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EDITORIAL

Stroke: Molecular Mechanisms and Therapies

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Despite decades of research using clinical and experimental models, stroke still remains one of the major health care problem with high rate of death and disability. Identifying new therapeutic targets and developing molecules that can manipulate the neurotoxic as well as protective mechanisms in post-stroke brain are still high-level priorities. Basic stroke research is exploding with many new discoveries. This special issue focusses on the molecular mechanisms and new therapeutic targets for stroke therapy.

Aneurysms formed due to weakened blood vessel walls are major proponents of stroke. The etiology of aneurysm formation that correlates with physical genetic factors is yet to be completely understood. On this topic, the review by Zhen Xu highlighted the importance of genetics and molecular mechanisms that contribute to intracranial aneurysm formation. Another major problem associated with the stroke clinical practice is to correctly identify the various subtypes of stroke to provide appropriate therapies. The review by Joseph Kamtchum-Tatuene discussed the state-of-art profiling of blood RNAs to identify a set of biomarkers that can be used for stroke diagnosis and therapy. In continuing this discussion, J. Weldon Furr's review showed that microRNAs in blood can be potential diagnostic biomarkers as well as they can be targeted to decrease the neuropathology in cerebral amyloid angiopathy.

New animal models to study the stroke outcomes are important. The article by Shingo Nishihiro used a chronic cerebral hypoperfusion rodent model to evaluate the role of high mobility box-1 in the formation of new blood vessels. Kristin Hillman used another robust new model of medial prefrontal stroke in adult mouse to show that cerebral ischemia also alters connectivity between cerebral cortex and hippocampus. Shyanne Page used an in vitro model that mimics blood–brain barrier (BBB) to demonstrate that HIF-1 signaling plays a role in BBB disruption following ischemic conditions.

The incidence of stroke is higher and the post-stroke recovery is lower in subjects with comorbid conditions like diabetes and hypertension. Hence, studies with diabetic and hypertensive rodent models offer invaluable translational potential for stroke drug development. In this regard, the review by Thierry Coppola highlighted the common targets that are therapeutically potential between diabetic and stroke subjects. *Stroke Treatment Academic Industry Roundtable* (STAIR) suggested that any new preclinical stroke therapeutic testing should be conducted in animals of both sexes as outcomes in males and females are quite different following stroke. The review by Ladonya Jackson showed that the post-stroke inflammatory responses which promote brain damage are different between male and female diabetic subjects. Ionic balance maintained by ion channels is known to be disrupted after stroke. Ashish Rehni's review shows that a specific acid-sensing ion channel plays a significant role in exacerbated brain damage seen in diabetic stroke subjects.

Many studies are evaluating novel targets that can be targeted to control post-stroke brain damage. If not controlled properly, post-ischemic neuroinflammation propels ischemic neuronal death rapidly. Many molecules which are the components of various inflammatory signaling pathways are potential targets to develop post-stroke drugs. In this regard, Saif Ahmad's article shows the importance of complement component C3 (controls innate immunity) in post-stroke inflammation. Recent studies show that various classes of noncoding RNAs are dysregulated after stroke and many of them have significant role in promoting post-stroke brain damage. In particular, a class of noncoding RNAs called long noncoding RNAs emerged as controllers of transcription. Aparna Akella's review highlighted the new avenues of modulating certain long noncoding RNAs as stroke therapeutic targets. As stroke leads to decreased blood flow, energy balance will be disrupted significantly. Preserving the function of mitochondria that controls energy flow is shown

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to be important for protecting white matter after stroke by Chinthasagar Bastian. The article by Jared Sperling showed important methods for studying mitochondrial respiration which has immense implications in post-stroke brain. Saif Ahmad showed that a novel molecule called AKBA effectively shuts down both inflammation and oxidative stress to protect brain endothelial cells under conditions of low oxygen and glucose. This shows the potential of this molecule in devising new strategies to protect blood vessels after stroke. Induction of ischemic tolerance might be a significant way to curtail the brain damage following an unavoidable incidence of stroke. Stefano Pianta showed that exercise promotes ischemic tolerance and the mechanism of this beneficial effect is by increasing the new blood vessel formation. Stem cells and resident progenitors play immense role in neuroplasticity after stroke. Koteswara Nalamolu showed that when stem cells are subjected to in vitro ischemia, they secrete exosomes that promote post-stroke recovery. Sarah Martha's article shows that molecules that control acid–base balance and electrolytes can be good therapeutic targets to preserve neurons in the ischemic brain.

Overall, this special issue is an effort to understand the mechanisms that lead to post-ischemic brain damage and discuss the new models and new therapeutic targets to protect brain after stroke.