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Mini-Review

How Factors Secreted From Astrocytes Impact Myelin Repair

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Over a century ago, hypertrophy of astrocytes was noted as a pathology of multiple sclerosis (MS) and was hypothesized to play an important role in this disease, yet the contribution of astrocytes has been largely underemphasized in the pathophysiology of CNS demyelination. Astrocytes perform many homeostatic functions within the developing and adult CNS, including enhancing formation and maintenance of the blood–brain barrier, moderating neuronal connections through the tripartite synapse, and perhaps even offering intercellular communication independently of neurons. Although there is a significant body of literature characterizing different types of MS lesions, the inflammatory demyelination in an active MS lesion is accompanied by the presence of macrophages, lymphocytes, and large reactive astrocytes. The astrocyte has long been viewed as a cell that promotes inflammation and demyelination, while also forming the glial scar, thus hindering remyelination and axon growth. Renewed interest in the astrocyte has been brought about by recent studies demonstrating that astrocytes can also function as cellular mediators of CNS myelination by promoting oligodendrocyte progenitor migration, proliferation, and differentiation. Thus, refining our knowledge of astrocytic functions in the regulation of CNS myelination may help us to better understand why remyelination fails in MS.

Key words: astrocyte; growth factor; oligodendrocyte progenitor cell; multiple sclerosis

Several exceptional reviews have previously focused on the roles of astrocytes in multiple sclerosis (MS), including their roles as antigen-presenting cells (APCs; Nair et al., 2008), their contribution during immune-mediated myelin pathology (Williams et al., 2007), and an historical perspective on how astrocytes first became a major cell type of interest for MS research (Lassmann, 2005). This Mini-Review focuses on astrocytes as producers of secreted factors that can either promote or impede myelination within the CNS and, more importantly, how astrocytes are currently thought to be involved in the myelin pathology of MS.

PLATELET-DERIVED GROWTH FACTOR

Platelet-derived growth factor (PDGF) was first identified from serum as a growth factor for smooth muscle (Coughlin et al., 1980) and is perhaps the best studied growth factor for oligodendrocytes, because expression of one of its receptors (PGDFαR) is a phenotypic marker for the oligodendrocyte progenitor cell (OPC; Hart et al., 1989). Currently, four PDGF monomers have been identified: PDGF-A, -B, -C, and -D, which are all expressed in the human CNS (Reigstad et al., 2005).

Astrocytes have been shown to express PDGF-A and -B chains to produce -AA (Pringle et al., 1989), -BB (Kernt et al., 2010), and -AB dimers (Silberstein et al., 1996). There are currently no reports of astrocytic production of either PDGF-C or PDGF-D. Production of PDGF-AB in primary astrocyte cultures is enhanced by the cytokines tumor necrosis factor-α (TNFα) and transforming growth factor-β (TGFβ), suggesting that astrocytic PDGF production in the CNS may be increased by inflammation (Silberstein et al., 1996). Astrocytes not only are a source of PDGF but also respond to PDGF and express the PDGFαR (Fruttiger et al., 1996).

Noble and Murray (1984) were among the first to demonstrate that astrocyte conditioned media could increase oligodendrocyte differentiation from optic nerve O-2A (for "oligodendrocyte: type II astrocyte") progenitor cells. Identification of PDGF as the factor responsible for proliferation of astrocytes and oligodendrocyte progenitors cells was initially made by Besnard and colleagues (1987). A subsequent study also reported that PDGF was produced by astrocytes in the developing optic nerve and controlled both O-2A cell proliferation and differentiation (Richardson et al., 1988). Around the same time, Raff and colleagues (1988) determined that the effect of astrocyte-derived PDGF in stimulating O-2A progenitor cells in vitro to either proliferate or

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differentiate into oligodendrocytes was influenced by the developmental age of the progenitor cells. This work corroborated in vivo developmental findings on the timing of myelination in the developing optic nerve and suggested that PDGF production by type 1 astrocytes coordinated the timing of oligodendrogenesis (Durand and Raff, 2000). PDGF has also been shown to enhance oligodendrocyte survival directly through activation of the JAK/STAT signaling pathway (Dell'Albani et al., 1998).

In the adult CNS, translating studies on the function of PDGF during CNS development into its role during myelin repair may not be reliable, insofar as the functions of PDGF in these two contexts may differ. PDGF-A expression, driven by the astrocyte [glial fibrillary acidic protein (GFAP)] promoter, resulted in enhanced proliferation of OPCs following focal demyelinating lesions induced by lysolecithin or intoxication with cuprizone, a copper chelator (Woodruff et al., 2004; Vana et al., 2007). It has also been reported that elevated expression of human (h)PDGF by astrocytes prevented oligodendrocyte apoptosis following cuprizone treatment (Vana et al., 2007). In addition, a single intracerebral injection of PDGF in a chemically induced demyelination rodent model (lysolecithin) increased numbers of mature oligodendrocyte and enhanced remyelination (Allamargot et al., 2001).

Translating the role of PDGF from cell culture and animal studies to human demyelinating diseases such as MS is supported, in part, through results pointing to common effects of PDGF on both human and rodent OPCs (Wilson et al., 2003). Similarly, expression of PDGFαR was noted on $NG2^+$ OPCs in acute white matter lesions from post-mortem human MS cases, although these progenitors were noticeably absent from chronic lesions (Wilson et al., 2006). Hence, PDGF-related signaling may foster myelin repair in the early stages of MS lesions, although the capacity to repair by this means may diminish with time as lesions outpace the number of PDGF-responsive OPCs, resulting in remyelination failure (Franklin, 2002).

FIBROBLAST GROWTH FACTOR-2

Fibroblast growth factor-2 (FGF-2), formerly known as basic FGF, is expressed at higher levels during the late embryonic period compared with the adult, with a widespread distribution of expression (Ernfors et al., 1990). During development, FGF-2 is expressed by both neurons and glia, yet expression of FGF-2 following myelin injury in the adult CNS is predominantly from astrocytes (Logan et al., 1992; Messersmith et al., 2000). The nadir of FGF-2 expression in murine CNS development is during the early postnatal period, a critical time of myelin formation. Interestingly, at postnatal day 9 (P9), intracerebroventricular injection of FGF-2 increased the number of immature oligodendrocytes while simultaneously reducing the overall numbers of mature oligodendrocytes in the anterior medullary velum (Goddard et al., 1999). A subsequent study by the same group also determined that, at high doses, FGF-2 leads to signaling cascades that disrupt myelin production in vivo (Goddard et al., 2001), an effect similar to that observed in culture (Bansal et al., 1996). Study of FGF-2 KO mice has revealed that these animals lack an overt myelin phenotype but do not exhibit the early overproduction of oligodendrocytes that is typically observed in postnatal development and is accompanied by a later increase in oligodendrocyte differentiation (Murtie et al., 2005). In contrast, under normal conditions, FGF receptor KO studies have demonstrated that a lack of FGF-2 signaling does not inhibit differentiation of oligodendrocytes (Kaga et al., 2006; Oh et al., 2003). This seemingly incongruous effect of FGF on oligodendrogenesis likely is due to simultaneous pleitropic effects of FGF on the regulation of other astrocytic factors (Bansal, 2002) and on multiple cells types, including astrocytes (Reuss et al., 2003), that also express FGF receptors (Bansal et al., 1996). Hence, future studies using cell-specific conditional KOs for FGF-2 receptors may bring to light cell-specific functions of FGF-2 and help to resolve the current disparity in the literature.

Although FGF-2 has been suggested as a growth factor for oligodendrocytes in vitro (Eccleston and Silberberg, 1985), application of FGF-2 to mature oligodendrocytes has been reported to result in loss of myelin gene expression (Fressinaud et al., 1995) and to trigger cell cycle reentry that leads to formation of a novel cellular phenotype with enhanced outgrowth of processes (Bansal and Pfeiffer, 1997; Fortin et al., 2005). It is also well known that FGF-2 can inhibit the terminal differentiation of OPCs into myelin-producing oligodendrocytes in purified OPC culture (McKinnon et al., 1990; Bansal and Pfeiffer, 1997) but not in cultures containing astrocytes (Bogler et al., 1990). Under certain pathological conditions, FGF-2 has also been shown to lead to apoptosis of oligodendrocytes (Muir and Compston, 1996). In the context of the immature oligodendrocyte (OPC), FGF-2 has been reported to stimulate the proliferation of OPCs in vitro (McKinnon et al., 1990).

FGF-2 transcript levels are increased in experimentally induced CNS demyelination (Hinks and Franklin, 1999) in reactive astrocytes localized to areas around demyelinating lesions and correlate with functional recovery of motor function in a virus-induced demyelination model (Messersmith et al., 2000). In both the cuprizone and the virus-induced demyelination models, FGF-2 KO animals were found to exhibit enhanced repopulation of lesions by oligodendrocytes (Armstrong et al., 2002). Intrathecal administration of a viral vector expressing FGF-2 has been reported to suppress the clinical signs of experimental autoimmune encephalomyelitis (EAE), an animal model of MS (Ruffini et al., 2001). Another study examining PDGF expression in an EAE model reported that FGF-2 expression was limited to the CNS, but no changes in either its expression or its receptors were observed in peripheral blood leukocytes (Koehler et al., 2008). However, virally driven FGF-2 expression in the previous study demonstrated that increases in FGF-2 outside the CNS could attenuate the

autoreactive T-cell response required for EAE (Ruffini et al., 2001).

It would seem that the data on FGF-2 are incongruous, but, instead, these studies likely point to important differences between the disease models themselves. For instance, EAE models of CNS demyelination are dependent on autoreactive T-cell responses, whereas cuprizone-induced demyelination does not evoke a robust peripheral T-cell response (Remington et al., 2007). Hence, the disparity in the role of FGF-2 in these various in vivo models may reflect separate and distinct actions of FGF-2 on peripheral immune responses and oligodendrocytes. However, the findings also leave us with an important question: how do we interpret the actions of FGF-2 on myelin and translate this to an understanding of FGF-2 in human demyelinating disease?

Only recently has FGF-2 been associated with myelin pathology in diseases such as MS. Measurement of FGF-2 in CSF samples from MS patients revealed that levels of FGF-2 were higher in patients with relapsing and remitting and secondary progressive disease types than in control cases (Sarchielli et al., 2008). Moreover, elevated FGF-2 levels were also detected during clinical relapse phases compared with stable or remission phases (Sarchielli et al., 2008). Although it has been proposed that FGF-2 signaling directly contributes to limited remyelination in MS, the promiscuity of FGF-2 signaling lends itself to many disparate processes, which likely contribute to the diverse findings related to this molecule and CNS myelination.

LEUKEMIA INHIBITORY FACTOR

Leukemia inhibitory factor (LIF) was first described in human lymphatic cell lines in 1970 (Granger et al., 1970) and is a neuropoeitic cytokine secreted by astrocytes that enhances cell growth (Smith and Silver, 1988). LIF expression by astrocytes occurs during embryonic development and is low or undetectable in adult tissues (Aloisi et al., 1994; Smith and Silver, 1988). LIF has recently emerged as an important mediator of myelin formation and promoter of oligodendrocyte survival (Barres et al., 1993; Kerr and Patterson, 2005). In vitro, LIF promotes myelination in mixed cortical neuron/glial cocultures (Stankoff et al., 2002) and has more recently been shown to mimic the effects of electrical stimulation and ATP required to promote myelination (Ishibashi et al., 2006). In the Ishibashi et al. study, the addition of astrocytes to cocultures of DRG neurons and mature oligodendrocytes, followed by electrical stimulation, induced astrocytic expression of LIF and promoted axon myelination (Ishibashi et al., 2006). Interestingly, in a similar assay, the addition of astrocytes derived from LIF knockout mice greatly impaired the activity-dependant myelinating events.

In the brains of LIF KO mice, reduced numbers of $GFAP^+$ astrocytes and lower myelin basic protein (MBP) levels have been observed compared with controls (Bugga et al., 1998). In EAE, exogenous LIF administration decreases disease severity and increases the numbers of mature oligodendrocytes (Butzkueven et al., 2002). Furthermore, anti-LIF neutralizing antibodies potentiated oligodendrocyte loss, enhanced demyelination, and exacerbated the symptoms of EAE (Butzkueven et al., 2006). In the cuprizone model of demyelination, LIF KO mice exhibit increased demyelination and oligodendrocyte loss compared with wild-type controls (Marriott et al., 2008). Similarly to the EAE results, exogenously administered LIF decreased demyelination in this model, without affecting the numbers of OPCs. Together these findings indicate that astrocyte-derived LIF works at the level of the mature oligodendrocyte and fosters remyelination, an important event that is seemingly absent in MS. To date, the role of astrocytes as producers of LIF in MS has not been explored.

CILIARY NEUROTROPHIC FACTOR

Ciliary neurotrophic factor (CNTF) is produced by astrocytes and neurons in the CNS and is characterized by its ability to promote the survival of neurons during development (Yokota et al., 2005). First identified in embryonic chick eye tissues, CNTF has also been shown to protect mature neurons during and following CNS injury (Dallner et al., 2002; Linker et al., 2002; Yokota et al., 2005). Further evidence suggests that CNTF also regulates astrocyte reactivity during CNS injury, although its exact mechanism of action remains unclear (Dallner et al., 2002).

In vitro studies examining the effects of CNTF on neuron/oligodendrocyte cocultures from mouse forebrain show a significant increase in myelin formation compared with controls (Stankoff et al., 2002). In detail, CNTF directly influences OPC survival (Dell'Albani et al., 1998; Albrecht et al., 2007) and oligodendrocyte differentiation, increasing the number of MOG^+ oligodendrocytes by nearly twofold (Stankoff et al., 2002). CNTF also promotes differentiation of O-2A progenitors, which differentiate into both oligodendrocytes and astrocytes, while also promoting survival of type 2 astrocytes (Hughes et al., 1988; Lillien et al., 1988). In vivo, mice recovering from viral-induced demyelination have a coincident increase in CNTF levels in the CNS (Albrecht et al., 2003). Indeed, astrocytes circumscribing demyelinated lesions have been reported to be the cellular source of CNTF (Albrecht et al., 2003). CNTF also directly influences myelination by promoting maturation of oligodendrocytes, which is mediated through the gp130-JAK pathway (Marmur et al., 1998). gp130 Is a signal-transducing receptor subunit of interleukin-6-type cytokines, which, in response to either LIF or CNTF, heterodimerizes with the LIF receptor, thus positively regulating myelination (Stankoff et al., 2002; Timmermann et al., 2002). Taken together, these finding suggest that CNTF may work in close association with other critical regulators of myelination, serving as an important

cytokine positively regulating myelination, highlighting the cross-talk between these molecules.

Mice lacking CNTF exhibit atrophy of dendritic processes and a loss of motor neurons over time compared with controls (Sendtner et al., 1996). Compared with wild-type control mice, CNTF KO mice have a more severe EAE phenotype characterized by enhanced demyelination, earlier clinical disease onset, and increased relapse frequency with prolonged disability (Linker et al., 2002, 2005). More recently, delivery of mesenchymal stem cells overexpressing CNTF reduces demyelination and promotes clinical recovery in EAE (Lu et al., 2009). Furthermore, CNTF KO mice have a reduction in OPCs throughout the spinal cord, which is suggested to at least contribute to the observed increased severity of the disease. Interestingly, CNTF KO mice have no myelin phenotype and possess similar numbers of mature oligodendrocytes, suggesting that CNTF is not required for differentiation and myelination but rather enhances these processes (Barres et al., 1996). In early-onset MS, a null mutation of the CNTF gene was identified in 2.4% of 288 patients studied. However, the incidence of this mutation was not significantly higher than in controls (Giess et al., 2002), and the disease course in patients with the mutation did not differ; indicating the mutation is not a sufficient risk factor for developing MS (Giess et al., 2002; Hoffmann et al., 2002).

INSULIN-LIKE GROWTH FACTOR-1

Insulin-like growth factor-1 (IGF-1) was first identified in 1976 as a component of serum and described as a protein having insulin-like activity that was unsuppressed by insulin antibodies (NSILA; Rinderknecht and Humbel, 1976). This polypeptide protein hormone is produced by astrocytes in the CNS, and Northern blot analysis in cultured rat astrocytes confirmed the presence of IGF-1 mRNA (Ballotti et al., 1987).

IGF-1 was first described as a potent inducer of oligodendrocyte development in cortically derived P1 rat oligodendrocyte cultures (McMorris et al., 1986). During development, IGF-1 influences oligodendrocyte differentiation and survival (Chesik et al., 2008). During adulthood, IGF-1 acts as a neurotrophic/neuroprotective factor by promoting cell survival and inhibiting apoptosis in several cell types, including neuronal cells in vitro (Aberg et al., 2006).

The cellular proliferation and survival effects of IGF-1 have been investigated through two possible signaling mechanisms, the PI3K [phosphoinositide-3 kinase)/Akt (a kinase and a transcription factor also known as protein kinase B (PKB)] pathway or activation of the MAPK/Erk (extracellular signal-regulated kinase) pathway (Aberg et al., 2006; Cui and Almazan, 2007). The first promotes survival and inhibits apoptosis, whereas the second enhances cell growth and division. Both require IGF-1 bound to cognate partner(s) (IGFBPs; Chesik et al., 2008; Wilczak et al., 2008). In pathology, IGFBP-1 is up-regulated in oligodendrocytes surrounding the myelin lesion and should be considered when addressing tissue repair and remyelination (Chesik et al., 2008).

The process of myelination can be activated by IGF-1 during development as well as after injury (Zeger et al., 2007). Studies using conditional *IGF-1R* gene KO mice demonstrated decreased brain volumes and cell counts in the corpus callosum and anterior commissure at various ages compared with wild-type mice (Zeger et al., 2007). Although astrocyte numbers remained normal, there was a marked decrease in the percentage of $NG2^+$ oligodendrocyte precursor cells and $CC1^+$ mature oligodendrocytes in the KO phenotype (Zeger et al., 2007). This observation can be attributed to a decrease in cellular proliferation combined with an increase in apoptosis, suggesting a direct role for IGF-1 in both oligodendrocytes and the process of myelination/remyelination (Zeger et al., 2007). When administered cuprizone, transgenic mice that continuously express IGF-1 showed an almost complete recovery by 5 weeks, whereas wild-type mice exhibited significant demyelination (Mason et al., 2000b). In EAE, IGF-1 treatment has been shown to decrease disease severity by reducing immune cell responses (Liu et al., 1997), and subcutaneous administration of IGF-1 also leads to an increase in the synthesis of myelin proteins (e.g., MBP, PLP, CNP), thereby promoting myelin formation (Yao et al., 1996). These data support a potential protective and regenerative role for IGF-1 in experimentally induced demyelination by preventing the loss of mature oligodendrocytes and stimulating the expression of myelin-related genes by the oligodendrocyte (Mason et al., 2000a).

EXTRACELLULAR MATRIX-RELATED MOLECULES

Extracellular Matrix (ECM)-related molecules are not conventionally considered growth factors (e.g., laminin and fibronectin) but are secreted by astrocytes and have been shown to influence myelination positively. Indeed, mutations in the human gene *LAMA2*, encoding the laminin $\alpha 2$ subunit, result in a form of muscular dystrophy that is accompanied by a disruption of normal myelination patterns (Jones et al., 2001). Similarly, myelin deficits in mice lacking laminin have also been reported (Chun et al., 2003). Laminins interact with integrin and dystroglycan receptors on the surface of oligodendrocytes and control OPC differentiation, migration, and myelin gene production (Milner et al., 1996; Colognato et al., 2007). Interestingly, αV integrin is the only ECM receptor on OPCs that is up-regulated following CNS demyelination (Zhao et al., 2009). More specifically, the lack of normal dystroglycan expression in oligodendrocytes results in the failure of these cells to differentiate, and blocking this receptor results in a deficit in which oligodendrocytes fail to produce adequate myelin sheets and initiate myelinating events in

cocultures containing dorsal root ganglion neurons (Colognato et al., 2007). In vivo, after experimentally induced focal demyelination injury, increased expression of ECM proteins by astrocytes, coupled with the increase in αV integrins on OPCs (Zhao et al., 2009), provides evidence that ECM molecules secreted by astrocytes can play important roles in CNS myelin repair.

BONE MORPHOGENIC PROTEINS

Bone morphogenic proteins (BMPs) were first described in X-ray diffraction studies of human fetal intervertebral discs in 1980 and are a group of signaling molecules collectively known as the TGF family of signaling molecules. BMPs are produced by astrocytes and exhibit repressive qualities on the development and differentiation of oligodendrocytes (See et al., 2007; See and Grinspan, 2009). During development, BMPs are highly expressed, whereas low levels of expression are present in the adult brain. BMPs are expressed by reactive, hypertrophic astrocytes during adult CNS injury and demyelination (See and Grinspan, 2009). BMP-2, and -4 specifically have been shown to block the process of oligodendrocyte differentiation (See and Grinspan, 2009). When BMP-2 or -4 is added to cultured OPCs, the number of cells expressing olig1/2 decreased and the number of $GFAP^+$ cells increased, suggesting that BMP-2 and -4 not only suppress oligodendrocyte differentiation but also enhance astrocyte differentiation (Mabie et al., 1997; Grinspan et al., 2000; Nakashima et al., 2001; Cheng et al., 2007). However, this inhibition can be overcome by forced expression of the transcription factors olig1 and olig2 (Cheng et al., 2007). olig2 Is required for the differentiation of oligodendrocytes and motor neurons; however, the functional role of olig1 is not as well characterized (Arnett et al., 2004). The olig2 KO phenotype is lethal because of an insufficient quantity of motor neurons, whereas the olig1 KO phenotype shows delayed development of oligodendrocytes with otherwise good healthy (Arnett et al., 2004). Recent work by Cao and colleagues has shown that reduced expression of olig1/2 facilitates the inhibitory effects of BMP-2 and -4 on oligodendrocyte differentiation (Cheng et al., 2007), indicating that increasing olig1/2 expression to impair BMP-2 and -4 signaling could facilitate endogenous remyelination. For example, in a rodent model of EAE, expression of BMP-4 is significantly elevated in areas of demyelination, and recovery is promoted when BMP signaling is blocked (See and Grinspan, 2009). Elevated BMP levels in the CNS during myelin injury may therefore impede the onset of white matter recovery.

ADDITIONAL ASTROCYTE-DERIVED FACTORS

The astrocyte-derived factors discussed in this Mini-Review were selected based on the current experimental data supporting both their expression by astrocytes as growth/inhibitory factors and their propensity to influence positively or negatively the OPCs and CNS myelination (Fig. 1). The molecules discussed to this point are among the best characterized astrocyte-secreted factors that influence CNS myelination, but it is also worth noting several additional, less well-studied, factors that have generated interest for their actions on OPCs and myelination. For instance, endothelin-1 is astrocyte derived and has recently been shown to increase OPC migration and differentiation, and an endothelin receptor antagonist inhibited OPC migration and differentiation (Gadea et al., 2009).

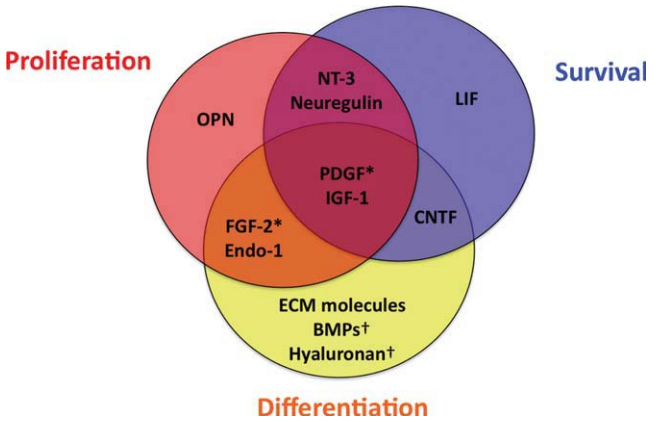

Fig. 1. Effects of astrocyte-secreted factors on oligodendrogenesis. This Venn diagram depicts the various astrocyte secreted factors that have been shown to influence oligodendrocyte progenitor cell (OPC) proliferation, differentiation, and/or survival. Molecules marked with a dagger (†) (BMPs and hyaluronan) are negative regulators of OPC differentiation, whereas molecules marked with an asterisk (*) (PDGF and FGF-2) have been shown to affect oligodendrogenesis both positively and negatively. Furthermore, this likely reflects the pleiotropic nature of these molecules not only on OPCs but on other cell types (e.g., endothelial, neurons, astrocytes, immune cells). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Another molecule of interest is osteopontin, a glycoprotein secreted by astrocytes that is up-regulated in animal models of myelin injury (Chabas et al., 2001; Selvaraju et al., 2004). Osteopontin has been shown to induce proliferation of OPCs, and recombinant osteopontin can enhance myelin formation in vitro (Selvaraju et al., 2004). Clinically, osteopontin is elevated during relapses in MS patients and is expressed in white matter lesions of postmortem MS brain tissues (Hur et al., 2007).

Neurotrophin-3 (NT-3) is another factor suggested to play a role in oligodendrocyte survival and proliferation as evidenced by the KO phenotype; fewer OPCs have been reported in the neonatal CNS of NT-3 KO and TrkC (NT-3 receptor) KO mice (Kahn et al., 1999). Furthermore, in a model of chemically induced demyelination, stereotaxic delivery of NT-3 into the corpus callosum increased the numbers of mature MBP^+ oligodendrocytes while significantly decreasing the volume of demyelinated lesions (Jean et al., 2003). Similarly, after a spinal cord contusion injury, transplanted grafts of fibroblasts expressing NT-3 and brain-derived

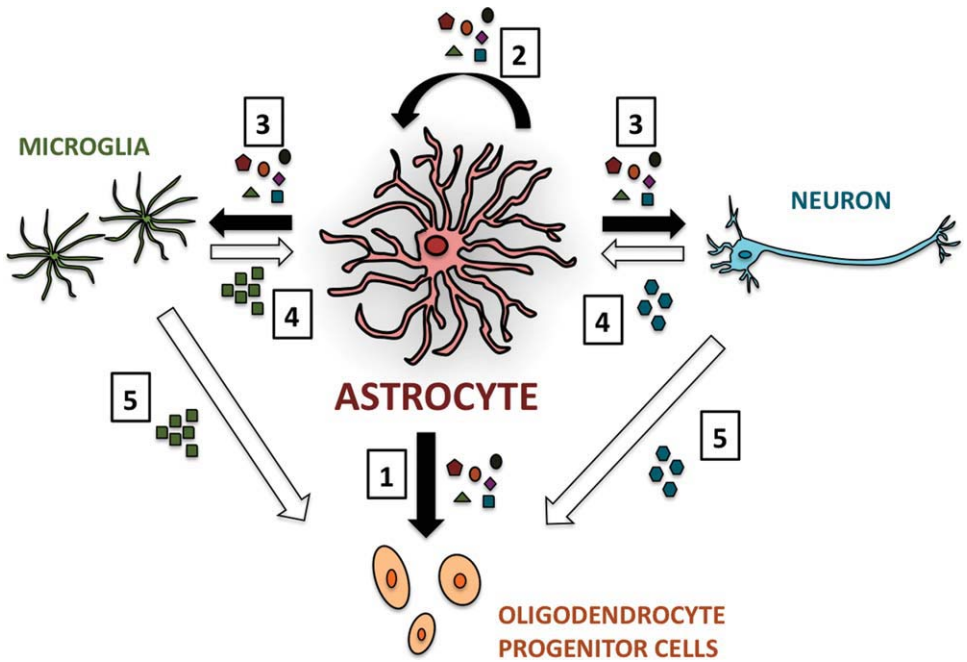

Fig. 2. Proposed model for influence of astrocyte-secreted factors on oligodendrocyte progenitor cell (OPC) growth, differentiation, and myelination. Factors released from the astrocyte, both during development and following CNS demyelination, can 1) directly influence the fate of the OPC; 2) signal in an autocrine manner, whereby the astrocyte-secreted factors bind to autocrine receptors on the astrocyte, altering the cell's biology and promoting the release of subsequent factors; 3) stimulate the release of factors from other cell types within the CNS (e.g., neurons and microglia) that can either signal back on the astrocyte (4) or directly influence the OPC (5). Inherent in this model are both positive and negative actions of secreted factors on the OPC. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

neurotrophic factor (BDNF) also increased proliferation of oligodendrocytes and promoted myelination of the regenerative axon (McTigue et al., 1998).

Neuregulins are a family of proteins that are homologous to the EGF family of trophic factors. Neuregulins have been shown to be necessary for oligodendrocyte development and to promote the proliferation and survival of OPCs while blocking OPC differentiation; however, this latter effect is dependent on the stage of development of the OPC (Canoll et al., 1996; Viehover et al., 2001). Interestingly, in the active and chronic MS lesion, expression of neuregulin by astrocytes is significantly decreased and has been suggested to contribute to the lack of remyelination that is observed in MS (Viehover et al., 2001).

Although the majority of factors discussed here have been reported to elicit positive effects on OPC growth and/or differentiation, other factors, such as BMPs (mentioned above), impair OPC development. Another example of this is hyaluronan, a glycosaminoglycan, made by astrocytes, that has been shown to be abundant in MS white matter lesions. Hyaluronan has also been shown to restrict remyelination following lysolecithin-induced injury by blocking the differentiation of OPCs (Back et al., 2005).

CONCLUSIONS

The diversity of factors generated by astrocytes that influence OPCs has led us to an emerging concept in glial biology: astrocytes produce secreted factors that orchestrate complex responses by many other cell types. In this model, the factors made by astrocytes influence the functions of other cells, including neurons, microglia, endothelial cells, and even neighboring astrocytes, that collectively impact the OPC and endogenous remyelinating potential of the CNS (Fig. 2). This model naturally leads us to consider how disease processes influence the factors expressed by astrocytes. Although many possible explanations exist, several recent studies have implicated histone dysregulation and transcriptional repression as potential mechanisms limiting the potential of OPCs to differentiate and remyelinate lesions in MS (Shen et al., 2008). We speculate that similar epigenetic changes might also regulate astrocytic gene expression, which, in turn, contributes to the failure of CNS myelin repair. Alternatively, astrocytic production of secreted factors may bring about epigenetic changes on other cell types, such as OPCs, that contribute to the disease process. Future studies specifically examining astrocytic gene expression could serve to unravel the signaling networks surrounding the OPC shortcomings of remyelination in MS.

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