Pericytes are vascular mural cells embedded within the basement membrane of blood microvessels. They are involved in regulating various aspects of vascular homeostasis, such as blood flow rate, vessel maturation, and blood–brain barrier integrity. However, how pericytes influence the brain parenchyma in normal and abnormal conditions remains to be fully understood. Three recent studies provide new knowledge for pericyte function with implications for stroke.

Although pericyte degeneration is now relatively well accepted as a cause of vascular dysfunction, mechanisms of pericyte death/damage remain to be elucidated. Shin et al (STAT1-mediated Bim expression promotes the apoptosis of retinal pericytes under high glucose conditions. Cell Death Dis. 2014;5:e986) revealed novel mechanism of pericyte death under hyperglycemic conditions. InS2Akita/+ mice, a mouse model of diabetes mellitus, exhibited an increase in TUNEL (Terminal Deoxynucleotidyl Transferase Mediated DUTP Nick End Labeling)-positive pericytes (ie, apoptotic pericytes) in retina. In addition, cultured mouse retinal pericytes showed a higher rate of apoptosis under high glucose conditions compared with normal culture conditions. As the underlying mechanisms, this study demonstrated that a proapoptotic protein Bim was elevated in retinal pericytes under diabetic conditions and then led to the accumulation of reactive oxygen species. Furthermore, high glucose conditions decreased the migration ability of pericytes, as well as the supportive effects on endothelial cells. Taken together, diabetic conditions provoke pericyte degeneration, which may eventually cause vascular dysfunction because of the disruption of pericyte–endothelial interactions.

Pericyte viability and survival should be tightly regulated by its local microenvironment. But what intra- and intercellular mechanisms are involved? A recent study by Wang et al (Notch3 establishes brain vascular integrity by regulating pericyte number. Development. 2014;141:307–317) demonstrated that Notch3 signaling promotes expansion of the brain pericyte population during development. This study used zebrafish as a model system to examine the roles of Notch3 on vascular development. Whole-mount in situ RNA hybridization confirmed that zebrafish brain pericytes express notch3, and the notch3 mutant zebrafish (nonsense mutation of notch3) showed a deficit of brain pericytes along with intraventricular hemorrhage because of blood–brain barrier disruption. On the contrary, when the Notch3 intracellular domain was overexpressed as a constitutively activation of Notch3, the pericyte deficiency phenotype in the mutant zebrafish was reduced. The Notch signaling pathway is a highly conserved cell signaling system and participates in several cell function, such as neurogenesis and angiogenesis. Among the Notch family, Notch3 is known to be related to the pathology of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy as the majority of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy have NOTCH3 missense mutations. Hence, these data may show a novel mechanism underlying the degradation of mural cells (pericytes and vascular smooth muscle cells) associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Pericyte dysfunction may participate in the progression of neurological diseases. Sagare et al (Pericyte loss influences Alzheimer-like neurodegeneration in mice. Nature Comm. 2013;4:2932) examined whether pericyte degeneration could influence Alzheimer disease-like neurodegeneration and contribute to disease pathogenesis. To address this question, the authors crossed transgenic mice overexpressing the Swedish mutation of human Aβ-precursor protein (APPsw/F) with pericyte-deficient platelet-derived growth factor receptor-β (Pdgfrβ−/−) mice. The APPsw/F mouse line is now widely used as a mouse model of Alzheimer disease, and Pdgfrβ−/− mice exhibit a moderate but age-dependent progressive loss of brain pericytes. Using this new transgenic mouse line, this study showed that the pericyte loss accelerated the Alzheimer disease pathology such as amyloid angiopathy and cerebral β-amyloidosis by diminishing clearance of soluble Aβ from the brain interstitial fluid. In addition, the pericyte deficiency in the APPsw/F mice led to progressive neuronal degeneration and vascular damage.

The concept of neurovascular unit emphasizes the importance of cell–cell interaction between all the brain cell types to maintain normal brain function. Within the neurovascular unit, pericytes are positioned at the interface between endothelial cells, astrocytes, and neurons. Therefore, pericytes may affect the function of multiple cell types, and as the findings introduced above suggest, pericyte dysfunction may cause or contribute to the progression of central nervous system diseases. These emerging data may eventually lead to novel mechanisms and targets for rescuing pericyte function in stroke.
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