NEURAL REGENERATION RESEARCH
January 2016, Volume 11, Issue 1
www.nrronline.org

SPECIAL ISSUE

The potential of neural transplantation for brain repair and regeneration following traumatic brain injury

Dong Sun*

Department of Neurosurgery, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA

How to cite this article: *Sun D (2016) The potential of neural transplantation for brain repair and regeneration following traumatic brain injury. Neural Regen Res 11(1):18-22.*

Funding: *This study was funded by the National Institutes of Health Grant No. NS078710.*

Abstract

Traumatic brain injury is a major health problem worldwide. Currently, there is no effective treatment to improve neural structural repair and functional recovery of patients in the clinic. Cell transplantation is a potential strategy to repair and regenerate the injured brain. This review article summarized recent development in cell transplantation studies for post-traumatic brain injury brain repair with varying types of cell sources. It also discussed the potential of neural transplantation to repair/promote recovery of the injured brain following traumatic brain injury.

Key Words: *traumatic brain injury; stem cells; neural transplantation; regeneration; functional recovery*

Correspondence to:
Dong Sun, M.D., Ph.D., dsun@vcu.edu.

orcid:
0000-0002-3837-7319 (Dong Sun)

doi: *10.4103/1673-5374.169605*
http:*//www.nrronline.org/*

Accepted: *2015-08-10*

Introduction

Following traumatic brain injury (TBI), the primary and secondary injury-induced neural tissue loss is permanent. As the mature mammalian brain has limited capacity to repair and replace the damaged neurons, neural transplantation is a prospective therapy for TBI as transplanted cells may differentiate into region-specific cells and integrate into the host tissue to replace the lost cells in the injured brain. Additionally, transplanted cells could provide trophic support to the host tissue to facilitate regeneration. Over the past decades, researchers have explored a wide array of cell sources for neural transplantation. These cells include embryonic stem cells isolated from fetal or embryonic tissue, mesenchymal stromal cells such as bone marrow stromal cells and umbilical cord cells, adult neural stem cells (NSCs) and, more recently, induced pluripotent stem cells (iPSCs) (**Figure 1**). The following sections will discuss the application of these cell types in the setting of TBI.

Embryonic Stem Cells

Embryonic stem (ES) cells are pluripotent stem cells that have unlimited capacity of self-renewal and can give rise to cells of all three primary germ layers. Due to their high plasticity, ES cells are the idea cell source for neural transplantation. When transplanted into normal or damaged CNS, human ES cells can differentiate, migrate and are capable of making innervations (Hentze et al., 2007). Thus far, ES cells derived from human or mouse fetal brains have been tested as transplantation cell source for TBI treatment in animal studies in different TBI models with varying results reported (Riess et al., 2002; Shear et al., 2004; Wennersten et al., 2004; Boockvar et al., 2005).

An earlier study showed that NSCs from human ES cells isolated from fetal brain were capable of survival for an extended period of time up to 6 weeks, migrating to the contralateral cortex and differentiating into neurons and astrocytes when transplanted into the injured brain following a cortical contusion injury (Wennersten et al., 2004). Gao et al. (2006) have reported that NSCs from human ES cells survive and differentiate to neurons after transplantation into the injured brain when examined at 2 weeks after cell injection, and the injured animals with cell transplantation had improved cognitive functional recovery. Shear et al. (2004) assessed the long-term survival, migration, differentiation and functional significance of NSCs derived from mouse fetal brain after transplanted into the injured brain up to 1 year post-transplantation. They found that the injured animals receiving transplants showed significant improvement in motor and spatial learning functions, and the transplanted cells migrated widely in the injured brain, with the majority of transplanted cells expressing NG2, an oligodendrocyte progenitor cell marker but not neuronal markers (Shear et al., 2004). Post-TBI neural transplantation of immortalized fetal ES-derived NSCs (C17.2 cells) has also shown improved motor function with the transplanted cells surviving for up to 13 weeks and differentiation into mature neurons and glial cells (Riess et al., 2002; Boockvar et al., 2005). *In vitro* modified ES cells either pre-differentiated into mature

neurons expressing neurotransmitters or over-expressing growth factors such as brain cell line-derived growth factor (GDNF), brain derived neurotrophic factor (BDNF), and human multi-neurotrophins showed beneficial effects when transplanted into the injured animals by promoting motor, and cognitive improvements concomitant with better graft survival and neuronal differentiation (Bakshi et al., 2006; Becerra et al., 2007; Ma et al., 2012; Blaya et al., 2015).

Taken together, these data suggest that post-TBI transplantation using ES-derived cells can restore motor and cognitive functions of the injured animals. However, the beneficial effect of the transplanted cells may be associated with neural trophic effect of the transplanted cells rather than directly neural replacement as long term survival and neuronal differentiation is rather limited. Skardelly et al. (2011, 2014) found that following transplantation of pre-differentiated human fetal ES cells, either focally into the injured rat brain or systemically following a controlled cortical injury, a transient increase of angiogenesis and reduced astrogliosis were observed together with improved long-term motor functional improvement, reduced brain injury lesion volume and increased neuronal survival in the border zone of the lesion; however, graft differentiation was rare, and some of the beneficial effects of cell transplantation were diminished at 12 weeks after transplantation. Further studies are needed to investigate how to prolong the survival of transplanted cells and improve their integration into functional neural circuitry by modulating the injured host environment. Caution must be taken when working with multipotent ES cells as undifferentiated ES cells have the risk of potential tumor formation (Riess et al., 2007).

Adult NSCs

Recent findings show that the mature mammalian CNS harbors multipotent stem cells capable of differentiation into a variety of specialized cells throughout life (Lois and Alvarez-Buylla, 1993; Gage et al., 1998). In the adult mammalian CNS, the NSCs/neural progenitor cells (NPCs) are primarily confined to the subventricular zone (SVZ) surrounding the lateral ventricle and the dentate gyrus (DG) of the hippocampus (Altman and Das, 1965; Lois and Alvarez-Buylla, 1993). Aside from these major neurogenic regions, adult neurogenesis in rodents has also been reported in other regions in the CNS including the striatum, substantia nigra, cortex and spinal cord (Weiss et al., 1996; Palmer et al., 1999; Lie et al., 2002). These adult derived NSCs express low levels of major histocompatibility complex antigens (Klassen et al., 2003) and display high survival rate. They become region-specific cells when transplanted into the normal adult rat brains (Gage et al., 1995; Zhang et al., 2003; Richardson et al., 2005). When transplanted into the injured brain in a rat experimental TBI model, we found that adult derived NSCs can survive for an extended period in the injured brain (Sun et al., 2011). Many cells migrated out of the injection site into surrounding areas expressing markers for mature astrocytes or oligodendrocytes. Electrophysiological studies showed that the transplanted cells possessed typical mature glial cell properties demonstrating that adult derived neural stem cells became region-specific functional cells (Sun et al., 2011).

In humans, multipotent stem/progenitors cells have been identified and successfully isolated from various regions of adult human brain including the hippocampus, SVZ, neocortex, and subcortical white matters from neurosurgical resection tissues (Kukekov et al., 1999; Roy et al., 2000; Arsenijevic et al., 2001; Brunet et al., 2002, 2003; Windrem et al., 2002; Nunes et al., 2003; Richardson et al., 2006). This has raised the possibility of using these cells as autologous cell sources for transplantation therapies. Indeed, Brunet et al. (2005) demonstrated that adult monkey NSCs/NPCs, derived from cortical biopsy, survived for at least 3 months and displayed a neuronal phenotype after re-implantation into the normal or ibotenic acid excitotoxic lesioned motor cortex of the donor brains (Brunet et al., 2005). These cells may also be possible to restore the anatomy and function of the injured CNS as shown in a study after grafting adult human NSCs/NPCs into the demyelinated rat spinal cord (Akiyama et al., 2001).

To date, very few studies have attempted to examine the behavior of adult derived human NSCs/NPCs in the injured mature CNS. Olstorn et al. (2007) recently reported that a small portion (4 ± 1%) of adult human NSCs/NPCs can survive for 16 weeks after transplantation into the posterior periventricular region in normal adult rats or rats with hippocampal CA1 ischemic injury. Although the results of this study are promising, questions remain whether these cells become anatomically and functionally integrated into the injured brain and whether the proportions of surviving cells can be increased by transplanting NSCs/NPCs at a different developmental stage.

Bone Marrow Stromal Cells (BMSCs)

Due to ethical and immunological concerns as well as the risk of tumorigenesis, the translational value of using ES cells for clinic application is limited. Autologous transplantation of NSCs isolated from neurosurgical removed brain tissue from TBI patients is an attractive strategy; however, thus far the success of long term cell survival and functional outcomes of these cells in the treatment of experimental TBI is rather limited. Due to these limitations, adult derived mesenchymal cells, particularly BMSCs, have received much attention.

BMSCs are undifferentiated cells with mixed cell population including stem and progenitor cells. These cells can be easily isolated from the mononuclear fraction of bone marrow from patients and be expanded in culture without ethical and technique concerns. Another advantage of considering BMSCs for cell transplantation is the low antigenicity due to their low expression of the major histocompatibility complex antigens (MHC Class II) (Le and Ringden, 2005). In addition, these cells produce high level of growth factors, cytokines and extracellular matrix molecules that could have potential neurotrophic or neuroprotective effects in the injured brain. As a matter of fact, all studies using BMSCs for neural transplantation have demonstrated that the beneficial effects of BSMCs are attributed to their neurotrophic, neuroprotective and anti-inflammatory effects rather than direct cell replacement (Li and Chopp, 2009; Zhang et al., 2013).

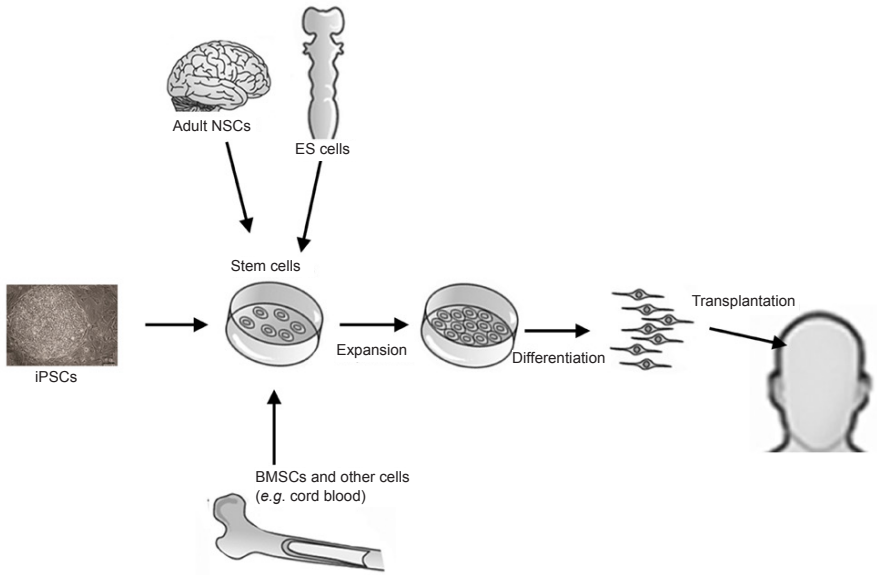

Figure 1 Schematic figure depicts the source of donor cells used for transplantation.

The potential of BMSCs for treating TBI has been extensively assessed in experimental TBI models. Cells were delivered either focally to the injured brain, or systemically through intravenous or intra-arterial injections at the acute or sub-acute phase after TBI and significant reduction of neurological deficits including motor and cognitive deficits was reported. For example, intracranial injection of rat BMSCs into the brain region adjacent to the brain lesion site or intravenous injection of cells at 24 hours after a controlled cortical contusion injury in rats were reported and they found that the injured animals had improved sensory motor functional improvement (Lu et al., 2001; Mahmood et al., 2001, 2003). When human BMSCs were combined with collagen scaffolds and transplanted into the injury cavity at 4 or 7 days following TBI, animals had significantly improved sensorimotor and spatial learning functions, together with reduced brain lesion volume and enhanced focal brain angiogenesis (Lu et al., 2007; Xiong et al., 2009). Co-transplantation of BMSCs with collagen scaffolds has also shown improved cell survival and neurite outgrowth and better functional recovery (Guan et al., 2013). The effect of BMSCs in improving sensorimotor function of injured animals was reported even when delivered at 2 months following TBI (Bonilla et al., 2009). Further studies have demonstrated that the beneficial effort of BMSCs in the injured brain is due largely to their production of bioactive factors which facilitates the endogenous plasticity and remodeling of the host brain (Li and Chopp, 2009). Although low number of BMSCs was found in the injured brain expressing neuronal or glial markers (Mahmood et al., 2001, 2003, 2006), no study has sufficiently demonstrated that MSCs can be fully differentiated into functional neurons *in vivo*. Taken together, extensively experimental studies have demonstrated the beneficial effects of BMSCs in the injured brain and highlight the potential of using BMSCs for TBI treatment in clinic.

Other Potential Types of Cells and Strategies for Cell Replacement Therapy

Apart from the aforementioned stem cells, in recent years researchers have explored several other type of stem or stem like cells for TBI application. Thus far, published data have reported that human amnion-derived multipotent progenitor cells significantly attenuated axonal degeneration, improved neurological function, and protected brain tissue morphology of the injured rats (Chen et al., 2009; Yan et al., 2013). Intravenous administration of human adipose-derived stem cells or culture medium into a controlled cortical impact rat model significantly improved motor and cognitive functions and reduced focal tissue damage and hippocampal cell loss (Tajiri et al., 2014).

The human umbilical cord blood is an abundant source of multiple stem cells, including hematopoietic stem cells, mesenchymal stem cells, unrestricted somatic stem cells, and embryonic-like stem cells. These cells can be easily harvested without ethical controversy and can be an attractive source of stem cells for brain repair. Thus far, studies have shown that these cells can survive at the injury sites and promote survival of local host neurons in ischemic and spinal cord injury animal models (Sun and Ma, 2013). In a small scale of clinic trial of using these cells for treating TBI patients, it was reported that patients treated with umbilical cord stem cells had improved neurological function and self-care compared to the control group with no cell transplantation (Wang et al., 2013). Similar to BMSCs, the reported beneficial effect of post-TBI transplantation with these cells is likely due to the neurotrophic effect of the transplanted cells, as direct neuronal differentiation and long term survival were rarely observed.

Compared to the aforementioned MSCs, peripheral blood derived MSCs may be a more approachable cell source. In a recent study, post-TBI transplantation of a subpopulation of human peripheral blood derived MSCs following *in vitro* priming resulted in improved cognitive function, decreased apoptosis of injured cortical brain tissue, and increased production of neurotrophic factors while some transplanted cells migrated to the site of injury with extended survival and neuronal differentiation at 3 months after injection into

the lateral ventricle (Nichols et al., 2013).

Recent development of somatic cell reprogramming which generates induced pluripotent stem cells (iPSCs) provides prospects for novel neural replacement strategies. Human iPSCs possess dual properties of unlimited self-renewal and the pluripotent potential to differentiate into multi-lineage cells without ethical concerns. More importantly, patient-specific iPSCs can serve as autologous cell source for transplantation without encountering graft rejection. These unique properties of iPSCs have raised the widespread hope that many neurological diseases including TBI might be cured or treated. Thus far rapid progress has been made in the field of reprogramming, however, the optimal source of somatic cells used for applications in neurological disorders has not yet been identified.

Compared to direct cell transplantation using exogenous cell source, *in situ* neuronal generation/cell replacement at the site of injury could be of greater potential for brain repair. Recent studies have reported *in vivo* reprogramming of astrocytes into neuroblasts by SOX2 overexpression (Niu et al., 2013), or by inhibiting Notch1 signaling in astrocytes (Magnusson et al., 2014). Moreover, reactive astrocytes in the cortex of injured or diseased mouse brain can be converted into functional neurons by overexpression of transcription factor NeuroD1 (Guo et al., 2014). 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

Extensive studies have shown the prospective of brain repair through cell replacement strategy using varying types of stem cells. However, to successfully repair and regenerate the injured brain with stem cells, many challenges must be overcome. One major challenge is the focal microenvironment of the site of injury. Following TBI, primary brain damage together with secondary tissue loss induced by ischemia, excitotoxicity, oxidative stress and inflammation creates a hostile environment preventing the survival and integration of the transplanted cells. Thus far, ample studies have supported the notion that the *in vivo* fate of transplanted cells is regulated by the intrinsic properties of grafted cells and the local environmental cues in the host. These challenges must be overcome in experimental TBI studies before moving forward stem cell therapies for treating the injured brain clinically.

References

Akiyama Y, Honmou O, Kato T, Uede T, Hashi K, Kocsis JD (2001) Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Exp Neurol 167:27-39.

Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124:319-335.

Arsenijevic Y, Villemure JG, Brunet JF, Bloch JJ, Deglon N, Kostic C, Zurn A, Aebischer P (2001) Isolation of multipotent neural precursors residing in the cortex of the adult human brain. Exp Neurol 170:48-62.

Bakshi A, Shimizu S, Keck CA, Cho S, LeBold DG, Morales D, Arenas E, Snyder EY, Watson DJ, McIntosh TK (2006) Neural progenitor cells engineered to secrete GDNF show enhanced survival, neuronal differentiation and improve cognitive function following traumatic brain injury. Eur J Neurosci 23:2119-2134.

Becerra GD, Tatko LM, Pak ES, Murashov AK, Hoane MR (2007) Transplantation of GABAergic neurons but not astrocytes induces recovery of sensorimotor function in the traumatically injured brain. Behav Brain Res 179:118-125.

Blaya MO, Tsoulfas P, Bramlett HM, Dietrich WD (2015) Neural progenitor cell transplantation promotes neuroprotection, enhances hippocampal neurogenesis, and improves cognitive outcomes after traumatic brain injury. Exp Neurol 264:67-81.

Bonilla C, Zurita M, Otero L, Aguayo C, Vaquero J (2009) Delayed intralesional transplantation of bone marrow stromal cells increases endogenous neurogenesis and promotes functional recovery after severe traumatic brain injury. Brain Inj 23:760-769.

Boockvar JA, Schouten J, Royo N, Millard M, Spangler Z, Castelbuono D, Snyder E, O'Rourke D, McIntosh T (2005) Experimental traumatic brain injury modulates the survival, migration, and terminal phenotype of transplanted epidermal growth factor receptor-activated neural stem cells. Neurosurgery 56:163-171.

Brunet JF, Pellerin L, Arsenijevic Y, Magistretti P, Villemure JG (2002) A novel method for in vitro production of human glial-like cells from neurosurgical resection tissue. Lab Invest 82:809-812.

Brunet JF, Pellerin L, Magistretti P, Villemure JG (2003) Cryopreservation of human brain tissue allowing timely production of viable adult human brain cells for autologous transplantation. Cryobiology 47:179-183.

Brunet JF, Rouiller E, Wannier T, Villemure JG, Bloch J (2005) Primate adult brain cell autotransplantation, a new tool for brain repair? Exp Neurol 196:195-198.

Chen Z, Tortella FC, Dave JR, Marshall VS, Clarke DL, Sing G, Du F, Lu XC (2009) Human amnion-derived multipotent progenitor cell treatment alleviates traumatic brain injury-induced axonal degeneration. J Neurotrauma 26:1987-1997.

Gage FH, Coates PW, Palmer TD, Kuhn HG, Fisher LJ, Suhonen JO, Peterson DA, Suhr ST, Ray J (1995) Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. Proc Natl Acad Sci U S A 92:11879-11883.

Gage FH, Kempermann G, Palmer TD, Peterson DA, Ray J (1998) Multipotent progenitor cells in the adult dentate gyrus. J Neurobiol 36:249-266.

Gao J, Prough DS, McAdoo DJ, Grady JJ, Parsley MO, Ma L, Tarensenko YI, Wu P (2006) Transplantation of primed human fetal neural stem cells improves cognitive function in rats after traumatic brain injury. Exp Neurol 201:281-292.

Guan J, Zhu Z, Zhao RC, Xiao Z, Wu C, Han Q, Chen L, Tong W, Zhang J, Han Q, Gao J, Feng M, Bao X, Dai J, Wang R (2013) Transplantation of human mesenchymal stem cells loaded on collagen scaffolds for the treatment of traumatic brain injury in rats. Biomaterials 34:5937-5946.

Guo Z, Zhang L, Wu Z, Chen Y, Wang F, Chen G (2014) In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. Cell Stem Cell 14:188-202.

Hentze H, Graichen R, Colman A (2007) Cell therapy and the safety of embryonic stem cell-derived grafts. Trends Biotechnol 25:24-32.

Klassen H, Imfeld KL, Ray J, Young MJ, Gage FH, Berman MA (2003) The immunological properties of adult hippocampal progenitor cells. Vision Res 43:947-956.

Kukekov VG, Laywell ED, Suslov O, Davies K, Scheffler B, Thomas LB, O'Brien TF, Kusakabe M, Steindler DA (1999) Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. Exp Neurol 156:333-344.

Le BK, Ringden O (2005) Immunobiology of human mesenchymal stem cells and future use in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 11:321-334.

Li Y, Chopp M (2009) Marrow stromal cell transplantation in stroke and traumatic brain injury. Neurosci Lett 456:120-123.

Lie DC, Dziewczapolski G, Willhoite AR, Kaspar BK, Shults CW, Gage FH (2002) The adult substantia nigra contains progenitor cells with neurogenic potential. J Neurosci 22:6639-6649.

Lois C, Alvarez-Buylla A (1993) Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. Proc Natl Acad Sci U S A 90:2074-2077.

Lu D, Mahmood A, Qu C, Hong X, Kaplan D, Chopp M (2007) Collagen scaffolds populated with human marrow stromal cells reduce lesion volume and improve functional outcome after traumatic brain injury. Neurosurgery 61:596-602.

Lu D, Mahmood A, Wang L, Li Y, Lu M, Chopp M (2001) Adult bone marrow stromal cells administered intravenously to rats after traumatic brain injury migrate into brain and improve neurological outcome. Neuroreport 12:559-563.

Ma H, Yu B, Kong L, Zhang Y, Shi Y (2012) Neural stem cells over-expressing brain-derived neurotrophic factor (BDNF) stimulate synaptic protein expression and promote functional recovery following transplantation in rat model of traumatic brain injury. Neurochem Res 37:69-83.

Magnusson JP, Goritz C, Tatarishvili J, Dias DO, Smith EM, Lindvall O, Kokaia Z, Frisen J (2014) A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science 346:237-241.

Mahmood A, Lu D, Lu M, Chopp M (2003) Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells. Neurosurgery 53:697-702.

Mahmood A, Lu D, Yi L, Chen JL, Chopp M (2001) Intracranial bone marrow transplantation after traumatic brain injury improving functional outcome in adult rats. J Neurosurg 94:589-595.

Mahmood A, Lu D, Qu C, Goussev A, Chopp M (2006) Long-term recovery after bone marrow stromal cell treatment of traumatic brain injury in rats. J Neurosurg 104:272-277.

Nichols JE, Niles JA, DeWitt D, Prough D, Parsley M, Vega S, Cantu A, Lee E, Cortiella J (2013) Neurogenic and neuro-protective potential of a novel subpopulation of peripheral blood-derived CD133+ ABCG2+CXCR4+ mesenchymal stem cells: development of autologous cell-based therapeutics for traumatic brain injury. Stem Cell Res Ther 4:3.

Niu W, Zang T, Zou Y, Fang S, Smith DK, Bachoo R, Zhang CL (2013) In vivo reprogramming of astrocytes to neuroblasts in the adult brain. Nat Cell Biol 15:1164-1175.

Nunes MC, Roy NS, Keyoung HM, Goodman RR, McKhann G, Jiang L, Kang J, Nedergaard M, Goldman SA (2003) Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. Nat Med 9:439-447.

Olstorn H, Moe MC, Roste GK, Bueters T, Langmoen IA (2007) Transplantation of stem cells from the adult human brain to the adult rat brain. Neurosurgery 60:1089-1098.

Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH (1999) Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. J Neurosci 19:8487-8497.

Richardson RM, Broaddus WC, Holloway KL, Sun D, Bullock MR, Fillmore HL (2005) Heterotypic neuronal differentiation of adult subependymal zone neuronal progenitor cells transplanted to the adult hippocampus. Mol Cell Neurosci 28:674-682.

Richardson RM, Holloway KL, Bullock MR, Broaddus WC, Fillmore HL (2006) Isolation of neuronal progenitor cells from the adult human neocortex. Acta Neurochir (Wien) 148:773-777.

Riess P, Molcanyi M, Bentz K, Maegele M, Simanski C, Carlitscheck C, Schneider A, Hescheler J, Bouillon B, Schafer U, Neugebauer E (2007) Embryonic stem cell transplantation after experimental traumatic brain injury dramatically improves neurological outcome, but may cause tumors. J Neurotrauma 24:216-225.

Riess P, Zhang C, Saatman KE, Laurer HL, Longhi LG, Raghupathi R, Lenzlinger PM, Lifshitz J, Boockvar J, Neugebauer E, Snyder EY, McIntosh TK (2002) Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury. Neurosurgery 51:1043-1052.

Roy NS, Benraiss A, Wang S, Fraser RA, Goodman R, Couldwell WT, Nedergaard M, Kawaguchi A, Okano H, Goldman SA (2000) Promoter-targeted selection and isolation of neural progenitor cells from the adult human ventricular zone. J Neurosci Res 59:321-331.

Shear DA, Tate MC, Archer DR, Hoffman SW, Hulce VD, LaPlaca MC, Stein DG (2004) Neural progenitor cell transplants promote long-term functional recovery after traumatic brain injury. Brain Res 1026:11-22.

Skardelly M, Gaber K, Burdack S, Scheidt F, Hilbig H, Boltze J, Forschler A, Schwarz S, Schwarz J, Meixensberger J, Schuhmann MU (2011) Long-term benefit of human fetal neuronal progenitor cell transplantation in a clinically adapted model after traumatic brain injury. J Neurotrauma 28:401-414.

Skardelly M, Gaber K, Burdack S, Scheidt F, Schuhmann MU, Hilbig H, Meixensberger J, Boltze J (2014) Transient but not permanent benefit of neuronal progenitor cell therapy after traumatic brain injury: potential causes and translational consequences. Front Cell Neurosci 8:318.

Sun D, Gugliotta M, Rolfe A, Reid W, McQuiston AR, Hu W, Young H (2011) Sustained Survival and Maturation of Adult Neural Stem/Progenitor Cells after Transplantation Into the Injured Brain. J Neurotrauma.

Sun T, Ma QH (2013) Repairing neural injuries using human umbilical cord blood. Mol Neurobiol 47:938-945.

Tajiri N, Acosta SA, Shahaduzzaman M, Ishikawa H, Shinozuka K, Pabon M, Hernandez-Ontiveros D, Kim DW, Metcalf C, Staples M, Dailey T, Vasconcellos J, Franyuti G, Gould L, Patel N, Cooper D, Kaneko Y, Borlongan CV, Bickford PC (2014) Intravenous transplants of human adipose-derived stem cell protect the brain from traumatic brain injury-induced neurodegeneration and motor and cognitive impairments: cell graft biodistribution and soluble factors in young and aged rats. J Neurosci 34:313-326.

Wang S, Cheng H, Dai G, Wang X, Hua R, Liu X, Wang P, Chen G, Yue W, An Y (2013) Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury. Brain Res 1532:76-84.

Weiss S, Dunne C, Hewson J, Wohl C, Wheatley M, Peterson AC, Reynolds BA (1996) Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. J Neurosci 16:7599-7609.

Wennersten A, Meier X, Holmin S, Wahlberg L, Mathiesen T (2004) Proliferation, migration, and differentiation of human neural stem/progenitor cells after transplantation into a rat model of traumatic brain injury. J Neurosurg 100:88-96.

Windrem MS, Roy NS, Wang J, Nunes M, Benraiss A, Goodman R, McKhann GM, Goldman SA (2002) Progenitor cells derived from the adult human subcortical white matter disperse and differentiate as oligodendrocytes within demyelinated lesions of the rat brain. J Neurosci Res 69:966-975.

Xiong Y, Qu C, Mahmood A, Liu Z, Ning R, Li Y, Kaplan DL, Schallert T, Chopp M (2009) Delayed transplantation of human marrow stromal cell-seeded scaffolds increases transcallosal neural fiber length, angiogenesis, and hippocampal neuronal survival and improves functional outcome after traumatic brain injury in rats. Brain Res 1263:183-191.

Yan ZJ, Zhang P, Hu YQ, Zhang HT, Hong SQ, Zhou HL, Zhang MY, Xu RX (2013) Neural stem-like cells derived from human amnion tissue are effective in treating traumatic brain injury in rat. Neurochem Res 38:1022-1033.

Zhang R, Liu Y, Yan K, Chen L, Chen XR, Li P, Chen FF, Jiang XD (2013) Anti-inflammatory and immunomodulatory mechanisms of mesenchymal stem cell transplantation in experimental traumatic brain injury. J Neuroinflammation 10:106.

Zhang RL, Zhang L, Zhang ZG, Morris D, Jiang Q, Wang L, Zhang LJ, Chopp M (2003) Migration and differentiation of adult rat subventricular zone progenitor cells transplanted into the adult rat striatum. Neuroscience 116:373-382.