Advancing stem cells: New therapeutic strategies for treating central nervous system disorders

Introduction

With stem cells' ability to initiate regenerative processes in the brain, stem cell transplantation may be a viable method for ameliorating neurological diseases and disorders. Prior research has demonstrated that cell-based therapies heal brain tissue by cell replacement and secretion of neurotrophic factors in various diseases such as ischemic stroke, traumatic brain injury, and Parkinson's disease (PD). Given the prevalence and severity of these maladies and the promising evidence regarding stem cell transplantation in preclinical animal models, further research and improvements to stem cell therapies are warranted. Moreover, alternative strategies to increase the limited available treatments for these and other brain diseases are welcomed. In this special issue, we explore new methods and knowledge to improve stem cell transplantation in diseases and conditions such as stroke, PD, and depression. Advancing the conventional idea regarding cell replacement in stem cell therapy, stem cells may also transfer healthy mitochondria to diseased ischemic neurons in stroke and improve the therapeutic time window of tissue plasminogen activator (tPA) in a conjunctive therapy for stroke, and human Wharton's Jelly-derived mesenchymal stromal cells (hWJ-MSCs) may rely mainly on trophic factor secretion to induce neuroprotective effects. In addition, trophic factors such as neurotrophin-4/5 (NT-4/5) and glial cell line-derived neurotrophic factor (GDNF) may enhance stem cell survival and differentiation to dopaminergic neurons for PD treatment, while encapsulating mesenchymal stem cells and GDNF-secreting cells may increase graft survival rates and their ability to promote neurogenesis and neurotrophic factor secretion in therapies for depression and PD. Of note, transfecting stem cells with a contrast agent such as a superparamagnetic iron oxide (SPIO) for tracking with magnetic resonance imaging (MRI) after transplantation may render these transplanted cells more vulnerable to toxicity in ischemic and hypoxic conditions. Moreover, other methods such as transient microglia depletion may protect against cosmic radiation-induced cognitive impairments, and focusing on the collaborative efforts between oligodendrocytes and the neurovascular unit cells to repair damaged white matter may improve therapies for white matter injury. The following ten reviews encompass pertinent investigations regarding regenerative therapies for several central nervous system (CNS) diseases and disorders. Ultimately, this editorial highlights innovative strategies and the current knowledge regarding the utility of stem cells and other cells such as microglia and oligodendrocytes in CNS repair, in the hopes of spawning novel therapies to bolster and increase the insufficient number of effective treatments for the aforementioned diseases and conditions.

Chapter 1 – Mitochondrial Targeting as a Novel Therapy for Stroke

Dr. Eleonora Napoli from the University of California, Davis, California, USA, and her collaborators from the University of South Florida (Florida, USA) show that mitochondrial dysfunction is central in ischemic injury, and recent findings of mitochondria transfer from stem cells to damaged cells pave the way for a novel promising strategy for stroke. Stroke is the second leading cause and death worldwide behind heart diseases. Interestingly, the transfer of healthy mitochondria in injured cells by promoting survival, reducing oxidative stress, and restoring bioenergetics proliferation could be an effective strategy for the treatment of stroke.

Chapter 2 – Healthy Mitochondria for Stroke Cells

Dr. Cesar V. Borlongan from the University of South Florida (Florida, USA) analyzes the mechanisms by which stem cells may serve as efficacious sources of healthy mitochondria for ischemic cells, not only neurons but also endothelial cells. By reducing neurovascular unit deficits, mitochondrial transfer could be a robust new tool for the treatment of stroke.

Chapter 3 – Combination Therapy for Ischemic Stroke: Novel Approaches to Lengthen Therapeutic Window of Tissue Plasminogen Activator

Dr. Ike Dela Peña from the University School of Pharmacy of Loma Linda (California, USA) explores different promising pharmacological and nondrug treatments to minimize adverse effects, mainly hemorrhagic transformation, associated with delayed tPA administration.

Chapter 4 – The Final Frontier: Transient Microglia-reduction after Cosmic Radiation Exposure Mitigates Cognitive Impairments and Modulates Phagocytic Activity

Dr. Susanna Rosi from the University of California of San Francisco (California, USA) shows that the temporary microglia depletion could prevent any deleterious cognitive impairments following exposure of cosmic radiation, suggesting a promising strategy to protect astronauts but also cancer patients.

Chapter 5 – Combination of Cell Transplantation and Glial Cell Line-Derived Neurotrophic Factor -Secreting Encapsulated Cells in Parkinson's Disease

Dr. Hans Widmer from the University of Bern (Bern, Switzerland) reports that a combination of rat fetal ventral mesencephalic (VM) tissue and encapsulated cells that secrete GDNF enhanced graft function in an animal model of PD. Therefore, facilitating graft survival may optimize the functional outcomes of the transplanted cells for PD.

Chapter 6 – White Matter Repair: Interaction between Oligodendrocytes and the Neurovascular Unit

Dr. Ken Arai *et al.* from the Neuroprotection Research Laboratory, Massachusetts General Hospital/ Harvard Medical School, focus on neuroprotective strategies, oligovascular signaling in stroke, and remodeling and recovery of the neurovascular unit. In this review, the authors examined the interaction between oligodendrocytes and other cells of the neurovascular unit and how they repair white matter injuries.

Chapter 7 – Human Wharton's Jelly-derived Mesenchymal Stromal Cell Transplant Reduces Ischemic Brain Injury through Glial Cell Line-Derived Neurotrophic Factor

Dr. Yun Wang *et al.* from the National Health Research Institutes of Miaoli (Taiwan) demonstrate that hWJ-MSC transplantation significantly decreased brain infarction and microglia activation in the penumbra leading to a significant reduction of neurological deficits. Interestingly, the incorporation of most of the grafted hWJ-MSCs into IBA1 (+) cells and the increase of GDNF expression in the host brain suggest that the protective effect of hWJ-MSCs may not be led to the survival of the grafted cells, but it may be due to the secretion of trophic factors.

Chapter 8 – Encapsulated Stem Cells Ameliorate Depressive-like Behavior via Growth Factor Secretion

Dr. Yohei Kin *et al.* from the Okayama University Graduate School of Medicine in collaboration with Dr. Borlongan from the University of South Florida examine deep brain stimulation and cell-based therapies for PD, ischemic stroke, and other neurological diseases. In this review, the authors discuss how encapsulating mesenchymal stem cells in cell transplantation treatments enhances these cells' ability to secrete neurotrophic factors, increase neurogenesis, and survive post-transplantation, which may be beneficial for treatment-resistant depression.

Chapter 9 – Effects of Labeling Human Mesenchymal Stem Cells with Superparamagnetic Iron Oxides on Cellular Functions and Magnetic Resonance Contrast in Hypoxic Environments and Long-term Monitoring

Dr. Samuel Grant and Dr. Teng Ma and their coworkers from the Florida Agricultural and Mechanical University–Florida State University College of Engineering and the National High Magnetic Field Laboratory in Florida State University specialize in developing techniques that utilize MRI to evaluate neurological diseases. In this review, they highlight how high amounts of SPIOs may decrease the survival rate of hMSCs in ischemic and hypoxic conditions, information which will be important for cell-based therapies for stroke and other ischemia-related maladies.

Chapter 10 – Neurotrophic Factor-based Strategies to Enhance Survival and Differentiation of Neural Progenitor Cells toward the Dopaminergic Phenotype

Dr. Stefano Di Santo and Dr. Widmer from the University of Bern (Switzerland) evaluate the application of NT-4/5 and GDNF in increasing the dopaminergic phenotypic expression of rat VM tissue as a new strategy of regenerative medicine for PD.

Conclusion

Stem cell therapies and relevant cell-based regenerative medicine approaches hold promise for improving the outcomes of CNS diseases and disorders and may be enhanced by additional knowledge, modification, and novel applications of stem cells, such as stem cell-mediated mitochondrial transfer and stem cell encapsulation. Furthermore, alternative approaches such as transient microglia depletion and emphasizing oligodendrocyte-associated white matter recovery

also appear to be effective potential strategies for CNS rehabilitation. Thus, future studies that improve our understanding of these methods will be necessary to enhance regenerative and neuroprotective therapies for stroke, PD, depression, cosmic radiation-induced cognitive impairment, white matter injury, and other related diseases and conditions in the clinic.

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Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_22_18

How to cite this article: Russo E, Lippert T, Tuazon JP, Borlongan CV. Advancing stem cells: New therapeutic strategies for treating central nervous system disorders. Brain Circ 2018;4:81-3.

Submission: 12-09-2018, Revised: 13-09-2018, Accepted: 13-09-2018