Stroke Literature Synopses: Basic Science

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Stroke is a multifactorial disease. Hence, potential therapeutic approaches can be found in multiple compartments and mechanisms. Three recent studies describe how new targets may be dissected in terms of preventing neuron death, ameliorating inflammation, and modifying thrombosis.

Irmady et al (MiR-592 regulates the induction and cell death–promoting activity of p75NTR in neuronal ischemic injury. J Neurosci. 2014;34:3419–3428) proposed that miR-592/p75NTR would be a therapeutic candidate to protect neurons from apoptosis after ischemic injury. p75NTR is a member of the tumor necrosis factor receptor superfamily, and this study showed that p75NTR expression increased after ischemic stress both in vivo and in vitro (eg, mouse brains in a focal ischemia model and cultured hippocampal slice or neurons after oxygen–glucose deprivation). Delivery of function-blocking antibodies for p75NTR reduced neuronal apoptosis in vivo, and furthermore, infarct volume by middle cerebral artery occlusion was significantly decreased in p75NTR knockout mice. Increased expression of p75NTR by ischemic insults may occur in a translation-dependent but not a transcription-dependent manner because the translation inhibitor cycloheximide but not the transcription inhibitor actinomycin D decreased the ischemia-induced p75NTR expression in neuron cultures. Finally, the authors demonstrated that transfection of miR-592 decreased the levels of p75NTR in neuronal cultures and the overexpression of miR-572 attenuated the ischemia-induced neuronal death in vitro. Hence, miR-572 could be a drug target for protecting neurons from ischemic stress by decreasing the levels of p75NTR.

Attenuating inflammatory responses is also important under acute phase after stroke. Shimamura et al (OPG/RANKL/RANK axis is a critical inflammatory signaling system in ischemic brain in mice. Proc Natl Acad Sci U S A. 2014;pii:201400544) examined the roles of osteoprotegerin after stroke. Osteoprotegerin is a soluble secreted protein, and a high-serum osteoprotegerin level is associated with a poor outcome in patients with stroke. Osteoprotegerin works as a decoy receptor for a receptor activator of nuclear factor-κB ligand (RANKL). Because the receptor activator of nuclear factor-κB (RANK) is a receptor for RANKL, osteoprotegerin inhibits the RANK/RANKL signaling. The authors first demonstrated that osteoprotegerin knockout mice showed a reduction in infarct volume and a decrease in cerebral edema after middle cerebral artery occlusion. To test whether an enhancement of RANKL/RANK signaling by osteoprotegerin deficiency was responsible for the reduction of infarct volume, the authors injected a neutralizing anti-RANKL antibody in the osteoprotegerin knockout mice. After middle cerebral artery occlusion, osteoprotegerin knockout mice treated with the neutralizing antibody exhibited an increase in infarct volume. Osteoprotegerin/RANKL/RANK was expressed in macrophage/microglia in ischemic brains, and the osteoprotegerin knockout mice showed a lower expression in inflammatory cytokines with the lower number of macrophage/microglia after stroke. Because RANKL did not show any direct effects in neuroprotection in neuron–glia mixed culture system, the neuroprotective effects of RANK/RANKL signaling may come from the inhibition of inflammatory cytokines in macrophage/microglia. Taken together, these data propose that osteoprotegerin/RANK/RANKL system would be an effective target to reduce inflammatory responses under acute phase of stroke.

Stroke is one of the atherothrombotic disorders, and therefore, thrombosis-related mechanisms might be also a target for drug discovery. Wang et al (Platelet-derived S100 family member myeloid-related protein-14 regulates thrombosis. J Clin Invest. 2014;pii:70966) reported a novel mechanism in arterial thrombotic occlusion. The authors examined the roles of myeloid-related protein (MRP) 14. MRP-14 is a member of the S100 family of calcium-modulated proteins and is known to be elevated in platelets from patients with acute myocardial infarction. MRP-14 complexes with MRP-8, and the MRP-8/MRP-14 heterodimer regulates myeloid cell function through binding to cell surface receptors such as CD36. The authors used MRP-14 knockout mice, which lack both MRP-8 and MRP-14 protein, to elucidate the effect of MRP-8/MRP-14 on the development of arterial thrombosis. Wild-type and MRP-14 knockout mice were subjected to the Rose Bengal model of thrombosis-related mechanisms might be also a target for drug discovery. Wang et al (Platelet-derived S100 family member myeloid-related protein-14 regulates thrombosis. J Clin Invest. 2014;pii:70966) reported a novel mechanism in arterial thrombotic occlusion. The authors examined the roles of myeloid-related protein (MRP) 14. MRP-14 is a member of the S100 family of calcium-modulated proteins and is known to be elevated in platelets from patients with acute myocardial infarction. MRP-14 complexes with MRP-8, and the MRP-8/MRP-14 heterodimer regulates myeloid cell function through binding to cell surface receptors such as CD36. The authors used MRP-14 knockout mice, which lack both MRP-8 and MRP-14 protein, to elucidate the effect of MRP-8/MRP-14 on the development of arterial thrombosis. Wild-type and MRP-14 knockout mice were subjected to the Rose Bengal model of thrombosis, and the authors showed that MRP-14 deficiency prolonged thrombotic occlusion time. Transfusion of wild-type platelets to the MRP-14 knockout mice shortened the prolonged time to carotid artery occlusion, indicating that platelet-derived MRP-14 is essential for thrombus formation. Therefore, MRP-14 would be positioned as a novel and targetable mediator of thrombosis.

Clinically effective stroke therapies are still limited, so basic and translational research should continue. The ideas described above warrant careful testing in preclinical model systems before clinical applications can be further considered.
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Stroke. 2014;45:e154; originally published online July 8, 2014; doi: 10.1161/STROKEAHA.114.006075
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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