Published in final edited form as:

Cell Mol Life Sci. 2014 March ; 71(6): 1055–1066. doi:10.1007/s00018-013-1488-9.

Crosstalk between cerebral endothelium and oligodendrocyte

Nobukazu Miyamoto¹, Loc-Duyen D. Pham¹, Ji Hae Seo^{1,2}, Kyu-Won Kim^{2,3,4}, Eng H. Lo¹, and Ken Arai¹

¹Neuroprotection Research Laboratory. Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, USA

²NeuroVascular Coordination Research Center, College of Pharmacy, Seoul National University, Seoul, Korea

³Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea

⁴Department of Internal Medicine, and Innovative Research Institute for Cell Therapy, Seoul National University Hospital, Seoul, Korea

Abstract

It is now relatively well accepted that the cerebrovascular system does not merely provide inert pipes for blood delivery to the brain. Cerebral endothelial cells may compose an embedded bunker of trophic factors that contribute to brain homeostasis and function. Recent findings suggest that soluble factors from cerebral endothelial cells nourish neighboring cells, such as neurons and astrocytes. Although data are strongest in supporting mechanisms of endothelial-neuron and/or endothelial-astrocyte trophic coupling, it is likely that similar interactions also exist between cerebral endothelial cells and oligodendrocyte lineage cells. In this mini-review, we summarize current advances in the field of endothelial-oligodendrocyte trophic coupling. These endothelial-oligodendrocyte interactions may comprise the oligovascular niche to maintain their cellular functions and sustain ongoing angiogenesis/oligodendrogenesis. Importantly, it should be noted that the cell-cell interactions are not static – the trophic coupling is disturbed under acute phase after brain injury, but would be recovered in the chronic phase to promote brain remodeling and repairing. Oligodendrocyte lineage cells play critical roles in white matter function, and under pathological conditions, oligodendrocyte dysfunction lead to white matter damage. Therefore, a deeper understanding of the mechanisms of endothelial-oligodendrocyte trophic coupling may lead to new therapeutic approaches for white matter related diseases, such as stroke or vascular dementia.

Keywords

oligodendrocytes; oligodendrocyte precursor cells; cerebral endothelial cells; oligovascular niche; neurovascular unit

1. Introduction

Brain physiology and pathophysiology are very complex. Several different types of brain cells may work together to maintain, remodel, and repair our brain functions. In this regard, the concept of “neurovascular unit” was raised as a new paradigm to understand the

pathology of central nervous system (CNS) diseases, such as stroke^{1–5}. This modular concept is defined at an intercellular level that comprises dynamic interactions between cerebral endothelial cells, glia, neurons, and the extracellular matrix. Dysfunctional crosstalk within the neurovascular unit may lead to multiple aspects of acute pathophysiology in CNS diseases. For example, impaired glutamate release-reuptake mechanisms in neurons and astrocytes can amplify excitotoxicity⁶. Perturbed signaling between cerebral endothelium and astrocytes (and sometimes pericytes) can disrupt blood-brain barrier integrity⁴. In addition, dysfunctional coupling between neuronal activation and vascular responses can also accelerate deleterious spreading depression⁷. Moreover, disordered signaling between all neurovascular and gliovascular elements may underlie the evolution of neuroinflammation and cell death⁸.

Besides the importance of cell-cell interaction, the neurovascular unit also emphasizes the distinct roles of cerebral endothelium on brain functions. Although cerebral vascular system is the major constituent of the brain, the cerebrovascular system was traditionally thought as a passive conduit for blood stream. However, recent research has proposed that this system plays more active roles in maintaining the CNS homeostasis. As mentioned, cerebral endothelial cells form the blood-brain barrier (BBB) with astrocytes and pericytes. The BBB constitutes anatomical, physiochemical, and biochemical barrier that controls the exchange of materials between blood, brain and cerebrospinal fluid. BBB breakdown due to endothelial dysfunction is frequently associated with a myriad of neurological pathologies, including chronic CNS diseases^{9–11}. Another example for the importance of cerebral vascular system is that cerebral endothelial cells nourish neighboring neurons. Through releasing trophic factors, cerebral endothelial cells guide developing axons¹², protect neurons against stress^{13, 14}, and provide a niche for supporting neural stem/progenitor cells (NSPCs)¹⁵. NSPCs were shown to have direct coupling with cerebral endothelial cells¹⁶, and in this so-called neurovascular niche, cell-cell signaling between cerebral endothelial cells and neuronal precursor cells help mediate and sustain pockets of ongoing neurogenesis and angiogenesis in adult brain^{15, 17}. Even under the remodeling phase after brain injury, these close relationships are maintained, and both neurogenesis and angiogenesis occur in the neurovascular niche to promote repairing of the brain. Indeed, angiogenic stimulation enhances neurogenesis after stroke^{15, 18}, and in turn, neuroblasts migrate along perivascular routes and the promotion of neurogenesis enhances vascular re-growth¹⁹.

For the most parts, research that studies mechanisms of trophic coupling in the neurovascular unit has mainly focused on endothelium-neuron and endothelium-astrocyte interactions. However, cell-cell interactions between endothelial cells and oligodendrocytes are likely to be important to maintain brain functions as well, especially in white matters. Recent papers indicate that some populations of oligodendrocyte lineage cells are located closely to cerebral endothelial cells^{20, 21} (Figure 1), and these cells may communicate each other via secreting soluble factors. In this mini-review, therefore, we attempt to overview key findings for the crosstalk between cerebral endothelial cells and oligodendrocytes.

2. Endothelium-Oligodendrocyte Signaling

2.1. Oligodendrocyte generation from neural stem cells

The interaction between brain microvascular endothelium and NSPCs is receiving a lot attention as a key mechanism of NSPC biology²². During embryonic development, interaction between endothelium and stem cells occurs in both the CNS and non-nervous tissues²². Endothelial cells modulate the behavior of NSPCs in the stem cell niche seen in subventricular zone (SVZ) or the hippocampal subgranular zone (SGZ)²³. These regions provide a specialized microenvironment, where NSPCs persist throughout their life. The SVZ contains a subpopulation of cells with astroglial properties (so-called type B cells),

which give rise to dividing intermediate progenitors or transient amplifying progenitors (so-called type C cells) to generate neuroblasts (so-called type A cells). The type B cells can also differentiate into oligodendrocyte lineage cells (i.e. migratory OPCs) through Olig2-expressing type C cells. These type-B-cells-derived OPCs leave the SVZ and migrate to the corpus callosum, the white matter tract in the striatum and fimbria fornix ²⁴. Thus far, at least two studies examined the cell-cell interaction between cerebral endothelium and NSPCs in generating oligodendrocytes. Chintawar et al.²⁵ investigated the interactions of human fetal neural precursor cells (hfNPCs) with human brain endothelial cells in their in vitro model systems. They found that in the in vitro sub-endothelial niche, NPCs interacted with endothelial cells to promote NPC differentiation into astrocytes, neurons, and even oligodendrocytes. This study proposed that the chemokine CCL2/MCP-1 mediated the interaction between endothelium and neural precursor cells for the differentiation into oligodendrocytes ²⁵. Another study by Plane et al. also examined the mechanisms of differentiation from postnatal murine forebrain neural stem cells. Interestingly, they showed that conditioned medium from endothelial cells promoted the differentiation of neural stem cells into oligodendrocyte lineage cells ²⁶. These two studies may suggest that cerebral endothelial cells participate in generating oligodendrocyte lineage cells from neural precursor cells under some conditions.

2.2. Signaling from cerebral endothelial cells to oligodendrocytes

In the developmental stage, most oligodendrocytes are generated from their precursors (oligodendrocyte precursor cells; OPCs). OPCs migrate to colonize the white matter brain (and sometimes gray matter as well) from their sites of origins (e.g. SVZ region) ^{27, 28}, and the differentiation into mature oligodendrocytes occurs in a multiple steps ²⁹. Many of OPCs differentiate into myelinating oligodendrocytes during development, but some populations of OPCs remain at the immature state and are widely distributed within the brain even after adolescence ³⁰. Several evidences indicate that OPCs persist in the adult SVZ ²⁴, and oligodendrocytes continue to be newly produced in the adult white matters ^{31–34}. These OPCs in the adult brains may participate in myelin repair after injury ^{35, 36}. Past studies have demonstrated that adult SVZ progenitors (i.e. type B cells) can generate new OPCs/oligodendrocytes after demyelinating lesions of the corpus callosum ^{37, 38}, seizures³⁹, or stroke ^{40–42}. As noted, these SVZ type B cells serve as primary precursors for new oligodendrocytes and give rise to young migrating oligodendrocytes through intermediate Olig2 transit-amplifying cells (so called type C cells) under normal and injured brains ²⁴. They are known to move out of the SVZ into the corpus callosum, neighboring striatum, and fimbria fornix to differentiate into non-myelinated and myelinated oligodendrocytes ⁴³. Compared with the large number of new neurons born in the SVZ, fewer OPCs/oligodendrocytes are normally produced from adult SVZ type B cells. This may be related to the slow turnover of oligodendrocytes in adult brain ³⁴. However, the number of OPCs/oligodendrocytes derived from SVZ type B cells are increased after a demyelinating lesion. Under the stress conditions, SVZ-generated oligodendrocytes express markers of myelin, suggesting that they contribute to the remyelination process ^{37, 38, 43, 44}.

Recently, the concept of oligovascular niche was proposed to understand the phenomena of trophic coupling between cerebral endothelium and oligodendrocyte precursors ⁴⁵. Cerebral endothelial cells may promote the proliferation of OPCs through releasing trophic factors, such as BDNF and bFGF, in vitro ⁴⁶. In addition, cerebral endothelial-derived VEGF-A increased the mobility of OPCs without affecting their proliferation ^{47, 48}. Importantly, sub-lethal oxidative stress decreased the levels of growth factor productions in endothelial cells, and the “sick” endothelial cells seemed no longer supportive for OPCs ⁴⁶. These results indicate that endothelium-oligodendrocyte trophic coupling would be disturbed during pathological conditions, which lead to white matter dysfunction. As noted, some OPCs are

located closely to cerebral endothelial cells in adult white matters (e.g. corpus callosum)²⁰, and therefore, cerebral endothelial cells may participate in the process of oligodendrocyte remodeling and repair under both normal and pathological conditions.

2.3. Signaling from oligodendrocytes to cerebral endothelial cells

Thus far, we have discussed how cerebral endothelial cells affect functions of oligodendrocyte lineage cells. But the trophic coupling between cerebral endothelial cells and oligodendrocytes should be “two-way”. Oligodendrocyte lineage cells could act as growth factor providers for neighboring cells⁴⁹. For example, oligodendrocytes synthesize defined growth factors and provide trophic signals to nearby neurons. Past studies show that oligodendrocyte-derived trophic factors, such as IGF1 and GDNF, promote neuronal survival and axonal outgrowth in vitro⁵⁰. Moreover, oligodendrocytes may serve as a principal metabolic supplier of lactate, which is integral for axonal energy support through monocarboxylate transporter 1⁵¹. Although there is little known about the mechanisms by which oligodendrocyte lineage cells affect vascular system, Pham et al. recently reported that after white matter injury, mature oligodendrocytes secreted a well-known angiogenic factor MMP-9 to promote vascular remodeling⁵². Hence, similar to the neurovascular niche, the oligovascular niche may provide an important mechanism for both angiogenesis and oligodendrogenesis in the adult white matter.

However, it should be noted that oligodendrocyte lineage cells might not always be supportive for cerebral vascular system. Very recently, OPCs were shown to release MMP-9 under acute phase of white matter injury²⁰. This OPC-derived MMP-9 initiated the early onset of BBB breakdown, which would progress to white matter dysfunction at the later time point²⁰. These findings suggest that the oligodendrocyte-endothelium interaction is not merely static. As the concept of neurovascular unit emphasizes, depending on the context, these cell-cell interactions can be both beneficial and detrimental. Under normal conditions, cell-cell trophic coupling is necessary for maintaining brain homeostasis. On the other hand, under the acute phase of neurodegenerative diseases, these cell-cell trophic coupling could be disrupted and leads to cellular dysfunction. However, in the chronic phase after brain injury, the cell-cell interaction may be recovered to some extent, and brains would try to repair their damaged function. Hence, understanding the precise mechanisms of oligodendrocyte-endothelium trophic coupling would lead us to find novel therapeutic approaches both in protecting white matters against stress under acute phase and in boosting white matter remodeling/repairing under chronic phase for white matter-related diseases, such as stroke and vascular dementia.

3. Possible mediators for oligodendrocyte-endothelial interaction

As mentioned, crosstalk between the vascular and neuronal compartments in the neurovascular niche is mediated by an exchange of soluble signals^{3, 4, 14, 53–57}. Many of these trophic factors may also affect oligodendrocyte lineage cells. Moreover, a growing literature suggests that similar to cerebral endothelium, oligodendrocyte lineage cells could work as a “bank” for trophic factors (Table). The precise regulatory mechanisms that underlie angiogenesis and oligodendrocytes in the oligovascular niche still require to be elucidated. However, we will try to summarize several candidates of mediators for the crosstalk between cerebral endothelium and oligodendrocytes in this section.

3.1 Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a member of the “neurotrophin” family of growth factors, which are related to the canonical nerve growth factor (NGF). BDNF is well known to act on neurons to support the survival of existing neurons and encourage the

growth and differentiation of new neurons and synapses^{58, 59}. BDNF can also modulate non-neuronal cell types. Irrefutably, BDNF is one of the major mediators for endothelium-oligodendrocyte interaction.

BDNF is known to regulate oligodendrocyte function in several ways. Firstly, BDNF promotes OPC proliferation and differentiation into mature oligodendrocytes. Cell culture and in vivo animal studies suggested that Trk-B receptor and ERK pathway mediated the supportive effects of BDNF^{60–63}. Secondly, even under pathological conditions, BDNF can be supportive for oligodendrocyte lineage cells. In in vivo white matter injury models (spinal cord injury or cuprizone-treated model), BDNF was shown to play an important role in regulating the numbers of oligodendrocyte lineage cells after demyelination^{64, 65}. Thirdly, BDNF may also work on neural stem cells (NSCs) to trigger the differentiation into oligodendrocyte lineage cells. Chen et al reported that BDNF enhanced the cell commitment of NSCs to neuronal and oligodendrocytic fates by activating Wnt/ β -catenin signaling pathway in vitro⁶⁶. Since cerebral endothelial cells are the major BDNF-producing cell type, cerebral endothelial cells may support oligodendrocyte lineage cells via BDNF signaling. As introduced in the previous section, endothelial-derived BDNF was shown to promote the proliferation of OPCs in vitro⁴⁶. But importantly, stressed endothelial cells secrete less BDNF and can no longer support OPCs⁴⁶, indicating that endothelial-oligodendrocyte interaction is highly dependent on their cellular conditions.

BDNF also promotes endothelial cell survival and induces angiogenesis in brain⁶⁷. While cell-cell trophic interactions are generally considered as “two-way”, there have been still no direct proofs that BDNF mediates signals from oligodendrocytes to endothelial cells. Nevertheless, several lines of evidence strongly support the idea that oligodendrocyte lineage cells would produce BDNF to support endothelial cells. In situ hybridization and immunocytochemical studies identified expressions of BDNF mRNA/protein in cultured basal forebrain oligodendrocytes^{68, 69}. The physiological relevance of these culture works is supported by detection of BDNF in oligodendrocytes in vivo. For example, BDNF mRNAs are localized in subpopulations of myelin-basic-protein-positive mature oligodendrocytes in the basal forebrain, cingulate cortex, and corpus callosum of postnatal day 7 rats⁶⁹. Similarly, BDNF mRNA and protein are also expressed in subsets of APC-positive oligodendrocytes of adult spinal cords^{70, 71}. The oligodendrocytic BDNF is bioactive because conditioned medium from oligodendrocyte cultures increased cholinergic neurons and the effect was partially blocked by co-treatment with anti-BDNF neutralizing antibody⁶⁹. Considering the fact that oligodendrocyte lineage cells are often located to cerebral endothelial cells, it would be reasonable to think that oligodendrocytic BDNF may regulate cerebral vascular system to some extent.

3.2 Fibroblast Growth Factor-2

Similar to BDNF, fibroblast growth factor-2 (FGF-2/bFGF) can be proposed as an important mediator for the endothelium-oligodendrocyte interaction. FGF-2 is a potent stimulator of endothelial cell migration, proliferation, sprouting, and tube formation. In addition, past studies have substantially revealed the roles of FGF-2 on oligodendrocyte function. FGF-2 by itself stimulates proliferation of late-stage OPCs and blocks their terminal differentiation into mature oligodendrocytes in vitro. Upon removal of FGF-2 from the cell culture medium of OPCs, the cells readily enter the terminal differentiation^{72–74}. In addition, FGF-2 cooperates with PDGF to up-regulate the expression of PDGF-receptor-alpha for OPC proliferation^{72, 75}. As for OPC migration, the importance of FGF signaling in early-stage OPCs has been evaluated both in vivo and in vitro. Using an in vivo transplantation approach, Osterhout et al. demonstrated that OPCs with dominant-negative FGF receptor 1 failed to migrate⁷⁶. Subsequent in vitro study showed that in response to FGF-2 stimulation, OPCs growing in an agarose drop successfully move out from the drop⁷⁷. Another study

suggested that FGF-2 also enhanced the migration of pre-OPCs from oligospheres, but might not induce the migration of late-stage OPCs⁷⁸. While still controversial, FGF-2 may affect OPC survival. FGF-2 can prevent OPCs from apoptotic stress⁷⁹, but this kind of protective effects were not observed in optic nerve OPCs⁸⁰. Since the cellular localization of FGF-2 is observed in cerebral endothelium both in normal and pathological conditions⁸¹, future studies are warranted to examine how FGF-2 modulate the dynamics of endothelium-oligodendrocyte crosstalk under normal conditions as well as acute/chronic phases after brain injury

3.3 Transforming Growth Factor-beta

Transforming growth factor-beta (TGF-beta), a prototypic member of a large family of pleiotropic cytokines, is also a potent modulator in the oligovascular niche. Many cells have been reported to produce TGF-beta, and TGF-beta would modulate several cellular functions in most cells⁸². In terms of endothelium-oligodendrocyte interaction, oligodendrocytes are reported to express TGF-beta in vitro cell culture systems⁸³ and in vivo spinal cords⁸⁴. TGF-beta contributes to angiogenesis by stabilizing newly formed capillary sprouts⁸⁵. Thus far, many studies in mouse and human have demonstrated its pivotal roles in modulating angiogenesis after brain injury, such as stroke⁸⁶⁻⁹¹. In addition, dysregulation of TGF-beta signaling may cause hereditary vascular disorders⁸². For example, mutations in TGF-beta receptors lead to hereditary hemorrhagic telangiectasia⁹², and in the cerebral white matter, accumulation of TGF-beta1 due to HtrA1 mutation is associated with a hereditary disorder CRASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy)⁹³. In contrast, the roles of TGF-beta on oligodendrocytic functions are still understudied. But TGF-beta was reported to affect the migration of cultured OPCs when they were maintained on astrocytes⁹⁴. Using the oligodendrocyte precursor cell line OLI-neu, TGF-beta was shown to upregulate a chondroitin sulfate proteoglycan DSD-1-PG on the cell surface⁹⁵, indicating that TGF-beta may modulate the cell adhesion property of OPCs to change cell motility.

3.4 Adrenomedullin

Adrenomedullin (AM) was originally isolated from pheochromocytoma cells⁹⁶. AM has a variety of actions on the vascular systems, such as endothelial survival/proliferation, vasodilatation, regulation of BBB permeability, and modulation of oxidative stress levels in endothelium^{97,98}. AM is secreted from various organs, and in the CNS, AM is mainly expressed in neurons and cerebral endothelium^{96,99}. AM has been shown to reduce the infarct volumes in transient stroke models^{100,101}. Under stroke conditions, AM expression is markedly increased via the hypoxia-inducible factor-1 signaling¹⁰², indicating that AM could work for vascular remodeling/repairing after brain injury. Interestingly, in the mouse model of chronic cerebral hypoperfusion (i.e. vascular dementia model), AM was demonstrated to be protective toward white matters¹⁰³, where most oligodendrocytes are populated. In addition, Uezono et al detected AM mRNAs in human oligodendroglial cell line, and showed the potential effects of AM in modulating oligodendrocyte function through AM receptors in oligodendrocytes¹⁰⁴. Importantly, past studies have demonstrated that AM increases several growth factors such as VEGF and FGF¹⁰⁵⁻¹⁰⁸. Hence, AM might work as a “master” modulator for growth factors in the oligovascular niche.

3.5 Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a primary regulator of angiogenesis by stimulating endothelial cell proliferation, migration, and tube formation⁵⁵. But it is now well recognized that VEGF is not solely an endothelial mediator, rather may represent one of the major mediators in the neurovascular unit¹⁰⁹⁻¹¹¹. For example, VEGF signaling plays a key role in neuronal migration and CNS development¹¹². In addition, VEGF may also affect

oligodendrocyte lineage cells. OPCs were positive for the VEGF receptor, Flk-1 (also known as KDR or VEGF-receptor 2)¹¹³, which is primarily responsible for VEGF-induced angiogenesis. Recent *in vitro* study suggested that VEGF-A significantly accelerated the motility of OPCs through Flk-1, and this effect was partly mediated by ROS production¹¹³. Importantly, conditioned media from cerebral endothelial cells promoted both OPC proliferation and migration. However, endothelial-derived VEGF-A may participate in the OPC migration but not proliferation¹¹⁴. In addition to VEGF-A, other VEGF families and VEGF receptors may also be involved in oligodendrocyte functions. Le Bras et al. demonstrated that VEGF-C promoted OPC proliferation through VEGF-receptor-3¹¹⁵. Taken together, these findings indicate that VEGFs/VEGF-receptors may play a central role in the endothelial-oligodendrocyte trophic coupling.

If VEGF is an important modulator for the oligovascular niche, we may need to consider the “biphasic actions” of VEGF to comprehend the dynamics of trophic coupling between cerebral endothelium and oligodendrocytes. Since VEGF is a primary regulator of angiogenesis, VEGF can trigger remodeling responses in endothelial cells (i.e. accelerating angiogenesis) after brain damage, such as stroke. Infusing VEGF into the lateral ventricles stimulated angiogenesis and decreased infarct volumes in rodent models of focal cerebral ischemia¹¹⁶. An increase in angiogenesis by VEGF in rats was also associated with reduced neurological deficits after stroke¹¹⁷. Similar effects were also reported in neonatal focal rodent stroke¹¹⁸. Moreover, in transgenic mice with overexpressing human VEGF165, brain microvessel density was significantly elevated compared to wild-type mice before ischemia, and the microvessel density was higher 3 days after stroke onset¹¹⁹. On the other hand, VEGF increases BBB permeability in the acute phase in stroke. VEGF administration worsens BBB leakage by ischemic insults^{120, 121}. Therefore, depending on the context of the microenvironment in the oligovascular niche, VEGF may regulate the endothelium-oligodendrocyte interaction to maintain and remodel white matter function.

3.6 Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) comprise a family of zinc endopeptidases, and their activities are tightly regulated by tissue inhibitor of metalloproteinases (TIMPs). This larger MMP network plays major roles in the physiology and pathology of the mammalian CNS, including stroke (MMP-2/3/7/9/13, TIMP-1/2¹²²), vascular dementia (MMP-2, 3, 9^{123, 124}), and CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy: TIMP-3¹²⁵). Similar to VEGF, MMPs are well-known biphasic modulators in the CNS. During the acute phase of stroke, MMP-2/3/9/13 are deleterious, i.e. they degrade the extracellular matrix that comprises the basal lamina, which could directly damage BBB¹²⁶. In addition, proteolysis of the neurovascular matrix by MMP-9 after stroke can trigger anoikis-like neuronal death¹²⁷. However, during delayed phases of stroke recovery, some of these proteinases (MMP-2/3/9) may play beneficial roles^{122, 126, 128}. In a mouse stroke model, peri-infarct cortical areas demonstrate a secondary elevation in MMP-9 in endothelial and glial cells within networks of regrowing microvessels¹²⁹. Inhibition of MMPs during this delayed phase disrupted brain repairing with the induction of hemorrhagic and malformed blood vessels. Moreover, signals of MMP-9 were observed in the migrating neuroblasts from the subventricular zone after brain injury, and inhibition of these MMPs also blocked the movement of these neuroblasts originally headed towards damaged brain¹³⁰.

As MMPs play multiple roles in the neurovascular unit, MMPs may mediate the crosstalk between cerebral endothelium and oligodendrocytes. Thus far, several studies imply the essential roles of MMP network in oligodendrocytic functions. For example, MMP-9 mediated oligodendrocytic process extension *in vitro* cell culture system¹¹⁶ and MMP-9 expression level was increased during myelin formation in the optic nerve *in vivo*¹¹⁷.

Moreover, after white matter injury, MMP-9 removed injury-induced deposition of inhibitory NG2 proteoglycan, which is an essential step for OPCs to differentiate into mature oligodendrocytes for remyelination¹³¹. In addition, MMP-12 was shown to cause demyelination, macrophage infiltration, and motor deficits in a mouse model of virus-induced multiple sclerosis¹³². Tissue inhibitor of metalloproteinases might be also involved in cellular function/survival of oligodendrocyte lineage cells. In a mouse model of focal stroke ischemia, TIMP-3 deficiency showed more number in immature oligodendrocytes after injury¹³³. Besides roles as a recipient cell for MMPs, oligodendrocyte lineage cells may in turn produce MMPs to send signals to cerebral endothelial cells. As noted, OPCs respond quickly to a stress stimulation after white matter damage and release MMP-9 to induce early BBB leakage in a mouse model of prolonged hypoperfusion model²⁰. On the other hand, under the chronic phase of white matter injury, oligodendrocytic MMP-9 may promote vascular remodeling⁵². Hence, as in the neurovascular unit, MMPs contribute to the dynamics of cellular interactions in the oligovascular niche due to their “biphasic property”.

4. Conclusions

The concept of neurovascular unit emphasizes that cell-cell interaction is critical to maintain normal brain function as well as brain remodeling after injury. Within the conceptual framework of neurovascular unit, cerebral endothelial cells are particularly important in releasing soluble factors to nourish neighboring cells, such as astrocytes or neurons. As we discussed in this mini-review, cerebral endothelial cells may also support oligodendrocyte lineage cells in the white matter. On the other hand, oligodendrocyte-derived factors can modulate cerebral vascular systems under some conditions. In the so-called oligovascular niche (i.e. microenvironment between cerebral endothelium and oligodendrocytes), cerebral endothelium and oligodendrocyte lineage cells may work together for white matter homeostasis (Figure 2). Although some key mediators for endothelium-oligodendrocyte crosstalk were briefly discussed in this mini-review, the precise underlying mechanisms still remain to be elucidated. Importantly, there may be overlap between factors in the oligovascular niche and the relatively more well-established neurovascular niche. Therefore, a deeper analysis, perhaps using subtractive approaches, may be required in order to rigorously define the regulatory signals that are truly unique to the oligovascular niche. As white matter injury is a key part of most CNS diseases, understanding the cell-cell interaction between cerebral endothelium and oligodendrocytes may lead us effective therapeutic approaches for white matter related diseases, such as stroke and vascular dementia.

Acknowledgments

Supported in part by National Institutes of Health, Research Abroad from the Uehara Memorial Foundation, National Research Foundation of Korea through the World Class University Program (R31-2008-000-10103-0), and the Global Research Laboratory Program (2011-0021874).

References

1. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. *Nat Rev Neurosci.* 2003; 4:399–415. [PubMed: 12728267]
2. del Zoppo GJ. Stroke and neurovascular protection. *N Engl J Med.* 2006; 354:553–555. [PubMed: 16467542]
3. Iadecola C. Neurovascular regulation in the normal brain and in alzheimer’s disease. *Nat Rev Neurosci.* 2004; 5:347–360. [PubMed: 15100718]
4. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. *Neuron.* 2008; 57:178–201. [PubMed: 18215617]

5. Lok J, Gupta P, Guo S, Kim WJ, Whalen MJ, van Leyen K, Lo EH. Cell-cell signaling in the neurovascular unit. *Neurochem Res.* 2007; 32:2032–2045. [PubMed: 17457674]
6. Besancon E, Guo S, Lok J, Tymianski M, Lo EH. Beyond nmda and ampa glutamate receptors: Emerging mechanisms for ionic imbalance and cell death in stroke. *Trends in pharmacological sciences.* 2008; 29:268–275. [PubMed: 18384889]
7. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nature medicine.* 2011; 17:439–447.
8. Iadecola C, Anrather J. The immunology of stroke: From mechanisms to translation. *Nature medicine.* 2011; 17:796–808.
9. Zlokovic BV. Neurovascular pathways to neurodegeneration in alzheimer's disease and other disorders. *Nat Rev Neurosci.* 2011; 12:723–738. [PubMed: 22048062]
10. Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R, Zlokovic BV. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron.* 2010; 68:409–427. [PubMed: 21040844]
11. Zlokovic BV. Neurodegeneration and the neurovascular unit. *Nat Med.* 2010; 16:1370–1371. [PubMed: 21135839]
12. Makita T, Sucov HM, Gariepy CE, Yanagisawa M, Ginty DD. Endothelins are vascular-derived axonal guidance cues for developing sympathetic neurons. *Nature.* 2008; 452:759–763. [PubMed: 18401410]
13. Dugas JC, Mandemakers W, Rogers M, Ibrahim A, Daneman R, Barres BA. A novel purification method for cns projection neurons leads to the identification of brain vascular cells as a source of trophic support for corticospinal motor neurons. *J Neurosci.* 2008; 28:8294–8305. [PubMed: 18701692]
14. Guo S, Kim WJ, Lok J, Lee SR, Besancon E, Luo BH, Stins MF, Wang X, Dedhar S, Lo EH. Neuroprotection via matrix-trophic coupling between cerebral endothelial cells and neurons. *Proc Natl Acad Sci U S A.* 2008; 105:7582–7587. [PubMed: 18495934]
15. Ohab JJ, Fleming S, Blesch A, Carmichael ST. A neurovascular niche for neurogenesis after stroke. *J Neurosci.* 2006; 26:13007–13016. [PubMed: 17167090]
16. Teng H, Zhang ZG, Wang L, Zhang RL, Zhang L, Morris D, Gregg SR, Wu Z, Jiang A, Lu M, Zlokovic BV, Chopp M. Coupling of angiogenesis and neurogenesis in cultured endothelial cells and neural progenitor cells after stroke. *J Cereb Blood Flow Metab.* 2008; 28:764–771. [PubMed: 17971789]
17. Kokovay E, Goderie S, Wang Y, Lotz S, Lin G, Sun Y, Roysam B, Shen Q, Temple S. Adult svz lineage cells home to and leave the vascular niche via differential responses to sdf1/cxcr4 signaling. *Cell Stem Cell.* 2010; 7:163–173. [PubMed: 20682445]
18. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, Tsukamoto Y, Iso H, Fujimori Y, Stern DM, Naritomi H, Matsuyama T. Administration of cd34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. *J Clin Invest.* 2004; 114:330–338. [PubMed: 15286799]
19. Thored P, Wood J, Arvidsson A, Cammenga J, Kokaia Z, Lindvall O. Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. *Stroke.* 2007; 38:3032–3039. [PubMed: 17901386]
20. Seo JH, Miyamoto N, Hayakawa K, Pham LD, Maki T, Ayata C, Kim KW, Lo EH, Arai K. Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. *J Clin Invest.* 2013; 123:782–786. [PubMed: 23281396]
21. Pham LD, Hayakawa K, Seo JH, Nguyen MN, Som AT, Lee BJ, Guo S, Kim KW, Lo EH, Arai K. Crosstalk between oligodendrocytes and cerebral endothelium contributes to vascular remodeling after white matter injury. *Glia.* 2012; 60:875–881. [PubMed: 22392631]
22. Scadden DT. The stem-cell niche as an entity of action. *Nature.* 2006; 441:1075–1079. [PubMed: 16810242]
23. Alvarez-Buylla A, Lim DA. For the long run: Maintaining germinal niches in the adult brain. *Neuron.* 2004; 41:683–686. [PubMed: 15003168]

24. 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]
25. Chintawar S, Cayrol R, Antel J, Pandolfo M, Prat A. Blood-brain barrier promotes differentiation of human fetal neural precursor cells. *Stem Cells.* 2009; 27:838–846. [PubMed: 19350685]
26. Plane JM, Andjelkovic AV, Keep RF, Parent JM. Intact and injured endothelial cells differentially modulate postnatal murine forebrain neural stem cells. *Neurobiol Dis.* 2010; 37:218–227. [PubMed: 19837162]
27. Thomas JL, Spassky N, Perez Villegas EM, Olivier C, Cobos I, Goujet-Zalc C, Martinez S, Zalc B. Spatiotemporal development of oligodendrocytes in the embryonic brain. *J Neurosci Res.* 2000; 59:471–476. [PubMed: 10679785]
28. Qi Y, Stapp D, Qiu M. Origin and molecular specification of oligodendrocytes in the telencephalon. *Trends Neurosci.* 2002; 25:223–225. [PubMed: 11972950]
29. Arai K, Lo EH. Oligovascular signaling in white matter stroke. *Biol Pharm Bull.* 2009; 32:1639–1644. [PubMed: 19801821]
30. Polito A, Reynolds R. Ng2-expressing cells as oligodendrocyte progenitors in the normal and demyelinated adult central nervous system. *J Anat.* 2005; 207:707–716. [PubMed: 16367798]
31. Blakemore WF. Observations on oligodendrocyte degeneration, the resolution of status spongiosus and remyelination in cuprizone intoxication in mice. *J Neurocytol.* 1972; 1:413–426. [PubMed: 8530973]
32. Prineas JW, Connell F. Remyelination in multiple sclerosis. *Ann Neurol.* 1979; 5:22–31. [PubMed: 426466]
33. Kaplan MS, Hinds JW. Gliogenesis of astrocytes and oligodendrocytes in the neocortical grey and white matter of the adult rat: Electron microscopic analysis of light radioautographs. *J Comp Neurol.* 1980; 193:711–727. [PubMed: 7440787]
34. McCarthy GF, Leblond CP. Radioautographic evidence for slow astrocyte turnover and modest oligodendrocyte production in the corpus callosum of adult mice infused with 3h-thymidine. *J Comp Neurol.* 1988; 271:589–603. [PubMed: 3385018]
35. Gensert JM, Goldman JE. Endogenous progenitors remyelinate demyelinated axons in the adult CNS. *Neuron.* 1997; 19:197–203. [PubMed: 9247275]
36. Chari DM, Blakemore WF. Efficient recolonisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. *Glia.* 2002; 37:307–313. [PubMed: 11870870]
37. Nait-Oumesmar B, Decker L, Lachapelle F, Avellana-Adalid V, Bachelin C, Van Evercooren AB. Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. *Eur J Neurosci.* 1999; 11:4357–4366. [PubMed: 10594662]
38. Picard-Riera N, Decker L, Delarasse C, Goude K, Nait-Oumesmar B, Liblau R, Pham-Dinh D, Evercooren AB. Experimental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice. *Proc Natl Acad Sci U S A.* 2002; 99:13211–13216. [PubMed: 12235363]
39. Parent JM, von dem Bussche N, Lowenstein DH. Prolonged seizures recruit caudal subventricular zone glial progenitors into the injured hippocampus. *Hippocampus.* 2006; 16:321–328. [PubMed: 16435310]
40. Li L, Harms KM, Ventura PB, Lagace DC, Eisch AJ, Cunningham LA. Focal cerebral ischemia induces a multilineage cytogenic response from adult subventricular zone that is predominantly gliogenic. *Glia.* 2010; 58:1610–1619. [PubMed: 20578055]
41. Zhang RL, Chopp M, Roberts C, Jia L, Wei M, Lu M, Wang X, Pourabdollah S, Zhang ZG. Ascl1 lineage cells contribute to ischemia-induced neurogenesis and oligodendrogenesis. *J Cereb Blood Flow Metab.* 2011; 31:614–625. [PubMed: 20736965]
42. Zhang RL, Chopp M, Roberts C, Wei M, Wang X, Liu X, Lu M, Zhang ZG. Sildenafil enhances neurogenesis and oligodendrogenesis in ischemic brain of middle-aged mouse. *PLoS One.* 2012; 7:e48141. [PubMed: 23118941]
43. Fancy SP, Zhao C, Franklin RJ. Increased expression of nkx2.2 and olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. *Mol Cell Neurosci.* 2004; 27:247–254. [PubMed: 15519240]

44. Petratos S, Gonzales MF, Azari MF, Marriott M, Minichiello RA, Shipham KA, Profyris C, Nicolaou A, Boyle K, Cheema SS, Kilpatrick TJ. Expression of the low-affinity neurotrophin receptor, p75(ntr), is upregulated by oligodendroglial progenitors adjacent to the subventricular zone in response to demyelination. *Glia*. 2004; 48:64–75. [PubMed: 15326616]
45. Arai K, Lo E. Oligovascular signaling in white matter stroke. *Biological & pharmaceutical bulletin*. 2009; 32:1639–1683. [PubMed: 19801821]
46. Arai K, Lo E. An oligovascular niche: Cerebral endothelial cells promote the survival and proliferation of oligodendrocyte precursor cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009; 29:4351–4356. [PubMed: 19357263]
47. Hayakawa K, Seo J, Pham L-D, Miyamoto N, Som A, Guo S, Kim K-W, Lo E, Arai K. Cerebral endothelial derived vascular endothelial growth factor promotes the migration but not the proliferation of oligodendrocyte precursor cells in vitro. *Neuroscience letters*. 2012; 513:42–48. [PubMed: 22342913]
48. Hayakawa K, Pham L-D, Som A, Lee B, Guo S, Lo E, Arai K. Vascular endothelial growth factor regulates the migration of oligodendrocyte precursor cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011; 31:10666–10736. [PubMed: 21775609]
49. Hansson E, Ronnback L. Glial neuronal signaling in the central nervous system. *FASEB J*. 2003; 17:341–348. [PubMed: 12631574]
50. Wilkins A, Majed H, Layfield R, Compston A, Chandran S. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: A novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci*. 2003; 23:4967–4974. [PubMed: 12832519]
51. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang PW, Pellerin L, Magistretti PJ, Rothstein JD. Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature*. 2012; 487:443–448. [PubMed: 22801498]
52. Pham LD, Hayakawa K, Seo JH, Nguyen MN, Som AT, Lee BJ, Guo S, Kim KW, Lo EH, Arai K. Crosstalk between oligodendrocytes and cerebral endothelium contributes to vascular remodeling after white matter injury. *Glia*. 2012
53. Zacchigna S, Lambrechts D, Carmeliet P. Neurovascular signalling defects in neurodegeneration. *Nat Rev Neurosci*. 2008; 9:169–181. [PubMed: 18253131]
54. Chopp M, Zhang ZG, Jiang Q. Neurogenesis, angiogenesis, and mri indices of functional recovery from stroke. *Stroke*. 2007; 38:827–831. [PubMed: 17261747]
55. Greenberg DA, Jin K. From angiogenesis to neuropathology. *Nature*. 2005; 438:954–959. [PubMed: 16355213]
56. Leventhal C, Rafii S, Rafii D, Shahar A, Goldman SA. Endothelial trophic support of neuronal production and recruitment from the adult mammalian subependyma. *Mol Cell Neurosci*. 1999; 13:450–464. [PubMed: 10383830]
57. Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, Vincent P, Pumiglia K, Temple S. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science*. 2004; 304:1338–1340. [PubMed: 15060285]
58. Acheson A, Conover JC, Fandl JP, DeChiara TM, Russell M, Thadani A, Squinto SP, Yancopoulos GD, Lindsay RM. A bdnf autocrine loop in adult sensory neurons prevents cell death. *Nature*. 1995; 374:450–453. [PubMed: 7700353]
59. Huang EJ, Reichardt LF. Neurotrophins: Roles in neuronal development and function. *Annu Rev Neurosci*. 2001; 24:677–736. [PubMed: 11520916]
60. Van't Veer A, Du Y, Fischer TZ, Boetig DR, Wood MR, Dreyfus CF. Brain-derived neurotrophic factor effects on oligodendrocyte progenitors of the basal forebrain are mediated through trkb and the map kinase pathway. *J Neurosci Res*. 2009; 87:69–78. [PubMed: 18752299]
61. Vondran MW, Clinton-Luke P, Honeywell JZ, Dreyfus CF. Bdnf+/- mice exhibit deficits in oligodendrocyte lineage cells of the basal forebrain. *Glia*. 2010; 58:848–856. [PubMed: 20091777]
62. Xiao J, Ferner AH, Wong AW, Denham M, Kilpatrick TJ, Murray SS. Extracellular signal-regulated kinase 1/2 signaling promotes oligodendrocyte myelination in vitro. *J Neurochem*. 2012; 122:1167–1180. [PubMed: 22784206]

63. Xiao J, Wong AW, Willingham MM, van den Buuse M, Kilpatrick TJ, Murray SS. Brain-derived neurotrophic factor promotes central nervous system myelination via a direct effect upon oligodendrocytes. *Neurosignals*. 2010; 18:186–202. [PubMed: 21242670]
64. VonDrán MW, Singh H, Honeywell JZ, Dreyfus CF. Levels of bdnf impact oligodendrocyte lineage cells following a cuprizone lesion. *J Neurosci*. 2011; 31:14182–14190. [PubMed: 21976503]
65. Nakajima H, Uchida K, Yayama T, Kobayashi S, Guerrero AR, Furukawa S, Baba H. Targeted retrograde gene delivery of brain-derived neurotrophic factor suppresses apoptosis of neurons and oligodendroglia after spinal cord injury in rats. *Spine (Phila Pa 1976)*. 2010; 35:497–504. [PubMed: 20190624]
66. Chen BY, Wang X, Wang ZY, Wang YZ, Chen LW, Luo ZJ. Brain-derived neurotrophic factor stimulates proliferation and differentiation of neural stem cells, possibly by triggering the wnt/ beta-catenin signaling pathway. *J Neurosci Res*. 2013; 91:30–41. [PubMed: 23023811]
67. Kermani P, Hempstead B. Brain-derived neurotrophic factor: A newly described mediator of angiogenesis. *Trends Cardiovasc Med*. 2007; 17:140–143. [PubMed: 17482097]
68. Dai X, Qu P, Dreyfus CF. Neuronal signals regulate neurotrophin expression in oligodendrocytes of the basal forebrain. *Glia*. 2001; 34:234–239. [PubMed: 11329185]
69. Dai X, Lercher LD, Clinton PM, Du Y, Livingston DL, Vieira C, Yang L, Shen MM, Dreyfus CF. The trophic role of oligodendrocytes in the basal forebrain. *J Neurosci*. 2003; 23:5846–5853. [PubMed: 12843289]
70. Dougherty KD, Dreyfus CF, Black IB. Brain-derived neurotrophic factor in astrocytes, oligodendrocytes, and microglia/macrophages after spinal cord injury. *Neurobiol Dis*. 2000; 7:574–585. [PubMed: 11114257]
71. Wetmore C, Olson L. Neuronal and nonneuronal expression of neurotrophins and their receptors in sensory and sympathetic ganglia suggest new intercellular trophic interactions. *J Comp Neurol*. 1995; 353:143–159. [PubMed: 7714245]
72. McKinnon RD, Matsui T, Dubois-Dalcq M, Aaronson SA. Fgf modulates the pdgf-driven pathway of oligodendrocyte development. *Neuron*. 1990; 5:603–614. [PubMed: 2171589]
73. Gard AL, Pfeiffer SE. Glial cell mitogens bfgf and pdgf differentially regulate development of o4+galc- oligodendrocyte progenitors. *Dev Biol*. 1993; 159:618–630. [PubMed: 8405684]
74. Bansal R, Pfeiffer SE. Inhibition of protein and lipid sulfation in oligodendrocytes blocks biological responses to fgf-2 and retards cytoarchitectural maturation, but not developmental lineage progression. *Dev Biol*. 1994; 162:511–524. [PubMed: 8150210]
75. Bogler O, Wren D, Barnett SC, Land H, Noble M. Cooperation between two growth factors promotes extended self-renewal and inhibits differentiation of oligodendrocyte-type-2 astrocyte (o-2a) progenitor cells. *Proc Natl Acad Sci U S A*. 1990; 87:6368–6372. [PubMed: 2201028]
76. Osterhout DJ, Ebner S, Xu J, Ornitz DM, Zazanis GA, McKinnon RD. Transplanted oligodendrocyte progenitor cells expressing a dominant-negative fgf receptor transgene fail to migrate in vivo. *J Neurosci*. 1997; 17:9122–9132. [PubMed: 9364059]
77. Milner R, Anderson HJ, Rippon RF, McKay JS, Franklin RJ, Marchionni MA, Reynolds R, French-Constant C. Contrasting effects of mitogenic growth factors on oligodendrocyte precursor cell migration. *Glia*. 1997; 19:85–90. [PubMed: 8989571]
78. Decker L, Avellana-Adalid V, Nait-Oumesmar B, Durbec P, Baron-Van Evercooren A. Oligodendrocyte precursor migration and differentiation: Combined effects of psa residues, growth factors, and substrates. *Mol Cell Neurosci*. 2000; 16:422–439. [PubMed: 11085879]
79. Yasuda T, Grinspan J, Stern J, Franceschini B, Bannerman P, Pleasure D. Apoptosis occurs in the oligodendroglial lineage, and is prevented by basic fibroblast growth factor. *J Neurosci Res*. 1995; 40:306–317. [PubMed: 7745624]
80. 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]
81. Issa R, AlQteishat A, Mitsios N, Saka M, Krupinski J, Tarkowski E, Gaffney J, Slevin M, Kumar S, Kumar P. Expression of basic fibroblast growth factor mRNA and protein in the human brain following ischaemic stroke. *Angiogenesis*. 2005; 8:53–62. [PubMed: 16132618]

82. ten Dijke P, Arthur HM. Extracellular control of tgfbeta signalling in vascular development and disease. *Nat Rev Mol Cell Biol.* 2007; 8:857–869. [PubMed: 17895899]
83. McKinnon RD, Piras G, Ida JA Jr, Dubois-Dalcq M. A role for tgfbeta in oligodendrocyte differentiation. *J Cell Biol.* 1993; 121:1397–1407. [PubMed: 8509457]
84. Hinks GL, Franklin RJ. Distinctive patterns of pdgf-a, fgf-2, igf-i, and tgfbeta1 gene expression during remyelination of experimentally-induced spinal cord demyelination. *Mol Cell Neurosci.* 1999; 14:153–168. [PubMed: 10532806]
85. Bottner M, Kriegstein K, Unsicker K. The transforming growth factor-betas: Structure, signaling, and roles in nervous system development and functions. *J Neurochem.* 2000; 75:2227–2240. [PubMed: 11080174]
86. Vivien D, Ali C. Transforming growth factor-beta signalling in brain disorders. *Cytokine & growth factor reviews.* 2006; 17:121–128. [PubMed: 16271500]
87. Krupinski J, Kumar P, Kumar S, Kaluza J. Increased expression of tgfbeta 1 in brain tissue after ischemic stroke in humans. *Stroke; a journal of cerebral circulation.* 1996; 27:852–857.
88. Ata AK, Funa K, Olsson Y. Expression of various tgfbeta isoforms and type i receptor in necrotizing human brain lesions. *Acta neuropathologica.* 1997; 93:326–333. [PubMed: 9113197]
89. Slevin M, Krupinski J, Slowik A, Kumar P, Szczudlik A, Gaffney J. Serial measurement of vascular endothelial growth factor and transforming growth factor-beta1 in serum of patients with acute ischemic stroke. *Stroke; a journal of cerebral circulation.* 2000; 31:1863–1870.
90. Zhang ZG, Zhang L, Jiang Q, Chopp M. Bone marrow-derived endothelial progenitor cells participate in cerebral neovascularization after focal cerebral ischemia in the adult mouse. *Circulation research.* 2002; 90:284–288. [PubMed: 11861416]
91. Krupinski J, Vodovotz Y, Li C, Slowik A, Beevers D, Flanders KC, Lip G, Kumar P, Szczudlik A. Inducible nitric oxide production and expression of transforming growth factor-beta1 in serum and csf after cerebral ischaemic stroke in man. *Nitric oxide : biology and chemistry/official journal of the Nitric Oxide Society.* 1998; 2:442–453. [PubMed: 10342487]
92. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: A clinical and scientific review. *Eur J Hum Genet.* 2009; 17:860–871. [PubMed: 19337313]
93. Hara K, Shiga A, Fukutake T, Nozaki H, Miyashita A, Yokoseki A, Kawata H, Koyama A, Arima K, Takahashi T, Ikeda M, Shiota H, Tamura M, Shimoe Y, Hirayama M, Arisato T, Yanagawa S, Tanaka A, Nakano I, Ikeda S, Yoshida Y, Yamamoto T, Ikeuchi T, Kuwano R, Nishizawa M, Tsuji S, Onodera O. Association of htra1 mutations and familial ischemic cerebral small-vessel disease. *N Engl J Med.* 2009; 360:1729–1739. [PubMed: 19387015]
94. Fok-Seang J, DiProspero NA, Meiners S, Muir E, Fawcett JW. Cytokine-induced changes in the ability of astrocytes to support migration of oligodendrocyte precursors and axon growth. *Eur J Neurosci.* 1998; 10:2400–2415. [PubMed: 9749768]
95. Schnadelbach O, Mandl C, Faissner A. Expression of dsd-1-pg in primary neural and glial-derived cell line cultures, upregulation by tgfbeta, and implications for cell-substrate interactions of the glial cell line oli-neu. *Glia.* 1998; 23:99–119. [PubMed: 9600379]
96. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, Eto T. Adrenomedullin: A novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun.* 1993; 192:553–560. [PubMed: 8387282]
97. Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, Eto T. Adrenomedullin: A novel hypotensive peptide isolated from human pheochromocytoma. 1993. *Biochem Biophys Res Commun.* 2012; 425:548–555. [PubMed: 22925672]
98. Kato J, Tsuruda T, Kita T, Kitamura K, Eto T. Adrenomedullin: A protective factor for blood vessels. *Arterioscler Thromb Vasc Biol.* 2005; 25:2480–2487. [PubMed: 16141406]
99. Serrano J, Alonso D, Fernandez AP, Encinas JM, Lopez JC, Castro-Blanco S, Fernandez-Vizarra P, Richart A, Santacana M, Uttenthal LO, Bentura ML, Martinez-Murillo R, Martinez A, Cuttitta F, Rodrigo J. Adrenomedullin in the central nervous system. *Microsc Res Tech.* 2002; 57:76–90. [PubMed: 11921358]
100. Dogan A, Suzuki Y, Koketsu N, Osuka K, Saito K, Takayasu M, Shibuya M, Yoshida J. Intravenous infusion of adrenomedullin and increase in regional cerebral blood flow and

- prevention of ischemic brain injury after middle cerebral artery occlusion in rats. *J Cereb Blood Flow Metab.* 1997; 17:19–25. [PubMed: 8978383]
101. Watanabe K, Takayasu M, Noda A, Hara M, Takagi T, Suzuki Y, Yoshia J. Adrenomedullin reduces ischemic brain injury after transient middle cerebral artery occlusion in rats. *Acta Neurochir (Wien).* 2001; 143:1157–1161. [PubMed: 11731867]
 102. Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin n-terminal 20 peptide (pamp), hypotensive and vasodilating peptides. *Peptides.* 2001; 22:1693–1711. [PubMed: 11754955]
 103. Maki T, Ihara M, Fujita Y, Nambu T, Miyashita K, Yamada M, Washida K, Nishio K, Ito H, Harada H, Yokoi H, Arai H, Itoh H, Nakao K, Takahashi R, Tomimoto H. Angiogenic and vasoprotective effects of adrenomedullin on prevention of cognitive decline after chronic cerebral hypoperfusion in mice. *Stroke.* 2011; 42:1122–1128. [PubMed: 21393586]
 104. Uezono Y, Nakamura E, Ueda Y, Shibuya I, Ueta Y, Yokoo H, Yanagita T, Toyohira Y, Kobayashi H, Yanagihara N, Wada A. Production of camp by adrenomedullin in human oligodendroglial cell line kg1c: Comparison with calcitonin gene-related peptide and amylin. *Brain Res Mol Brain Res.* 2001; 97:59–69. [PubMed: 11744163]
 105. Maki T, Ihara M, Fujita Y, Nambu T, Harada H, Ito H, Nakao K, Tomimoto H, Takahashi R. Angiogenic roles of adrenomedullin through vascular endothelial growth factor induction. *Neuroreport.* 2011; 22:442–447. [PubMed: 21558971]
 106. Schwarz N, Renshaw D, Kapas S, Hinson JP. Adrenomedullin increases the expression of calcitonin-like receptor and receptor activity modifying protein 2 mRNA in human microvascular endothelial cells. *J Endocrinol.* 2006; 190:505–514. [PubMed: 16899583]
 107. Iimuro S, Shindo T, Moriyama N, Amaki T, Niu P, Takeda N, Iwata H, Zhang Y, Ebihara A, Nagai R. Angiogenic effects of adrenomedullin in ischemia and tumor growth. *Circ Res.* 2004; 95:415–423. [PubMed: 15242974]
 108. Ichikawa-Shindo Y, Sakurai T, Kamiyoshi A, Kawate H, Iinuma N, Yoshizawa T, Koyama T, Fukuchi J, Iimuro S, Moriyama N, Kawakami H, Murata T, Kangawa K, Nagai R, Shindo T. The gpcr modulator protein ramp2 is essential for angiogenesis and vascular integrity. *J Clin Invest.* 2008; 118:29–39. [PubMed: 18097473]
 109. Rosenstein JM, Krum JM. New roles for vegf in nervous tissue--beyond blood vessels. *Exp Neurol.* 2004; 187:246–253. [PubMed: 15144851]
 110. Lambrechts D, Carmeliet P. VEGF at the neurovascular interface: Therapeutic implications for motor neuron disease. *Biochim Biophys Acta.* 2006; 1762:1109–1121. [PubMed: 16784838]
 111. Chow J, Ogunshola O, Fan SY, Li Y, Ment LR, Madri JA. Astrocyte-derived vegf mediates survival and tube stabilization of hypoxic brain microvascular endothelial cells in vitro. *Brain Res Dev Brain Res.* 2001; 130:123–132.
 112. Carmeliet P, Stenkebaum E. Vascular and neuronal effects of vegf in the nervous system: Implications for neurological disorders. *Semin Cell Dev Biol.* 2002; 13:39–53. [PubMed: 11969370]
 113. Hayakawa K, Pham LD, Som AT, Lee BJ, Guo S, Lo EH, Arai K. Vascular endothelial growth factor regulates the migration of oligodendrocyte precursor cells. *J Neurosci.* 2011; 31:10666–10670. [PubMed: 21775609]
 114. Hayakawa K, Seo JH, Pham LD, Miyamoto N, Som AT, Guo S, Kim KW, Lo EH, Arai K. Cerebral endothelial derived vascular endothelial growth factor promotes the migration but not the proliferation of oligodendrocyte precursor cells in vitro. *Neurosci Lett.* 2012; 513:42–46. [PubMed: 22342913]
 115. Le Bras B, Barallobre MJ, Homman-Ludiye J, Ny A, Wyns S, Tammela T, Haiko P, Karkkainen MJ, Yuan L, Muriel MP, Chatzopoulou E, Breant C, Zalc B, Carmeliet P, Alitalo K, Eichmann A, Thomas JL. Vegf-c is a trophic factor for neural progenitors in the vertebrate embryonic brain. *Nat Neurosci.* 2006; 9:340–348. [PubMed: 16462734]
 116. Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, Greenberg DA. Vegf-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. *J Clin Invest.* 2003; 111:1843–1851. [PubMed: 12813020]

117. Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, Bruggen N, Chopp M. Vegf enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. *J Clin Invest.* 2000; 106:829–838. [PubMed: 11018070]
118. Dzierko M, Derugin N, Wendland MF, Vexler ZS, Ferriero DM. Delayed vegf treatment enhances angiogenesis and recovery after neonatal focal rodent stroke. *Transl Stroke Res.* 2013; 4:189–200. [PubMed: 23926451]
119. Wang Y, Kilic E, Kilic U, Weber B, Bassetti CL, Marti HH, Hermann DM. Vegf overexpression induces post-ischaemic neuroprotection, but facilitates haemodynamic steal phenomena. *Brain.* 2005; 128:52–63. [PubMed: 15509618]
120. Fagan SC, Hess DC, Hohnadel EJ, Pollock DM, Ergul A. Targets for vascular protection after acute ischemic stroke. *Stroke.* 2004; 35:2220–2225. [PubMed: 15284446]
121. Hansen TM, Moss AJ, Brindle NP. Vascular endothelial growth factor and angiopoietins in neurovascular regeneration and protection following stroke. *Curr Neurovasc Res.* 2008; 5:235–244.
122. Rosell A, Lo EH. Multiphasic roles for matrix metalloproteinases after stroke. *Curr Opin Pharmacol.* 2008; 8:82–89. [PubMed: 18226583]
123. Rosenberg GA, Sullivan N, Esiri MM. White matter damage is associated with matrix metalloproteinases in vascular dementia. *Stroke.* 2001; 32:1162–1168. [PubMed: 11340226]
124. Nakaji K, Ihara M, Takahashi C, Itohara S, Noda M, Takahashi R, Tomimoto H. Matrix metalloproteinase-2 plays a critical role in the pathogenesis of white matter lesions after chronic cerebral hypoperfusion in rodents. *Stroke.* 2006; 37:2816–2823. [PubMed: 17008622]
125. Monet-Lepretre M, Haddad I, Baron-Menguy C, Fouillot-Panchal M, Riani M, Domenga-Denier V, Dussaule C, Cognat E, Vinh J, Joutel A. Abnormal recruitment of extracellular matrix proteins by excess notch3 ecd: A new pathomechanism in cadasil. *Brain.* 2013; 136:1830–1845. [PubMed: 23649698]
126. Morancho A, Rosell A, Garcia-Bonilla L, Montaner J. Metalloproteinase and stroke infarct size: Role for anti-inflammatory treatment? *Ann N Y Acad Sci.* 2010; 1207:123–133. [PubMed: 20955435]
127. Gu Z, Kaul M, Yan B, Kridel SJ, Cui J, Strongin A, Smith JW, Liddington RC, Lipton SA. S-nitrosylation of matrix metalloproteinases: Signaling pathway to neuronal cell death. *Science.* 2002; 297:1186–1190. [PubMed: 12183632]
128. Zhao BQ, Tejima E, Lo EH. Neurovascular proteases in brain injury, hemorrhage and remodeling after stroke. *Stroke.* 2007; 38:748–752. [PubMed: 17261731]
129. Zhao BQ, Wang S, Kim HY, Storrie H, Rosen BR, Mooney DJ, Wang X, Lo EH. Role of matrix metalloproteinases in delayed cortical responses after stroke. *Nat Med.* 2006; 12:441–445. [PubMed: 16565723]
130. Lee SR, Kim HY, Rogowska J, Zhao BQ, Bhide P, Parent JM, Lo EH. Involvement of matrix metalloproteinase in neuroblast cell migration from the subventricular zone after stroke. *J Neurosci.* 2006; 26:3491–3495. [PubMed: 16571756]
131. Larsen PH, Wells JE, Stallcup WB, Opdenakker G, Yong VW. Matrix metalloproteinase-9 facilitates remyelination in part by processing the inhibitory ng2 proteoglycan. *J Neurosci.* 2003; 23:11127–11135. [PubMed: 14657171]
132. Hansmann F, Herder V, Kalkuhl A, Haist V, Zhang N, Schaudien D, Deschl U, Baumgartner W, Ulrich R. Matrix metalloproteinase-12 deficiency ameliorates the clinical course and demyelination in theiler's murine encephalomyelitis. *Acta Neuropathol.* 2012; 124:127–142. [PubMed: 22271152]
133. Yang Y, Jalal FY, Thompson JF, Walker EJ, Candelario-Jalil E, Li L, Reichard RR, Ben C, Sang QX, Cunningham LA, Rosenberg GA. Tissue inhibitor of metalloproteinases-3 mediates the death of immature oligodendrocytes via tnfr-alpha/tace in focal cerebral ischemia in mice. *J Neuroinflammation.* 2011; 8:108. [PubMed: 21871134]
134. Byravan S, Foster LM, Phan T, Verity AN, Campagnoni AT. Murine oligodendroglial cells express nerve growth factor. *Proc Natl Acad Sci U S A.* 1994; 91:8812–8816. [PubMed: 8090729]

135. Wilkins A, Chandran S, Compston A. A role for oligodendrocyte-derived igf-1 in trophic support of cortical neurons. *Glia*. 2001; 36:48–57. [PubMed: 11571783]
136. Gonzalez D, Dees WL, Hiney JK, Ojeda SR, Saneto RP. Expression of beta-nerve growth factor in cultured cells derived from the hypothalamus and cerebral cortex. *Brain Res*. 1990; 511:249–258. [PubMed: 2334846]
137. Raabe TD, Clive DR, Wen D, DeVries GH. Neonatal oligodendrocytes contain and secrete neuregulins in vitro. *J Neurochem*. 1997; 69:1859–1863. [PubMed: 9349528]
138. Deadwyler GD, Pouly S, Antel JP, Devries GH. Neuregulins and erbb receptor expression in adult human oligodendrocytes. *Glia*. 2000; 32:304–312. [PubMed: 11102970]
139. Strelau J, Unsicker K. Gdnf family members and their receptors: Expression and functions in two oligodendroglial cell lines representing distinct stages of oligodendroglial development. *Glia*. 1999; 26:291–301. [PubMed: 10383048]
140. Kim JB, Lim CM, Yu YM, Lee JK. Induction and subcellular localization of high-mobility group box-1 (hmgbl) in the postischemic rat brain. *J Neurosci Res*. 2008; 86:1125–1131. [PubMed: 17975839]

Figure 1. Oligodendrocyte precursor cells (red: PDGF-R-alpha antibody) are often located closely to cerebral endothelial cells (green: CD31). Adult rat brain, corpus callosum region. Scale bar = 10 μ m.

Figure 2. Proposed model for endothelium-oligodendrocyte crosstalk

In the so-called oligovascular niche (a micro-environment between cerebral endothelial cells and oligodendrocyte lineage cells), these cells exchange soluble factors to maintain white matter homeostasis. But after brain injury, the trophic coupling would be disrupted, which lead to white matter dysfunction. In addition, some factors such as VEGF and MMP-9 may actively worsen pathological processes (e.g. BBB breakdown).

Table 1

Table Releasing factors from oligodendrocyte lineage cells

Releasing factor	Cellular type
BDNF	cultured rat oligodendrocytes ⁶⁸
	immortalized oligodendroglial cell line (N19) ¹³⁴
	MBP-positive oligodendrocytes in rat brain ⁶⁹
IGF-1	cultured rat OPCs ¹³⁵
NGF	cultured rat OPCs ¹³⁶
	cultured rat oligodendrocytes ^{68, 136}
	immortalized oligodendroglial cell line (N19) ¹³⁴
	MBP-positive oligodendrocytes in rat brain ⁶⁹
NT-3	cultured rat oligodendrocytes ⁶⁸
	MBP-positive oligodendrocytes in rat brain ⁶⁹
Neuregulin	cultured rat OPCs ¹³⁷
	cultured adult human oligodendrocytes ¹³⁸
GDNF	cultured rat oligodendrocytes ^{50, 139}
	cultured rat OPCs ¹³⁹
	transformed oligodendroglial cell line OLN-93 ¹³⁹
	immortalized oligodendrocyte precursor cell line OLI-neu ¹³⁹
TGF-beta	cultured rat OPCs ⁸³
HMGB-1	oligodendrocyte-like cells in rat brain ¹⁴⁰
AM	human oligodendroglial cell line KG1C ¹⁰⁴
MMP-9	cultured rat OPCs ²⁰
	MOBP-positive oligodendrocytes ²¹