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Previews

Pericytes: Unsung heroes in myelin repair after neonatal brain hypoxia

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Preterm infants can face lasting neurodevelopmental challenges due to hypoxia-induced injury of the cerebral white matter. In this issue of *Neuron*, Ren et al.[1] identify microvascular pericytes as unexpected targets for growth hormone signaling, which enhances angiogenesis and remyelination after hypoxic injury in the developing mouse brain.

Cerebral white matter is very energy efficient during signal transduction in the adult brain. However, there is a considerable energy investment in the creation of myelinated axons during development. During their differentiation into mature oligodendrocytes, oligodendrocyte precursor cells (OPCs) undergo an enormous expansion of membrane area to create the myelin sheaths that enwrap axons. This process must develop alongside a vascular network to support the surge in energy demand. Remarkably, OPCs can sense local oxygen tension through hypoxia-inducible factor and release Wnt1 to promote angiogenesis during myelination.[2] The orchestration of this oligovascular crosstalk occurs when infants are most susceptible to hypoxic conditions, which can arise from a variety of perinatal complications that affect respiration or cardiovascular function. Compared to other brain regions, white matter is also uniquely sensitive to hypoxia, as oligodendrocytes and axons are very susceptible to oxidative and excitotoxic injury. Hypoxia also inhibits the differentiation of OPCs, suppressing the normal developmental trajectory of myelination. Despite some capacity for repair and remyelination, these early life injuries are incompletely resolved and often result in lasting neurological deficits.

Adding insult to injury, white matter already contains some of the sparsest capillary networks in the brain. The most studied white matter tract in rodent models, the corpus callosum, contains roughly half the vascular density of the overlying cerebral cortex. Further, white matter often sits in watershed regions at the distal edge of arterial perfusion territories, which become the most hypoxic during reduced blood flow or oxygenation. It is therefore logical to assume that approaches to promote vascularization in white matter will boost blood supply and facilitate the repair of injured tissue.

In this issue of *Neuron*, Ren et al.[1] report that growth hormone production induced by hypoxia promotes an increase in capillary density and myelination in white matter of the neonatal mouse brain. Growth hormone (somatropin) is involved in central nervous system development, neuroprotection, and repair after injury.[3] Its expression is elevated in mouse pups and in umbilical cord blood of human newborns that experienced perinatal hypoxia, suggesting a potential role in white matter repair in neonates. In an initial key experiment to build therapeutic relevance, the authors administered recombinant growth hormone to mouse pups during or after a 7-day period of hypoxia. Growth hormone treatment consistently elevated microvascular density in the corpus callosum, ameliorated myelin loss, and reduced functional deficit in adolescence (Figure 1A). Recombinant growth hormone is already US Food and Drug Administration-approved and used in human pediatric populations for the treatment of many conditions involving growth deficiency, making it a candidate for drug repurposing in perinatal hypoxia.

A logical assumption would be that growth hormone acts directly upon OPCs to promote remyelination. Surprisingly, transcriptomic and protein analyses revealed that the growth hormone receptor (GHR) transcript was almost entirely absent in OPCs, oligodendrocytes, other glia, and neurons but highly expressed by a subset of microvascular pericytes (Figure 1B). Pericytes are a type of mural cell that line the abluminal surface of brain capillaries to serve key functions in angiogenesis, development of the blood-brain barrier (BBB), and blood flow regulation.[4] The identity of GHR-expressing pericytes was verified by gene expression, cellular morphology, and vascular localization using novel fluorescent GHR reporter mice. Numerous growth factors have been linked to pericyte proliferation and migration during angiogenesis, with the most well-studied being platelet-derived growth factor B (PDGF-BB). PDGF-BB is released by endothelial cells during angiogenesis and deposited in the vascular basement membrane as a migratory signal for pericytes, which express high levels of the PDGF-BB receptor (PDGFRβ). However, the role of growth hormone in pericyte-endothelial dynamics remained obscure.

Ren et al. manipulated GHR-expressing pericytes to test their role in myelination. They first deleted GHR expressing cells

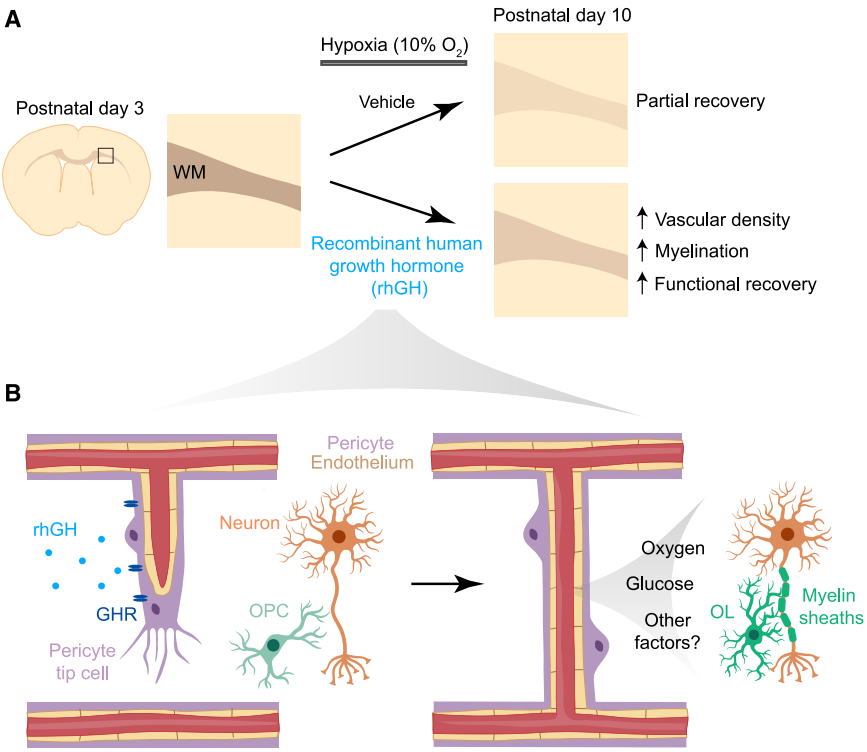

Figure 1. Growth hormone acts on pericytes to enhance vascularization and blood supply to hypoxic white matter

(A) Recombinant human growth hormone (rhGH) treatment of mouse pups experiencing 7 days of hypoxia results in augmented microvascular density and myelination in white matter, as well as improved functional recovery at adolescence.

(B) A subset of pericytes express growth hormone receptor (GHR) and appear to be angiogenic tip cells that guide the formation of anastomotic connections in capillary networks of white matter. This growth hormone-induced neovascularization supports remyelination during hypoxia by improving blood flow and metabolic supply.

using diphtheria toxin receptor-mediated ablation and found marked reductions in myelination, even in the absence of hypoxia. However, GHR is expressed in the liver and skeletal muscle and possibly at lower levels in other brain cells. Therefore, they honed their genetic manipulations by conditionally deleting GHR in PDGFRβ- or neural/glial antigen 2 (NG2)-expressing cells using two Cre mouse lines. Again, these manipulations led to loss in myelination without perturbing the number of oligodendroglia or compromising BBB function. PDGFRβ and NG2 are expressed by pericytes, but neither are specific only to pericytes. In fact, NG2 is also expressed by OPCs. However, while these Cre drivers are individually imperfect, the combination of their use and similarity in outcomes lends confidence to the idea that brain pericytes were a target for growth hormone. They further deleted GHR from OPCs and found no change in myelination, driving home the idea that growth hormone effects on myelin worked indirectly through pericytes. Critically, throughout these exhaustive *in vivo* genetic manipulations in pericytes, there was consistent reduction of microvascular density in the corpus callosum. Moreover, the knockout of GHR in pericytes abolished hypoxia-induced angiogenesis, confirming a key role of GHR signaling in neovascularization of white matter.

In addition to serving as conduits for blood supply, blood vessels also support neuronal viability through non-nutritive roles. There is growing evidence that pericytes secrete growth factors and other molecules to support neuronal health[5–7] and OPC maturation.[8] Ren et al. therefore tested whether GHR-expressing pericytes released paracrine signals to influence OPCs after treatment with growth hormone using an *in vitro* co-culture model with pericytes and OPCs physically separated but sharing the same media. These experiments suggested that GH-treated pericytes did not secrete additional factors into the media to promote OPC maturation or myelin basic protein expression. They concluded that the salutary effects of growth hormone *in vivo* were likely mediated through improved blood flow to white matter (Figure 1B).

The authors then examined how GHR-expressing pericytes might contribute to angiogenesis. Interestingly, some GHR-positive pericytes exhibited a "tip cell" like morphology typically ascribed to sprouting endothelial cells. Using *in vivo* two-photon imaging, they observed pericyte dynamics that mimicked those of endothelial tip cells, with actively extending and retracting filopodia. These pericyte tip cells lacked the canonical endothelial marker, CD31, but expressed PDGFRβ. Further, GHR-expressing pericytes migrated in advance of endothelial cells to create bridging anastomotic connections. As mentioned above, current knowledge is that endothelial tip cells lead the angiogenic process, and pericytes follow behind to suppress endothelial proliferation and stabilize microvascular structure. However, the findings of Ren et al. recast pericytes and endothelial cells as equal partners in the growth and guidance of nascent capillaries. In fact, other *ex vivo* and *in vivo* imaging studies of developmental angiogenesis have also observed instances where pericytes lead or migrate neck-to-neck with endothelial cells during sprout formation.[9,10] Angiogenic sprouts can also emerge from the location of pericyte somata, suggesting that pericytes are not always suppressors of endothelial proliferation.[10] These findings do not contest the leading role of endothelial tip cells but suggest that pericyte tip cells are probably involved in certain steps of capillary network construction, such as short-range anastomotic connections to enhance capillary density.

These fascinating results open the door to many new questions and opportunities. First, although there was a lack of evidence for paracrine signaling between pericytes and OPCs *in vitro*, crosstalk between cells *in vivo* is far more complex and cells are in closer proximity. Future studies could delve deeper into how

growth hormone signaling intersects with recently discovered pericyte-secreted factors that support neuronal viability and function. Second, could newly formed vessels also aid remyelination by serving as scaffolds for migration of new OPCs? This would be another non-nutritive way vessels can support myelination. Third, how does growth factor signaling in pericytes intersect with the delicate balance between oxygen tension, oxygen sensing by OPCs, and release of angiogenic factors?[2] Fourth, does growth factor signaling promote angiogenesis in the corpus callosum preferentially, or does it influence vascular density in white and gray matter throughout the central nervous system? Finally, do the effects of growth factor on white matter vascularization extend into the adult and aged brain? Progressive rarefaction of capillaries in white matter contributes to cognitive impairment and dementia, and therapeutic avenues to prevent or restore blood flow loss would be profoundly beneficial in this context as well. In sum, the studies of Ren et al. have identified pericytes as an under-recognized player in oligo-vascular crosstalk that is vital to myelination during normal development and repair after injury.

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DECLARATION OF INTERESTS

The authors have no financial or non-financial conflicts of interest.

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Attention: The blue spot reveals one of its secrets

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The locus coeruleus is the seat of a brain-wide neuromodulatory circuit. Using optogenetic and electrophysiological tools to selectively interrogate noradrenergic neurons in non-human primates, Ghosh and Maunsell show how locus coeruleus neurons contribute to a specific aspect of visual attention.

The locus coeruleus (LC) is a small nucleus in the vertebrate brainstem that plays an outsized role in regulating behavior. The LC is the major source of noradrenaline in the brain and projections from LC neurons reach almost every place in the central nervous system, including the cerebral cortex, thalamus, midbrain, cerebellum, brainstem, and spinal cord.[1] The release of noradrenaline by the LC is a fundamental component of the sympathetic response to stress and promotes a wide range of physiological responses for arousal, including regulation of the sleep-to-wake transition, motivation, and orienting, as well as sensory, cognitive, and memory processes.[2] The range of brain functions touched by LC neurons is both extraordinary and enigmatic, but more recent circuit-targeting tools have started to reveal individual pieces of this puzzle. In this issue of *Neuron*, Ghosh and Maunsell[3] combine optogenetic and electrophysiological approaches in the non-human primate to provide compelling evidence that the LC contributes to visual attention in a specific, targeted manner.

To be attentive, one must first be responsive to stimulus events, and in