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# The Potential of Stem Cells in Treatment of Traumatic Brain Injury

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## Abstract

**Purpose of Review—**Traumatic brain injury (TBI) is a global public health concern, with limited treatment options available. Despite improving survival rate after TBI, treatment is lacking for brain functional recovery and structural repair in clinic. Recent studies have suggested that the mature brain harbors neural stem cells which have regenerative capacity following brain insults. Much progress has been made in preclinical TBI model studies in understanding the behaviors, functions, and regulatory mechanisms of neural stem cells in the injured brain. Different strategies targeting these cell population have been assessed in TBI models. In parallel, cell transplantation strategy using a wide range of stem cells has been explored for TBI treatment in pre-clinical studies and some in clinical trials. This review summarized strategies which have been explored to enhance endogenous neural stem cell-mediated regeneration and recent development in cell transplantation studies for post-TBI brain repair.

**Recent Findings—**Thus far, neural regeneration through neural stem cells either by modulating endogenous neural stem cells or by stem cell transplantation has attracted much attention. It is highly speculated that targeting neural stem cells could be a potential strategy to repair and regenerate the injured brain.

**Summary—**Neuroprotection and neuroregeneration are major aspects for TBI therapeutic development. With technique advancement, it is hoped that stem cell-based therapy targeting neuroregeneration will be able to translate to clinic in not so far future.

### Keywords

Traumatic brain injury; Neural stem cells; Endogenous neurogenesis; Subventricular zone; Hippocampus; Cell transplantation; Cognitive function

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Compliance with Ethical Standards

**Conflict of Interest** Nicole M. Weston and Dong Sun declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

Traumatic brain injury (TBI) is a global public health concern, with limited treatment options available. In the USA alone, between 3.2 and 5.3 million people suffer long-term cognitive impairments as a result of TBI [1]. While there have been significant improvement in reducing TBI-related mortality in the past 10 years, approximately 80,000 individuals in the USA annually sustain TBIs that result in significant long-term deficits involving sensory motor and memory functions. TBI causes significant brain tissue damage of both neuronal and white matter with resultant of brain atrophy and neurological functional impairment. Due to the complicity and heterogeneity of TBI, despite intensive research, there is still no effective therapy for TBI. Current strategies are mostly focused on reducing secondary injuries. Strategies targeting regeneration and repair are limited. Recent identification of functional neural stem cells in the mature mammalian brain and technique advancement in generating neural stem cells in culture dish have raised the possibility of developing stem cell-based therapy to repair and regenerate the injured brain following TBI. Two approaches targeting stem cells for neural regeneration either modulating endogenous neural stem cells or utilizing exogenous stem cells are gaining increasing attention. This article summarized studies targeting stem cells as therapy for TBI with manipulation of endogenous or exogenous stem cells in both pre-clinical and clinical settings.

## Targeting Endogenous Neural Stem Cells

### Adult Neural Stem Cells, their Development Process, and Functional Roles in the Normal Brain

Neural stem cells (NSCs) are pluripotent cells residing in the CNS that have unlimited potential of self-renewal and can generate both neurons and glia cell types. Within the adult mammalian brain, NSCs and their fate committed progenitor cells are primarily located in the subventricular zone (SVZ) that surrounds the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus [2, 3]. NSCs in the SVZ generate new neurons migrating along rostral migratory stream to olfactory bulb becoming olfactory granule or periglomerular neurons while NSCs from the DG migrate laterally from the birth place of SGZ to the granular cell layer and differentiate into DG granule cells [4–7]. The developmental stage of adult generated neurons is well characterized in the DG. Briefly, after generation, while more than half of newborn cells are subsequently undergoing apoptosis within the 1st month due to limited trophic support, those survived new neurons project their axons into the hilus and dendrites into the molecular layer with dendritic protrusions typically appearing during the third week [8]. The maturation stage of these cells to begin displaying enhanced excitability and plasticity is between 3 and 7 weeks aligning with the start of dendritic protrusions development [9–13]. The survival and integration during this time point act as rate-limiting steps for the amount of new cells that will be involved in successful maturation and contribution to the circuitry which would make up 6% of the total granule cell population in the DG [7, 8, 14, 15].

The integration of new neurons from the SVZ to the olfactory bulb circuitry holds similarities to the DG neurogenic niche in that less than half of new neurons from the SVZ survive beyond week 4 of maturation [16]. A majority of cells mature into olfactory granule

cells, while the rest differentiate into periglomular neurons (PGNs). Located in the deepest layer, the granule cells are a population of inhibitory interneurons that are very homogenous among one another and extend their dendrites into the external plexiform layer of the olfactory bulb typically maturing at an earlier time point of 2 weeks. Alternatively, those that turn into the PGNs are more differentiated from each other and are located at a superficial location with the olfactory bulb receiving more direct sensory information. [17–19]. The PGNs typically take about 4 weeks to develop their dendritic and axonal structures.

A key difference between the two neurogenic regions is that the olfactory bulb replaces existing neurons with these new neurons, while the dentate gyrus has continuous addition and integration of new neurons [4, 18, 20–22]. The sequential steps of functional maturation directly involve the formation of synapses and fine tuning for these new cells to be dynamically incorporated into the circuit. New neurons form synaptic connections with both afferent and efferent pathways of existing neural circuit and continuously introduce structural plasticity throughout the adulthood. The integration of these new neurons requires a level of plasticity to functionally contribute to the circuit, especially since this ongoing endogenous neurogenesis has functional implications for these regions [23]. Specifically, adult NSC-derived new neurons in the DG play important roles in hippocampal dependent learning and memory functions, particularly in pattern separation and new memory formation [24–27], whereas new olfactory interneurons generated from the SVZ NSCs are necessary in maintaining normal structure and function of the the olfactory bulb as well as several selected olfactory behaviors, such as olfactory discrimination, new order acquisition, and short-term olfactory memory functions [28–30].

Generation of new neurons involves different stages: proliferation or generation of new cells, migration to the appropriate targeted areas, and differentiation into proper neuronal cell types and integration into preexisting neural circuitry. These stages are influenced by many factors including environmental factors such as stress, physical exercise, or enrichment; biochemical factors such as growth factors, steroids, and neurotransmitters; and disruption of normal brain function from disease or injury such as TBI [5, 31–34].

## Adult Neural Stem Cell Response Following TBI

NSCs in the SVZ and hippocampus are versatile responding to many types of stimulants. Enhanced activation of NSCs has been observed in multiple types of experimental TBI models including fluid percussive injury (FPI) [35, 36], controlled cortical impact injury (CCI) [37, 38], closed head weight drop injury [39], and acceleration-impact injury [40]. In all reported studies, the most common and prominent endogenous cell response following TBI is an increase in cell proliferation in both neurogenic regions of the DG and SVZ. Increased generation of new neurons resulted from the TBI-enhanced NSC proliferation was also observed particularly in the hippocampus in these models in the more severely injured animals [39, 41]. Further studies have found that injury-induced new granule neurons sending out axonal projections into the targeted CA3 region suggesting their integration into the existing hippocampal circuitry [41, 42], and this injury-enhanced endogenous NSC response is directly related to the innate cognitive functional recovery following TBI in rodents [43, 44•].

In the human brain, the degree and function of adult neurogenesis are less clear. From autopsy human brain samples, NSCs with proliferative capacity have been found in the SVZ and the hippocampus [45, 46]. However, it is reported that the extent of neurogenesis in the SVZ and migration of new neurons from SVZ to olfactory bulbs and neocortex are rather limited and are only observed in the early childhood [47–49]. However, a recent study has reported a substantial degree of hippocampal neurogenesis in human brains and that the rate of neurogenesis is comparable between middle-aged humans and mice [50]. Thus far, convincing evidence of TBI-induced neurogenesis in human brain is lacking due to difficulties of obtaining human brain samples as well as technical challenges to birth-dating NSCs. Nevertheless, neurons expressing immature neuronal markers were reported in human brains in regions around lesions of focal infarction [51], TBI [52], and subarachnoid hemorrhage [53].

From rodent to human, these above mentioned studies indicated a potential that NSCs from the SVZ and DG may be utilized to develop therapies targeting these cell population to aid in the functional recovery of the injured brain.

## Targeting Neural Stem Cell Population for Endogenous Neural Repair Following TBI

Although TBI enhances endogenous NSCs response, the capacity of this self-repair is limited, with the low survival rate of these newly generated cells and particularly when the hostile environment produced by mass cell death and inflammation is still present following TBI. To utilize this endogenous repair mechanism for the injured brain, varying strategies that can promote proliferation, neuronal differentiation, survival, and migration of NSCs have been explored in recent experimental studies and have shown varying degrees of beneficial effects in improving sensory-motor and cognitive functional recovery of the injured animals.

**Biochemical Approach—**During developmental stage, neurotrophic and growth factors are essential for cell proliferation, differentiation, and survival. In the injured brain, supplementing these factors such as basic fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, brain-derived neurotrophic factor etc. have shown functions recapitulating the developmental stage with enhancement of proliferation, survival of NSCs in the hippocampus and the SVZ, and ultimately improve recovery of cognitive functions of the injured animals [54–57].

Unlike pre-clinical studies, utility of direct application of growth factors for clinic use is limited due to the invasive delivery method. Small molecules which act as agonist mimicking growth factor functions could be more applicable to clinic with better penetration through blood brain barrier and longer half life. Several small moleculars such as a synthetic neurotrophin TrkB receptor agonist, 7,8-dihydroxyflavone; a small-molecule p75NTR signaling modulator, LM11A-31; cerebrolysin, a small neuropeptide derived from purified porcine brain proteins which has similar properties as the endogenous neurotrophic factors; and a small molecule peptide 6, which corresponds to an active region of human ciliary neurotrophic factor (CNTF), have shown different degrees of enhancing NSC proliferation, new neuron survival, and improving functional recovery of the injured animals in different

TBI pre-clinical models [58–62]. Cerebrolysin has shown enhancing cognitive improvements in mild TBI patients in a clinical trial [63].

Apart from growth factors and their mimics, several pharmacology agents and FDA-approved drugs have been identified with functions stimulating endogenous NSC response and improving cognitive recovery of injured animals following TBI. These include erythropoietin (EPO), a hormone-stimulating production of erythrocytes [64, 65]; thymosin β4, a small peptide G-actin sequestering molecule [66]; P7C3 class of aminopropyl carbazole agents [67]; statins, a class of hydroxymethylglutaryl-coenzyme A reductase inhibitors for treating hyperlipidemia; tissue plasminogen activator (tPA), the drug for early stroke treatment; selective serotonin reuptake inhibitor imipramine and fluoxetine; NeuroAid (MLC901), a traditional Chinese medicine used for stroke and angiotensin II receptor type 2 (AT2) agonists [68–74].

**Physical or Other Radical Approaches—**NSCs in the hippocampus respond to physiological stimuli such as physical exercise and environmental enrichment with increased proliferation rate in normal situation [34, 75]. When applied these stimuli to the injured animals at appropriate time following TBI, they show beneficial effect by further increasing generation of new neurons in the hippocampus and improving cognitive recovery [76–78]. Similar positive results were also observed following a transcranial low light laser therapy [76].

In summary, strategies that can significantly influence NSC functions including proliferation, neuronal differentiation, and survival of newly generated neurons have shown beneficial effect in improving the functional recovery of the injured brain. These suggest that targeting endogenous repair mechanisms via neural stem cells has potential for treating the injured brain following TBI.

## Exogenous Stem Cells Via Neural Transplantation for Post-TBI Brain Repair and Regeneration

Following TBI, injury-induced neural tissue loss is permanent. Given the limited population of the endogenous NSCs, neural transplantation supplementing exogenous stem cells to the injured brain is a potential therapy for post-TBI brain repair. Specifically, the introduced cells will not only be able to replace the lost neural population, but also provide neurotrophic support in hopes of reestablishing and stabilizing the injured brain. Thus far, several categories of cells have been tested for post-TBI stem cell therapy including embryonic stem cells, adult-derived NSCs, induced pluripotent stem cells, and mesenchymal stromal cells.

### Embryonic Stem Cells

Embryonic stem (ES) cells derived from fetal or embryonic brains are strongly considered for neural transplantation due to their high degree of plasticity and having the ability to unlimited self-renew and differentiation into all three germinal layers. These cells can differentiate, migrate, and make innervations when implanted into a recipient brain [79]. In pre-clinical TBI studies, NSCs isolated from human fetal brain were capable of survival for

an extended period, migrating to the contralateral cortex and differentiating into neurons and astrocytes after transplantation into the injured brain following a focal brain injury [80]. Transplanted NSCs from human ES cells can differentiate into mature neurons and release growth factors improving cognitive functional recovery of the injured host [81]. Long-term survival of grafted NSCs derived from mice fetal brains is reported up to 1 year with extensive migration in the injured brain and maturation into neurons or glial cells accompanied by improved motor and spatial learning functions of the host [82–84]. Furthermore, ES cells over-expressing growth factors or pre-differentiated into neurotransmitter expressing mature neurons following in vitro manipulation have shown better graft survival and neuronal differentiation after transplanted into the injured brain, and the recipients have enhanced recovery in motor and cognitive functions [85–88].

Although ES cells have high survival and plasticity in neural transplantation, the ethical controversies, risk of transplant rejection, and the possibility of teratoma development limit their clinical application for TBI.

## Adult Neural Stem Cells

As mentioned above, mature mammalian CNS harbors NSCs. Apart from participating endogenous repair, these adult-derived NSCs are capable of becoming region-specific cells when transplanted into the normal adult rodent brains [89–91]. We have found that after transplantation into the injured brain following TBI, these cells can survive for a long period and become region-specific functional cells [92]. Transplantation of the adult-generated NSCs in mouse TBI models has shown improvements of learning deficits [93, 94].

Neural stem/progenitor like cells have been isolated from adult human brain from various regions from neurosurgical resection tissues, and they can become mature neurons and glia in culture dishes [95–102]. As their adult origin, these cells may be possibly used as autologous cell sources for neural transplantation therapies to regenerate the injured CNS as demonstrated in a study after grafting adult human-derived NSCs into the demyelinated rat spinal cord [103]. However, due to their adult origin, these cells show less plasticity when compared to the ES cells. It was reported that only a small portion (4 ± 1%) of cultured adult human NSCs from surgically removed tissue can survive up to 16 weeks following transplantation into the posterior periventricular region in naïve rat brain or in the hippocampal CA1 region following ischemic injury in rat [104]. With such limitation, the application of adult NSCs for TBI in clinic is unrealistic.

## Induced Pluripotent Stem Cells

Most recently and more ethically appealing, induced pluripotent stem cells (iPSCs) have allowed scientists to explore manipulating this highly plastic population. These somatic cell-derived iPSCs can provide large quantities of pluripotent cells that have high plasticity generating cells for all three germ layers including neurons and glia (Takahashi and Yamanaka, 2006). More importantly, iPSCs can be derived from patients themselves and have potential for autologous transplantation, avoiding ethical and graft rejection concerns. These unique properties of iPSCs have raised hope that many neurological diseases including TBI might be cured or treated. Thus far, the prospective of iPSCs for treating TBI

has just begun to be explored. In TBI experimental studies, only two publications were found in PubMed reporting the use of iPSCs for post-TBI transplantation, these studies mainly reported the feasibility of using iPSCs providing very limited information about the fate of transplanted iPSCs in the injured brain [105, 106].

## Mesenchymal Derived Stem Cells

Stem cell therapy using mesenchymal stem cells (MSCs) has been extensively tested in many neurological disorders including TBI in pre-clinical models and clinical trials in recent years. Cells tested in TBI studies include bone marrow stromal cells (BMSCs), human amnion-derived multipotent progenitor cells, human adipose-derived stem cells, human umbilical cord blood, and peripheral blood-derived MSCs [107–109, 110•, 111–113]. These mesenchymal derived cells are undifferentiated cells with mixed cell population including stem and progenitor cells. In culture condition, they can be induced to differentiate into neuronal phenotype. These cells produce high level of growth factors, cytokines, and extracellular matrix molecules with potential neurotrophic or neuroprotective effects in the injured brain [114, 115]. Among the MSCs, the potential of BMSCs for TBI has been extensively tested. Studies have reported that cells being delivered directly into the injured brain, or via intravenous or intra-arterial injections during the acute, sub-acute, or chronic phase after TBI, significant decrease of neurological deficits in motor and cognitive functions was observed [111–113, 116]. The beneficial effort of MSCs is due primarily to the bioactive factors they produced to facilitate the endogenous plasticity and remodeling of the host brain rather than direct neural replacement as direct neuronal differentiation and long-term survival were rarely observed [114]. This is further approved by a recent study showing that administration of cell-free exosomes derived from human BMSCs can improve functional recovery of injured animals following TBI [117].

## Combinational of Stem Cells with Biomaterials

Albeit the multiple cell sources for cell replacement therapeutics, structural damage at the site of injury following TBI often creates a hostile environment preventing long-term survival and integration of the transplanted cells. A large component necessary for cell survival, appropriate incorporation, and maintaining healthy is the conducive extracellular environment. For the injured brain, supplementing appropriate extracellular matrix could aid in recovery of the injured microenvironment and promoting survival, differentiate, and integration of the transplanted cells. There has been a great extent of work done in the field of bioengineering deploying collagen, a major component of the extracellular matrix, for tissue regeneration due to its abundance and accessibility to create a suitable matrix [118]. In TBI models, studies have found that animals that received transplantation of ES-derived NSCs with fibronectin can increase survival and migration of NSCs in the injured brain [119], whereas co-trans plantation of BMSCs with collagen scaffold in the cortex showed increased axonal sprouting in the cortical spinal tract and better improvement of motor and cognitive functional recovery compared to animals with BMSCs only [120, 121]. For effective bioengineer/stem cell transplantation therapy, the ideal substrate should be derived from or most similar to the brain extracellular matrix, and be injectable specifically with the fluidity of the matrix and appreciatively fitting more irregular grooves and folds that are expected in the injured brain [122]. These brain-derived extracellular matrices that are being

developed are classified as hydrogels [123]. In our own hands, we found that transplantation of ES cell-derived NSCs with injectable hydrogels into the injured cavity in cerebral cortex can significantly reduce the injury cavity size and encourage extensive formation of vasculatures and survival of transplanted cells at the site of injury in rats following a cortical impact injury (unpublished data). These studies emphasized the importance of stabilizing extracellular environment for successful stem cell transplantation therapy.

## Other Stem Cell Strategies for TBI

### In Situ Conversion of Glial Cells into Functional Neurons.

Today, significant progress has been made in the field of somatic cell reprogramming. Apart from generating iPSCs in culture dish, current reprogramming techniques enable direct in situ conversion of glial cells into functional neurons, thus creating true autologous cell replacement therapy bypassing neural transplantation procedure. Following brain injury, the glial scar at the site of injury forms a physical and chemical barrier preventing neural regeneration. Direct conversion of glial cells at the scar site into functional neurons can not only solve the inhibitory issue of the scaring tissue but also provide localized functional neurons. Recent studies have successfully provided insight of in situ conversion of glial cells via delivery of neurogenic transcription factors [124, 125]. Reprog ramming of astrocytes into neuroblasts and mature neurons has been achieved by SOX2 overexpression [126, 127•], or by inhibiting Notch1 signaling in astrocytes [128]. Moreover, reactive astrocytes in the cortex of injured or diseased mice brain can be converted into functional neurons by overexpression of transcription factor NeuroD1 [129••]. Following TBI, viral transduction of reprogramming transcription factors Oct4, Sox2, Klf4, and c-Myc can convert reactive astrocytes at the injury site into iPSCs which can further differentiate into both functional neurons and glia in situ filling up the injury cavity [130••]. These studies suggest that direct reprogramming of reactive glial cells to functional neurons at the site of brain injury could be a more attractive strategy for post-TBI brain repair.

## Conclusion and Perspectives

Significant progress has been made in stem cell-based therapy targeting neural regeneration in stroke and neurodegenerative diseases in both preclinical and clinical studies. Extensive studies have shown the prospective of stem cell therapy for treating the injured brain. However, due to the complicity and heterogeneity of brain trauma, post-TBI neural repair and regeneration are still a far reaching goal. There are many unmet challenges for successful stem cell therapy. For endogenous repair through adult neurogenesis, strategies guiding migration of new neurons to the site of injury and promoting long-term survival are necessary. For stem cell transplantation, as the intrinsic properties of grafted cells and the local host environment determine the fate of transplanted cells, an optimal cell source and a controlled host environment are necessary for successfully neural transplantation. These challenges must be addressed in preclinical TBI studies before stem cell-based therapies can be applied to clinic.

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•• Of major importance

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