The Editorial for this Special Issue

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This special issue of *Translational Stroke Research* focusing on “Protein Misfolding and Organelle Stress after Brain Ischemia” grew, in part, from a symposium presented at the XXVth International Symposium on Cerebral Blood Flow, Metabolism and Function held in Barcelona, Spain, in May of 2011. Both that symposium and this special issue seek to raise awareness in the field of how brain ischemia as a multifactorial condition affects all subcellular organelles.

For some time, the idea has dominated the field that ischemia-induced neuronal death was due mainly to activation of pro-death pathways such as free radical production or apoptosis or due merely to a single event such as the endoplasmic reticulum (ER) or mitochondrial failure. While these clearly are important aspects of ischemic damage, the latest studies suggest that brain ischemia leads to protein misfolding and deposition, and multiple organelle stress. To survive this nasty environment, postischemic neurons must cope with repair and eliminate irreparable damaged organelles and toxic materials by upregulation of cellular defense systems such as molecular chaperones and cellular degradation pathways. Furthermore, excessive cellular digestion might also contribute to neuronal damage.

Growing evidence supports that many established ischemic damaging events converge to generate multiple organelle damage. These detrimental events include protein misfolding and aggregation, synaptic dysfunction, translational arrest, ER stress, mitochondrial dysfunction, acidosis, reactive oxygen species (ROS), dysfunction of protein quality control systems, and impairment of protein degradation pathways. Collectively, these lead to dramatic deposition of misfolded proteins on

multiple organelle membranes. Postischemic neurons respond to overload of misfolded proteins by (1) shutting off protein synthesis to reduce the load of the major cellular unfolded nascent polypeptides, (2) expression of molecular chaperones that prevent misfolded protein-induced toxicity and to repair organelle damage, and (3) upregulating protein degradation pathways for eliminating damaged organelles.

The multiple organelle damage occurs mainly in neurons that are destined to die such as CA1 neurons after transient cerebral ischemia and penumbral neurons after focal brain ischemia [1]. There are other important aspects of brain ischemia research. These may include stroke biomarker discovery, inflammatory reaction, immune responses, autoantibodies, stem cell-based therapy, antibody therapy, personalized medicine, stroke prevention, and long-term stroke recovery. These interesting topics can be found in *Translational Stroke Research* (e.g., [2–12]).

In this special issue, we are fortunate to gather reports from workers at the leading edge of these issues. Luo et al. discuss protein misfolding, aggregation, and autophagy after brain ischemia. DeGracia and colleagues present original studies of the protein synthesis system in reperfused neurons, including HuR function and translational state analysis following global brain ischemia and reperfusion, and mRNA redistribution during permanent focal cerebral ischemia. Liu et al. provide a timely update on the roles of the heat shock proteins Hsp70, Hsp 27, and HO-1 (Hsp32) and their therapeutic potential. Petegnief et al. provide a critical assessment of SIRT1 regulation and modulation of stroke outcome that contains several important observations on open questions and unresolved issue. Kucharz et al. review the recently discovered fission and fusion of the neuronal ER and what role this plays in the neuronal stress response to ischemia. Kristian et al. provide a deep analysis of mitochondrial dysfunction and NAD⁺ metabolism alterations in pathophysiology of acute brain injury. Sun and colleagues expand the

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understanding of ER stress to encompass the effects and roles of DHA as an ER stress inhibitor. Swanson et al. present an up-to-date discussion on the links between mitochondrial dysfunction and nuclear poly(ADP-ribose) polymerase-1. Pattinson provides an update on pseudo-continuous arterial spin labelling MRI for noninvasive, whole-brain serial quantification of cerebral blood flow following aneurysmal subarachnoid hemorrhage. Researchers from the Fiskum Laboratory report their original study of augmentation of normal and glutamate-impaired neuronal respiratory capacity by exogenous alternative biofuels. Colbourne et al. present their study of bipyridine, an iron chelator, showing that it does not lessen intracerebral iron-induced damage or improve outcome after intracerebral hemorrhagic stroke in rats. Lin et al. present their study that fatty acid methyl esters and Solutol HS15 confer neuroprotection after focal and global cerebral ischemia. Lipton brings together evidence to present the novel view that lysosomes may form a common final pathway for many upstream damage mechanisms, leading to cell death under mild ischemic conditions.

Together, these articles illustrate the multifactorial nature of ischemic injury, which affects all the levels of organization in the brain, from physiological, cellular, organellar, to molecular. The recognition that ischemic injury encompasses the many structural and functional levels of brain organization is certain to impact future therapeutic efforts, which, to this point, have not been successful by targeting only single damage mechanisms. A possible clinical approach to multiple organelle damage may be early diagnosis and a combination therapy to prevent or target multiple organelle damage after brain ischemia or to enhance endogenous stress responses. Another approach suggests that it may be possible to consider all of the changes as the aggregate competition between cell-damaging and cell-protective responses, where the crucial therapeutic target will not be any single substrate but the combined dynamics of the entire injured cell [13].

Therefore, this special issue is timely in bringing together information pertinent to multiple organelle damage in postischemic brain and to disseminate these findings to foster further interest and research recognizing this multiangled viewpoint.

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Conflict of Interest The authors declare no conflict of interest.

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