MicroRNAs are small noncoding RNA molecules that play key roles in regulating gene expression. Although accumulating evidence has revealed that microRNAs contribute to several physiological responses, roles of microRNAs in stroke pathology still remain unclear. Three recent articles introduced below used animal stroke models to study how microRNAs regulate vascular function after ischemic stress in brain. 

Li et al (MicroRNA-107 contributes to post-stroke angiogenesis by targeting Dicer-1. Sci Rep. 2015;5:13316. doi: 10.1038/srep13316.) examined the roles of miR-107 in cerebrovascular system in stroke brain. miR-107 is a hypoxic responsive microRNA and is known to be linked to angiogenesis. The authors showed that in a rat stroke model (permanent middle cerebral artery occlusion by filament insertion from common carotid artery), the expression level of miR-107 increased in ischemic boundary zones, where poststroke angiogenesis would actively occur. Downregulation of miR-107 by lateral injection of antagonmir-107 reduced the number of capillaries in the boundary zone, but upregulation by agomir-107 injection increased. Also in cell culture system, miR-107 level in cultured brain endothelial cells increased after oxygen–glucose deprivation. And the matrigel and transwell migration assays confirmed that miR-107–overexpressed cells exhibited more in vitro angiogenic responses but miR-107–downregulated cells showed opposite responses. miR-107 may regulate the expression of VEGF164 and VEGF165 via a transcription factor Dicer-1 in endothelial cells. The authors used miRanda, RNAhybrid, and TargetScan approaches to confirm that Dicer 1 possesses a specific binding site for miR-107. And, by manipulating expressions of miR-107 or Dicer 1, the authors showed that miR-107 in fact upregulated VEGF164 and VEGF165 by suppressing Dicer 1, which would eventually lead to poststroke angiogenesis.

MicroRNAs may also contribute to other poststroke recovery responses. Caballero-Garrido et al (In vivo inhibition of miR-155 promotes recovery after experimental mouse stroke. J Neurosci. 2015;35:12446–12464. doi: 10.1523/JNEUROSCI.1641-15.2015.) investigated how in vivo inhibition of miR-155 would affect on brain recovery after experimental cerebral ischemia. miR-155 is specifically expressed in hematopoietic cells or in cells that are related to vascular remodeling, including endothelial cells. The research team previously demonstrated that miR-155 negatively regulates proangiogenic signaling pathways in cultured mouse brain endothelial cells, and this study used a mouse model of distal middle cerebral artery occlusion (dMCAO) to test the hypothesis that miR-155 would also coordinate vascular function after stroke in vivo. The authors injected a novel second-generation–specific inhibitor for miR-155 to MCAO mice at 48 hours after stroke onset. The inhibitor was injected intravenously, and it successfully crossed the blood–brain barrier to brain parenchyma. miR-155 inhibitor-injected MCAO mice exhibited improved blood flow and microvascular integrity along with preserved capillary tight junctions. In addition, infarct size and neuronal damage in the peri-infarct area were reduced by the miR-155 inhibitor. Because of the preservation of brain tissue, the miR-155 inhibitor-injected MCAO mice also showed efficient functional recovery compared with control-injected MCAO mice.

MicroRNAs may also play a key role in stem cell therapy for stroke. Chen et al (MiR-126 contributes to human umbilical cord blood cell induced neurorestorative effects after stroke in type-2 diabetic mice [published online ahead of print August 24, 2015]. Stem Cells. doi:10.1002/stem.2193.) treated human umbilical cord blood cells (HUCBCs) to type 2 diabetes mellitus (DM) mice (db/db) at 3 days after distal MCAO surgery. MiR-126 is known to facilitate angiogenesis, and past studies showed that miR-126 is closely associated with DM, for example, miR-126 level is significantly decreased in the circulating CD34-positive peripheral blood mononuclear cells in patients with DM. This study showed that type 2 DM stroke mice exhibited decreased level of miR-126 expression in blood serum and ischemic tissue, but HUCBC treatment recovered the miR-126 expression. However, miR-126–deficient HUCBCs did not increase miR-126 expression level in the recipient animals. Correspondingly, vascular deficits and neurological dysfunction by ischemic stress in db/db mice were suppressed by HUCBC treatment, but these supportive effects were not observed in miR-126–deficient HUCBCs. The authors confirmed the key roles of HUCBC’s miR-126 on vascular and neural function in vitro as well, for example, HUCBC-induced angiogenesis and neurogenesis in cell cultures were abolished when miR-126 was knocked down in HUCBCs. Together, these data support the idea that miR-126 is a key microRNA that regulates neuronal and vascular function in DM brains after stroke.

These 3 studies demonstrate novel mechanisms of microRNAs in stroke pathology. Further investigation into the roles of those 3 microRNAs above may eventually yield new therapeutic targets for stroke.
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