INTRODUCTION

Over the past several decades, study of central nervous system (CNS) pathologies has focused on intra-neuronal mechanisms. In recent years, however, this neuron-based model has gradually shifted to a more integrated paradigm that emphasizes cell–cell interactions. The concept of the "neurovascular unit" emphasizes the importance of multiple brain cell types in many CNS diseases (Fig. 1; the reader is encouraged to seek more detailed reviews on this broad topic). Briefly, this neurovascular paradigm is underscored by dynamic interactions between cerebral endothelial cells, astrocytes, neurons, and the extracellular matrix. Perhaps, the role of the cerebral endothelium is especially important. Traditionally, cerebral endothelial cells have been thought as inert pipes for blood flow to the brain. But, recent findings suggest that cerebral endothelium may be an endocrine organ embedded within the brain itself. Endothelial-derived growth factors may nourish neighboring cells. Although data are strongest in terms of supporting endothelial–neuronal interactions, it is likely that similar interactions occur in white matter as well. In this mini-review, we summarize recent advances in the dissection of cell–cell interactions in white matter. We examine two key concepts. First, trophic interactions between vessels and oligodendrocytes (OLGs) and oligodendrocyte precursor cells (OPCs) play critical roles in white matter homeostasis. Second, cell–cell trophic coupling is disturbed under diseased conditions that incur oxidative stress. White matter pathophysiology is very important in stroke. A deeper understanding of the mechanisms of oligovascular signaling in normal and pathologic conditions may lead us to new therapeutic targets for stroke and other neurodegenerative diseases.

Key words  oligovascular signaling; white matter injury; stroke; oligovascular niche; oligodendrocyte; neurovascular unit

Oligovascular Signaling in White Matter Stroke

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Stroke is one of the leading causes of death and disability in developed countries. Since protecting neurons alone is not sufficient for stroke therapy, research has shifted to the rescue of multiple cell types in the brain. In particular, attention has focused on the study of how cerebral blood vessels and brain cells communicate with each other. Recent findings suggest that cerebral endothelial cells may secrete trophic factors that nourish neighboring cells. Although data are strongest in terms of supporting endothelial–neuronal interactions, it is likely that similar interactions occur in white matter as well. In this mini-review, we summarize recent advances in the dissection of cell–cell interactions in white matter. We examine two key concepts. First, trophic interactions between vessels and oligodendrocytes (OLGs) and oligodendrocyte precursor cells (OPCs) play critical roles in white matter homeostasis. Second, cell–cell trophic coupling is disturbed under diseased conditions that incur oxidative stress. White matter pathophysiology is very important in stroke. A deeper understanding of the mechanisms of oligovascular signaling in normal and pathologic conditions may lead us to new therapeutic targets for stroke and other neurodegenerative diseases.

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Stroke is the third leading cause of death and a leading cause of adult disability in developed countries. Under stroke conditions, brain function is perturbed due to cerebral ischemia (lack of blood supply to the brain) caused by thrombosis/embolism or hemorrhage. In central areas of ischemic regions, blood flow deficits are severe and brain cells die rapidly. In peripheral areas (the so-called penumbra), blood flow deficits are relatively mild, so that therapeutic salvage is theoretically possible. Thus far, for acute stroke therapy, only thrombolytic therapy with tissue-plasminogen activator has been approved by the FDA to be effective in targeting the salvageable ischemic penumbra. Although many advances have been made in terms of the basic molecular mechanisms underlying neuronal death, clinically effective neuroprotective drugs in stroke have not yet been discovered. There are at least two potential issues worth examining further. One is that, as described above, a singular focus on saving neurons alone might not be sufficient. Perhaps seeking a broader “neurovascular protection” is required? As shown in Fig. 1, many parallel deleterious events are activated under stroke conditions, resulting in neurovascular damage. A second issue is that most of our research to date is only focused on gray matter. But without considering the oligodendrocytes (OLGs) and their precursor cells (oligodendrocyte precursor cells; OPCs) in white matter, we may not be able to truly save the brain.

In this mini-review, we will briefly explore current knowledge on trophic coupling in white matter under normal and stroke conditions. First, the basic steps involved in OLG maturation will be introduced. OLG is one of the major cell types in the CNS white matter, and OLG differentiation/maturation in adult brain is an important event for white matter maintenance and repair. Next, we will overview the phenomena of white matter damage in stroke. Under ischemic conditions, several deleterious signal cascades are activated and OLGs eventually die. On the other hand, in the penumbra, the number of OPCs may even increase as the brain attempts to repair itself. Finally, we will survey recent data to support the idea that cell–cell trophic coupling in white matter is critical for maintaining white matter homeostasis. We will mainly discuss the interaction between cerebral endothelium and OLG/OPC (i.e., oligovascular signaling). Under stroke conditions, oligovascular coupling is interrupted, and this may contribute to white matter injury. Taken together, understanding the mechanisms of oligovascular signaling in stroke may lead us to new approaches for stroke therapy.

1. OLIGODENDROCYTE LINEAGE AND GROWTH FACTORS

In CNS white matter, oligodendrocytes (OLGs) form myelin sheaths that encircle axonal bundles. OLGs differentiate from their precursor cells (oligodendrocyte precursor cells; OPCs). The maturation of OPCs into mature OLGs occurs in a multiple steps defined by the expression of specific cell-surface receptors. Overall, there are four stages in this maturation process; oligodendrocyte-type 2 astrocyte (O-2A) cells, pro-OLGs, immature OLGs, and mature OLGs (Fig. 2). During this complex process of OPC/OLG maturation, multiple growth factors are likely to contribute to proliferation, differentiation, and cytoprotection. Basic fibroblast growth factor (bFGF, also know FGF-2) and platelet-derived growth factor (PDGF) are the most documented growth factors known to promote the proliferation of O-2A cells. bFGF has also been shown to upregulate PDGF-receptor expression in O-2A cells/pro-OLGs, and to block the maturation step from pro-OLGs to immature OLGs. Interestingly, pro-OLGs in vitro undergo a transient phenotypic reversion to the less mature stage (O-2A cells) in response to PDGF but not bFGF. Insulin-like growth factor 1 (IGF-1) is also a well examined OPC proliferation and OLG myelination factor. Moreover, it has shown that IGF-1 also protects cultured OLGs and their precursor cells from apoptosis induced by tumor necrosis factor (TNF)-alpha, glutamate, and growth factor deprivation. In addition, other growth factors such as neuregulin, ciliary neurotrophic factor (CNTF), brain-derived growth factor (BDNF), and nerve growth factor may also be involved in the regulation of OLG development/survival. Altogether, a complex network of feedback and interplay between different growth factor may be quite important in the promotion of this OPC/OLG maturation process. The reader is encouraged to seek more detailed reviews describing these various mechanisms.

If growth factors mediate OPC/OLG survival and maturation during development, it may be reasonable to hypothesize that analogous cell–cell interactions help maintain white matter function even in adult brain. Without support from neighboring cell, OLGs and OPCs may not survive, resulting in white matter dysfunction. Before discussing the trophic cou-
pling between OLG/OPC and other brain cells, we will briefly overview key events of white matter injury under stroke conditions of ischemic stress.

2. WHITE MATTER DAMAGE IN STROKE

Gray matter and white matter are the major two components of the CNS. The ratio between white matter and gray matter in human neocortex is approximately 1. But this ratio is much smaller in rodent neocortex, where white matter only comprises 10—15% of total volume.37 White matter primarily consists of axonal bundles ensheathed with myelin. Myelin is synthesized by OLGs that tend to be arranged in rows parallel to axonal tracts. Just before and after birth, OPCs multiply rapidly and mature into OLGs. The OLGs then develop processes that form the myelin sheaths. Although this standard model emphasizes the central role of OLGs, recent data now suggest that even in adult brain, OPCs may also be involved in white matter maintenance. Subpopulations of OPCs persist throughout the adult brain.25—31 These OPCs are thought to contribute to myelin maintenance and repair by generating new OLGs. Therefore, under pathologic conditions such as stroke, OLG/OPC dysfunction and death may contribute to white matter damage.

White matter is especially susceptible to stroke.32—34 Because white matter blood flow is lower than in gray matter and there is little collateral blood supply in deep white matter, white matter ischemia is typically severe with rapid cell swelling and tissue edema.35 Minor white matter strokes often cause extensive neurological deficits by interrupting the passage of large axonal bundles such as those within the internal capsule.21 Axons contain abundant mitochondria, which is an organelle for a source of reactive oxygen species. In fact, free radical scavenging significantly reduces white matter injury in rodent stroke models.35—38 Furthermore, white matter ischemia activates several kinds of proteases, which weaken the structural integrity of axons and myelin sheath. Neurofilaments are major structural components of white matter axons, and calpains have been demonstrated to be involved in neurofilament degradation under ischemic conditions.39 Matrix metalloproteinases (MMPs) can directly attack myelin components such as myelin-basic protein.40 Ischemia-induced degradation of myelin-basic protein is reduced in MMP-9 knockout mice.41 Importantly, chronic white matter lesions are associated with upregulation of MMPs in autopsy-sampled brains from patients with vascular dementia.42

Like neurons in gray matter, axons and OLGs are vulnerable to damage by excitatory amino acids, oxidative stress, trophic factor deprivation, and activation of apoptotic pathways.43—45 Because a single OLG myelinates multiple axons, damage to only one OLG can cause dysfunction in many different neuronal pathways (Fig. 3). Therefore, protecting OLGs is a reasonable therapeutic approach for white matter stroke treatment. Thus far, using in vitro and in vivo experimental systems, several pathways have been demonstrated in OLG death/damage under stroke conditions.43,45 (Fig. 3). The mechanisms of glutamate-induced excitatory/oxidative stress are well examined. After cerebral ischemia, loss of energy stores induces ionic imbalances, which then promote reversal of the Na⁺-dependent glutamate transporter GLT1, resulting in extracellular glutamate accumulation. In fact, GLT1 block-
ers threo-beta-benzylxy aspartate (TBOA) and dihydroykinic acid (DHKA) are both confirmed to protect white matter against ischemic stress in mouse optic nerves.46,47 OLGs express AMPA/kainate receptors, and overactivation of these receptors can also mediate Na⁺ and Ca²⁺ influx leading to OLG death.48,49 Furthermore, the cystine-glutamate exchange antipporter in OLGs may also contribute to glutamate-induced OLG death. Excessive glutamate blocks the antiporter, which in turn induces glutathione depletion that augments oxidative stress.50 Recently, it has been shown that OLGs also express N-methyl-D-aspartic acid (NMDA) receptors.51—53 NMDA receptors of OLGs are activated by glutamate in white matter ischemia,51 and activation of these receptors can also lead to rise of intracellular Ca²⁺ concentration.53 However, the involvement of NMDA receptor in glutamate-induced OLG death is still controversial,47 and therefore further studies are warranted to examine whether the NMDA receptor in OLGs can be a therapeutic target for white matter damage in stroke patients. Since a number of pathways is involved in OLG damage/death under pathologic conditions, the reader is encouraged to seek more detailed review regarding these complex mechanisms.43—45,54

In contrast to axonal response, the role of OPCs under stroke conditions in adult brain is mostly unknown. OPCs in culture are susceptible to oxidative stress such as oxygen-glucose deprivation.55,56 Hence it is possible that OPCs are also damaged during acute stroke in vivo. During stroke recovery, OPCs might contribute to myelin repair by generating new OLGs as a source of remyelination and remodeling.57—60 Furthermore, a recent study suggested that OPCs may also serve as a precursor pool for cortical projection neurons in adult brain.51 Therefore, it is reasonable to think that OPCs play critical roles in the recovery phase in stroke. In fact, experimental evidence is now starting to show that myelin repair can occur in peri-infarct areas in rodent stroke models, as judged by upregulated gene expression of proteolipid protein (PLP) and myelin basic protein (MBP), which are the major protein components of CNS myelin.62,63 Furthermore, using a rat MCAO model, elevations in the number of OPCs and a gradual recovery of OLGs can be found in the peri-infarct area after stroke.64 Taken together, both OLGs and OPCs might comprise interesting targets of the treatment for white matter injury.

3. CELL–CELL INTERACTION IN WHITE MATTER AND NEW CONCEPT OF OLIGOVASCULAR NICHE

Whereas protecting OPCs and OLGs are clearly important per se, it is likely that cell–cell interactions in the white matter may also be extremely important under normal and diseased conditions. In this section, we will briefly examine the recently proposed concept of “oligovascular niche”.

The main cell types comprising white matter are the neuronal axon, OLG (myelin), astrocyte, and endothelial cell (Fig. 3). As in gray matter, there is close anatomical and perhaps functional contact between all these cells. Astrocytes are in close apposition to OLGs within the white matter,65 and couple with OLGs through gap junctions to maintain their functions.66 Furthermore, using astrocyte-OLG coculture system, astrocytes have been shown to promote OLG survival through an alpha6 integrin-laminin-dependent
mechanism. Astrocyte-derived soluble factors are also implied to be supportive to both OLGs and OPCs. Conditioned media from astrocyte cultures have been demonstrated to support OLGs/OPCs survival. In turn, recent findings suggest that OLGs not only myelinate axons but also maintain their functional integrity and survival thorough OLG-specific proteins and/or trophic factor release. Thus far, PLP (and its smaller isoform DM20) and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) are well documented myelin-associated proteins expressed in OLGs to affect axonal functions. Mice with mutations for those genes revealed that axonal support by OLGs is independent of myelin assembly. Myelinating OLGs also provide trophic support for axons by secreting soluble factors. To date, BDNF, NT3, NGF, and PDGF are reported as OLG-axon signaling mediators. The reader is encouraged to seek more detailed reviews describing the events in white matter ischemia.

Fig. 3. Schematic of the Adult White Matter under Stroke Conditions

The main components of white matter are the neuronal axon, oligodendrocyte (myelin), astrocyte, and endothelium. Similar to gray matter, cell–cell interactions are important to maintain white matter function. Under ischemic conditions, several deleterious factors/cascades are activated. As in the neurovascular unit, several events occur due to ischemic stress. Glutamate efflux, oxidative stress, and proteinase activation eventually induce cell death. Importantly, deleterious factors secreted by one cell type may affect another cell type. For example, cerebral endothelial cells secrete MMPs after ischemic injury. These MMPs, in turn, damage the myelin sheath produced by oligodendrocytes. Moreover, under ischemic conditions, trophic support from astrocyte/endothelium to myelinated axons is disturbed by oxidative stress. The reader is encouraged to seek more detailed reviews describing the events in white matter ischemia.

Fig. 4. Schematic of the Oligovascular Signaling in Adult White Matter

In the oligovascular niche, oligogenesis and angiogenesis might occur to maintain white matter homeostasis. Oligodendrocyte precursor cells (OPCs) are thought to contribute to myelin maintenance and repair by generating new mature oligodendrocytes (OLGs). In addition, trophic coupling may also exist between cerebral endothelial cells and mature OLGs. Under diseased conditions such as stroke, multiple deleterious factors directly attack OLGs and OPCs, which are vulnerable to oxidative stress. Moreover, oxidative stress can disturb the trophic coupling between cerebral endothelial cells and OLGs/OPCs, resulting in further white matter damage.
conditions, cerebral endothelium secretes trophic factors to support neighboring neurons.1,8,9 This trophic coupling creates a neurovascular niche, wherein cell–cell signaling between cerebral endothelium and neuronal precursor cells help mediate and sustain pockets of ongoing neurogenesis and angiogenesis.4,5,80—83 Therefore, endothelial dysfunction results in not only lack of blood supply to the brain but also loss of trophic coupling in many aspects. Although the concept of the neurovascular unit is usually used to discuss phenomena in the gray matter,2—4,6 it obviously should apply for white matter physiology and pathology as well.

To date, cell–cell interactions between cerebral endothelium and OLG/OPC are not well understood. However, a recent study suggests the existence of an “oligovascular niche”, whereby cerebral endothelial cells support the survival and proliferation of OPCs.55 Cross-talk between the vascular and neuronal compartments in the neurovascular niche is mediated by an exchange of soluble signals, and this phenomenon is partly mediated by the ability of cerebral endothelium to secrete a rich repertoire of trophic factors.8,84,85 Similarly, endothelial-derived growth factors such as BDNF and FGF-2 promote OPC proliferation.55 Importantly, these trophic coupling might be interrupted under pathological conditions. Non-lethal oxidative stress reduces the expression of several growth factors in cultured cerebral endothelial cells.8,55 Also, in a mouse stroke model, BDNF and NGF expression in core infarct areas are significantly decreased.86 Moreover, although healthy endothelium can support OPCs even under ischemic conditions, sick endothelium no longer support OPCs.55 In stroke patients and rodent stroke models, endothelial dysfunction is often observed by cerebral small-vessel disease in white matter ischemia.87—89 Therefore, disruption of endothelium-OPC/OLG coupling should be one of the major causes for the pathogenesis and progression of white matter lesion in CNS diseases including stroke. Thus far, there is no direct evidence showing OPCs support endothelial functions including angiogenesis. Also, endothelium-OLG trophic coupling has not been experimentally proved yet. However, it is well known that both cerebral endothelium and OLG/OPC secrete many kinds of growth factors.8,55,90 Therefore, it is possible that there is two-way trophic coupling between these cells in white matter (Fig. 4).

Compared to the mechanisms of cell–cell interaction in gray matter, trophic coupling in white matter remains relatively understudied and poorly understood. For the neurovascular niche, matrix and trophic interactions between endothelial cells and neurons sustain neurogenesis and angiogenesis.83—85 and may also protect neurons against oxidative and metabolic insults.8,9 Analogous interactions within a widely distributed oligovascular niche may provide a similar mechanism for sustaining white matter renewal and integrity. Further studies are warranted to dissect how these mechanisms function in normal brain, and how disruptions in oligovascular signaling may underlie white matter disease and neurodegeneration. Finally, to develop new stroke therapy, one may need to define these mechanisms in aged brains. Aging is the major risk factor for stroke, and it has recently shown that ischemic injury to white matter is an age-dependent process.47,51 How these mechanisms of oligovascular signaling are affected by aging and metabolic disease should be extremely important.

4. CONCLUSIONS

The development of stroke therapies is very challenging. Over the past many decades, a large number of neuroprotection trials have unfortunately failed. Researchers are now changing their research direction from single neuron protection to overall neurovascular protection. In addition to this trend, however, we might also need to take white matter protection into account because white matter damage is a clinically important part of stroke. Needless to say, singular OLG protection may also not be enough. Cell–cell interactions within an oligovascular niche may be crucial for white matter function and dysfunction. In this mini-review, we have surveyed key events in white matter damage in stroke along with the possible role of oligovascular signaling. We have mostly discussed cerebral endothelial cells and OLGS/OPCs in white matter. But clearly, the integrity of interactions within all brain cell types including axonal compartments and astrocytes will also be important in white matter. A systematic dissection of cell–cell trophic signaling in both gray and white matter may provide more novel opportunities for discovering treatments for stroke, and perhaps even other CNS disorders.

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