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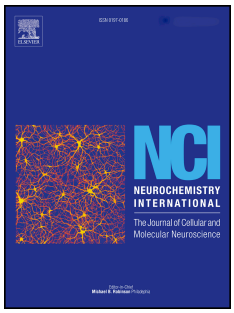

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Cellular and Molecular Mechanisms of Neuroprotection and Plasticity after Traumatic Brain Injury

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TBI and its sequel of pathological events are a major health concern among younger as well as older individuals [1, 2]. Most often, post-TBI functional consequences can be seen for many decades. These include motor/cognitive dysfunction and development of neurodegenerative diseases [3-6]. Several pathologic mechanisms including inflammation, oxidative stress, ER stress, mitochondrial damage and apoptosis synergistically mediate the secondary neuronal death that is responsible for the long-term neurological dysfunction after TBI [7]. This special issue is a timely effort to bring together some of the recent advances in the understanding of the mechanisms that lead to post-TBI dysfunction and experimental TBI therapies.

In several cases, TBI leads to long-term depression in humans, but the mechanisms are not completely understood. Phosphodiesterase-4 inhibitors (PDE4) are known to promote antidepressant-like effects and Jindal et al. showed that treating rats subjected to impact accelerated TBI with a next generation PDE4 inhibitor called etazolate significantly reversed post-TBI behavioral deficits probably by modulating oxidative stress and nitrosative stress.

Despite decades of research, a therapy that can minimize post-TBI neuronal death leading to better functional recovery in humans is still elusive. Hence, understanding the molecular mechanisms that leads to secondary brain damage might promote development of new TBI therapies. In mammals, <2% of the transcriptional output is represented by protein-coding RNAs (mRNAs) while the remaining >98% are noncoding RNAs (ncRNAs) of various classes. The ncRNAs are thought to control both transcription and translation and hence understanding their functional roles is important to decipher the mechanisms of secondary brain damage after TBI. The review by Chandran et al. discusses the functions of various classes of ncRNAs including microRNAs and long noncoding RNAs in controlling various pathophysiologic mechanisms that are beneficial like neuroprotection, angiogenesis, blood vessel integrity and plasticity, as well as destructive like BBB dysfunction, inflammation, gliosis and neuronal death. The review also discusses the role of ncRNAs in inducing tolerance to brain damage.

Ionic imbalance after brain injury leads to edema that is a major promoter of brain damage. In addition, blood-brain barrier (BBB) disruption also leads to secondary brain damage by promoting infiltration of macrophages, neutrophils and cytotoxic T-cells into brain parenchyma. The study by Zhang J et al. shows that controlling Na^+-K^+-$2Cl^-$ cotransporter which plays a central role in ionic balance prevents BBB disruption leading to better functional outcome after CCI injury in mice. This study shows the promise of therapeutic development of drugs to modulate ion channels to promote recovery after TBI.

Increased levels of reactive oxygen species (ROS) leads to oxidative stress which is a known proponent of neuronal death after TBI. The transcription factor Nrf2 induces the transcription of several antioxidant genes and thus helps to dispose the ROS after an injury. In addition, endoplasmic reticulum (ER) dysfunction leads to accumulation of misfolded/unfolded proteins that increase the load on the ubiquitin-proteasomal system (UPS) leading to ER stress. Oxidative stress and ER stress are co-incidental