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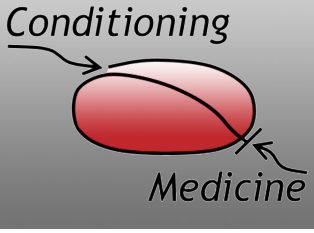

EDITORIAL| OPEN ACCESS

Cell Signaling: A Window to View Brain and Heart Homeostasis, Disease and Treatment

Cesar V. Borlongan[1], Guest Editor

The brain and heart consist of many cell types that are intricately involved in the homeostasis and pathological condition of the central nervous system and the cardiovascular system. Compelling evidence indicates that cells centrally and peripherally may contribute to both brain and heart function. In this special issue of *Conditioning Medicine*, the theme of central and peripheral cell signaling pathways is given much attention to solicit critical and innovative discussion on emerging hypotheses about brain and heart homeostasis, disease, and treatment.

In the first article, Dr. Joo Eun Jung from the Department of Neurology in the McGovern Medical School at the University of Texas Health Science Center at Houston, and Dr. Eng Lo from the Neuroprotection Research Laboratory, Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, highlight multiple signaling molecules and pathways triggered by ischemic preconditioning, a therapeutic approach involving a sub-lethal insult that enables resistance to a subsequent lethal injury, including cerebral ischemia, hemorrhage, neonatal hypoxic injury, and trauma. In particular, the authors advance the concept that c-Jun N-terminal kinase (JNK), a member of the mitogen-activated protein kinases (MAPKs), is activated by various cellular stresses including ischemic injury. Because JNK signaling may regulate neuronal death in many central nervous system injuries, they hypothesize that this pathway is involved in neuronal survival in brain preconditioning. Their review paper discusses clinical and laboratory evidence supporting the role of JNK in effective ischemic preconditioning against stroke.

In the second article by Dr. Elga Esposito and colleagues from the Neuroprotection Research Laboratory, Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, the authors also examine a potential signaling pathway that may mediate the effects of ischemic preconditioning, but also pursue pathways that may be involved in postconditioning to better understand these therapeutic strategies for cerebral ischemia. The authors place the neurovascular unit as a key entity in building the concept of "help-me signaling" pathway, whereby injured neurons propel extracellular signals that alter glial and vascular cells into therapeutic phenotypes. They further highlight that this therapeutic pathway may be mediated by intra-cellular, as well as by non-cell autonomous exchange of inter-cellular help-me signals between cellular components of the neurovascular unit. The authors focus on specific help-me signals, such as CCL2, TNFα, VEGF, and extracellular microvesicles, as likely candidate targets for probing both ischemic preconditioning and postconditioning mechanism of action.

In the third paper, Dr. Dmitriy Atochin and her colleagues from the Pirogov Russian National Research Medical University and Research Center of Neurology in Moscow, and the Cardiovascular Research Center, Massachusetts General Hospital, and Harvard Medical School detail an innovative mechanism of action mediating cardiac preconditioning and postconditioning. Here, the authors review the role of RISK, SAFE, and eNOS pathways in conditioning cardiac protection, mechanisms by which the signaling pathways interact, and the physiological consequences of these interactions. The RISK pathway is a combination of two parallel cascades, PI3K-Akt and MEK1-ERK1/2; the The SAFE pathway involves TNFa, JAK, and STAT3; and the eNOS signaling cascade is based on the protein kinase G (PKG) and involves nitric oxide. The authors suggest that these signaling pathways may provide molecular-targeted therapy with cardioprotective potential employing preconditioning and postconditioning paradigms.

The fourth article Dr. José Juan Antonio Ibarra Arias and Elisa García from the Centro de Investigación en Ciencias de la Salud (CICSA), FCS at the Universidad Anáhuac México Campus Norte in Mexico, describe the role of inflammatory signaling pathways in spinal cord injury. Here, they discuss laboratory evidence supporting the neuroprotective role of immunization with neural-derived peptides in spinal cord injury. They suggest that a close examination of the severity of the inflammatory response after the injury may

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provide a better prognosis of the disease pathology and treatment with immunization. Specifically, they reveal that expression of inflammation-related genes (IL-6, IL-12, IL-1β, IFNɣ, TNFα, IL-10, IL-4, and IGF-1) may differ between moderate and severe spinal cord injured animals treated with the immunization peptides. This paper argues for a critical evaluation of inflammatory signaling pathways after spinal cord injury in order to better cater protective autoimmunity.

Finally, in the fifth article, Dr. Susanna Rosi from the Department of Physical Therapy and Rehabilitation Science, University of California, San Francisco, presents new laboratory evidence closely implicating the role of aging in traumatic brain injury. In particular, she shows that peripherally-derived monocytes can closely approximate the resulting inflammatory response from TBI, which is exacerbated by aging. That peripherally-derived monocytes ($CCR2^{+}$) permeate the brain and exacerbate cognitive impairments in chronic TBI, especially in aged animals, indicates that these monocytes can serve as a biomarker for TBI, which should allow a better understanding of TBI pathology and aid in developing anti-inflammatory-based treatments.

Altogether these studies indicate the importance of interrogating the cell signaling pathways associated with functional, as well as dysfunctional brain and heart, in revealing novel concepts of disease onset and progression, and subsequent treatments for these pathological conditions. These cell signaling pathways, while largely developed in ischemic conditioning models (Jung et al., 2018; Esposite et al., 2018; Baranich et al., 2018), may be extended to general neuroprotection as seen in spinal cord injury and traumatic brain injury (Ibarra et al., 2018; Rosi et al., 2018).

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