Review Article

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White-matter repair: Interaction between oligodendrocytes and the neurovascular unit

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Abstract:

There are currently no adequate treatments for white-matter injury, which often follows central nervous system maladies and their accompanying neurodegenerative processes. Indeed, the white matter is compromised by the deterioration of the blood–brain barrier and the demyelination of neuronal axons. Key repairs to the white matter are mediated by oligodendrocyte lineage cells after damaging events. Oligodendrocytes are supported by other cells in the neurovascular unit and these cells collaborate in processes such as angiogenesis, neurogenesis, and oligodendrogenesis. Understanding the various interactions between these cells and oligodendrocytes will be imperative for developing reparative therapies for impaired white matter. This minireview will discuss how oligodendrocytes and oligodendrocyte lineage cells mend damage to the white matter and restore brain function ensuing neural injury.

Keywords:

Myelination, neurovascular unit, oligodendrocyte, oligodendrocyte precursor cell, white-matter repair

Introduction

To better comprehend stroke pathology, the notion of the neurovascular unit (NVU) was created which encompasses how various cell types communicate to mediate regular brain processes.[1,2] The idea of the NVU has been connected to central nervous system (CNS) diseases and the corresponding injury and recovery phases, and how glial cells play a role in neurodegeneration, advancing the initial concept of the NVU as the interplay between gray matter neurons in stroke's acute stage.

With their ability to generate myelin sheaths composed of hydrophobic membranes, oligodendrocytes in the white matter facilitate the saltatory conduction that propagates nerve signals and is necessary for neuronal communication. The initial construction of the nervous system and healing white matter postinjury especially require proper oligodendrocyte myelination. Oligodendrocytes and their lineage cells are implicated in ameliorating white-matter damage, though the precise mechanisms are uncertain. Here, we discuss how oligodendrocytes function in neurogenesis, angiogenesis, and oligodendrogenesis, and interact with other NVU-associated cells.

Neurons and Oligodendrocytes

By devastating cortical neurons and stymieing action potential conduction in the axons of connecting neurons, CNS injuries including trauma, neurodegenerative diseases, and stroke may impair neural networks. Inhibiting signal transduction can exacerbate axon damage by increasing white-matter levels of calcium ions and neurotransmitters, which demyelinates the surrounding neurons, kills oligodendrocytes, and incapacitates

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axons.[3,4] Oligodendrocytes are centralized near neuronal axons to support them through various means such as by supplying glucose, as evidenced by electromyography (EMG) studies involving the corpus callosum, which may implicate the oligodendrocytes' ability to preserve neurons during ischemic stroke and other situations with minimal glucose.[5] Neurons can also aid oligodendrocytes such as by secreting growth factors such as neuregulin, which mitigates injury-induced damage to the CNS[6,7] and boosts oligodendrocyte myelin production,[8] and releasing neurotransmitters that enable oligodendrocyte lineage cells to proliferate, migrate, and differentiate.[9-13] Subjecting mice to ischemic stress reduces oligodendrocytes and myelin, demonstrating that neural injuries interfere with the mutual benefits between neurons and oligodendrocytes.[14] Additional interactions between the two cell types during disease states are further implicated, as damage to the white matter is abated by preemptively adding a GluN2C/D-negative allosteric modulator incorporating N-methyl-D-aspartate (NMDA) glutamate receptors.

Damage to neuronal axons and myelin sheaths triggers the proliferation, migration, and differentiation of oligodendrocyte precursor cells (OPCs), which repair injuries to myelinated axons with the cooperation of other cells. Endogenous myelin-associated inhibitors (MAIs), which originate from myelin and are overexpressed by oligodendrocyte lineage cells and astroglial cells during CNS damage, include chondroitin sulfate proteoglycans, oligodendrocyte myelin glycoprotein, Nogo-A, and myelin-associated glycolin, and counter the regrowth of axons critical to the post white-matter injury restoration of myelinated axons, neural plasticity, and neuronal function.[15,16] By binding to MAI receptor complexes on neuronal axons and activating inhibitory signaling avenues including the Rho/Rho-associated coiled-coil containing protein kinase (Rho/ROCK) pathway, MAIs preclude axons from expanding. Through alternate downstream pathways, the neuronal receptor paired Ig-like receptor B, which has common ligands with Nogo-66 receptor-1 (NgR1), can prevent the lengthening of axons.[17-19] Axonal growth is also blocked by a combination of the Rho/ROCK pathway and interactions between the sphingosine-1-phosphate receptor 2 in neurons and a specific Nogo-A region.[20] By helping NgR1 mature and utilizing the Rho/ROCK pathway, the nociception receptor ORL1 also hampers axon extension.[21] Delivering NgR1 decoys systemically in older mice improves motor function and white-matter restoration after stroke and increases the quantity of mature OPCs, illustrating that impeding MAI-related downstream signaling avenues can ameliorate white-matter damage.[22] Healing white-matter injury via increasing oligodendrocytes and restoring neuronal axons will conceivably benefit from regulating MAI-related signaling, given the involvement of MAIs in promoting CNS stability.

Neuronal activity-induced neural plasticity demonstrates the interplay between neurons and oligodendrocytes necessary to mend white-matter damage. Investigations incorporating human magnetic resonance imaging (MRI) have mainly observed this plasticity thus far, initially only exploring gray matter until advances in MRI technology featuring structural MRI analysis and increased spatiotemporal resolution enabled effective evaluation of white-matter plasticity in relation to CNS activity. Rearrangement of neural networks to link different areas of the CNS pertinent to various tasks is possible based on functional MRIs demonstrating a connection between organizing fiber tracts and practicing a musical instrument.[23] Indeed, EMG and MRI data convey that even brief stimuli can cause alterations in white-matter structures.[24] Thus, white-matter plasticity can potentially be attributed to modifying present myelin or the adaptability of recently synthesized myelin, and neuronal stimuli can augment this plasticity and organize neural connections.[25] In fact, learning motor-based tasks requires the generation of new oligodendrocytes in white matter, as revealed by animal studies utilizing MRI and histological analyses.[26,27] Activating S1 pyramidal neurons in the corpus callosum of mice increases axon myelination and OPC count, signifying that myelination following neuronal stimulation is a specific event in which the activation of both white-matter axons and gray-matter neurons contributes to plasticity and myelin formation in neural cells in white matter.[28] Repairing white-matter injury will necessitate a precise understanding of this relationship between myelin and neurons.

The Cerebrovascular System and Oligodendrocytes

The blood–brain barrier (BBB) mediates the transfer of molecules between the cerebrospinal fluid, blood, and the brain, comprises several NVU components, and is part of the cerebral vascular system, which regulates homeostasis of the CNS in addition to blood circulation. Neurodegenerative diseases compromise tight junctions and consequently, deteriorate the BBB,[29-32] so comprehending how this affects the cerebral vascular system and its related processes will be imperative.

With the localization of oligodendrocytes around cerebral endothelial cells, it is conceivable that oligodendrocyte lineage cells also monitor the BBB and endothelial cell processes, in addition to pericytes and astrocytes.[33-36] BBB impairment appears to follow diminished communication between endothelial cells and oligodendrocytes, as exhibited in mice with either oligodendrocytes

hyperactivated by HRas or oligodendrocytes lacking neurofibromatosis type 1.[37] OPCs produce transforming growth factor-β1, which utilizes the MEK/ERK pathway and increases tight junction proteins, thus bolstering the BBB.[36] Angiogenesis also implicates the roles of OPCs, as the formation of blood vessels during early development requires endothelial cell–OPC communication, and OPCs under low oxygen conditions produce Wnt7a and Wnt7b which facilitate endothelial cell proliferation *in vitro* and angiogenesis *in vivo*.[38] Nogo signaling pathways in the brains of postnatal mice, in which blood vessels are still developing, exhibit how oligodendrocytes can also inhibit angiogenesis through negative regulation.[39,40] Blood vessels increase when Nogo-A is reduced via gene knockout, inhibition by an antibody, or knockdown induced by a virus. Moreover, adding the antibody to Nogo-A nullifies Nogo-A-mediated obstruction of brain microvascular endothelial cell migration. Matrix metalloproteinase-9 (MMP-9) released by oligodendrocytes following damage to white matter alter vascular structures, indicating that these oligodendrocyte-induced effects on angiogenesis may also apply to injured white matter.[35] In contrast, conditions of inflammation and oxidative stress trigger OPCs to produce exceedingly large quantities of MMP-9, disrupting the BBB.[41] For white-matter restoration, it will be important to elucidate which specific pathways and mediators control which OPC effects on the cerebrovascular system.

While oligodendrocytes can regulate components of the cerebrovascular system such as the BBB, the cerebrovascular system can also control aspects of oligodendrocytes, as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) manufactured by cerebral endothelial cells enable OPCs to survive and increase in number.[42] OPCs migrate without proliferating when in the presence of vascular endothelial growth factor A (VEGF-A).[43] Moreover, endothelial cell-derived extracellular vesicles are speculated to carry FGF, BDNF, and VEGF-A to OPCs.[44] Additionally, endothelial cells modulate the centralization of oligodendrocyte lineage cells via stromal cell-derived factor 1 (SDF-1) stimulation of the Wnt-chemokine receptor 4.[45] Endothelial progenitor cells (EPCs) modified with the SDF-1 gene enhance remyelination and proliferation of OPCs,[46] in addition to elevating the amount of blood vessels.[47] Secretomes from EPCs may also treat white-matter afflictions, helping OPCs mature and enabling both endothelial cells and OPCs to proliferate in *in vivo* and *in vitro* settings.[48]

As mediators of the BBB, cerebral blood flow, and other aspects of the cerebrovascular system, the mural cells known as pericytes are found within the basal membrane of blood vessel endothelial cells and promote functional white-matter tissue.[49] The localization of OPCs and pericytes in the cerebral white matter's peri-vascular area and close proximity to each other indicate that they likely swap soluble factors to communicate,[50] but the exact process in which they interact is undetermined. Moreover, pericytes release growth factors such as BMP4 and TGFβ-1 which regenerate oligodendrocytes[51] and help OPCs migrate during the initial formation of the cerebral cortex,[52] respectively. OPC maturation to oligodendrocytes is also facilitated by pericyte-induced growth factors, whose generation is mediated by protein A-kinase anchor protein.[53] Following injury to white matter, interplay in the peri-vascular region between pericytes, oligodendrocyte lineage cells, and other NVU-related cells leads to the creation of new blood vessels and oligodendrocytes, which implies that future therapies for treating white-matter damage should bolster the beneficial interactions between these cells.

Glial Cells and Oligodendrocytes

Glial cell types include oligodendrocyte lineage cells, microglia, and astrocytes, and the latter two promote the proliferation and differentiation of OPCs via noncell autonomous means, aside from regulating other brain processes.

Given their close distance to oligodendrocytes, astrocytes can attach to these cells via gap junctions and utilize Cx43 hemichannels to transfer small molecules such as ATP.[9,54-56] In an ischemic environment, glutamate transporters in astrocytes expel glutamate, which prevents OPCs from differentiating[57] by activating oligodendrocyte lineage cells' NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors.[58-60] Furthermore, OPC differentiation can be facilitated by precluding the release of glutamate by blocking the Cx43 hemichannel.[61] Cx43 may be key to ameliorating white-matter damage, as its modulation may enable the remyelination of damaged axons and the generation of new oligodendrocytes. Aside from detrimental factors, astrocytes also release beneficial growth factors after nervous tissue damage that promote regenerative processes. For instance, the quantity of oligodendrocytes in white-matter increase upon astrocyte secretion of BDNF in a cerebral hypoperfusion mouse model.[33] Additionally, astrocytes derived from induced pluripotent stem cells assist with OPC maturation and secrete tropic factors that boost oligodendrogenesis.[62]

During diseased states, such as those featuring reduced oligodendrocytes and myelination, microglia may modulate oligodendrocytes and promote remyelination by eliminating apoptotic cells and defective myelin. Microglial cells then convert to the M2-anti-inflammatory state (M2) from their M1-pro-inflammatory state (M1),

during the remyelination process.[63] This M2 microglia phenotype augments the differentiation of oligodendrocytes in both *in vivo* and *in vitro* situations[63] and shifting between the two phenotypes may increase oligodendrocytes poststroke. OPC proliferation and mature oligodendrocyte count rises upon administration of the peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, in stroke-afflicted mice.[64] Rosiglitazone increases M2 microglia and decreases M1 microglia, which enables OPCs to differentiate.[64] Following demyelination in axons, activated microglial cells can localize at the demyelinated region and utilize neural stem and progenitor cells to produce additional OPCs from the corpus callosum's subventricular zone.[65] Of note, OPC generation is diminished when microglial activation is hindered and OPCs are killed when M1 microglia utilize TLR4 signaling pathways.[66] Thus, healing white-matter injury and initiating remyelination may benefit from employing the conversion between microglial phenotypes.

Conclusion

The white matter is characterized by myelin sheaths, a critical component produced by oligodendrocytes that facilitate the efficient transmission of electrical signals and enable communication between gray-matter neurons throughout various areas. Oligodendrocyte quantities rely on OPCs, which possess the ability to divide and generate more oligodendrocytes, unlike mature oligodendrocytes. However, cells of the oligodendrocyte lineage rely on other cells in the NVU, which assist in regenerating oligodendrocytes following damage to white matter and perform other tasks to help oligodendrocytes. In turn, oligodendrocytes aid other NVU cells in preserving healthy white matter. Angiogenesis and neurogenesis may also be useful for treating white-matter injury, given that oligodendrogenesis may not be sufficient to fully repair damage. Further knowledge regarding cooperative events between various cells during angiogenesis, oligodendrogenesis, and neurogenesis will be critical for developing reparative white-matter therapies. Moreover, as stem cell transplants induce endogenous brain repair via various regenerative pathways,[67] they may complement other methods for white-matter recovery. While oligodendrocytes protect white matter in collaboration with other NVU cells, their exact roles and the mechanisms underlying oligodendrogenesis post white-matter injury are still uncertain, and can be explored in future investigations.

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Conflicts of interest

There are no conflicts of interest.

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