Currently, there are no clinically effective neuroprotectants not only for stroke, but also more broadly across all central nervous system disorders. Fundamentally, it is now recognized that regardless of the specific disorder, there may be unifying mechanisms that are common to protecting neurons against injury and disease. Three recent studies suggest novel therapeutic approaches for neuroprotection in animal models of neurodegeneration. Further investigation of these pathways may eventually yield ideas and targets with relevance for stroke as well.

Lee et al (Parthanatos mediates AIMP2-activated age-dependent dopaminergic neuronal loss. Nat Neurosci. 2013;16:1392–1400) reported that aminocacyl-tRNA synthetase complex interacting multifunctional protein-2 (AIMP2) causes a selective, age-dependent, progressive loss of dopaminergic neurons. AIMP2 is a parkin substrate that is present in Lewy body inclusions of the Parkinson disease substantia nigra. Mutations in the ubiquitin E3 ligase PARKIN are an important cause of familial Parkinson disease, and AIMP2 is a strong candidate as a pathogenic parkin substrate. AIMP2 levels are known to be elevated in both patients with Parkinson disease and animal models. This study prepared a novel transgenic mouse line with AIMP2 overexpression and showed that AIMP2 accumulation leads to an age-dependent degeneration of dopaminergic neurons, which eventually cause Parkinson disease–like symptoms such as striatal dopaminergic deficits and dysfunctional motor coordination. As an underlying mechanism in AIMP2-induced dopaminergic neuronal damage, the authors demonstrated that AIMP2 activates poly ADP ribose polymerase1 (PARP1), which is one of the major molecules for apoptosis. Importantly, knockout or inhibition of PARP1 prevented the AIMP2-mediated dopaminergic neuronal death. Therefore, brain-permeable PARP inhibitors could be effective for neuroprotection in some neurodegenerative diseases.

Mechanisms for neuronal death may depend on neuronal cell types. Saxena et al (Neuroprotection through excitability and mTOR required in ALS motoneurons to delay disease and extend survival. Neuron. 2013;80:80–96) examined endogenous neuroprotection mechanisms in motoneurons using transgenic mice with mutant superoxide dismutase1 (SOD1), which are widely used as a mouse model of familial amyotrophic lateral sclerosis. In early postnatal stages (postnatal day =7), a subpopulation of α-motoneurons exhibited misfolded SOD1 accumulation. The vulnerability of motoneurons may be related to their lower excitability because enhancing motoneuron excitability promoted the viability of motoneurons and reversed the misfolded SOD accumulation. On the contrary, direct pharmacological inhibition of excitability in motoneurons enhanced misfolded SOD1 accumulation and endoplasmic reticulum stress. In addition, when the mammalian target of rapamycin (mTOR) inhibitor rapamycin was chronically treated, the familial amyotrophic lateral sclerosis transgenic mice showed the disease progression such as misfolded SOD accumulation and increased endoplasmic reticulum stress in the vulnerable motoneurons. Taken together, these results suggest that excitability signaling leading to mTOR activation would be a critical mechanism for neuroprotection in motoneurons in the amyotrophic lateral sclerosis (ALS) model mice. Thus, endogenous neuroprotection pathways may be valuable therapeutic targets for neuroprotection in central nervous system diseases.

When we seek neuroprotection, we may also need to pay attention to neuronal axons that are enwrapped by myelin sheath. Laterza et al (iPSC-derived neural precursors exert a neuroprotective role in immune-mediated demyelination via the secretion of LIF. Nat Commun. 2013;4:2597) reveal novel mechanisms by which transplanted mouse induced pluripotent stem cell (iPSC)-derived neural stem/precursor cells (miPSC-NPCs) exert the neuroprotective effect in a mouse model of multiple sclerosis. Compared with sham-treated multiple sclerosis mice, miPSC-NPC–treated multiple sclerosis mice promoted the functional recovery and exhibited a better preservation of myelin/axonal integrity. Because the transplanted miPSC-NPCs persisted undifferentiated within perivascular infiltrates, the neuroprotective effects were at least partly mediated via the secretion of a specific neurotrophin by the miPSCs-NPCs. In vitro and in vivo examinations demonstrated that miPSC-NPC–derived leukemia inhibitory factor promoted remyelination. iPSCs have opened a new avenue of translational research in the cell transplantation approaches, and this study expands the therapeutic potential of iPSCs for neuroprotection in myelin disorder diseases.

Although clinical trials of neuroprotectants have failed in our stroke field to date, the search for effective drugs to protect neurons must continue. In this regard, the findings introduced above should be helpful because they provide a deeper understanding of fundamental mechanisms that may eventually lead to new ways to achieve neuroprotection in patients with stroke.