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Stroke Literature Synopses: Basic Science (2014/August)

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The mitochondrion is a membrane-bounded cell organelle, which plays critical roles in cellular survival by supplying energy or mediating intracellular signaling pathway. Mitochondrial dysfunction has been implicated in many CNS disorders including stroke. Three recent studies elucidate novel mechanisms for how mitochondria are involved in neuronal damage under diseased conditions.

Li et al. (A TIGAR-regulated metabolic pathway is critical for protection of brain ischemia. The Journal of Neuroscience. 2014;34:7458-7471) demonstrated that TP53-induced glycolysis and apoptosis regulator (TIGAR) protects neurons against ischemic stress. TIGAR has been reported to block glycolysis by reducing the levels of Fru-2,6-P_2 and therefore increase the flow of pentose phosphate pathway. The western blots and immunostaining analyses found that TIGAR was highly expressed in brain neurons and was rapidly upregulated in response to ischemia/reperfusion insults. In addition, both in animal and cellular stroke models, ischemia/reperfusion or oxygen-glucose-deprivation (OGD)/reoxygenation stress increased mitochondrial localization of TIGAR. To explore the roles of TIGAR in cerebral ischemic injury, the authors injected lentiviral vectors encoding TIGAR or sh-TIGAR into mouse lateral ventricle and striatum, and then subjected the mice to stroke insults. Compared to control-lentiviral-vector-injected mice, overexpression of TIGAR reduced the infarct size, neurological deficits, and brain edema, whereas TIGAR knockdown aggravated the damage. Similarly, in their neuronal cell culture system, overexpression of TIGAR increased the cell viability under OGD/reoxygenation conditions, whereas knockdown of TIGAR decreased the cell viability. Furthermore, overexpression of TIGAR in neuron cultures prevented the decreases in mitochondrial transmembrane potential caused by OGD/reoxygenation insults. Therefore, the TIGAR-regulated metabolic pathway may be a new therapeutic target for stroke.

Mitochondria maintain intra-cellular homeostasis, and as needed, they mediate pro-apoptotic signaling by releasing apoptosis-inducing factor (AIF), which plays crucial roles in caspase-independent neuronal death. Doti et al. (Inhibition of the AIF/CypA complex protects against intrinsic death pathways induced by oxidative stress. Cell Death and Disease. 2014;5:e993) showed that the AIF amino-acid residues 370-394 mediates the protein complex formation of AIF with cytosolic cyclophilin A (CypA). AIF is a mitochondrial flavoprotein, and after release from the mitochondria, it binds to CypA to initiate the

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translocation to the nucleus, where the AIF/CypA complex generates a lethal DNA-degrading complex. The authors designed AIF peptide AIF(370-394), which targets the AIF-binding site on CypA. To evaluate the neuroprotective potency of AIF/CypA complex formation inhibition, the AIF peptide was applied to HT-22 neuronal cell lines, wherein glutamate-induced oxidative stress causes AIF-dependent cell death. Firstly, the authors confirmed that CypA knockdown by CypA-siRNA gene silencing blocked glutamate-induced nuclear translocation of AIF and protected HT-22 neuronal cells against glutamate-induced oxidative stress. Similarly, AIF(370-394)-transfected HT-22 exhibited less glutamate-induced nuclear translocation of AIF and more resistance to glutamate-induced oxidative stress. Furthermore, the decrease of mitochondrial membrane potential by glutamate treatment was significantly attenuated in the HT-22 cells transfected with AIF(370-394). Hence, drugs or peptides that inhibit AIF/CypA complex formation may act as a promising neuroprotectant against ischemic stress.

Axonal degeneration is one of the major hallmarks of neuronal damage in stroke. Ohno et al. (Mitochondrial immobilization mediated by syntaphilin facilitates survival of demyelinated axons. Proceedings of the National Academy of Sciences. 2014;111:9953-9958) defined the roles of mitochondrial volume and distribution in axonal degeneration following CNS demyelination. Most axonal mitochondria do not appear to translocate and are located at their stationary sites on microtubules, and syntaphilin tethers/immobilizes axonal mitochondria to microtubles at the stationary sites. This study compared mitochondrial function in wild-type axons with the one in syntaphilin-deficient axons. The volume of mitochondrial stationary sites was increased in demyelinated CNS axons in wild-type white matters. In contrast, although the size of mitochondrial stationary sites was similar in wild-type and syntaphilin-deficient myelinated axons, demyelinated syntaphilin-deficient axons exhibited similar size of mitochondrial stationary sites as myelinated syntaphilin-deficient axons. Correspondingly, compared to wild-type mice, larger axonal pathology was observed in the demyelinated corpus callosum of syntaphilin-deficient mice. Failure to increase mitochondrial volume in the syntaphilin-deficient demyelinated axons may reduce ATP production and increase axonal Na^+, leading to augmented axonal degeneration. In fact, a Na^+ channel blocker flecainide was beneficial for the survival of demyelinated syntaphilin-deficient axons. Taken together, therapeutic stabilization of mitochondria-microtuble docking interactions would prevent or reduce degeneration of demyelinated axons.

Clinically effective neuroprotectants in the stroke field are not yet developed. However, the ideas described above propose novel therapeutic approaches in targeting mitochondria to protect neurons against ischemic insults. Future studies are warranted to pursue this direction in preclinical and clinical studies.