor (CNTF) [35–37].

Another major function of astrocytes is maintenance of the BBB. The BBB is a selective physical barrier that regulates traffic between the circulation and the CNS parenchyma. Structurally, the BBB is composed of capillaries surrounded by perivascular macrophages and astrocytic endfeet. Capillaries in the CNS are more restrictive than in the rest of the body due to the presence of tight junctions [38]. These tight junctions limit the entry of large hydrophilic molecules (proteins) across the BBB but allow diffusion of small gaseous molecules (O₂ and CO₂) and smaller lipophilic compounds that easily pass through the endothelial cell membrane [39]. Larger molecules are able to pass through the BBB via specific transporters located on CNS endothelial cells.

The role of astrocytes in the BBB is primarily a regulatory one. Astrocytic endfeet surround CNS capillaries and perivascular macrophages allowing for astrocytes to directly modulate BBB function. Interleukin (IL)-6, tumor necrosis factor- α (TNF- α), and IL-1 β are released by astrocytes during inflammation and increase BBB permeability by acting specifically on endothelial cells and tight junctions [40–42]. Astrocytes also can tighten the BBB via tumor growth factor- β (TGF- β) secretion [39]. The ability of astrocytes to modulate BBB permeability has significant implications during inflammation by potentially allowing the influx of immune cells, ions, and toxic molecules into the CNS.

Astrocytes as Immune Cells

Long regarded as immunocompromised, the CNS is now considered to be a site of rapid and potent immune responses. Not only do circulating immune cells readily enter the CNS during periods of inflammation [43,44], but CNS-resident cells are also vital players in CNS immunity. Microglia, for instance, are of hematopoietic origin and are regarded as the resident macrophages of the CNS. Astrocytes, on the other hand, are of neural origin yet exhibit a multitude of immune functions that are characteristic of peripheral immune cells.

Increasing evidence suggests that astrocytes contribute to both innate and adaptive immunity in the CNS.

The innate immune system is the initial non-specific response to foreign pathogens. At the onset of an infection, various pattern recognition receptors (PRRs) are activated and trigger a cascade of immune pathways. The most well-known class of PRRs is the toll-like receptors (TLR). Murine astrocytes express all 9 TLR but show the greatest expression of TLR3 *in vivo* [45]. TLR3 binds double-stranded RNA (dsRNA) and its expression by astrocytes suggests an active role for these cells in the CNS anti-viral immune response. Another type of PRR, which may play a role in recognition of dsRNA, is PKR (dsRNA-dependent protein kinase). PKR has been demonstrated to be instrumental in the dsRNA response in cultured astrocytes [46]. Astrocytes also express a variety of other PRR including scavenger receptors, mannose receptors, and complement receptors [47].

One of the primary functions of the innate immune response is to induce the adaptive immune response to mount a specific response. Despite the relative lack of professional antigen presenting cells (APC) and circulating lymphocytes in the naive CNS, resident CNS cells are able to elicit a potent cell-mediated immune response. Many of the studies regarding CNS adaptive immunity have focused on hematopoietically-derived microglia, which are able to take up antigens and present them to T cells [48,49]. Although they are derived from neuroectodermal lineage, astrocytes also exhibit APC functions. For example, astrocytes express major histocompatibility complex (MHC) class I and class II molecules *in vitro* [50] and upregulate expression of the costimulatory molecules CD80 (B7-1) and CD86 (B7-2) upon *in vitro* treatment with interferon (IFN)- γ [51]. Functional studies indicate that IFN- γ -treated astrocytes are able to activate both CD8⁺ [52] and CD4⁺ T cells [51,53] *in vitro*. However, the role of astrocyte-mediated antigen presentation *in vivo* is less clear. Intrathecal administration of IFN- γ induces MHC class II expression on astrocytes supporting *in vitro* findings [54]. Also, Barcia et al. [55] demonstrated that astrocytes do in fact form immunological synapses with T cells *in vivo*. Still, *in vivo* astrocyte APC function is controversial given the more efficient antigen presentation function of microglia and other infiltrating APC.

In addition to direct activation of T cells, astrocytes also provide a suitable environment for T cell activation. During inflammation, astrocytes are producers of a variety of cytokines including IL-1, IL-6, TNF- α , IL-10, and TGF- β [56]. Depending on the inflammatory environment, these cytokines could drive the immune response toward a T_H1, T_H2, or T_H17 response. Astrocytes also play a role in attracting T cells within the CNS via chemokine production. For example, astrocytes have been shown to be major producers of RANTES (CCL5), MCP-1 (CCL2), IL-8 (CXCL8), and IP-10 (CXCL10) [56]. Such production of chemokines may have significant effects on migration of lymphocytes across the BBB due to the proximity of astrocytic end feet to blood vessels. Furthermore, astrocyte expression of adhesion molecules like intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) likely aids in migration of T cells and may stabilize interactions between T cells and APC in the CNS [44,57].

This review challenges the traditional view that astrocytes simply support neuronal function. Instead, astrocytes appear to play an active role in both the naive and inflamed CNS. The sections below will examine how astrocytes exhibit a dual role during the development of MS. Both protective and adverse affects of astrocyte function will be examined in the context of demyelination (Figure 1) and remyelination (Figure 2) during MS. Due to the limited amount of data available from human MS studies, we will also focus our discussion to include data from *in vitro* studies and animal models of MS and other CNS inflammatory conditions. The models discussed will include experimental autoimmune encephalomyelitis

(EAE), Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), and chemically-induced demyelination (cuprizone, lysolecithin, etc). *In vitro* models presented involve cytokine-activated astrocytes from both human and rodent CNS sources.

Adverse Effects of Astrocytes on CNS Immunopathogenesis

Antigen Presentation and Direct Activation of T cells

One way in which astrocytes may promote the pathogenesis of MS is by priming encephalitogenic T cells to target various myelin epitopes. As mentioned earlier, astrocytes act as non-professional APC and do in fact express the proper machinery to activate autoreactive T cells [51,58]. In human MS tissue, astrocytes have been shown to express MHC class I, class II, CD80, and CD86 [59–62]. Still, there is controversy as to whether astrocytes express these molecules during MS as others have demonstrated a lack of MHC and co-stimulatory molecule expression by astrocytes in frozen MS tissue [63–65]. One reason for the discrepancies may be due to the wide range of pathologies observed during MS, each of which may require a different astrocytic response. In EAE models, astrocyte expression of MHC and co-stimulatory molecules is dependent on species, strain, and peptide used to initiate disease [60,66–68].

While the above studies suggest that astrocytes have the potential to activate autoreactive T cells, *in vitro* studies demonstrate a more definitive functional role for astrocyte-mediated T cell activation. Murine astrocytes stimulated with IFN- γ induced the proliferation of proteolipid protein (PLP)- and myelin oligodendrocyte glycoprotein (MOG)-specific CD4⁺ T cells [69,70]. If astrocytic expression of CD80 was blocked, T cell activation was not observed, indicating an important role for astrocyte co-stimulatory molecule expression in the activation of autoreactive T cells. In addition, astrocytes from mice deficient in CIIA (MHC class II transactivator) failed to activate MOG-specific CD4⁺ T cells due to the lack of MHC class II expression [71]. This suggests that, like professional APC, murine astrocytes are able to activate encephalitogenic CD4⁺ T cells through the classical MHC class II pathway. It is important to note that there are species differences involved in astrocyte activation of T cells. For example, IFN- γ treatment is not necessary for rat astrocytes to activate myelin basic protein (MBP)-specific T cells *in vitro* [72]. Also, human astrocytes do not effectively activate encephalitogenic T cells *in vitro* and may even inhibit their function [73].

Contributing to the ability of astrocytes to activate T cells is their inducible expression of adhesion molecules. Two adhesion molecules in particular, ICAM-1 (intracellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1), play crucial roles in the extravasation and homing of T cells through the CNS parenchyma. ICAM-1 and VCAM-1 bind LFA-1 (CD11a/CD18) and VLA-4 (very late antigen-4) on activated lymphocytes, respectively. In MS tissue, ICAM-1 expression was observed in astrocytes at the edges of demyelinated lesions [74]. VCAM-1, however, has not been identified on astrocytes during MS but is expressed by astrocytes during EAE [57]. *In vitro* stimulation of astrocytes by TNF- α , IL-1 β , or IFN- γ leads to upregulation of both ICAM-1 and VCAM-1 [53,75]. It should be noted that in addition to astrocytes, microglia and endothelial cells also express adhesion molecules during MS and EAE [57,76]. Despite the overlapping functions of these cell types, the role of astrocyte adhesion molecule expression is likely crucial for the infiltration of T cells given their proximity to the BBB.

To fully understand the role of astrocyte activation of T cells, it is important to address whether CNS antigen presentation is required for demyelinating disease. In MS, it is likely that autoreactive T cells are primed in peripheral lymph nodes by myelin antigens released from the CNS or from cross-reactive mimicked epitopes [77]. These autoreactive T cells

subsequently migrate across the BBB and initiate myelin destruction. Due to the difficulty in examining human CNS tissue, animal models may shed some light onto this subject. EAE models are characterized by peripheral administration of myelin-derived peptides and adjuvant, resulting in peptide-specific T cell activation in the draining lymph nodes. Still, studies using CIIA-deficient mice indicate that while CNS antigen presentation is in fact necessary for the development of EAE [78], astrocyte-specific deficiency of CIIA does not affect susceptibility to EAE [71]. This suggests that astrocytes are not necessary for CNS antigen presentation during EAE most likely due to the presence of more efficient APCs in the CNS such as microglia, macrophages, and dendritic cells. Our laboratory has shown that dendritic cells migrate into the CNS and are potent antigen presenting cells during EAE [8]. Thus, while astrocytes are fully capable of priming T cells during EAE, this process is not necessary to initiate disease. Rather, astrocyte-mediated activation of autoreactive T cells may play a role in the potentiation and exacerbation of ongoing disease.

Astrocyte-derived Cytokines and Chemokines Drive Inflammation

In addition to a potential role in directly priming autoreactive T cells, astrocytes also provide a suitable environment for T cell activation. Although MS and EAE have long been thought to be mediated by IFN- γ producing T_H1 cells, more recent evidence implicates the T_H17 lineage of T cells in driving the pathogenesis of demyelinating disease [79,80]. Accordingly, astrocytes play a role in the activation of both T_H1 and T_H17 T cells by secreting IL-12 and IL-23 [81]. IL-12 is essential for driving the production of T_H1 cells [82] whereas IL-23 is required for the expansion of T_H17 cells *in vivo* [83]. *In vitro* studies demonstrate that astrocyte-mediated production of IL-23 is critical for the activation of IL-17-producing T cells [84]. *In vivo*, however, astrocyte production of IL-23 may not be required for driving T_H17 responses in the CNS. Instead, bone marrow chimera studies suggest that microglia-derived IL-23 is necessary for the development of EAE [85]. Thus, while astrocytes are able to promote T_H17 responses in the CNS, it appears that their production of IL-23 is not necessary to induce EAE.

Although IL-17 production has largely been associated with T cells, a recent study demonstrated that astrocytes also produce this cytokine in postmortem MS tissue [80]. IL-17 has been shown to be responsible for neutrophil recruitment, chemokine production, and dendritic cell maturation in other autoimmune diseases [86]. However, the exact role of IL-17 in MS is not fully understood and, therefore, it is difficult to delineate the significance of astrocyte-derived IL-17. Astrocytes also have the potential to secrete other inflammatory cytokines such as IL-1, IL-6, and TNF- α [56] although it is not known whether these cytokines are actually produced *in vivo* by astrocytes during demyelinating disease. Because disease is initiated by T cells, it is likely that astrocytes are activated to release cytokines in response to T cell-derived factors and therefore, would perpetuate immune-mediated demyelination.

Perhaps the primary way in which astrocytes perpetuate immune-mediated demyelination is via chemokine production. Cerebrospinal fluid (CSF) from MS patients displays elevated levels of a variety of chemokines including IP-10 (CXCL10), Mig (CXCL9), RANTES (CCL5), and MIP-1 α (CCL3) [87–89]. While few studies have examined astrocyte chemokine production in MS tissue, it appears that astrocytes are the major producers of chemokines in MS. IP-10, for example, is elevated in astrocytic processes, particularly around blood vessels. Interestingly, IP-10 specifically recruits activated T_H1 cells into the CNS, suggesting astrocytes may be key in promoting the influx of autoreactive T cells. Near the edge of demyelinated lesions, astrocytes express high levels of SDF-1 (CXCL12) and MCP-1 (CCL2) leading to the recruitment of macrophages, microglia, and lymphocytes towards MS lesions [90–92]. *In vitro* studies confirm that human astrocytes secrete IP-10, MCP-1, and SDF-1 in response to inflammatory cytokines IL-1 β , TNF- α , and IFN- γ .

[90,93,94] again suggesting that astrocyte-induced immunopathology may be a consequence of activation by infiltrating T cells.

More extensive examination of astrocyte chemokine production has been conducted in animal models. Specific contributions of chemokines have been delineated using a variety of EAE models [95]. The IFN- γ -inducible chemokines MCP-1, IP-10, and GRO- γ (CXCL3) are all prominent in EAE lesions and are highly localized to astrocytes [96–98]. Fractalkine (CX3CL1), which recruits T cells and monocytes, is increased in astrocytes during MOG-induced EAE in rats [99] although fractalkine-deficient mice are still susceptible to EAE [100]. It is possible that redundant and compensatory mechanisms are taking place in these fractalkine-deficient mice as many chemokines have overlapping functions. Interestingly, in relapsing EAE, a sudden and drastic increase in MCP-1, IP-10, RANTES, and MIP-1a were observed in both brains and spinal cords at the initiation of relapse [98] indicating temporal regulation of chemokine expression during EAE. It is not known whether astrocytes are responsible for the production of these chemokines during relapse. *In vitro* data suggests that astrocytes secrete MCP-1 and IP-10 in response to IFN- γ and TNF- α [101,102], all of which are simultaneously expressed in the CNS during relapsing EAE.

Similar chemokine production is also observed in TMEV-infected mice. Intracranial TMEV infection induces a biphasic disease in which the first phase involves a potent T cell-mediated anti-viral response. Following the initial response, the virus persistently infects microglia and astrocytes culminating in epitope spreading, molecular mimicry, and TMEV-IDD [103,104]. During both the initial phase of infection and the later demyelinating phase, MIP-1 α , MCP-1, IP-10, and RANTES are prominently expressed in the CNS and likely play an instrumental role in the migration of virus-specific T cells [105,106]. *In vitro* infection of astrocytes by TMEV induces RANTES, MCP-1, and IP-10 production through a PKR-dependent pathway [107,108]. In addition, activation of AP-1 (activator protein-1) and NF- κ B (nuclear factor- κ B) is required for TMEV-induced, astrocyte production of chemokines [109]. Whether astrocyte-derived chemokines play any role *in vivo*, however, is not well understood. Astrocytes from TMEV-susceptible SJL mice demonstrate enhanced production of MIP-2 (CXCL2) following infection *in vivo* whereas MIP-2 production was not observed in astrocytes from TMEV-resistant BALB/c mice [110]. MIP-2 targets neutrophils and may play a significant role in initiating the anti-viral response in the CNS. The different chemokine responses between astrocytes from susceptible and resistant mouse strains suggest that astrocyte-derived cytokines may play a role in the migration of inflammatory cells into the CNS during TMEV infection.

Viral Infection Activates Innate Immune Function in Astrocytes

At the early stages of a viral infection, innate immune responses are required to initiate the cellular immune response. In the case of virally-induced demyelinating disease, it is likely that these innate responses are necessary for the recruitment and activation of potentially autoreactive T cells in the CNS. Astrocytes exhibit innate immune function and subsequently may drive virally-induced demyelination such as that observed in TMEV-IDD. Two molecules in particular have been shown to play a role in the astrocyte response to TMEV infection *in vitro*: PKR and TLR3. TMEV infection induces the production of type-I interferons (IFN- α and IFN- β) and IL-6 in primary astrocyte cultures primarily by PKR and, to a lesser extent, TLR3 stimulation [107]. Type-I interferons are important for early control of viral infection by inhibiting translation of viral proteins and promoting degradation of dsRNA. However, in combination with IL-6, astrocyte-derived type-I interferons increase MHC class I and II expression, ultimately leading to a pro-inflammatory response within the CNS [111]. Whether these astrocyte-mediated innate immune responses play any role in driving autoreactive T cells during TMEV-IDD is still not known.

In MS patients, recent evidence suggests a role for the human endogenous retrovirus HERV-W in exacerbating disease. Although segments of the HERV-W genome are found in various human tissue, a majority of these genes are functionally defective. However, one HERV-W gene product, syncytin-1, has been implicated in astrocyte-mediated pathology of MS. Syncytin-1 is a membrane glycoprotein that binds its receptor ASCT2, a amino acid transporter [112]. Interestingly, syncytin-1 mRNA and protein expression was significantly higher in cortical white matter of MS patients [113]. *In vitro* studies demonstrate that syncytin-1 induced the expression of inducible nitric oxide synthase in cultured astrocytes [114] potentially providing a link between HERV-W and oligodendrocyte damage. Furthermore, mice that over-expressed syncytin-1 under the GFAP promoter demonstrated neuroinflammation and a decrease in myelin proteins in the brain. These findings suggest that astrocyte responses to syncytin-1 may contribute to inflammatory demyelination in MS patients.

Protective Effects of Astrocytes on CNS Immunopathogenesis

Astrocytes Promote Anti-inflammatory Responses

In addition to data supporting the role of astrocytes as pro-inflammatory mediators of CNS tissue damage, many studies have demonstrated the ability of these cells to limit T cell-mediated neuroinflammation. Early *in vitro* studies suggested that murine astrocytes were inefficient at stimulating T_H1 responses and inhibited IL-12 production from microglia, but were efficient APC for the restimulation of T_H2 cells and producers of cytokines such as IL-10 and TGF- β [115–117]. It is generally accepted that the production of T_H2-type cytokines with anti-inflammatory properties can restrict tissue damage by down-regulating the effects of pro-inflammatory cytokines and inhibiting APC function [118,119]. More recent studies support the notion that astrocytes induce a mixed T_H1/T_H17/T_H2 cytokine profile in antigen-specific T cells. Although astrocytes stimulated *in vitro* production of IFN- γ and IL-17 in myelin-antigen-specific lymphocytes [84] and CD4⁺ T cells [70], they also sustained IL-4 and IL-5 generation [70], indicating the potential of astrocytes to limit inflammation in the CNS. Likewise, while TLR activation can cause pro-inflammatory cytokine release from astrocytes (as discussed above), activated TLR3 expression on poly I:C-treated adult human astrocytes also promoted increased production of anti-inflammatory cytokines IL-9, IL-10 and IL-11, and down-regulated the p40 subunit of IL-12 and IL-23 [120]. In addition, many molecules associated with neuroprotection were induced following TLR3 activation of astrocytes including neurotrophin-4 (NT-4), BDNF, CNTF, and LIF [120]. The observation that astroglial TLR3 expression is detected in late stage MS lesions [121] is in accordance with the idea that TLR3 activation in astrocytes promotes an anti-inflammatory and neuroprotective response over a pro-inflammatory response, but this has yet to be tested functionally or in an *in vivo* type setting.

Astrocyte Suppression of T cell Activation Limits Neuroinflammation

Other studies have indicated that cytokine-treated rat and human astrocytes inhibit antigen-specific T cell proliferation [122,123]. In one study, activated and resting astrocytes were shown to mediate the upregulation of CTLA-4 (cytotoxic T lymphocyte antigen-4) on already activated T_H1 and T_H2 cells in the presence of antigen [124,125]. CTLA-4 binds to costimulatory molecules, CD80 and CD86, with a 10 to 100-fold higher affinity than CD28 [125]. While CD28 signaling enhances T cell activation, CTLA-4 signals attenuate T cell proliferation and cytokine production without causing apoptosis. Thus, as a result of astrocyte-mediated CTLA-4 upregulation, the authors reported suppression of antigen-specific T_H1 and T_H2 cell activation and effector function [124]. In an unrelated study, astrocytes were shown to induce T cell unresponsiveness with an additional ability to trigger suppressor activity in both rat and human lymphocytes [126]. These astrocyte-induced

regulatory cells inhibited proliferation of fresh responder lymphocytes and decreased the severity of rat EAE when injected intravenously 7 days after immunization [126]. Moreover, a more recent study has found that activated astrocytes secrete IL-27 protein *in vitro*, which has been found to induce a suppressive effect on T_H17 cells and to limit CNS inflammation in both active and adoptive transfer EAE [127]. While more studies are required to explore the implications of the above discussed *in vitro* and EAE findings, these data indicate that depending on the cellular environment and the expression of other molecules, astrocytes can either promote or suppress neuroinflammation.

Adverse Effects of Astrocytes that Limit Remyelination and CNS Repair

Astrocytes Inhibit Remyelination by Forming a Glial Scar

In addition to exacerbating the myelin-specific immune response, astrocytes can contribute to the pathogenesis of MS by inhibiting remyelination. One way in which this occurs is through the formation of a glial scar, a physical barrier around demyelinated lesions and is primarily composed of interwoven astrocytic processes held together by tight junctions [128,129]. Astrocytes within the glial scar display highly filamentous processes with increased expression of GFAP, nestin, and vimentin [130]. Numerous biochemical changes occur during the formation of the glial scar including the production of proteases, cytokines, and trophic factors. These glial scars are evident in tissue from MS patients and mice with EAE and surround areas of demyelination [131,132]. It appears that the purpose of the scar is to seclude the area of CNS damage to prevent widespread tissue damage. However, as described below, a result of the glial scar's rigidity is that it prevents both OPCs and axons from entering demyelinated plaques thereby inhibiting remyelination.

Astrocytes Prevent OPC Migration and Maturation

To ensure successful and effective remyelination, it is necessary for OPCs to migrate from the subventricular zones to areas of demyelination. *In vitro* studies demonstrate that OPC and Schwann cell migration is inhibited by astrocytes [133,134]. This is apparent *in vivo*, as OPCs are unable to migrate over long distances (> 2 mm) through the astrocyte-rich CNS parenchyma [135]. Accordingly, transplanted OPCs and Schwann cells preferentially migrate toward demyelinated areas along astrocyte-deficient pathways in rodent spinal cord [136,137]. In EAE, OPCs are observed along side astrocytes around demyelinated lesions but very few actually penetrate the glial scar [138].

Once at the site of demyelination, OPCs must mature to become myelinating oligodendrocytes. Astrocytes are able to inhibit myelination by secreting FGF-2, which promotes OPC proliferation and survival, but prevents OPC maturation. During murine hepatitis virus (MHV)-induced demyelination, astrocyte-production of FGF-2 corresponds to elevated numbers of OPCs around demyelinated lesions [139]. While these studies demonstrate that FGF-2 promotes remyelination, neonatal rats receiving exogenous administration of FGF-2 show segments of nerve fibers lacking myelin [140] suggesting that overproduction of FGF-2 by astrocytes may be detrimental to remyelination.

Another molecule that appears to play a significant role in preventing OPC maturation is hyaluronan, a glycosaminoglycan found throughout the extracellular matrix and white matter areas of the CNS [141]. Its receptor, CD44, is expressed on astrocytes in normal white matter [142] and in astrocytes, OPCs, and T cells in both MS and EAE CNS tissue [143,144]. Hyaluronan, on the other hand, is not elevated in MS patients but has been shown to be produced by astrocytes and some OPCs during MOG-induced EAE [145]. Those oligodendrocytes that co-localized with hyaluronan displayed an immature phenotype and did not express markers of mature oligodendrocytes such as galactocerebrosidase and MBP. It is not known how the hyaluronan-CD44 interaction inhibits OPC maturation but direct

treatment of OPCs with hyaluronan *in vitro* prevented maturation [145]. These findings suggest that astrocytes directly inhibit OPC maturation and subsequent remyelination.

Axonal Regeneration is Blocked by Astrocyte-Associated Molecules

As mentioned earlier, astrocytes which make up the glial scar help form a physical barrier around areas of demyelination. Consequently, axon regeneration is prevented from occurring near demyelinated plaques. When newly formed axons come in contact with the glial scar environment, growth cone migration is stalled for indefinite periods of time [146]. Amazingly, growth cones that have been arrested for one year are still able to form mature synapses with the addition of BDNF indicating that astrocyte-mediated inhibition of axon growth is reversible [147]. *In vitro* studies support the inhibitory nature of astrocytes as axons regenerate poorly on three-dimensional neonatal rodent astrocyte cultures [148] and on astrocytes from glial scars [149]. Further examination has demonstrated that this inhibition is mediated by astrocyte-derived chondroitin sulphate proteoglycans (CS-PGs). These molecules are up-regulated around glial scars in CNS white matter [150] and play a role in inhibiting axon regeneration in MS [151]. Three types of CS-PGs are preferentially localized to astrocytes *in vivo*: neurocan, brevican, and NG2. Neurocan (secreted) and brevican (cell-bound) are the major proteoglycan produced by astrocytes *in vitro* and both have been shown to inhibit axon growth following CNS injury [152,153]. Although it is not known whether these specific molecules play a role in MS, mice deficient in both neurocan and brevican display enhanced axon regeneration following spinal cord lesioning [154].

NG2 is most often regarded as a marker for OPCs in the adult CNS as it often co-localizes with A2B5 and PDGF receptor [155]. At the edges of a glial scar, NG2-positive cells are found in great numbers. While many of these cells are likely OPCs, recent evidence suggests that NG2-positive cells are also able to become astrocytes *in vivo* [156]. Therefore, astrocyte-derived NG2 may provide inhibitory signals to axon regeneration. NG2 has been shown to be expressed by both OPCs and astrocytes adjacent to areas of demyelination [157]. *In vitro* studies demonstrate that NG2 is inhibitory to the growth of axons and that this inhibition could be overcome by anti-NG2 antibody treatment in astrocyte cell lines [158]. The negative effects of NG2 on axon regeneration are not limited to astrocytes, however. OPC-derived NG2 contributes to the inhibition of axon regeneration as immature oligodendrocytes have been shown to prevent axon growth *in vitro* [159].

Aside from CS-PGs, other less studied inhibitory molecules are found to be expressed by astrocytes during demyelinating disease. Ephrins and their receptors (Ephs), for example, are secreted by astrocytes in normal CNS and are increased in MS lesions [160]. Functionally, astrocyte-derived ephrin-B2 helps form the glial scar by creating a basal lamina around areas of injury thereby physically limiting axon growth [161]. Furthermore, ephrins induce growth cone collapse through activation of axon-bound Eph tyrosine-receptor kinase receptors [162]. Another molecule that inhibits axon growth is Nogo-A and its receptor NgR. Nogo-A is primarily expressed on oligodendrocytes at the edges of demyelinated lesions in MS tissue [163] and has been shown to prevent axon growth in EAE [164]. A 66-amino acid segment of Nogo-A, known as Nogo-66, is expressed on axons and mediates growth cone collapse through activation of NgR. Interestingly, astrocytes express NgR, its co-receptor TROY, and an adapter LINGO in MS lesions [165]. The NgR-TROY-LINGO interaction is inhibitory to axon growth and the simultaneous expression of these three molecules by astrocytes in MS supports the idea that astrocytes prevent remyelination.

Protective Effects of Astrocytes that Promote Neuroprotection and Myelin Repair

An experimental model involving the ablation of astrocytes following CNS insult revealed protective roles for reactive astrocytes in the inflamed CNS [47]. Transgenic mice expressing herpes simplex virus-thymidine kinase (HSV-TK) under the GFAP promoter were engineered and treated with the antiviral drug gancyclovir (GCV), which causes HSV-TK-expressing cells to metabolize the drug into toxic nucleotide analogs. Following CNS insult, astrocytes proliferate and are preferentially killed in GCV-treated GFAP-TK mice [166]. The ablation of these cells resulted in enhanced neuronal damage, improper scar formation with extended inflammation, and a persistence of infiltrate entering through the BBB. Thus, these results suggest that astrocytes perform protective functions following CNS injury such as influencing neuronal survival and limiting further tissue damage and lymphocyte infiltration through scar formation and BBB repair.

Extracellular Matrix-Related Factors can Favor Remyelination and Neuroprotection

Astrocytes express matrix metalloproteinases (MMPs), which are key factors in extracellular matrix remodeling [167]. As the BBB is breached during CNS injury, MMPs allow immune cell extravasation, but not all MMPs are detrimental for tissue repair. For example, MMP-9 has been shown to mediate oligodendrocyte process outgrowth [168] and MMP-9 knock out mice exhibit impaired remyelination following a demyelinating insult [169]. Deficiencies in remyelination in these mice can thus be attributed to the failure of debris clearance and/or inhibition of oligodendrocyte process extension. MMP activity is negatively regulated by tissue inhibitors of metalloproteinases (TIMPs), which are also expressed by astrocytes located in demyelinating lesions of mice with EAE [170]. During the course of EAE, TIMP-1 knock out mice display enhanced immune cell infiltration and activation, and myelin repair deficiencies [171]. Thus, in the CNS TIMP-1 plays a role in BBB maintenance and can exhibit neuroprotective properties. These results suggest that depending on the specific MMP being expressed and whether a favorable balance between MMP expression and TIMP [143] inhibition is reached, astrocytic expression of these factors can favor remyelination and neuroprotection. During MS, it appears that a lack of balance between these factors may contribute to the persistence of disease, as several studies have reported upregulated expression of MMPs and a static or reduced production of their inhibitors in patients with the disease [143].

Astrocyte-Derived Chemokines Support Progenitor Cell Migration and Differentiation

Astrocyte-derived chemokines function not only to promote the recruitment of immune cells into the CNS, but also influence the migration of neural precursors and OPCs towards damaged areas in the CNS and/or support their differentiation into mature cell types. MCP1 is upregulated in various neuroinflammatory conditions and secreted by astrocytes with a major role in promoting the migration of neural progenitor cells to the site of injury [172–175], and enhancing differentiation of these cells [175]. SDF-1 α expression was detected in astrocytes within MS lesions [90], and has been demonstrated *in vitro* to inhibit primary rat oligodendrocyte progenitor cell migration, and to augment their differentiation into mature oligodendrocytes to support remyelination [176]. Astrocytes expressing GRO- α (CXCL1) were detected in MS lesions and found associated with oligodendrocytes reactive for CXCR2, the receptor for GRO- α . CXCR2 signaling has been demonstrated to be important for the maintenance and differentiation of oligodendrocyte cells, as well as for myelination in the adult CNS [177]. Thus, together these results indicate a potential role for GRO- α , an astrocyte-derived chemokine, in the generation of mature oligodendrocytes and new myelin following a neuroinflammatory attack.

Astrocyte-derived Cytokines Promote Myelin Repair and Neuroprotection

GRO- α was recently found to increase oligodendrocyte progenitor proliferation in slice cultures of human fetal cortical brain tissue, and this effect was mediated through an ERK1/2-dependent pathway and secretion of IL-6 from astrocytes [178]. IL-6 has been associated with the inflammatory response and reactive gliosis. However, there is also evidence that IL-6 can mediate remyelination and neuroprotection. IL-6 treatment of TMEV-infected mice or mice with EAE resulted in decreased demyelination in both diseases [179,180], and the fact that IL-6 null mice are resistant to EAE [181] suggests that the pro-inflammatory versus protective role of IL-6 may be a timing issue. Increased numbers of astrocytes expressing IL-6 protein have been correlated with increased oligodendrocyte preservation near inactive demyelinated lesions in MS tissue [182], which is suggestive of a survival role for IL-6 once the inflammatory response has subsided. *In vitro* data has suggested both a survival and differentiation effect of an IL6RIL6 chimeric protein on primary rat OPCs [183]. In addition to its effects on oligodendrocyte lineage cells, IL-6 has also been shown to promote the release of neurotrophins (i.e. NT-3, NT-4/5, and NGF) from astrocytes to support neuronal regeneration [184]. Moreover, it is now understood that IL-6 amplifies the expression and activation of neuronal adenosine A(1) receptors enabling neuronal protection from glutamate toxicity during CNS insults [185] and further supporting the importance of astrocyte-derived IL-6 for CNS repair.

Expression of IL-11, another cytokine of the IL-6 family, was recently localized to activated astrocytes within the myelinated regions between active and chronic lesions in MS tissue [186]. Oligodendrocytes and OPC expressed the receptor IL11-R α in MS tissue and in human cultures *in vitro* [186]. IL-11-treatment increased survival and maturation of human oligodendrocyte cells *in vitro* and enhanced myelin synthesis in rodent neuron-oligodendrocyte progenitor co-cultures [186]. Furthermore, it was determined that IL-11 can be induced in astrocytes in response to activation with IL-1 β or TGF- β , two cytokines involved in astrogliosis during CNS inflammation [187,188].

LIF is a member of the IL-6 cytokine family that has been shown to have both positive [189] and negative [190] effects on oligodendrocyte myelination. A recent study showed this effect to be concentration dependent, such that low concentrations (less than 5 ng/ml) promoted myelination while higher concentrations inhibited myelin formation in co-cultures of neurons and oligodendrocytes [191]. Moreover, astrocytes added to these cultures released LIF in response to axon impulse activity and enhanced myelination by an ATP-receptor-dependent mechanism [191]. These results support a positive role for astrocytes in mediating myelination, but depending on the local concentration of LIF *in vivo*, its release by astrocytes could also inhibit myelination and remyelination.

Like IL-6, IL-1 β can be produced by astrocytes and appears to play a dual role in the response to CNS injury, having been implicated in both the induction and repair of CNS inflammation. The role of IL-1 β in the activation of astrocytes has been linked to the restoration of the BBB following CNS insult [188]. IL-1 β -null mice exhibited decreased astrocyte reactivity and increased permeability of the BBB following induction of a demyelinating insult compared to wild type controls [188]. Using these knock out mice, it has also been noted that IL-1 β plays a role in supporting oligodendrocyte generation and remyelination through the induction of CNTF [192] and IGF-I [193]. While both astrocytes and microglia produce IL-1 β [192,193], astrocytes are the primary cellular source of CNTF [194] and IGF-I [193] following injury. IGF-I supports the survival of oligodendrocyte lineage cells, promotes the proliferation and differentiation of OPC, and regulates myelin synthesis in mature oligodendrocytes [195]. Moreover, IGF-I has been described as a potent neurotrophic factor [196].

Astrocytic CNTF induction requires IL-1 β signaling following CNS injury [192] and expression of this IL-6 family member has been detected in remyelinating spinal cord regions of mice recovering from a viral demyelinating model [197]. CNTF has been shown to promote the survival of both neuronal and glial cell types [35,198] and has also been implicated in the promotion of perinatal and adult OPC differentiation *in vitro* [189,199,200]. An autocrine/paracrine loop for CNTF release by astrocytes has been described [201] and factors released by CNTF-treated astrocytes also mediate neuroprotection [202], and oligodendrocyte progenitor survival [203] and proliferation [197]. FGF-2, a growth factor that promotes oligodendrocyte progenitor proliferation, is one such factor that is produced by astrocytes in response to CNTF stimulation [197].

Overall the potential of the above-mentioned cytokines to positively regulate oligodendrocyte function and CNS repair has been well demonstrated. However, as also discussed, most of these cytokines have additional effects on immune cells and can be detrimental to CNS tissue during inflammation. Thus, caution must be taken in developing treatment strategies to optimize the reparative effects and diminish the damaging effects.

Conclusions: Implications for Therapy

In recent years, investigators in the field of neuroimmunology have depicted the astrocyte as both an ally and an enemy in the fight against CNS immune infiltration and the restoration of neuronal function (Figures 1 and 2). Some experimental evidence implicates astrocytes as mediators of neuroinflammation that impede remyelination and neuronal repair. Other evidence suggests that astrocytes limit the detrimental effects of pro-inflammatory factors while providing support and protection for oligodendrocytes and neurons. Thus, targeting the astrocyte population for therapeutic intervention of neuroinflammatory and neurodegenerative diseases is a challenging endeavor. Based on research discussed here, ablating astrocytic function completely would be detrimental for CNS repair, as astrocytes are important for the confinement of lesions and the restoration of CNS homeostasis. Therefore, selective targeting of astrocyte function to minimize the damaging effects is most ideal for the development of astrocyte-specific therapies for MS and other similar CNS diseases. However, the conflicting dual roles that many astrocyte-derived factors have been demonstrated to play in the regulation of inflammation and neural repair, contribute to the difficult task of therapy design.

Several therapies that have been tested in MS-models, human clinical trials, and/or are approved for use by MS patients have been reported to regulate astrocytes in ways that may contribute to their beneficial effects. IFN- β is an approved drug for MS that has been shown *in vitro* to inhibit proliferation [204] and nitric oxide (NO) production by astrocytes [205]. Increased survival of astrocytes [206] and their production of oligodendrocyte growth factors such as NGF [207] have also been reported. Taken together, these data suggest that IFN- β targets a somewhat limited repertoire of astrocyte functions, at least *in vitro*.

Treatment with statins, or HMG-CoA reductase inhibitors, which decrease leukocyte infiltration into the CNS [208], led to decreased gadolinium-enhancing lesions in MS patients during clinical trials [209]. Administration of a statin drug to cultured neonatal rat astrocytes *in vitro* significantly decreased IFN- γ -induced MHC class II expression in astrocytes [210], which is similar to an effect observed following IFN- β treatment [211]. Moreover, a statin-induced decrease in MHC class II expression in microglia has also been demonstrated [212]. Since microglia display more potent APC functions and astrocyte APC function is most likely not required to initiate disease, the implications of decreased MHC class II on astrocytes is uncertain.

Retinoic acid (RA) is another potential therapy, shown to inhibit clinical signs of EAE, with effects on both microglia and astrocytes *in vitro*. The production of NO and TNF- α were inhibited in both primary cell-types stimulated with LPS, whereas only microglia exhibited decreased production of IL-1 β and IL-12 p40 and increased secretion of MCP-1 [213]. However, RA in combination with a peroxisome proliferator-activated receptor- α (PPAR- α) agonist cooperatively inhibited IL-1 β , IL-6 and MCP-1 in addition to NO and TNF- α in LPS-stimulated astrocytes [214]. PPARs are hormone receptors with roles in glucose and lipid metabolism that have also been shown to protect against the development of EAE [215] and to inhibit pro-inflammatory cytokine production from activated CD4⁺ T cells [216]. By themselves, PPAR- α agonists inhibited astrocyte production of NO, TNF- α , IL-1 β , and IL-6 *in vitro*, however the significance of these effects *in vivo* are not known.

Therapies designed and approved for the treatment of MS are restricted mainly to anti-inflammatory drugs with limited benefit. Whereas many cytokine and chemokine manipulations have proven beneficial in animal models of MS, these same therapies have not translated into favorable treatments for human MS. A reason for these discrepancies may be that specific cytokines or factors (some of which are regulated by astrocytes) are required at different time periods following injury in order for disease resolution to occur. Molecules that are useful early in demyelinating disease for immune suppression may be harmful later during lesion resolution, and vice versa. It is clear that astrocytes play a crucial role in both the pathogenesis and resolution of demyelinating disease. However, the conflicting and dual effects of many astrocyte-derived factors on the regulation of inflammation and neural repair contribute to the difficult task of therapy design. Dissecting out which factors are most beneficial at specific stages during disease and understanding the variable degrees of astrocyte function during lesion evolution are critical areas of further research.

Acknowledgments

This work was supported by research grants from the National Institutes of Health, the National Multiple Sclerosis Society (NMSS) and the Myelin Repair Foundation. TJF is supported by NMSS Postdoctoral Fellowship FG 1648A1/1.

References

1. 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;19:578–587. [PubMed: 3524414]
2. McFarland HF, Martin R. Multiple sclerosis: a complicated picture of autoimmunity. *Nat Immunol* 2007;8:913–919. [PubMed: 17712344]
3. Bruck W, Kuhlmann T, Stadelmann C. Remyelination in multiple sclerosis. *J Neurol Sci* 2003;206:181–185. [PubMed: 12559508]
4. Gensert JM, Goldman JE. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. *Neuron* 1997;19:197–203. [PubMed: 9247275]
5. Bjartmar C, Trapp BD. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. *Curr Opin Neurol* 2001;14:271–278. [PubMed: 11371748]
6. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowski M, Lira SA, Gorman D, Kastelein RA, Sedgwick JD. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003;421:744–748. [PubMed: 12610626]
7. Babbe H, Roers A, Waisman A, Lassmann H, Goebels N, Hohlfeld R, Friese M, Schroder R, Deckert M, Schmidt S, Ravid R, Rajewsky K. Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. *J Exp Med* 2000;192:393–404. [PubMed: 10934227]

8. Bailey SL, Schreiner B, McMahon EJ, Miller SD. CNS myeloid DCs presenting endogenous myelin peptides 'preferentially' polarize CD4(+) T(H)-17 cells in relapsing EAE. *Nat Immunol* 2007;8:172–180. [PubMed: 17206145]
9. Ziemssen T, Ziemssen F. The role of the humoral immune system in multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). *Autoimmun Rev* 2005;4:460–467. [PubMed: 16137612]
10. He F, Sun YE. Glial cells more than support cells? *Int J Biochem Cell Biol* 2007;39:661–665. [PubMed: 17141551]
11. Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: redefining the functional architecture of the brain. *Trends Neurosci* 2003;26:523–530. [PubMed: 14522144]
12. Chao, TI.; Rickmann, M.; Wolff, JR. The synapse-astrocyte boundary: anatomical basis for an integrative role of glia in synaptic transmission. In: Volterra, A.; Magistretti, P.; Haydon, P., editors. *Tripartate Synapses: Synaptic Transmission with Glia*. Oxford University Press; Oxford, New York: 2002. p. 3-23.
13. Butt AM, Duncan A, Berry M. Astrocyte associations with nodes of Ranvier: ultrastructural analysis of HRP-filled astrocytes in the mouse optic nerve. *J Neurocytol* 1994;23:486–499. [PubMed: 7983475]
14. Eng LF. Glial fibrillary acidic protein (GFAP): the major protein of glial intermediate filaments in differentiated astrocytes. *J Neuroimmunol* 1985;8:203–214. [PubMed: 2409105]
15. Liedtke W, Edelmann W, Bieri PL, Chiu FC, Cowan NJ, Kucherlapati R, Raine CS. GFAP is necessary for the integrity of CNS white matter architecture and long-term maintenance of myelination. *Neuron* 1996;17:607–615. [PubMed: 8893019]
16. McCall MA, Gregg RG, Behringer RR, Brenner M, Delaney CL, Galbreath EJ, Zhang CL, Pearce RA, Chiu SY, Messing A. Targeted deletion in astrocyte intermediate filament (Gfap) alters neuronal physiology. *Proc Natl Acad Sci USA* 1996;93:6361–6366. [PubMed: 8692820]
17. Nawashiro H, Messing A, Azzam N, Brenner M. Mice lacking GFAP are hypersensitive to traumatic cerebrospinal injury. *Neuroreport* 1998;9:1691–1696. [PubMed: 9665584]
18. Messing A, Goldman JE, Johnson AB, Brenner M. Alexander disease: new insights from genetics. *J Neuropathol Exp Neurol* 2001;60:563–573. [PubMed: 11398833]
19. Menn B, Garcia-Verdugo JM, Yaschine C, Gonzalez-Perez O, Rowitch D, Alvarez-Buylla A. Origin of oligodendrocytes in the subventricular zone of the adult brain. *J Neurosci* 2006;26:7907–7918. [PubMed: 16870736]
20. Jessen KR, Mirsky R. Nonmyelin-forming Schwann cells coexpress surface proteins and intermediate filaments not found in myelin-forming cells: a study of Ran-2, A5E3 antigen and glial fibrillary acidic protein. *J Neurocytol* 1984;13:923–934. [PubMed: 6398831]
21. Bertelli E, Regoli M, Gambelli F, Lucattelli M, Lungarella G, Bastianini A. GFAP is expressed as a major soluble pool associated with glucagon secretory granules in A-cells of mouse pancreas. *J Histochem Cytochem* 2000;48:1233–1242. [PubMed: 10950880]
22. von Boyen GB, Steinkamp M, Reinshagen M, Schafer KH, Adler G, Kirsch J. Proinflammatory cytokines increase glial fibrillary acidic protein expression in enteric glia. *Gut* 2004;53:222–228. [PubMed: 14724154]
23. Korfias S, Stranjalis G, Papadimitriou A, Psachoulia C, Daskalakis G, Antsaklis A, Sakas DE. Serum S-100B protein as a biochemical marker of brain injury: a review of current concepts. *Curr Med Chem* 2006;13:3719–3731. [PubMed: 17168733]
24. Chaudhry FA, Lehre KP, van Lookeren Campagne M, Ottersen OP, Danbolt NC, Storm-Mathisen J. Glutamate transporters in glial plasma membranes: highly differentiated localizations revealed by quantitative ultrastructural immunocytochemistry. *Neuron* 1995;15:711–720. [PubMed: 7546749]
25. McKinnon PJ, Margolskee RF. SC1: a marker for astrocytes in the adult rodent brain is upregulated during reactive astrocytosis. *Brain Res* 1996;709:27–36. [PubMed: 8869553]
26. Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. *Glia* 2007;55:1263–1271. [PubMed: 17659525]
27. Kang J, Jiang L, Goldman SA, Nedergaard M. Astrocyte-mediated potentiation of inhibitory synaptic transmission. *Nat Neurosci* 1998;1:683–692. [PubMed: 10196584]

28. Liberto CM, Albrecht PJ, Herx LM, Yong VW, Levison SW. Pro-regenerative properties of cytokine-activated astrocytes. *J Neurochem* 2004;89:1092–1100. [PubMed: 15147501]
29. Martin DL. Synthesis and release of neuroactive substances by glial cells. *Glia* 1992;5:81–94. [PubMed: 1349588]
30. Haydon PG. Neuroglial networks: neurons and glia talk to each other. *Curr Biol* 2000;10:R712–714. [PubMed: 11050407]
31. Dreyfus CF, Dai X, Lercher LD, Racey BR, Friedman WJ, Black IB. Expression of neurotrophins in the adult spinal cord in vivo. *J Neurosci Res* 1999;56:1–7. [PubMed: 10213469]
32. Schwartz JP, Nishiyama N. Neurotrophic factor gene expression in astrocytes during development and following injury. *Brain Res Bull* 1994;35:403–407. [PubMed: 7532097]
33. Nakayama T, Momoki-Soga T, Inoue N. Astrocyte-derived factors instruct differentiation of embryonic stem cells into neurons. *Neurosci Res* 2003;46:241–249. [PubMed: 12767487]
34. Gard AL, Burrell MR, Pfeiffer SE, Rudge JS, Williams WC. Astroglial control of oligodendrocyte survival mediated by PDGF and leukemia inhibitory factor-like protein. *Development* 1995;121:2187–2197. [PubMed: 7635062]
35. Barres BA, Schmid R, Sendtner M, Raff MC. Multiple extracellular signals are required for long-term oligodendrocyte survival. *Development* 1993;118:283–295. [PubMed: 8375338]
36. Sendtner M, Kreutzberg GW, Thoenen H. Ciliary neurotrophic factor prevents the degeneration of motor neurons after axotomy. *Nature* 1990;345:440–441. [PubMed: 2342575]
37. Chernausk SD. Insulin-like growth factor-I (IGF-I) production by astroglial cells: regulation and importance for epidermal growth factor-induced cell replication. *J Neurosci Res* 1993;34:189–197. [PubMed: 8450562]
38. Wolburg H, Lippoldt A. Tight junctions of the blood-brain barrier: development, composition and regulation. *Vascul Pharmacol* 2002;38:323–337. [PubMed: 12529927]
39. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 2006;7:41–53. [PubMed: 16371949]
40. Schwaninger M, Sallmann S, Petersen N, Schneider A, Prinz S, Libermann TA, Spranger M. Bradykinin induces interleukin-6 expression in astrocytes through activation of nuclear factor-kappaB. *J Neurochem* 1999;73:1461–1466. [PubMed: 10501190]
41. Didier N, Romero IA, Creminon C, Wijkhuisen A, Grassi J, Mabondzo A. Secretion of interleukin-1beta by astrocytes mediates endothelin-1 and tumour necrosis factor-alpha effects on human brain microvascular endothelial cell permeability. *J Neurochem* 2003;86:246–254. [PubMed: 12807444]
42. Kim JH, Kim JH, Park JA, Lee SW, Kim WJ, Yu YS, Kim KW. Blood-neural barrier: intercellular communication at glio-vascular interface. *J Biochem Mol Biol* 2006;39:339–345. [PubMed: 16889675]
43. Kleine TO, Benes L. Immune surveillance of the human central nervous system (CNS): different migration pathways of immune cells through the blood-brain barrier and blood-cerebrospinal fluid barrier in healthy persons. *Cytometry A* 2006;69:147–151. [PubMed: 16479603]
44. Ransohoff RM, Kivisakk P, Kidd G. Three or more routes for leukocyte migration into the central nervous system. *Nat Rev Immunol* 2003;3:569–581. [PubMed: 12876559]
45. Carpentier PA, Begolka WS, Olson JK, Elhofy A, Karpus WJ, Miller SD. Differential activation of astrocytes by innate and adaptive immune stimuli. *Glia* 2005;49:360–374. [PubMed: 15538753]
46. Scumpia PO, Kelly KM, Reeves WH, Stevens BR. Double-stranded RNA signals antiviral and inflammatory programs and dysfunctional glutamate transport in TLR3-expressing astrocytes. *Glia* 2005;52:153–162. [PubMed: 15920723]
47. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends Immunol* 2007;28:138–145. [PubMed: 17276138]
48. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* 2005;308:1314–1318. [PubMed: 15831717]
49. Carson MJ, Reilly CR, Sutcliffe JG, Lo D. Mature microglia resemble immature antigen-presenting cells. *Glia* 1998;22:72–85. [PubMed: 9436789]

50. Wong GH, Bartlett PF, Clark-Lewis I, Battye F, Schrader JW. Inducible expression of H-2 and Ia antigens on brain cells. *Nature* 1984;310:688–691. [PubMed: 6433204]
51. Nikcevich KM, Gordon KB, Tan L, Hurst SD, Kroepfl JF, Gardinier M, Barrett TA, Miller SD. Interferon-gamma activated primary murine astrocytes express B7 costimulatory molecules and prime naive antigen-specific T cells. *J Immunol* 1997;158:614–621. [PubMed: 8992975]
52. Sedgwick JD, Mossner R, Schwender S, ter Meulen V. Major histocompatibility complex-expressing nonhematopoietic astroglial cells prime only CD8 + T lymphocytes: astroglial cells as perpetuators but not initiators of CD4 + T cell responses in the central nervous system. *J Exp Med* 1991;173:1235–1246. [PubMed: 1827142]
53. Tan LJ, 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;160:4271–4279. [PubMed: 9574529]
54. Vass K, Lassmann H. Intrathecal application of interferon gamma. Progressive appearance of MHC antigens within the rat nervous system. *Am J Pathol* 1990;137:789–800. [PubMed: 2121041]
55. Barcia C, Thomas CE, Curtin JF, King GD, Wawrowsky K, Candolfi M, Xiong WD, Liu C, Kroeger K, Boyer O, Kupiec-Weglinski J, Klatzmann D, Castro MG, Lowenstein PR. In vivo mature immunological synapses forming SMACs mediate clearance of virally infected astrocytes from the brain. *J Exp Med* 2006;203:2095–2107. [PubMed: 16923851]
56. Dong Y, Benveniste EN. Immune function of astrocytes. *Glia* 2001;36:180–190. [PubMed: 11596126]
57. Gimenez MA, Sim JE, Russell JH. TNFR1-dependent VCAM-1 expression by astrocytes exposes the CNS to destructive inflammation. *J Neuroimmunol* 2004;151:116–125. [PubMed: 15145610]
58. Wong GH, Bartlett PF, Clark-Lewis I, Battye F, Schrader JW. Inducible expression of H-2 and Ia antigens on brain cells. *Nature* 1984;310:688–691. [PubMed: 6433204]
59. Hoftberger R, Aboul-Enein F, Brueck W, Lucchinetti C, Rodriguez M, Schmidbauer M, Jellinger K, Lassmann H. Expression of major histocompatibility complex class I molecules on the different cell types in multiple sclerosis lesions. *Brain Pathol* 2004;14:43–50. [PubMed: 14997936]
60. Traugott U, McFarlin DE, Raine CS. Immunopathology of the lesion in chronic relapsing experimental autoimmune encephalomyelitis in the mouse. *Cell Immunol* 1986;99:395–410. [PubMed: 3093105]
61. Zeinstra E, Wilczak N, De Keyser J. Reactive astrocytes in chronic active lesions of multiple sclerosis express co-stimulatory molecules B7-1 and B7-2. *J Neuroimmunol* 2003;135:166–171. [PubMed: 12576238]
62. Zeinstra E, Wilczak N, Streefland C, De Keyser J. Astrocytes in chronic active multiple sclerosis plaques express MHC class II molecules. *Neuroreport* 2000;11:89–91. [PubMed: 10683836]
63. Bo L, Mork S, Kong PA, Nyland H, Pardo CA, Trapp BD. Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions. *J Neuroimmunol* 1994;51:135–146. [PubMed: 8182113]
64. Hayashi T, Burks JS, Hauser SL. Expression and cellular localization of major histocompatibility complex antigens in active multiple sclerosis lesions. *Ann NY Acad Sci* 1988;540:301–305. [PubMed: 3061338]
65. Windhagen A, Newcombe J, Dangond F, Strand C, Woodroffe MN, Cuzner ML, Hafler DA. Expression of costimulatory molecules B7-1 (CD80), B7-2 (CD80), and interleukin 12 cytokine in multiple sclerosis lesions. *J Exp Med* 1995;182:1985–1996. [PubMed: 7500044]
66. Cross AH, Ku G. Astrocytes and central nervous system endothelial cells do not express B7-1 (CD80) or B7-2 (CD86) immunoreactivity during experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2000;110:76–82. [PubMed: 11024536]
67. Butter C, O'Neill JK, Baker D, Gschmeissner SE, Turk JL. An immunoelectron microscopical study of the expression of class II major histocompatibility complex during chronic relapsing experimental allergic encephalomyelitis in Biozzi AB/H mice. *J Neuroimmunol* 1991;33:37–42. [PubMed: 2056070]

68. Issazadeh S, Navikas V, Schaub M, Sayegh M, Khoury S. Kinetics of expression of costimulatory molecules and their ligands in murine relapsing experimental autoimmune encephalomyelitis in vivo. *J Immunol* 1998;161:1104–1112. [PubMed: 9686568]
69. Tan LJ, Vanderlugt CL, McRae BL, Miller SD. Regulation of the effector stages of experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance induction. III. A role for clonal anergy/deletion. *Autoimmunity* 1998;27:13–28. [PubMed: 9482204]
70. Kort JJ, Kawamura K, Fugger L, Weissert R, Forsthuber TG. Efficient presentation of myelin oligodendrocyte glycoprotein peptides but not protein by astrocytes from HLA-DR2 and HLA-DR4 transgenic mice. *J Neuroimmunol* 2006;173:23–34. [PubMed: 16386804]
71. Stuve O, Youssef S, Slavin AJ, King CL, Patarroyo JC, Hirschberg DL, Brickey WJ, Soos JM, Piskurich JF, Chapman HA, Zamvil SS. The role of the MHC class II transactivator in class II expression and antigen presentation by astrocytes and in susceptibility to central nervous system autoimmune disease. *J Immunol* 2002;169:6720–6732. [PubMed: 12471103]
72. Fontana A, Fierz W, Wekerle H. Astrocytes present myelin basic protein to encephalitogenic T-cell lines. *Nature* 1984;307:273–276. [PubMed: 6198590]
73. Xiao BG, Diab A, Zhu J, van der Meide P, Link H. Astrocytes induce hyporesponses of myelin basic protein-reactive T and B cell function. *J Neuroimmunol* 1998;89:113–121. [PubMed: 9726833]
74. Sobel RA, Mitchell ME, Fondren G. Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. *Am J Pathol* 1990;136:1309–1316. [PubMed: 1972610]
75. Rosenman SJ, Shrikant P, Dubb L, Benveniste EN, Ransohoff RM. Cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1) by astrocytes and astrocytoma cell lines. *J Immunol* 1995;154:1888–1899. [PubMed: 7530745]
76. Cannella B, Raine CS. The adhesion molecule and cytokine profile of multiple sclerosis lesions. *Ann Neurol* 1995;37:424–435. [PubMed: 7536402]
77. Hemmer B, Archelos JJ, Hartung HP. New concepts in the immunopathogenesis of multiple sclerosis. *Nat Rev Neurosci* 2002;3:291–301. [PubMed: 11967559]
78. Tompkins SM, Padilla J, Dal Canto MC, Ting JP, Van Kaer L, Miller SD. De novo central nervous system processing of myelin antigen is required for the initiation of experimental autoimmune encephalomyelitis. *J Immunol* 2002;168:4173–4183. [PubMed: 11937578]
79. Harrington LE, Mangan PR, Weaver CT. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. *Curr Opin Immunol* 2006;18:349–356. [PubMed: 16616472]
80. Tzartos JS, Friese MA, Craner MJ, Palace J, Newcombe J, Esiri MM, Fugger L. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol*. 2007
81. Constantinescu CS, Tani M, Ransohoff RM, Wysocka M, Hilliard B, Fujioka T, Murphy S, Tighe PJ, Sarma JD, Trinchieri G, Rostami A. Astrocytes as antigen-presenting cells: expression of IL-12/IL-23. *J Neurochem* 2005;95:331–340. [PubMed: 16086689]
82. O'Garra A, Arai N. The molecular basis of T helper 1 and T helper 2 cell differentiation. *Trends Cell Biol* 2000;10:542–550. [PubMed: 11121747]
83. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McClanahan T, Kastelein RA, Cua DJ. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* 2005;201:233–240. [PubMed: 15657292]
84. Miljkovic D, Momcilovic M, Stojanovic I, Stosic-Grujicic S, Ramic Z, Mostarica-Stojkovic M. Astrocytes stimulate interleukin-17 and interferon-gamma production in vitro. *J Neurosci Res* 2007;85:3598–3606. [PubMed: 17969033]
85. Becher B, Durell BG, Noelle RJ. IL-23 produced by CNS-resident cells controls T cell encephalitogenicity during the effector phase of experimental autoimmune encephalomyelitis. *J Clin Invest* 2003;112:1186–1191. [PubMed: 14561703]
86. Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. *Nat Immunol* 2007;8:345–350. [PubMed: 17375096]
87. Sorensen TL, Tani M, Jensen J, Pierce V, Lucchinetti C, Folcik VA, Qin S, Rottman J, Sellebjerg F, Strieter RM, Frederiksen JL, Ransohoff RM. Expression of specific chemokines and chemokine

- receptors in the central nervous system of multiple sclerosis patients. *J Clin Invest* 1999;103:807–815. [PubMed: 10079101]
88. Simpson JE, Newcombe J, Cuzner ML, Woodroffe MN. Expression of the interferon-gamma-inducible chemokines IP-10 and Mig and their receptor, CXCR3, in multiple sclerosis lesions. *Neuropathol Appl Neurobiol* 2000;26:133–142. [PubMed: 10840276]
 89. Balashov KE, Rottman JB, Weiner HL, Hancock WW. CCR5(+) and CXCR3(+) T cells are increased in multiple sclerosis and their ligands MIP-1alpha and IP-10 are expressed in demyelinating brain lesions. *Proc Natl Acad Sci USA* 1999;96:6873–6878. [PubMed: 10359806]
 90. Calderon TM, Eugenin EA, Lopez L, Kumar SS, Hesselgesser J, Raine CS, Berman JW. A role for CXCL12 (SDF-1alpha) in the pathogenesis of multiple sclerosis: regulation of CXCL12 expression in astrocytes by soluble myelin basic protein. *J Neuroimmunol* 2006;177:27–39. [PubMed: 16782208]
 91. Tanuma N, Sakuma H, Sasaki A, Matsumoto Y. Chemokine expression by astrocytes plays a role in microglia/macrophage activation and subsequent neurodegeneration in secondary progressive multiple sclerosis. *Acta Neuropathol(Berl)* 2006;112:195–204. [PubMed: 16733654]
 92. Van Der Voorn P, Tekstra J, Beelen RH, Tensen CP, Van Der Valk P, De Groot CJ. Expression of MCP-1 by reactive astrocytes in demyelinating multiple sclerosis lesions. *Am J Pathol* 1999;154:45–51. [PubMed: 9916917]
 93. Salmaggi A, Gelati M, Dufour A, Corsini E, Pagano S, Bacalini R, Ferrero E, Scabini S, Silei V, Ciusani E, De Rossi M. Expression and modulation of IFN-gamma-inducible chemokines (IP-10, Mig, and I-TAC) in human brain endothelium and astrocytes: possible relevance for the immune invasion of the central nervous system and the pathogenesis of multiple sclerosis. *J Interferon Cytokine Res* 2002;22:631–640. [PubMed: 12162873]
 94. Barna BP, Pettay J, Barnett GH, Zhou P, Iwasaki K, Estes ML. Regulation of monocyte chemoattractant protein-1 expression in adult human non-neoplastic astrocytes is sensitive to tumor necrosis factor (TNF) or antibody to the 55-kDa TNF receptor. *J Neuroimmunol* 1994;50:101–107. [PubMed: 8300851]
 95. Karpus WJ, Ransohoff RM. Chemokine regulation of experimental autoimmune encephalomyelitis: temporal and spatial expression patterns govern disease pathogenesis. *J Immunol* 1998;161:2667–2671. [PubMed: 9743321]
 96. Ransohoff RM, Hamilton TA, Tani M, Stoler MH, Shick HE, Major JA, Estes ML, Thomas DM, Tuohy VK. Astrocyte expression of mRNA encoding cytokines IP-10 and JE/MCP-1 in experimental autoimmune encephalomyelitis. *FASEB J* 1993;7:592–600. [PubMed: 8472896]
 97. Carter SL, Muller M, Manders PM, Campbell IL. Induction of the genes for Cxcl9 and Cxcl10 is dependent on IFN-gamma but shows differential cellular expression in experimental autoimmune encephalomyelitis and by astrocytes and microglia in vitro. *Glia* 2007;55:1728–1739. [PubMed: 17902170]
 98. Glabinski AR, Tani M, Strieter RM, Tuohy VK, Ransohoff RM. Synchronous synthesis of alpha- and beta-chemokines by cells of diverse lineage in the central nervous system of mice with relapses of chronic experimental autoimmune encephalomyelitis. *Am J Pathol* 1997;150:617–630. [PubMed: 9033275]
 99. Sunnemark D, Eltayeb S, Nilsson M, Wallstrom E, Lassmann H, Olsson T, Berg AL, Ericsson-Dahlstrand A. CX3CL1 (fractalkine) and CX3CR1 expression in myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis: kinetics and cellular origin. *J Neuroinflamm* 2005;2:17.
 100. Cook DN, Chen SC, Sullivan LM, Manfra DJ, Wiekowski MT, Prosser DM, Vassileva G, Lira SA. Generation and analysis of mice lacking the chemokine fractalkine. *Mol Cell Biol* 2001;21:3159–3165. [PubMed: 11287620]
 101. Hurwitz AA, Lyman WD, Berman JW. Tumor necrosis factor alpha and transforming growth factor beta upregulate astrocyte expression of monocyte chemoattractant protein-1. *J Neuroimmunol* 1995;57:193–198. [PubMed: 7706436]
 102. Hayashi M, Luo Y, Laning J, Strieter RM, Dorf ME. Production and function of monocyte chemoattractant protein-1 and other beta-chemokines in murine glial cells. *J Neuroimmunol* 1995;60:143–150. [PubMed: 7642742]

103. Croxford JL, Olson JK, Miller SD. Epitope spreading and molecular mimicry as triggers of autoimmunity in the Theiler's virus induced demyelinating disease model of multiple sclerosis. *Autoimmun. Rev* 2002;1:251–260.
104. Miller SD, Vanderlugt CL, Begolka WS, Pao W, Yauch RL, Neville KL, Katz-Levy Y, Carrizosa A, Kim BS. Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. *Nat Med* 1997;3:1133–1136. [PubMed: 9334726]
105. Hoffman LM, Fife BT, Begolka WS, Miller SD, Karpus WJ. Central nervous system chemokine expression during Theiler's virus-induced demyelinating disease. *J Neurovirol* 1999;5:635–642. [PubMed: 10602404]
106. Murray PD, Krivacic K, Chernosky A, Wei T, Ransohoff RM, Rodriguez M. Biphasic and regionally-restricted chemokine expression in the central nervous system in the Theiler's virus model of multiple sclerosis. *J Neurovirol* 2000;6 Suppl 1:S44–52. [PubMed: 10871765]
107. Carpentier PA, Williams BR, Miller SD. Distinct roles of protein kinase R and toll-like receptor 3 in the activation of astrocytes by viral stimuli. *Glia* 2007;55:239–252. [PubMed: 17091495]
108. Palma JP, Kim BS. Induction of selected chemokines in glial cells infected with Theiler's virus. *J Neuroimmunol* 2001;117:166–170. [PubMed: 11431017]
109. Kwon D, Fuller AC, Palma JP, Choi IH, Kim BS. Induction of chemokines in human astrocytes by picornavirus infection requires activation of both AP-1 and NF-kappa B. *Glia* 2004;45:287–296. [PubMed: 14730702]
110. Rubio N, Sanz-Rodriguez F, Lipton HL. Theiler's virus induces the MIP-2 chemokine (CXCL2) in astrocytes from genetically susceptible but not from resistant mouse strains. *Cell Immunol* 2006;239:31–40. [PubMed: 16684516]
111. Carpentier PA, Duncan DS, Miller SD. Glial toll-like receptor signaling in central nervous system infection and autoimmunity. *Brain Behav Immun* 2008;22:140–147. [PubMed: 17920811]
112. Mattson MP, Taub DD. Ancient viral protein enrages astrocytes in multiple sclerosis. *Nat Neurosci* 2004;7:1021–1023. [PubMed: 15452568]
113. Antony JM, van Marle G, Opii W, Butterfield DA, Mallet F, Yong VW, Wallace JL, Deacon RM, Warren K, Power C. Human endogenous retrovirus glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. *Nat Neurosci* 2004;7:1088–1095. [PubMed: 15452578]
114. Antony JM, Ellestad KK, Hammond R, Imaizumi K, Mallet F, Warren KG, Power C. The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes. *J Immunol* 2007;179:1210–1224. [PubMed: 17617614]
115. Aloisi F, Ria F, Penna G, Adorini L. Microglia are more efficient than astrocytes in antigen processing and in Th1 but not Th2 activation. *J Immunol* 1998;160:4671–4680. [PubMed: 9590212]
116. Aloisi F, Penna G, Cerase J, Menendez IB, Adorini L. IL-12 production by central nervous system microglia is inhibited by astrocytes. *J Immunol* 1997;159:1604–1612. [PubMed: 9257819]
117. 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;21:141–147. [PubMed: 10689302]
118. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383:787–793. [PubMed: 8893001]
119. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* 1996;17:138–146. [PubMed: 8820272]
120. Bsibsi M, Persoon-Deen C, Verwer RW, Meeuwssen S, Ravid R, Van Noort JM. Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators. *Glia* 2006;53:688–695. [PubMed: 16482523]
121. Bsibsi M, Ravid R, Gveric D, van Noort JM. Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* 2002;61:1013–1021. [PubMed: 12430718]

122. Meinl E, Aloisi F, Ertl B, Weber F, De Waal Malefyt R, Wekerle H, Hohlfeld R. Multiple sclerosis. Immunomodulatory effects of human astrocytes on T cells. *Brain* 1994;117:1323–1332. [PubMed: 7820569]
123. Weber F, Meinl E, Aloisi F, Nevinny-Stickel C, Albert E, Wekerle H, Hohlfeld R. Human astrocytes are only partially competent antigen presenting cells. Possible implications for lesion development in multiple sclerosis. *Brain* 1994;117:59–69. [PubMed: 7511974]
124. Gimsa U, Oren A, Pandiyan P, Teichmann D, Bechmann I, Nitsch R, Brunner-Weinzierl MC. Astrocytes protect the CNS: antigen-specific T helper cell responses are inhibited by astrocyte-induced upregulation of CTLA-4 (CD152). *J Mol Med* 2004;82:364–372. [PubMed: 15007511]
125. Chambers CA, Krummel MF, Boitel B, Hurwitz A, Sullivan TJ, Fournier S, Cassell D, Brunner M, Allison JP. The role of CTLA-4 in the regulation and initiation of T cell responses. *Immunol Rev* 1996;153:27–46. [PubMed: 9010718]
126. Trajkovic V, Vuckovic O, Stosic-Grujicic S, Miljkovic D, Popadic D, Markovic M, Bumbasirevic V, Backovic A, Cvetkovic I, Harhaji L, Ramic Z, Mostarica SM. Astrocyte-induced regulatory T cells mitigate CNS autoimmunity. *Glia* 2004;47:168–179. [PubMed: 15185395]
127. Fitzgerald DC, Ciric B, Touil T, Harle H, Grammatikopolou J, Das Sarma J, Gran B, Zhang GX, Rostami A. Suppressive effect of IL-27 on encephalitogenic Th17 cells and the effector phase of experimental autoimmune encephalomyelitis. *J Immunol* 2007;179:3268–3275. [PubMed: 17709543]
128. Eng LF, Reier PJ, Houle JD. Astrocyte activation and fibrous gliosis: glial fibrillary acidic protein immunostaining of astrocytes following intraspinal cord grafting of fetal CNS tissue. *Prog Brain Res* 1987;71:439–455. [PubMed: 3588961]
129. Reier PJ, Houle JD. The glial scar: its bearing on axonal elongation and transplantation approaches to CNS repair. *Adv Neurol* 1988;47:87–138. [PubMed: 3278533]
130. Norton WT, Aquino DA, Hozumi I, Chiu FC, Brosnan CF. Quantitative aspects of reactive gliosis: a review. *Neurochem Res* 1992;17:877–885. [PubMed: 1407275]
131. Holley JE, Gveric D, Newcombe J, Cuzner ML, Gutowski NJ. Astrocyte characterization in the multiple sclerosis glial scar. *Neuropathol Appl Neurobiol* 2003;29:434–444. [PubMed: 14507335]
132. Smith ME, Eng LF. Glial fibrillary acidic protein in chronic relapsing experimental allergic encephalomyelitis in SJL/J mice. *J Neurosci Res* 1987;18:203–208. [PubMed: 3682026]
133. Fok-Seang J, Smith-Thomas LC, Meiners S, Muir E, Du JS, Housden E, Johnson AR, Faissner A, Geller HM, Keynes RJ. An analysis of astrocytic cell lines with different abilities to promote axon growth. *Brain Res* 1995;689:207–223. [PubMed: 7583324]
134. Wilby MJ, Muir EM, Fok-Seang J, Gour BJ, Blaschuk OW, Fawcett JW. N-Cadherin inhibits Schwann cell migration on astrocytes. *Mol Cell Neurosci* 1999;14:66–84. [PubMed: 10433818]
135. Franklin RJ, Gilson JM, Blakemore WF. Local recruitment of remyelinating cells in the repair of demyelination in the central nervous system. *J Neurosci Res* 1997;50:337–344. [PubMed: 9373042]
136. Baron-Van Evercooren A, Avellana-Adalid V, Ben Younes-Chennoufi A, Gansmuller A, Nait-Oumesmar B, Vignais L. Cell-cell interactions during the migration of myelin-forming cells transplanted in the demyelinated spinal cord. *Glia* 1996;16:147–164. [PubMed: 8929902]
137. Blakemore WF, Crang AJ. The relationship between type-1 astrocytes, Schwann cells and oligodendrocytes following transplantation of glial cell cultures into demyelinating lesions in the adult rat spinal cord. *J Neurocytol* 1989;18:519–528. [PubMed: 2809635]
138. Bannerman P, Hahn A, Soulika A, Gallo V, Pleasure D. Astrogliosis in EAE spinal cord: derivation from radial glia, and relationships to oligodendroglia. *Glia* 2007;55:57–64. [PubMed: 17009237]
139. Messersmith DJ, Murtie JC, Le TQ, Frost EE, Armstrong RC. Fibroblast growth factor 2 (FGF2) and FGF receptor expression in an experimental demyelinating disease with extensive remyelination. *J Neurosci Res* 2000;62:241–256. [PubMed: 11020217]
140. Goddard DR, Berry M, Butt AM. In vivo actions of fibroblast growth factor-2 and insulin-like growth factor-I on oligodendrocyte development and myelination in the central nervous system. *J Neurosci Res* 1999;57:74–85. [PubMed: 10397637]

141. Sherman LS, Struve JN, Rangwala R, Wallingford NM, Tuohy TM, Kuntz CT. Hyaluronate-based extracellular matrix: keeping glia in their place. *Glia* 2002;38:93–102. [PubMed: 11948803]
142. Quackenbush EJ, Cruz TF, Moscarello MA, Letarte M. Identification of three antigens in human brain associated with similar antigens on human leukaemic cells. *Biochem J* 1985;225:291–299. [PubMed: 3856426]
143. Williams A, Piaton G, Lubetzki C. Astrocytes—friends or foes in multiple sclerosis? *Glia* 2007;55:1300–1312. [PubMed: 17626262]
144. Soilu-Hanninen M, Laaksonen M, Hanninen A. Hyaluronate receptor (CD44) and integrin alpha4 (CD49d) are up-regulated on T cells during MS relapses. *J Neuroimmunol* 2005;166:189–192. [PubMed: 15990174]
145. Back SA, Tuohy TM, Chen H, Wallingford N, Craig A, Struve J, Luo NL, Banine F, Liu Y, Chang A, Trapp BD, Bebo BF Jr, Rao MS, Sherman LS. Hyaluronan accumulates in demyelinated lesions and inhibits oligodendrocyte progenitor maturation. *Nat Med* 2005;11:966–972. [PubMed: 16086023]
146. Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci* 2004;5:146–156. [PubMed: 14735117]
147. Kobayashi NR, Fan DP, Giehl KM, Bedard AM, Wiegand SJ, Tetzlaff W. BDNF and NT-4/5 prevent atrophy of rat rubrospinal neurons after cervical axotomy, stimulate GAP-43 and Talphal-tubulin mRNA expression, and promote axonal regeneration. *J Neurosci* 1997;17:9583–9595. [PubMed: 9391013]
148. Fawcett JW, Housden E, Smith-Thomas L, Meyer RL. The growth of axons in three-dimensional astrocyte cultures. *Dev Biol* 1989;135:449–458. [PubMed: 2776978]
149. McKeon RJ, Hoke A, Silver J. Injury-induced proteoglycans inhibit the potential for laminin-mediated axon growth on astrocytic scars. *Exp Neurol* 1995;136:32–43. [PubMed: 7589332]
150. McKeon RJ, Jurynek MJ, Buck CR. The chondroitin sulfate proteoglycans neurocan and phosphacan are expressed by reactive astrocytes in the chronic CNS glial scar. *J Neurosci* 1999;19:10778–10788. [PubMed: 10594061]
151. Sobel RA. The extracellular matrix in multiple sclerosis: an update. *Braz J Med Biol Res* 2001;34:603–609. [PubMed: 11323746]
152. Asher RA, Morgenstern DA, Fidler PS, Adcock KH, Oohira A, Braistead JE, Levine JM, Margolis RU, Rogers JH, Fawcett JW. Neurocan is upregulated in injured brain and in cytokine-treated astrocytes. *J Neurosci* 2000;20:2427–2438. [PubMed: 10729323]
153. Yamada H, Fredette B, Shitara K, Hagihara K, Miura R, Ranscht B, Stallcup WB, Yamaguchi Y. The brain chondroitin sulfate proteoglycan brevican associates with astrocytes ensheathing cerebellar glomeruli and inhibits neurite outgrowth from granule neurons. *J Neurosci* 1997;17:7784–7795. [PubMed: 9315899]
154. Quaglia X, Beggah AT, Seidenbecher C, Zurn AD. Delayed priming promotes CNS regeneration post-rhizotomy in Neurocan and Brevican-deficient mice. *Brain* 2008;131:240–249. [PubMed: 18065437]
155. Stallcup WB, Beasley L. Bipotential glial precursor cells of the optic nerve express the NG2 proteoglycan. *J Neurosci* 1987;7:2737–2744. [PubMed: 3305800]
156. Zhu X, Bergles DE, Nishiyama A. NG2 cells generate both oligodendrocytes and gray matter astrocytes. *Development* 2008;135:145–157. [PubMed: 18045844]
157. Trotter J. NG2-positive cells in CNS function and the pathological role of antibodies against NG2 in demyelinating diseases. *J Neurol Sci* 2005;233:37–42. [PubMed: 15949494]
158. Fidler PS, Schuette K, Asher RA, Dobberty A, Thornton SR, Calle-Patino Y, Muir E, Levine JM, Geller HM, Rogers JH, Faissner A, Fawcett JW. Comparing astrocytic cell lines that are inhibitory or permissive for axon growth: the major axon-inhibitory proteoglycan is NG2. *J Neurosci* 1999;19:8778–8788. [PubMed: 10516297]
159. Chen ZJ, Ughrin Y, Levine JM. Inhibition of axon growth by oligodendrocyte precursor cells. *Mol Cell Neurosci* 2002;20:125–139. [PubMed: 12056844]
160. Sobel RA. Ephrin A receptors and ligands in lesions and normal-appearing white matter in multiple sclerosis. *Brain Pathol* 2005;15:35–45. [PubMed: 15779235]

161. Bundesen LQ, Scheel TA, Bregman BS, Kromer LF. Ephrin-B2 and EphB2 regulation of astrocyte-meningeal fibroblast interactions in response to spinal cord lesions in adult rats. *J Neurosci* 2003;23:7789–7800. [PubMed: 12944508]
162. Wahl S, Barth H, Ciossek T, Aktories K, Mueller BK. Ephrin-A5 induces collapse of growth cones by activating Rho and Rho kinase. *J Cell Biol* 2000;149:263–270. [PubMed: 10769020]
163. Satoh J, Onoue H, Arima K, Yamamura T. Nogo-A and nogo receptor expression in demyelinating lesions of multiple sclerosis. *J Neuropathol Exp Neurol* 2005;64:129–138. [PubMed: 15751227]
164. Karnezis T, Mandemakers W, McQualter JL, Zheng B, Ho PP, Jordan KA, Murray BM, Barres B, Tessier-Lavigne M, Bernard CC. The neurite outgrowth inhibitor Nogo A is involved in autoimmune-mediated demyelination. *Nat Neurosci* 2004;7:736–744. [PubMed: 15184901]
165. Satoh J, Tabunoki H, Yamamura T, Arima K, Konno H. TROY and LINGO-1 expression in astrocytes and macrophages/microglia in multiple sclerosis lesions. *Neuropathol Appl Neurobiol* 2007;33:99–107. [PubMed: 17239012]
166. Bush TG, Puvanachandra N, Horner CH, Polito A, Ostensfeld T, Svendsen CN, Mucke L, Johnson MH, Sofroniew MV. Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron* 1999;23:297–308. [PubMed: 10399936]
167. Gardner J, Ghorpade A. Tissue inhibitor of metalloproteinase (TIMP)-1: the TIMPed balance of matrix metalloproteinases in the central nervous system. *J Neurosci Res* 2003;74:801–806. [PubMed: 14648584]
168. Uhm JH, Dooley NP, Oh LY, Yong VW. Oligodendrocytes utilize a matrix metalloproteinase, MMP-9, to extend processes along an astrocyte extracellular matrix. *Glia* 1998;22:53–63. [PubMed: 9436787]
169. Larsen PH, Wells JE, Stallcup WB, Odenakker G, Yong VW. Matrix metalloproteinase-9 facilitates remyelination in part by processing the inhibitory NG2 proteoglycan. *J Neurosci* 2003;23:11127–11135. [PubMed: 14657171]
170. Pagenstecher A, Stalder AK, Kincaid CL, Shapiro SD, Campbell IL. Differential expression of matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase genes in the mouse central nervous system in normal and inflammatory states. *Am J Pathol* 1998;152:729–741. [PubMed: 9502415]
171. Crocker SJ, Whitmire JK, Frausto RF, Chertboonmuang P, Soloway PD, Whitton JL, Campbell IL. Persistent macrophage/microglial activation and myelin disruption after experimental autoimmune encephalomyelitis in tissue inhibitor of metalloproteinase-1-deficient mice. *Am J Pathol* 2006;169:2104–2116. [PubMed: 17148673]
172. Belmadani A, Tran PB, Ren D, Miller RJ. Chemokines regulate the migration of neural progenitors to sites of neuroinflammation. *J Neurosci* 2006;26:3182–3191. [PubMed: 16554469]
173. Yan YP, Sailor KA, Lang BT, Park SW, Vemuganti R, Dempsey RJ. Monocyte chemoattractant protein-1 plays a critical role in neuroblast migration after focal cerebral ischemia. *J Cereb Blood Flow Metab* 2007;27:1213–1224. [PubMed: 17191078]
174. Liu XS, Zhang ZG, Zhang RL, Gregg SR, Wang L, Yier T, Chopp M. Chemokine ligand 2 (CCL2) induces migration and differentiation of subventricular zone cells after stroke. *J Neurosci Res* 2007;85:2120–2125. [PubMed: 17510981]
175. Xu Q, Wang S, Jiang X, Zhao Y, Gao M, Zhang Y, Wang X, Tano K, Kanehara M, Zhang W, Ishida T. Hypoxia-induced astrocytes promote the migration of neural progenitor cells via vascular endothelial factor, stem cell factor, stromal-derived factor-1 α and monocyte chemoattractant protein-1 upregulation in vitro. *Clin Exp Pharmacol Physiol* 2007;34:624–631. [PubMed: 17581219]
176. Maysami S, Nguyen D, Zobel F, Pitz C, Heine S, Hopfner M, Stangel M. Modulation of rat oligodendrocyte precursor cells by the chemokine CXCL12. *Neuroreport* 2006;17:1187–1190. [PubMed: 16837851]
177. Padovani-Claudio DA, Liu L, Ransohoff RM, Miller RH. Alterations in the oligodendrocyte lineage, myelin, and white matter in adult mice lacking the chemokine receptor CXCR2. *Glia* 2006;54:471–483. [PubMed: 16886211]

178. Filipovic R, Zecevic N. The effect of CXCL1 on human fetal oligodendrocyte progenitor cells. *Glia* 2008;56:1–15. [PubMed: 17910053]
179. Rodriguez M, Pavelko KD, McKinney CW, Leibowitz JL. Recombinant human IL-6 suppresses demyelination in a viral model of multiple sclerosis. *J Immunol* 1994;153:3811–3821. [PubMed: 7930598]
180. Willenborg DO, Fordham SA, Cowden WB, Ramshaw IA. Cytokines and murine autoimmune encephalomyelitis: inhibition or enhancement of disease with antibodies to select cytokines, or by delivery of exogenous cytokines using a recombinant vaccinia virus system. *Scand J Immunol* 1995;41:31–41. [PubMed: 7824886]
181. Eugster HP, Frei K, Kopf M, Lassmann H, Fontana A. IL-6-deficient mice resist myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. *Eur J Immunol* 1998;28:2178–2187. [PubMed: 9692887]
182. Schonrock LM, Gawlowski G, Bruck W. Interleukin-6 expression in human multiple sclerosis lesions. *Neurosci Lett* 2000;294:45–48. [PubMed: 11044583]
183. 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;21:602–615. [PubMed: 12504593]
184. 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;26:191–200. [PubMed: 10340760]
185. Biber K, Pinto-Duarte A, Wittendorp MC, Dolga AM, Fernandes CC, Von Frijtag Drabbe Kunzel J, Keijser JN, de Vries R, Ijzerman AP, Ribeiro JA, Eisel U, Sebastiao AM, Boddeke HW. Interleukin-6 Upregulates Neuronal Adenosine A(1) Receptors: Implications for Neuromodulation and Neuroprotection. *Neuropsychopharmacol*. 2007 Epub ahead of print.
186. Zhang Y, Taveggia C, Melendez-Vasquez C, Einheber S, Raine CS, Salzer JL, Brosnan CF, John GR. Interleukin-11 potentiates oligodendrocyte survival and maturation, and myelin formation. *J Neurosci* 2006;26:12174–12185. [PubMed: 17122042]
187. Logan A, Berry M, Gonzalez AM, Frautschy SA, Sporn MB, Baird A. Effects of transforming growth factor beta 1 on scar production in the injured central nervous system of the rat. *Eur J Neurosci* 1994;6:355–363. [PubMed: 8019673]
188. Herx LM, Yong VW. Interleukin-1 beta is required for the early evolution of reactive astrogliosis following CNS lesion. *J Neuropathol Exp Neurol* 2001;60:961–971. [PubMed: 11589427]
189. 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;22:9221–9227. [PubMed: 12417647]
190. Park SK, Solomon D, Vartanian T. Growth factor control of CNS myelination. *Dev Neurosci* 2001;23:327–337. [PubMed: 11756748]
191. Ishibashi T, Dakin KA, Stevens B, Lee PR, Kozlov SV, Stewart CL, Fields RD. Astrocytes promote myelination in response to electrical impulses. *Neuron* 2006;49:823–832. [PubMed: 16543131]
192. 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;165:2232–2239. [PubMed: 10925311]
193. Mason JL, Suzuki K, Chaplin DD, Matsushima GK. Interleukin-1beta promotes repair of the CNS. *J Neurosci* 2001;21:7046–7052. [PubMed: 11549714]
194. Stockli KA, Lillien LE, Naher-Noe M, Breitfeld G, Hughes RA, Raff MC, Thoenen H, Sendtner M. Regional distribution, developmental changes, and cellular localization of CNTF-mRNA and protein in the rat brain. *J Cell Biol* 1991;115:447–459. [PubMed: 1918150]
195. McMorris FA, Mozell RL, Carson MJ, Shinar Y, Meyer RD, Marchetti N. Regulation of oligodendrocyte development and central nervous system myelination by insulin-like growth factors. *Ann N Y Acad Sci* 1993;692:321–334. [PubMed: 8215042]
196. Chesik D, Wilczak N, De Keyser J. The insulin-like growth factor system in multiple sclerosis. *Int Rev Neurobiol* 2007;79:203–226. [PubMed: 17531843]

197. Albrecht PJ, Murtie JC, Ness JK, Redwine JM, Enterline JR, Armstrong RC, Levison SW. Astrocytes produce CNTF during the remyelination phase of viral-induced spinal cord demyelination to stimulate FGF-2 production. *Neurobiol Dis* 2003;13:89–101. [PubMed: 12828933]
198. Richardson PM. Ciliary neurotrophic factor: a review. *Pharmacol Ther* 1994;63:187–198. [PubMed: 7809179]
199. Mayer M, Bhakoo K, Noble M. Ciliary neurotrophic factor and leukemia inhibitory factor promote the generation, maturation and survival of oligodendrocytes in vitro. *Development* 1994;120:143–153. [PubMed: 8119123]
200. Talbott JF, Cao Q, Bertram J, Nkansah M, Benton RL, Lavik E, Whittemore SR. 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;204:485–489. [PubMed: 17274982]
201. Sendtner M, Carroll P, Holtmann B, Hughes RA, Thoenen H. Ciliary neurotrophic factor. *J Neurobiol* 1994;25:1436–1453. [PubMed: 7852996]
202. Albrecht PJ, Dahl JP, Stoltzfus OK, Levenson R, Levison SW. Ciliary neurotrophic factor activates spinal cord astrocytes, stimulating their production and release of fibroblast growth factor-2, to increase motor neuron survival. *Exp Neurol* 2002;173:46–62. [PubMed: 11771938]
203. Albrecht PJ, Enterline JC, Cromer J, Levison SW. CNTF-activated astrocytes release a soluble trophic activity for oligodendrocyte progenitors. *Neurochem Res* 2007;32:263–271. [PubMed: 17004130]
204. Malik O, Compston DA, Scolding NJ. Interferon-beta inhibits mitogen induced astrocyte proliferation in vitro. *J Neuroimmunol* 1998;86:155–162. [PubMed: 9663561]
205. Stewart VC, Giovannoni G, Land JM, McDonald WI, Clark JB, Heales SJ. Pretreatment of astrocytes with interferon-alpha/beta impairs interferon-gamma induction of nitric oxide synthase. *J Neurochem* 1997;68:2547–2551. [PubMed: 9166751]
206. Barca O, Ferre S, Seoane M, Prieto JM, Lema M, Senaris R, Arce VM. Interferon beta promotes survival in primary astrocytes through phosphatidylinositol 3-kinase. *J Neuroimmunol* 2003;139:155–159. [PubMed: 12799034]
207. McLaurin J, Antel JP, Yong VW. Immune and non-immune actions of interferon-beta-1b on primary human neural cells. *Mult Scler* 1995;1:10–19. [PubMed: 9345464]
208. Neuhaus O, Stuve O, Zamvil SS, Hartung HP. Are statins a treatment option for multiple sclerosis? *Lancet Neurol* 2004;3:369–371. [PubMed: 15157852]
209. Vollmer T, Key L, Durkalski V, Tyor W, Corboy J, Markovic-Plese S, Preiningerova J, Rizzo M, Singh I. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. *Lancet* 2004;363:1607–1608. [PubMed: 15145635]
210. Zeinstra E, Wilczak N, Chesik D, Glazenburg L, Kroese FG, De Keyser J. Simvastatin inhibits interferon-gamma-induced MHC class II up-regulation in cultured astrocytes. *J Neuroinflammation* 2006;3:16. [PubMed: 16859542]
211. Satoh J, Paty DW, Kim SU. Counteracting effect of IFN-beta on IFN-gamma-induced proliferation of human astrocytes in culture. *Mult Scler* 1996;1:279–287. [PubMed: 9345430]
212. Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, Bravo M, Mitchell DJ, Sobel RA, Steinman L, Zamvil SS. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* 2002;420:78–84. [PubMed: 12422218]
213. Xu J, Drew PD. 9-Cis-retinoic acid suppresses inflammatory responses of microglia and astrocytes. *J Neuroimmunol* 2006;171:135–144. [PubMed: 16303184]
214. Xu J, Chavis JA, Racke MK, Drew PD. Peroxisome proliferator-activated receptor-alpha and retinoid X receptor agonists inhibit inflammatory responses of astrocytes. *J Neuroimmunol* 2006;176:95–105. [PubMed: 16764943]
215. Lovett-Racke AE, Hussain RZ, Northrop S, Choy J, Rocchini A, Matthes L, Chavis JA, Diab A, Drew PD, Racke MK. Peroxisome proliferator-activated receptor alpha agonists as therapy for autoimmune disease. *J Immunol* 2004;172:5790–5798. [PubMed: 15100326]

216. Marx N, Kehrle B, Kohlhammer K, Grub M, Koenig W, Hombach V, Libby P, Plutzky J. PPAR activators as antiinflammatory mediators in human T lymphocytes: implications for atherosclerosis and transplantation-associated arteriosclerosis. *Circ Res* 2002;90:703–710. [PubMed: 11934839]

Figure 1. The dual role of astrocytes in autoimmune demyelination

Astrocytes promote demyelination by enhancing the immune response. Autoreactive T cells are activated through expression of MHC class II, co-stimulatory molecules, and adhesion molecules by astrocytes [1]. Astrocyte-derived cytokines IL-12 and IL-23 promote T_H1 and T_H17 responses, respectively [2]. During viral-induced demyelination, stimulation of TLR3 (toll-like receptor 3) and PKR (dsRNA-dependent protein kinase) induce production of type-I interferons (IFN- α/β) and IL-6 [3]. These innate responses aid in initiating a cell-mediated, autoimmune response. Astrocytes also recruit T cells, macrophages, and microglia to inflammatory lesions by producing chemokines [4]. Conversely, astrocytes also inhibit aspects of the immune response, thereby inhibiting demyelination. Through CTLA-4 expression and production of anti-inflammatory cytokines (IL-10, IL-4, IL-5, TGF- β , and IL-27), astrocytes are able to diminish autoreactive Th1 and Th17 responses [5]. Also, TLR3 activation has been shown to trigger the release of anti-inflammatory cytokines and to inhibit the release of pro-inflammatory cytokines IL-12 and IL-23 [6]. Finally, TIMPs (tissue inhibitors of metalloproteinases) antagonize MMPs (matrix metalloproteinases) activity resulting in decreased ability of autoreactive T cells to migrate to sites of demyelination [7].

Inhibiting Remyelination

Promoting Remyelination

Figure 2. The dual role of astrocytes in remyelination

Astrocytes modulate remyelination by acting on both axon regeneration and oligodendrocyte progenitor cells (OPCs). Chondroitin sulphate proteoglycans (CS-PGs) and NOGO-A receptor (NgR) inhibit axon growth following injury [1]. Both of these molecules are associated with astrocytes in the glial scar, a physical barrier around demyelinated lesions. Astrocytes also release ephrins which bind to receptors on axons, inducing collapse of growth cones on regenerating axons [2]. OPCs are also targets of astrocyte modulation. Fibroblast growth factor-2 (FGF-2), a potent mitogen for OPCs, can actually inhibit remyelination by preventing OPC maturation [3]. For successful remyelination, OPCs must proliferate, migrate to sites of demyelination, and mature into myelinating oligodendrocytes. Accordingly, astrocytes-derived factors promote OPC migration via chemokines [4], proliferation (IL-6, IL-11, IGF-I) [5], and maturation (IL-11 and LIF) [6]. In addition, TLR3 activation can release neurotrophic factors NT-3, BDNF, and CNTF to promote OPC survival [7]. Astrocytes also are able to limit myelin damage by taking up extracellular glutamate, which would normally induce excitotoxicity in oligodendrocytes [8].