Editorial

Critical Appraisal of Ischemic Stroke Pathophysiology: Road to Cerebral Resuscitation? Part II

There is no doubt that ischemic stroke prevention, management and treatment necessitate a better understanding of its pathophysiology. Part 1 of this theme issue described the role of thrombomodulin, calcium and inflammation in ischemic stroke, and covered topics related to mechanisms of neurovascular dysfunction and synaptic and extrasynaptic glutamate signaling in cerebral ischemia. This second part of the theme issue focuses more specifically on the role of obesity, hypertension, hypercholesterolemia, leukocytes and microglial activation in ischemic stroke.

Obesity, hypertension and hypercholesterolemia, are long known as important risk factors for atherosclerosis, and this may lead to ischemic events. Mia-Jeanne van Rooy and Etheresia Pretorius discuss the role of inflammation with regards to reactive oxygen species (ROS) and nitric oxide (NO) in conjunction with ROS, as well as inflammatory cytokines, linked to obesity, hypertension and hypercholesterolemia. The risk factors may ultimately lead to atherosclerosis and ischemic events, including transient ischemic attacks (TIA's), thrombotic stroke and myocardial infarction. Therefore, atherosclerosis is not the result of only one risk factor, but a combination of various physiological and inflammatory response processes.

Mounting preclinical evidence highlights the importance of leukocytes in the injury response induced by cerebral ischemic reperfusion. Clinical evidence also supports a role for leukocytes as a determinant of stroke outcome. In 'Leukocyte-mediated tissue injury in ischemic stroke', Stephen Rodrigues, and Neil Granger summarize evidence that implicates leukocytes in the pathophysiology of stroke and address some of the mediators that contribute to the recruitment and activation of leukocytes in the post-ischemic brain. The products of leukocyte activation that may account for the deleterious effects of this cell population in stroke is also discussed. Recently tested compounds that afford protection against the neurological deficits and tissue injury induced by stroke are addressed within the context of potential development of novel strategies for stroke treatment.

CD147, a transmembrane glycoprotein, is expressed on all leukocytes, platelets, and endothelial cells. Increased expression of CD147 has been implicated in the pathogenesis of a number of diseases, such as asthma-mediated lung inflammation, rheumatoid arthritis, multiple sclerosis, myocardial infarction and ischemic stroke. Therapeutictargeting of CD147 has yielded encouraging effects in a number of experimental models of human diseases, suggesting CD147 as an attractive target for treatment of inflammation-related diseases. In their article 'CD147: a novel modulator of inflammatory and immune disorders', Xiaolei Zhu, Zifang Song, and Guohong Li review the current understanding of CD147 expression and functions in inflammatory and immune responses and potential implications for treatment of inflammatory disorders, including ischemic stroke.

Microglia are the resident immune cells of the central nervous system, and they respond to stroke by assuming an activated phenotype that releases cytotoxic cytokines, reactive oxygen species, proteases, and other factors. Redundancy in cytotoxic microglial responses suggest that the most effective therapeutic approach may be to target the global gene expression changes involved in microglial activation. In 'Targeting microglial activation in stroke therapy: Pharmacological tools and gender effects', Yanting Chen, Seok Joon Won, Yun Xu, and Raymond Swanson review the preclinical studies supporting efficacy of drugs targeting the microglial activation after stroke. They also review recent advances in the understanding of sex differences in the CNS inflammatory response, as these differences are likely to influence the efficacy of drugs targeting post-stroke brain inflammation.

Age and high blood pressure are responsible for silent structural and functional cerebral changes leading to white matter lesions and cognitive impairment. However, the clinical significance and pathological substrate of white matter lesions are incompletely understood. In her article 'Essential hypertension, cerebral white matter pathology and ischemic stroke', Cristina Sierra highlights some strong evidence to support the fact that cerebral white matter lesions in hypertensive patients should be considered a silent early marker of brain damage.

In the next article 'Role of Connexins and Pannexins in ischemic stroke', Juan Orellana *et al.* review the current findings on the regulation of connexin- and pannexin-based channels in ischemic stroke and how they contribute to cell damage observed in pathology. Further, they hypothesize that the development of new drug modulators using *in silico* devices for connexin and pannexin-based channels will be crucial for future therapies against stroke.

Mitochondria are key element for the maintenance of life and also the "gatekeeper" of cell death pathways. They are highly dynamic and exhibit a delicate balance between fusion and fission, which is very crucial for the maintenance of normal cellular homeostasis and physiology. In their article entitled 'Drp1 in ischemic neuronal death: An unusual suspect', Pradeep, Bhargy Sharma, and Rajanikant G. K. focuss on the mitochondrial fission protein, dynamin-related protein 1 (Drp1) and discuss the pathophysiological role of Drp1 in ischemic stroke.

The next article entitled 'Instructions from the vascular system - Directing neural stem cell fate in health and disease', focuses on recent findings about cell- or blood-derived factors in the vascular system supporting stem cell niche maintenance or activation for tissue homeostasis and repair. The authors compare common hallmarks of vascular system - stem cell interactions of different stem cell niches focusing on adult neural stem cells (NSCs) after CNS injury and disease.

In the concluding article, contributed by Gjumrakch Aliev *et al.,* authors postulate that chronic vascular hypoperfusion is a part of the common underlying mechanisms involved in the initiation and development of neurodegenerative disorders such as stroke, arteriosclerosis and AD. They hypothesize that the central initiating factor for vascular abnormality is mitochondrial damage and its preventation may lead to new and more effective treatment strategies for these devastative diseases in the near future.

The selected articles capture some of the state-of-the-art research issues in ischemic stroke and neuroprotection field and aid in expanding our understanding of disease mechanisms. The editors hope that this issue will serve to illustrate and help future researchers on this topic. The editors wish to express their sincere appreciation to all of those who helped in this project in one way or another. Special recognition is due to Prof. Atta-ur-Rahman, Editor-in-Chief for his confidence, support and great patience throughout the whole publication process. Very special thanks go to our anonymous referees for their professional and timely reviews. The editors are grateful to all authors for their scholarly contribution to this special theme issue.

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