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Updates on and Advances in Therapeutic Strategies for Traumatic Brain Injury

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Traumatic brain injury (TBI) is a debilitating injury that affects numerous individuals, as it may result from trauma sustained by motor vehicle accidents, sports injuries, combat, or other events. The long-term effects of TBI are debilitating and pervasive and can impact an individual's family, career, and overall ability to function in society. This special issue of *Cell Transplantation* is dedicated to providing new information related to biological therapies for TBI and factors contributing to disability, including discussions about inflammation, the elucidation of new molecular targets, alterations in gene expression, cell therapy, neurogenesis, and therapeutic molecules. This special issue underscores the need for more investigation of TBI and presents a wide array of research currently being conducted.

Galgano et al. open the issue by providing background information and reviewing the current clinical treatment modalities for TBI, including surgical interventions and postinjury seizure prophylaxis. Mild TBI is discussed in a second review by Fehily et al., and the final review discusses how changes in dopamine levels may exacerbate the pathogenesis and pathophysiology of TBI.

In a study of military personnel with TBI, Devoto et al. discuss the role of inflammation in long-term behavioral and neurological deficits resulting from the injury. The researchers found a relationship between chronic inflammation and brain dysfunction and a relationship between the comorbidity of TBI and post-traumatic stress disorder (PTSD) and inflammation.

Other studies in the issue focused on beneficial molecules in TBI therapy. Merkel et al. found that dexamethasone may be a viable option for curbing TBI-associated cocaine dependence, as individuals with TBI are often susceptible to substance abuse. *Withania somnifera*, a root extract commonly used in traditional medicine, was evaluated as a potential neuroprotective agent for TBI by Saykally et al. Lastly, Allitt et al. found that progesterone helped improve the response profile (neuronal firing) in the cortex of a rat model of TBI.

Transplantation studies using extracellular matrix (ECM) and cells are also included in the current issue. Wu et al. used ECM derived from porcine (pig) brains to transplant TBI-modeled mice and found that neurobehavioral function was improved and lesion volume was reduced. Focused ultrasound and magnetic targeting of human neural progenitor cells in rats was explored by Shen et al., who showed that migration of therapeutic cells to the brain was improved. Beretta et al. also transplanted therapeutic cells for a murine model of TBI. Using human neural stem cells (hNSCs), the researchers showed that performance on hippocampal-based memory tasks was improved. Likewise, Wang et al. transplanted a rat model of TBI with mouse-derived neural stem cells (NSCs), which resulted in decreased apoptosis and improved neurological function, as evidenced by neurological severity scores (NSS). The findings in these studies raise the question of whether various pathological features and functional deficits that result from TBI could be improved using a cell-based therapeutic.

Wang et al. further evaluated apoptosis in TBI by testing whether suppression of a member of the tripartite motif (TRIM) protein family, Trim32, could inhibit apoptosis post-TBI. Using TBI rats, the group showed that Trim32 downregulation facilitated recovery of neurological function, as determined by NSS and that suppression of apoptosis was likely the mechanism by which this improvement was achieved. Alteration of protein and gene expression is another topic in this special issue that was next explored by Baek et al., who sought to uncover how gene expression patterns changed in the brain following spinal cord injury (SCI). SCI is another debilitating and trauma-based injury that has an effect on the brain. The group identified several pathways that were altered postinjury and concluded that

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gene expression plays a significant role in the pathophysiology of central nervous system injuries. Shojo et al. used a fluid percussion TBI model to examine the role of two inflammatory signaling molecules, prostaglandin and cyclooxygenase 1, in TBI-related neuroinflammation. The results underscore a need to identify therapeutic targets in future research endeavors.

Also employing the fluid percussion injury model, Shapiro sought to show how hippocampal neurogenesis is altered following TBI. In a brief report, the researcher showed that neurogenesis was significantly decreased at later time points postinjury and postulated that changes in levels of cytokines, chemokines, and growth factors produce an inhospitable environment, thus resulting in stymied neurogenesis.

There is currently a need for more clinical trials for TBI, and there exists a lack of trials that use regenerative medicine techniques. This special issue introduces a myriad of possible therapeutic agents and/or methods and underscores the need for further investigation for this condition.