Stroke Literature Synopses: Basic Science

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Neurons are the signaling unit of neurotransmission and play a key role to the function of the nervous system. As the concept of neurovascular unit emphasizes, the surrounding cell types (eg, cerebral endothelial cells, glial cells, etc) support neuronal survival and function. However, how neurons affect cellular function of neighboring cells is still mostly unknown. Four recent studies suggest novel roles of neurons in regulating glial and endothelial function in brain.

Akiyama et al (Trans-regulatoin of oligodendrocyte myelination by neurons through small GTPase Arf6-regulated secretion of fibroblast growth factor-2, Nat Commun. 2014;5:4744 doi: 10.1038/ncomms5744) examined how neurons affect function of oligodendrocyte precursor cells. This study focused on the roles of ADP-ribosylation factor 6 (Arf-6), which predominantly localizes to the plasma membrane. Neuronal Arf-6 is known to contribute to neurite outgrowth and spine formation. In this study, the authors generated conditional knockout mice lacking Arf6 in neurons and showed that neuronal Arf-6 is important for oligodendrocyte myelination during development. In contrast, mice lacking Arf6 in oligodendrocytes exhibited normal oligodendrocyte myelination. In vitro cell culture experiments demonstrated the underlying mechanisms. Cultured neurons lacking Arf-6 secreted less fibroblast growth factor-2 and no longer supported oligodendrocyte precursor cell migration in vitro. However, neuron-derived factors may not always be supportive for neighboring cells. Jonas et al (Axonally derived matrilin-2 induces proinflammatory responses that exacerbate autoimmune neuroinflammation, J Clin Invest. 2014;124:5042–5056. doi: 10.1172/JCI71385) reported that neurons may exacerbate inflammatory responses under pathological conditions. This study examined the roles of matrilin-2 (MATN-2) that is a family of noncollagenous extracellular matrix. In mice with experimental autoimmune encephalomyelitis, MATN-2 was upregulated and released by neurons after acute axonal damage. In vitro neuron-macrophage coculture experiments showed that neuronal MATN-2 induced proinflammatory responses in macrophages through toll-like receptor-associated signaling pathways. In fact, compared with wild-type mice, mice lacking Matn2 exhibited reduced severity after induction of experimental autoimmune encephalomyelitis.

In addition to neuron-derived factors, neuronal activity itself may affect surrounding microenvironments. Lacoste et al (Sensory-related neural activity regulates the structure of vascular networks in the cerebral cortex. Neuron. 2014;83:1117–1130. doi: 10.1016/j.neuron.2014.07.034) examined the roles of neurons on vascular patterning, which is critical for maintaining brain function because brains are vulnerable to ischemia. The authors developed a novel integrative approach combining mouse genetics, high-resolution 3D imaging, and computational image analysis to simultaneously assess neuronal and vascular components. In this study, the mouse barrel cortex region was used as a model system because there is a somatotopic sensory map in which 1 whisker is represented by 1 barrel. Reduction of sensory-related neural activity by whisker plucking led to a reduction of vascular network formation. In contrast, enhancement of sensory-related neural activity by whisker stimulation increased vascular density and branching. Similarly, Hill et al (Modulation of oligodendrocyte generation during a critical temporal window after NG2 cell division, Nat Neurosci. 2014;17:1518–1527. doi: 10.1038/nn.3815) showed that neural activity also influenced oligodendrocyte formation in vivo. This study monitored the mouse barrel cortex region after the sensory deprivation by whisker clipping. In the developing mouse brain, the majority of divided NG2 cells (also known as polydendrocytes or oligodendrocyte precursor cells) differentiate into oligodendrocytes. But after whisker removal, the density of oligodendrocytes was smaller in the deprived somatosensory cortex. Because the density of caspase-3-positive NG2 cells was higher in the affected region, reduction of sensory-related neural activity would increase death of divided NG2 cells that were in the process for oligodendrocyte differentiation.

The findings described above indicate that neurons are important for cell–cell homeostasis in the brain. But after stroke or brain injury, neurons may release signals that either amplify injury or promote recovery in neighboring cells. Further investigation into the neuronal release of help-me or harm-me signals on surrounding environments may eventually yield new therapeutic targets for stroke.
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Stroke. published online January 13, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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