Commentary

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Wiring and plumbing: Oligodendrocyte precursors and angiogenesis in the oligovascular niche

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Abstract

For efficient stroke recovery, the entire neurovascular unit must be repaired. A recent study underscores this concept by highlighting the importance of cellular crosstalk for white mater remodeling. In developing brains and in brains injured by hypoxia, interactions between oligodendrocyte precursors and endothelium play an essential role for physiological and compensatory angiogenesis. Further studies are warranted to build on these emerging findings in the oligovascular niche in order to identify novel therapeutic targets for stroke and other CNS diseases.

Keywords

Angiogenesis, cell-cell interaction, neurovascular unit, oligodendrocyte precursor cell, oligovascular niche, white matter

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Text

In 2001, the concept of the neurovascular unit was proposed at an NINDS workshop to encourage a broader approach in stroke research. Stroke is no longer a purely "neuron death" disease. Instead, mechanisms in all neuronal, glial and vascular cell types must be assessed in order to understand the pathological pathways of cerebrovascular injury.[1] Furthermore, cell-cell signaling in the entire neurovascular unit is also essential for stroke recovery, comprising multifactorial pathways of neuroplasticity, glial reactions and compensatory angiogenesis.[2,3]

In white matter, stroke recovery should be based on re-establishing the "wiring and plumbing". Axons must be properly remyelinated to renormalize neuronal network connectivity, and blood vessels must be repaired to regain the metabolic supply of oxygen and glucose. In this regard, functional interactions between endothelium and peri-vascular cells may be essential. It has been proposed that besides astrocytes and pericytes, a subset of oligodendrocyte precursor cells (OPCs) is also closely located adjacent to blood microvessels, and in this microenvironment or so-called oligovascular niche, cerebral endothelial cells and OPCs communicate closely in order to maintain the blood-brain barrier (BBB) and sustain OPC homeostasis.[4,5] A recent paper by Chavali et al has now expanded upon these findings to show that cell-cell signaling between OPCs and endothelium play a critical role in angiogenesis as well.[6]

In the study, the authors first showed that OPCs contact sprouting endothelial tip cells in neonatal white matter in mouse, ferret, and human brains. Then, using the cre-flox system, they generated two transgenic mouse lines; one with decreased OPC density (*Olig2*-cre:*Sox10*-lox-GFP-STOP-lox-DTA) and the other with increased OPC density (*Olig2*-cre:*Braf*-V600E-flox/-). In these mouse models, increased or decreased OPC density induced matching changes in white matter vascular investment during brain development. *Wnt* signaling was involved because a conditional knockout of *Wnt* in OPCs resulted in diminished white matter sprouting, angiogenesis and vascular

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growth in neonatal mice. Importantly, the authors showed that these pathways also participate in white matter repair after brain injury. Conditional knockout of *Wnt7a/7b* in OPCs significantly dampened compensatory angiogenesis in cerebral white matter of neonatal mice subjected to hypoxia. These exciting findings are consistent with another recent study showing that aberrant Wnt signaling in OPCs causes dysfunctional vascular detachment of OPCs that then leads to disruption of endothelial tight junction integrity.[7]

OPCs are active during developmental stages, but some OPC pools remain in adult brains and these cells underlie white matter homeostasis.[8] Because oligodendrocytes are required for myelination and because oligodendrocytes cannot proliferate, OPCs play an indispensable role in controlling the oligodendrocyte population for myelin renewal. In damaged white matter, OPCs should be essential for remyelination and axonal recovery. The paper by Chavali et al demonstrate that OPCs may also contribute to angiogenesis and vascular repair. Promoting angiogenesis is an important part of pro-recovery therapies in stroke.[9,10] It is also increasingly recognized that white matter repair is an important target for vascular dementia.[11] Therefore, the findings from Chavali et al may provide new mechanistic opportunities to therapeutically manipulate both "wiring and plumbing" for stroke and cerebrovascular disease.

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