

Editorial

Stem Cells in Traumatic Brain Injury Therapy

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Traumatic brain injury (TBI) is a serious public health and socioeconomic problem throughout the world. Each year, TBI contributes to a substantial number of cases of permanent disability and even death. According to CDC data, about 1.7 million TBI occur every year in the U.S. and at least 5.3 million Americans currently live with disabilities resulting from TBI. In addition, it is also the leading killer of young children. As a result with improving medical technology as well as an improved understanding of TBI, the survival rate of patients with severe TBI has increased significantly. However, a majority of these survivors suffer from varying types of disabilities, such as body motor dysfunction, language and communication difficulties, and psychological and social cognitive defects. Currently, the typical treatments for TBI involve surgery or conservative symptomatic treatment, focusing on preventing secondary injury during the early stages and individually tailored rehabilitation therapies including physical therapy and occupational therapy during late stages. However, these aforementioned therapies have been shown to not be as effectively beneficial for moderately to severely injured patients. In addition, the development of several pharmacological agents, in an attempt to prevent the secondary injury associated with TBI, has also proven to be ineffective [1,2].

Stem cell research and application has continuously widened the margin for formulating new therapies in the hopes of stunting neurological disease and injury. Supported by animal experiments that indicate some CNS damage may be preventable or reversible by stem cell-based approaches, stem cell therapy has been already been applied in clinical trials involving various neurological diseases, such as stroke [3], ALS [4], and PD [5]. From these experimental and clinical trials, two main hypotheses have emerged: 1) cell replacement, i.e. replenish dead or degenerated neurons by exogenous cells to reconstruct damaged neural circuit; 2) cell support or protection, i.e. prevent further cell death/degeneration by modifying microenvironment around vulnerable neurons with secreted trophic factors or cytokines from grafted cells. Other possible hypotheses involve the suppression of neuroinflammation [6] and stimulation of endogenous neurogenic niche for self-regenerative recovery [7].

At present, few clinical trials are undergoing or have been completed for TBI therapy with stem cells [8]. Not only are there ethical issues to consider, by TBI are very inherently complex in nature. Pathophysiological mechanisms and symptomatic manifestations are heterogeneous in TBI, in correspondence

to a wide range of causes (direct impact, rapid acceleration or deceleration, penetrating object and blast waves), which generate various clinical outcomes resulting in different prognoses. Generally, TBI is categorized by mechanical mechanism (closed vs penetrating), by clinical severity (Glasgow coma scale [GCS]), and by assessment of structural damage (neuroimaging) [9]. Because of these varying factors, the heterogeneity of TBI must be considered for the generation of stem cell therapy strategies. For example, ischemic brain damage derived from TBI has extensive similarities with the damage incurred by stroke. In this manner, stem cell treatment on this specific TBI scenario may be able to utilize results and conclusions from previous stroke studies, which have been and continue to be widely studied pre-clinically and clinically.

Stem cell selection for the TBI therapy also needs to be carefully considered based on TBI scenarios and potential therapeutic mechanisms. For example, with TBI resulting in neuronal loss caused by structural damage, the primary target is neural circuit reconstruction to restore function. Because neural stem cells (NSCs, adult or from embryonic) or any other multipotent progenitor cells are able to differentiate into mature neurons and be integrated into host neural circuits to execute related functions, NSCs have been regarded as a reasonable starting place for neural circuit restoration. However, although animal studies demonstrate that transplanted NSCs are indeed able to differentiate into neurons and integrate into host neural circuits, cell replacement may not be the mechanism for observed therapeutic efficacy in several neurological disease animal models [10,11]. More likely, these observed cases of restoration are results of cell support or protection mechanisms and endogenous neurogenic niche stimulation [7]. However, cell replacement strategy is possibly the only approach for the successful recovery of chronic TBI with resulting brain damage. Another stem cell selection example regarding TBI with diffuse axonal injury (DAI) is to reduce axon degeneration by protecting vulnerable axons in order to promote axonal regeneration and remyelination. In this particular case, oligodendrocyte progenitors (OPs) may be an optimal agent to utilize. However in most cases, selective white matter pathways are vulnerable under various TBI conditions and locating these pathways is important for cell delivery. One beneficial feature about OPs is that they have demonstrated the propensity to migrate extensively along white matter pathways

in our experimental DAI model, which suggests that fewer transplantation sites would be needed for cell delivery. OPs have shown promising preclinical results for demyelination diseases and also spinal cord injury so therefore, there is optimism regarding the potential success for the usage of OPs in TBI therapy [12,13]. Additionally, the therapeutic window selection for TBI also needs to be investigated if cell support or protection is regarded as the optimal strategy, in order to judge whether the stem cells would need to be given as early as possible.

Although CNS is an “immune privileged” organ, immune rejection still occurs in stem cell allogeneic transplantation. This is one particular reason why present clinical trial on TBI stem cell therapy is currently using bone marrow mononuclear cell (BMMNC) with autologous transplantation method [8]. The advantages of using autologous BMMNC are: 1) relatively easy collection, 2) rich sources and 3) no immune rejection. The main possible therapeutic mechanism for BMMNC is cell support and protection, which means that BMMNCs need to be delivered acutely or subacutely after TBI. The best way to solve immune rejection for NSCs, OPs, and other possible stem cells that are collected with great difficulty for autologous transplantation is to employ pluripotent stem (iPS) cell technology. This technology offers a promising strategy for stem cell therapy on neurological diseases and injuries, i.e. personalized regenerative medicine. iPS cells produced from patients’ skin fibroblasts or even peripheral blood cells through transcription factor-mediated reprogramming are able to yield required NSCs, OPs, or any other types of cells for autologous transplantation [14]. However, one possible concern regarding iPS cells is the potential for these cells to be subject to sizeable genetic and epigenetic abnormalities, as they have been shown to be susceptible to in recent studies [15].

In conclusion, although there are still many factors to consider regarding stem cell-based therapy, it appears that this method of therapy is a very promising approach for TBI treatment in the future.

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