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Review

Astrocytes in multiple sclerosis: A product of their environment

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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].

$CD4^+$ 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 inflamma-

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tory 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, Camillio 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 processes 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 glial fibrillary acidic protein (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 MS 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] and 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 upregulation of GFAP, other less specific astrocyte markers have also been examined. For example, S100β 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 bi-directional 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 (O_2 and CO_2) 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 (TNF)-α, and IL-1β 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 (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 dsRNA-dependent protein kinase (PKR). 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

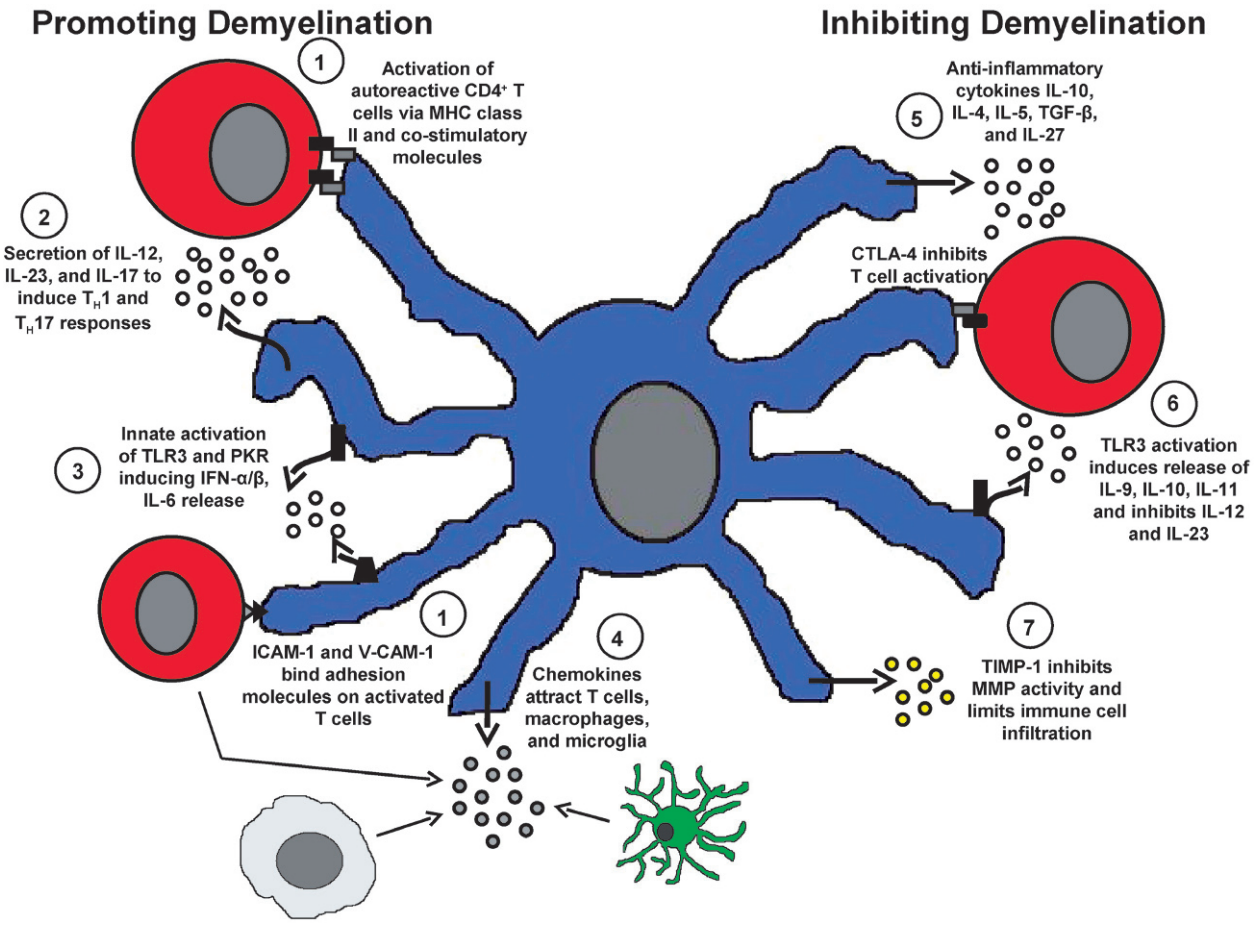

Figure 1. The dual role of astrocytes in autoimmune demyelination. Astrocytes promote demyelination by enhancing the immune response. Autoreactive T cells are activated through expression of MHC class II, co-stimulatory molecules, and adhesion molecules by astrocytes [1]. Astrocyte-derived cytokines 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].

(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 (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 (Fig. 1) and remyelination (Fig. 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.

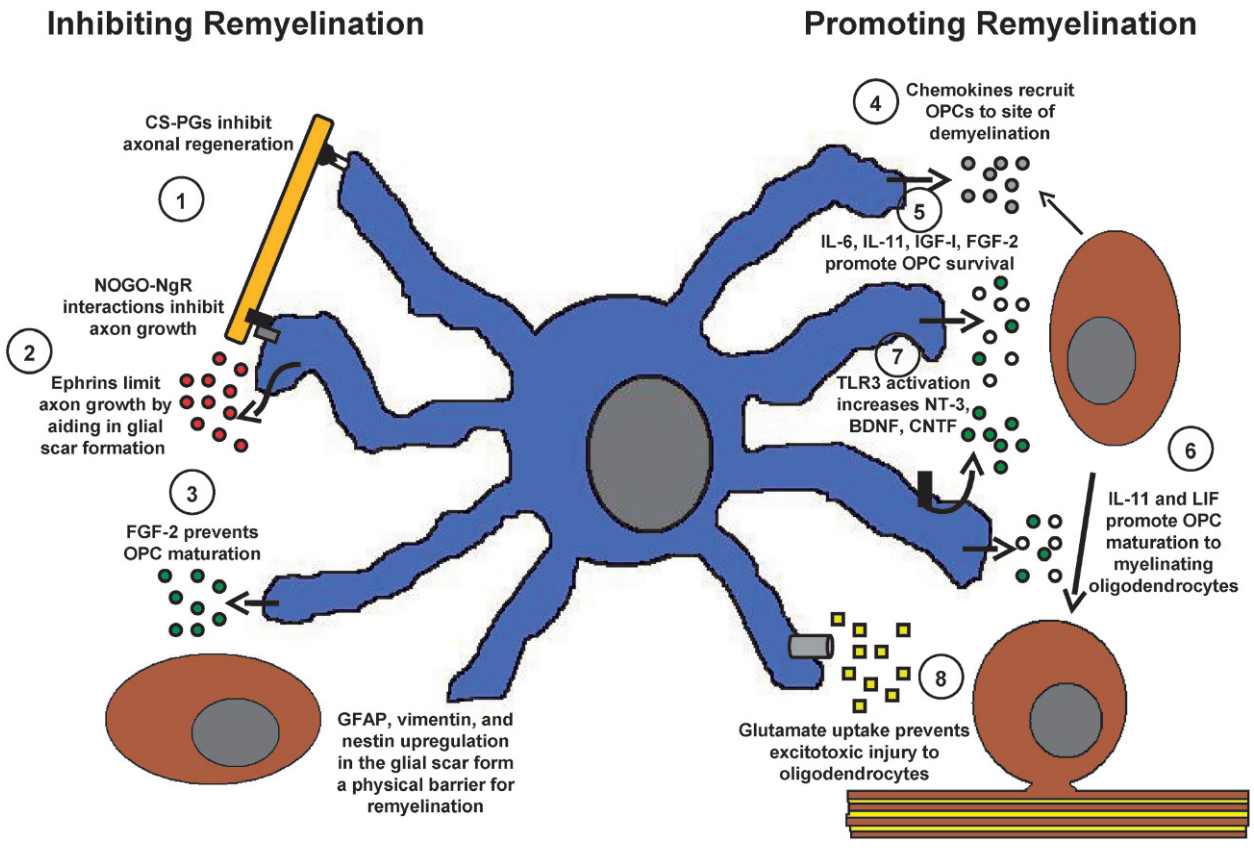

Figure 2. The dual role of astrocytes in remyelination. Astrocytes modulate remyelination by acting on both axon regeneration and oligodendrocyte progenitor cells (OPCs). Chondroitin sulphate proteoglycans (CS-PGs) and NOGO-A receptor (NgR) inhibit axon growth following injury [1]. Both of these molecules 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].

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 and VCAM-1, play crucial roles in the extravasation and homing of T cells through the CNS parenchyma. ICAM-1 and VCAM-1 bind lymphocyte function-associated antigen (LFA)-1 (CD11a/CD18) and very late antigen (VLA)-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-1β, 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 the 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-1α (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-1β, 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-1α 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 Theiler's murine encephalomyelitis virus (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-1α, 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 activator protein (AP)-1 and nuclear factor (NF)-κB 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

In 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 to 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 expres-

sion 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 cytotoxic T lymphocyte antigen (CTLA)-4 on already activated T_H1 and T_H2 cells in the presence of antigen [124, 125]. CTLA-4 binds to co-stimulatory 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 alongside 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 mater 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 itself, 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 astrocytes-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 proteoglycans 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 receptors [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 astro-

cytes 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-1α 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-Rα 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-1β 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-1β 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-1β in the activation of astrocytes has been linked to the restoration of the BBB following CNS insult [188]. IL-1β-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-1β 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-1β [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-1β 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 (Fig. 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-1β 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-1β, 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-1β, 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.

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