Advancing age is major risk factor for development of many central nervous system diseases, including stroke. Three recent studies provide novel mechanisms for how aging causes brain dysfunction with implications for potential targets for stroke therapy.

Liu et al (Neuronal necrosis is regulated by a conserved chromatin-modifying cascade. Proc Natl Acad Sci U S A. 2014;111:13960–13965) examined signaling mechanisms that cause neuronal necrosis. The authors generated a transgenic fly line with the rat glutamate receptor 1 Lurher mutant, which exhibits high permeability to calcium. JIL-1 is the Drosophila homolog of mitogen- and stress-activated protein kinase 1/2 (MSK1/2), and the mutations of JIL-1 in the transgenic flies suppressed the calcium-overloaded–induced neuronal necrosis. JIL-1 can phosphorylate histon H3 serine 28 (H3S28ph) and then displace Polycomb repressive complex 1 (PRC1) from chromatin. The authors demonstrated that mutations of PRC1 enhanced neuronal necrosis in the Drosophila model. To further examine the mechanisms of neuronal necrosis, the authors examined the roles of Trithorax (Trx), which counteracts with PRC1 to regulate transcription. Trx plays an important role in chromatin structure, and H3S28ph-mediated PRC1 loss disinhibits Trx in neuronal necrosis. In the Drosophila model, mutants of Trx suppressed the neuronal necrosis, but overexpression of Trx enhanced necrosis. Finally, to evaluate the roles of JIL1(MSK1/2)/PRC1/Trx cascade in mammalian neuronal necrosis, the authors used in vitro rat neuron system (glutamate-induced cell death) and in vivo rodent brain ischemia models (transient global ischemia/reperfusion in mouse, permanent middle cerebral artery occlusion model in rat). In these models, MSK1/2/PRC1/Trx cascade indeed mediated the glutamate-induced neuronal necrosis. Glutamate-induced neuronal necrosis via calcium overload causes brain dysfunction in stroke, and Bm1, which is the core component of PRC1, is known to be downregulated in aged brain. Therefore, this study implies novel targets/biomarkers for stroke therapy in aged patients.

Age-related synaptic dysfunction is thought to cause neurological degeneration in age-related diseases. Samuel et al (LKB1 and AMPK regulate synaptic remodeling in old age. Nat Neurosci. 2014;17:1190–1197) identified molecular mechanisms that lead to the age-associated synaptic dysfunction in the outer retina. As a candidate molecule, the authors focused on the roles of the serine/threonine kinase LKB1. LKB1 is a multifunctional enzyme that plays important roles in cellular energy homeostasis, cell proliferation, polarity, and axon outgrowth. First, the authors showed that LKB1 deletion in retinal progenitors (LKB1<sup>−/−</sup>) induced numerous horizontal and bipolar cell sprouts even in young mice, which resembled those of aged wild-type mice. Staining with synaptic markers revealed that sprouts in young LKB1<sup>−/−</sup> and aged wild-type mice were dotted with numerous ectopic synapses. Electrophysiological approaches also confirmed that young LKB1<sup>−/−</sup> mice exhibited alterations in retinal function similar to those in aged wild-type mice. Rods are photoreceptors that form synapses in the outer retina, and deletion of LKB1 in rods alone (LKB1<sup>−/−</sup>) also induced sprouting of both rod bipolar and horizontal cells. In addition, LKB1<sup>−/−</sup> mice exhibited similar numbers of ectopic synapses as LKB1<sup>−/−</sup> or aged wild-type mice. Finally, the authors assessed the roles of AMPK, a downstream component of LKB1 signaling pathway. In old retina, the decrease in AMPK activation was confirmed, and AMPK inactivation induced ectopic synapse formation at levels similar to those in the LKB1 mutants or aged wild-type animals. On the other hand, infection of constitutively active form of AMPK reduced ectopic synapse formation in LKB1<sup>−/−</sup> mice. Taken together, these results suggest that LKB1/AMPK signaling is involved in age-related changes of retinal synapses, and therefore, this pathway may be a novel target for neuronal protection in age-related diseases, including stroke.

In the brain, protein waste removal is partly performed by paravascular pathways. Kress et al (Impairment of paravascular clearance
pathways in the aging brain [published online ahead of print September 10, 2014]. Ann Neurol. doi: 10.1002/ana.24271) demonstrated that advancing age was associated with a decline in the efficiency of exchange between the subarachnoid cerebrospinal fluid (CSF) and the brain parenchyma. The paravascular pathways facilitate convective exchange of water and soluble contents between CSF and interstitial fluid (ISF). The authors evaluated the CSF–ISF exchange and interstitial solute clearance in young (2–3 months), middle-aged (10–12 months), and old (18–20 months) wild-type mice. To evaluate paravascular CSF penetration into the brain parenchyma in vivo, fluorescent CSF tracers were infused into the subarachnoid CSF of the cisterna magna. In middle-aged and, to a greater extent, in old brains, CSF tracer penetration both along paravascular pathways and across the pial surface was reduced. Similarly, the interstitial solute clearance was also impaired in the aged brains. In addition, in vivo 2-photon microscopic analyses confirmed the age-associated changes in the paravascular CSF–ISF exchange. To examine the underlying mechanisms, the authors focused on the roles of aquaporin-4. Aquaporin-4 is a water channel that is localized to perivascular astrocytic feet. Aquaporin-4 is known to support the paravascular bulk flow of CSF and ISF, and the authors showed that the age-associated loss of perivascular aquaporin-4 polarization along the penetrating arteries accompanied with the impairment of CSF–ISF exchange in aged brains.

The findings described above imply that compared with young brains, aged brains may respond differently to stress. Therefore, future studies using aged animals are warranted to pursue effective therapeutic approaches for stroke patients.
Stroke Literature Synopses: Basic Science
Ken Arai

Stroke. 2014;45:e247-e248; originally published online November 11, 2014;
doi: 10.1161/STROKEAHA.114.007417
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
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:
http://stroke.ahajournals.org/content/45/12/e247

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/