Stem Cells and Cloning: Advances and Applications

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REVIEW

Therapeutic Application of Stem Cells in the Repair of Traumatic Brain Injury

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Abstract: Traumatic brain injury is the main cause of injury-related deaths and disabilities throughout the world, which is characterized by a disruption of the normal physiology of the brain following trauma. It can potentially cause severe complications such as physical, cognitive, and emotional impairment. In addition to understanding traumatic brain injury pathophysiology, this review explains the therapeutic potential of stem cells following brain injury in two pathways: response of endogenous neurogenic cells and transplantation of exogenous stem cell therapy. After traumatic brain injuries, clinical evidence indicated that endogenous neural progenitor cells might play an important role in regenerative medicine to treat brain injury. This is due to an increased neurogenic regeneration ability of these cells following brain injury. Besides, exogenous stem cell transplantation has also accelerated immature neuronal development and increased endogenous cellular proliferation in the damaged brain region. Therefore, a better understanding of the endogenous neural stem cell's regenerative ability and the effect of exogenous stem cells on proliferation and differentiation ability may help researchers to understand how to increase functional recovery and tissue repair following injury.

Keywords: traumatic brain injury, stem cell therapy, neural stem cells, endogenous neurogenesis, cell transplantation

Introduction

Traumatic brain injury is one of the main causes of deaths, disabilities, and hospitalization in the world. In the USA, around 30% of all injury-related deaths are due to traumatic brain injury.[1] Globally, traumatic brain injury affects the lives of about 10 million people each year.[2] It happened as the brain tissue is damaged by an external force, the result of direct impact, rapid acceleration or deceleration, a piercing object, and blast waves from an explosion.[3] Visual impairment, cognitive dysfunction, hearing loss, and mental health disorders are among the most common complications affecting traumatic brain injury patients and their families. The pathophysiology of traumatic brain injury is not clear since the structure of the brain is complex with many cell types such as neurons, astrocytes, oligodendrocytes, microglia, and multiple subtypes of these cells. Traumatic brain injury occurs in two phases. These are primary (acute) and secondary (late) brain injuries. The primary injury is the initial blow to the head; in this phase, brain tissue and cells such as neurons, glial cells, endothelial cells, and the blood–brain barrier are damaged by mechanical injury. The secondary injury occurs after primary injury and in these late phases, several toxins are released from the injured cells leading to the formation of cytotoxic cascades, which increase the initial brain damage.[4] The primary brain injury causes the dysfunction of the blood–brain barrier and initiates local inflammation and secondary neuronal injury. In addition, severe and long-term inflammation causes severe neurodegenerative and inflammatory diseases. Repairing of tissue damage needs the inhibition of secondary injury and rapid regeneration of injured tissue.[5] Depending on the nature of the injury, neurons and neuroglial cells may be damaged; excessive bleeding may happen, axons may be destroyed and a contusion may occur.[6] Moreover, the pathogenesis of traumatic brain injury involves blood–brain barrier damage, neural inflammation, and diffuse neuronal degeneration.[7] Unlike other organs, it has long been thought that mature brain tissue cannot be able to repair itself after injury.[8] However, the current research indicated that multipotent neural stem/

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progenitor cells are residing in some areas of the brain throughout the lifespan of an animal, implying the mature brain's ability to produce new neurons and neuroglial cells.[9] In the previous decades, several studies have shown that the mature neurons in the hippocampal dentate gyrus of the brain play significant roles in hippocampal-induced learning and memory activities,[9] while new olfactory interneurons produced from the subventricular zone are essential for the appropriate functioning of the olfactory bulb network and some specific olfactory behaviors.[10] After traumatic brain injuries, clinical evidence indicated that endogenous neural progenitor cells might play an important role in regenerative medicine to treat brain injury because an increased neurogenic regeneration ability has been reported in different types of brain injury models of animal and human studies.[11] Nowadays, there is a new therapeutic approach for traumatic brain injury that involves the use of stem cells for neural regeneration and restoration. Exogenous stem cell transplantation has been found to accelerate immature neuronal development and increase endogenous cellular proliferation in the damaged brain region.[12] A better understanding of the endogenous neural stem cell's regenerative ability as well as the effect of exogenous neural stem cells on proliferation and differentiation may help researchers better understand how to increase functional recovery and brain tissue repair following injury. Therefore, in this study, we discussed the therapeutic effects of stem cells in the repair of traumatic brain injury.

Endogenous Neurogenic Stem Cells in Normal Animal Brain

Traumatic brain injury causes severe stress on the brain, making it extremely hard to keep appropriate cognitive abilities. Even though many organs in the body, for example, the skin, can regenerate following injury, the brain tissue may not easily repair. In the adult brain, endogenous neural stem cells are primarily localized to the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus.[13] In the subventricular zone, neural stem/progenitor cells generate neuronal and oligodendroglial progenies.[14] Most of the new neurons produced from the subventricular zone migrate via the rostral migratory stream, eventually becoming olfactory interneurons in the olfactory bulb.[15] A few subventricular zone-derived new neurons travel into cortical areas for an unknown cause but may be related to tissue repair or renewal mechanisms.[16] Similarly, newly produced dentate gyrus cells travel laterally into the dentate granule cell layer and become fully mature in a few weeks through a process known as adult hippocampus neurogenesis.[17] However, it is still unknown whether these neural stem cells in the subventricular zone and dentate gyrus regions can replace the lost neurons following injury.

So far, several studies have assessed the degree of neurogenesis in these two areas and have demonstrated that significant numbers of new cells are continuously generated.[9,18] For example, the rat dentate gyrus generates about 9000 new cells each day or 270,000 cells every month.[18] A current clinical finding indicated that the whole granular cell population in the deep layer and half of the superficial layer of the olfactory bulb were replaced by newly produced mature neurons for a year.[19] A similar study also revealed that adult-produced neurons account for around 10% of the overall number of dentate granule cells in the hippocampus and they are uniformly distributed along the anterior-posterior axis of the dentate gyrus.[19] After the finding of continuous adult neurogenesis during the lifetime in the adult animal brain, the functional roles and the significance of this adult neurogenesis, mainly hippocampal neurogenesis concerning learning and memory processes, have been widely explored. Previous studies showed factors that increase hippocampal neurogenesis such as exposure to enriched environments, physical activity, or growth factor therapy may improve cognitive abilities.[20–22]

The newly formed granular cells in the mature dentate gyrus can become functional neurons in the normal hippocampus by demonstrating passive membrane characteristics, generating action potentials, and receiving functional synaptic inputs, as seen in the adult dentate gyrus neurons.[23] For instance, mouse strains hereditarily having poor levels of neurogenesis carry out low learning activities than those with a higher level of baseline neurogenesis.[23–25] A variety of physical and chemical signals influence the proliferation and maturational destiny of cells in the subventricular zone and dentate gyrus. For instance, biochemical variables including serotonin, glucocorticoids, ovarian hormones, and growth factors strongly regulate the proliferative response, implying that cell proliferation in these areas has a significant physiological role.[26,27] Besides, physical factors such as exercise and stress produce changes in cell proliferation implying a significant role in network adaptation.[28,29] For example, physical exercise might cognitively and physically enhance the production of cells and neurogenesis within the subventricular zone and dentate gyrus, but stress inhibits this

type of cellular activity. Furthermore, the physiologic role of these new cells depends on the number of cells being produced, survival rate, differentiation ability, and integration of cells into existing neuronal circuity.[24,30]

Response of Neural Stem Cells After Traumatic Brain Injuries

The subventricular zone and hippocampus contain neural stem cells that respond to a variety of stimuli. Different kinds of experimental traumatic brain injury models such as fluid percussive injury,[31,32] controlled cortical impact injury,[33,34] closed-head weight drop injury,[35] and acceleration-impact injury[36] have shown increased neural stem cells' activation. All of these experimental studies have shown the most prevalent and notable endogenous cell response after traumatic brain injury is an elevated cell proliferation within neurogenic areas of the dentate gyrus and subventricular zone. It is well accepted that enhanced production of new neurons following the traumatic brain injury was detected predominantly in the hippocampus in the more seriously injured animals in many experimental studies.[37] More studies have discovered that injury-enhanced new granule neurons send out axonal projections into the targeted CA3 region implying their integration into the existing hippocampal circuitry,[37,38] and this injury-induced endogenous neurogenic stem cells' response is directly associated with the inherent cognitive functional recovery after traumatic brain injury of rodents.[39,40]

In the human brain, the extent and physiology of the adult neural generation are not well understood. A study on human brain samples taken from the autopsy revealed neural stem cells with proliferative ability have been observed within the subventricular zone and the hippocampus.[41,42] Conversely, a more recent study has shown that neurogenesis in the subventricular zone and movement of new neurons from the subventricular zone to the olfactory bulbs and neocortex are restricted and only seen in the early childhood period.[43,44] Therefore, credible evidence of traumatic brain injury-initiated neurogenesis in the human brain is inadequate because of the difficulties of collecting human brain samples and technical challenges to birth-dating neural stem cells.

Exogenous Stem Cells Therapy in Traumatic Brain Injury

After traumatic brain injury, injury-initiated neural cell loss is permanent. Given the restricted amount of endogenous neurogenic stem cells, neural transplantation supplementing exogenous stem cells to the damaged brain tissue is a potential treatment for post-traumatic brain injury regeneration.[45] Especially, the transplanted cells will not only be able to replace the damaged neural cells but also give neurotrophic support in hopes of reestablishing and stabilizing the damaged brain tissue.[45] Clinical evidence revealed intervention with stem cell secretome may significantly improve neural inflammation after traumatic brain injury and other neurological deficits in humans.[46] Besides, the combined effects of bioscaffold and exosomes can aid in the transportation of stem cells to damaged areas as well as enhance their survival and facilitate successful treatment.[47] Despite the rapid progression of brain infarction, the decreased proliferation of neural stem cells, and the delayed initiation of neurological recovery were observed in the aged rat model compared with a young rat after stroke, the restorative capability of the brain by stem cell therapy is still present in the aged rat.[48] Compared to stem cell monotherapies which are still uniformly failed in clinical practice, combination therapy with hypothermia has potential therapeutic effects on the physiology of the aged brain and may be required for effective protection of the brain following stroke.[49] After several years of biomaterials study for regeneration of peripheral nerve, a new 3D printing strategy is developing as a good substitution for nerve autograft over large gap injuries. The applications of 3D printing technologies can help in improving long-distance peripheral nerve regeneration since it is a leading device to give one path for better nerve guidance.[50] Up to now, various categories of stem cell therapy have been tested for post-traumatic brain injury. These include embryonic stem cells, adult-derived neural stem cells, mesenchymal stem cells, and induced pluripotent stem cells.

Embryonic Neural Stem Cells

Embryonic stem cells obtained from fetal or embryonic brain tissues are highly considered for neural transplantation because of their ability of plasticity and have the capacity to self-repair and differentiation into all germinal layers. They can differentiate, migrate, and innervate as transplanted into a receiver brain tissue.[51] In previous clinical brain injury studies, neural stem cells derived from the embryonic human brain could survive for a long time, migrating to the contralateral cortex and differentiating into mature neural cells and microglia following transplantation into the damaged

brain tissue.[52] Implanted neurogenic stem cells obtained from human fetal stem cells may differentiate into adult neurons and release growth factors increasing the cognitive functional recovery of the damaged brain.[53] Interestingly, the long-term survival rate of transplanted neural stem cells obtained from mice embryonic brains was seen for up to 1 year with a high degree of migration in the damaged brain and maturation into neurons or neuroglial cells along with enhanced motor and spatial learning functions of the brain tissue.[54–56] In addition, embryonic stem cells expressing growth factors or early differentiated into neurotransmitter expressing adult neurons after in vitro manipulation have revealed improved transplant survival and neuronal differentiation following grafted into the damaged brain, and the receivers have better recovery in motor and cognitive activities.[57–59] Even though embryonic stem cells have a high rate of survival and plasticity in neuronal transplantation, the ethical concerns, risk of transplant rejection, and the likelihood of teratoma development restrict their therapeutic use for traumatic brain injury.[45]

Adult Neural Stem Cells

Neural stem cells are multipotent cells that can differentiate into neural cells but have a limited ability to differentiate into other tissue types.[60] Neurogenic stem cells are located in the subventricular zones of the lateral ventricle, the hippocampal dentate gyrus, and other areas of the brain like the cerebral cortex, amygdala, hypothalamus, and substantia nigra. They could be isolated, developed in culture media, and produce many neural lineages that can be used in the treatment of neurological disorders as an important element of cellular-replacement therapy.[61] Adult neural stem cells were transplanted into damaged parts of the brain in a traumatic brain injury rat model. These cells survived the transplantation process and moved to a damaged site when expressing markers for adult microglia and oligodendrocytes.[62] Interestingly, one most recent study indicated that Korean red ginseng extract-mediated astrocytic heme oxygenase-1 induction contributes to the proliferation and differentiation of adult neural stem cells by upregulating astrocyte–neuronal system cooperation.[63] Another study revealed that following neural stem cell transplantation to the hippocampal region, injured rats had developed better cognitive function.[64] The administration of combined therapies such as human neural stem/progenitor cells and curcumin-loaded noisome nanoparticles significantly improve brain edema, gliosis, and inflammatory responses in the traumatic brain injury rat model.[65] Furthermore, in traumatic brain injury rat models, as neural stem cells were injected intravenously, they resulted in a decreased neurologic impairment and less edema because of the anti-inflammatory and anti-apoptotic features of neural stem cells.[60,66] The ideal transplantation timeframe is 7–14 days,[60] beyond which the glial scar forms, restricting perfusion and graft survival.[67] The ability to transport cells to the desired location is a key obstacle with neural stem cell transplantation. Neural stem cells can be administered intrathecally, intravenously, and intra-arterial infusion. Conversely, a nanofiber scaffold implantation was proposed by Walker et al as a new strategy to be implemented to give the support essential for cell proliferation, which provides direction to future research.[68]

Mesenchymal Stem Cells

Mesenchymal stem cells are multipotent stromal that can differentiate into mesenchymal and non-mesenchymal tissue, such as neural tissue.[69] They are obtained from different types of tissues.[70] The accessibility, availability, and differentiation ability of these cells have drawn the attention of researchers performing studies in regenerative medicine. A previous study revealed the differentiation capacity of mesenchymal stem cells into neuronal cells. This study found that when rat and human mesenchymal stem cells are exposed to various experimental culture conditions, they can differentiate into neural and neuroglial cells.[69] Besides, mesenchymal stem cells have also been demonstrated to enhance the proliferation and differentiation of native neural stem cells; the mechanism of which may be directly associated with chemokines produced by mesenchymal stem cells or indirectly through stimulation of adjacent astrocytes.[70] In addition to their capacity to differentiate, mesenchymal stem cells selectively move to damaged tissues in traumatic brain injury rat models, where they develop into neurons and astrocytes and enhance motor function.[71] The possible mechanism of action through which this occurs is linked to chemokines, growth factors,[72] and adhesion factors, like the vascular cell adhesion molecule (VCAM-1), which permits mesenchymal stem cells to adhere to the endothelium of damaged organ.[73] Mesenchymal stem cell transplantation has become a potential and safe treatment of choice for traumatic brain injuries because of its anti-inflammatory capability by regulating leukocyte and inflammatory factors such as IL-6, CRP, and

TNF-a.[74,75] Treatment with mesenchymal stem cell-derived extracellular vesicles greatly increased neurogenesis and neuroplasticity in a pig model of hemorrhagic stroke and traumatic brain damage.[76] Currently, stem cell therapy using mesenchymal stromal cells has been widely investigated in preclinical models and clinical trials for the treatment of several neurological illnesses, including traumatic brain injury. Mesenchymal stem cells investigated for the treatment of traumatic brain injury in these clinical trials include bone marrow-derived stem cells, amnion-derived multipotent progenitor cells, adipose-derived stem cells, umbilical cord-derived stem cells, and peripheral blood-derived stem cells.[77–79] Those undifferentiated mesenchymal-derived cells have a heterogeneous cell population that includes stem and progenitor cells. They can be stimulated to differentiate into a neuronal cell phenotype in vitro. In the damaged brain tissue, these cells can generate a large number of growth factors, cytokines, and extracellular matrix substances that have neurotrophic or neuroprotective effects.[80,81]

Bone Marrow-Derived Mesenchymal Stem Cells

From all mesenchymal stem cells, the effect of bone marrow-derived mesenchymal stem cells on traumatic brain injury has been fully investigated. According to previous studies, mesenchymal stem cells injected directly into the injured brain, or through intravenous or intra-arterial injections during the acute, sub-acute, or chronic phase following traumatic brain injury, have been shown to significantly reduce neurological abnormalities in motor and cognitive abilities.[77–79,82] The therapeutic effect of mesenchymal stem cells is mostly because of the bioactive molecules they produced to facilitate the endogenous plasticity and remodeling of the recipient brain tissue instead of direct neural repair as direct neuronal differentiation and long-term viability were rarely seen.[80] A more recent study found that the injection of cell-free exosomes obtained from human bone marrow-derived mesenchymal stromal cells can increase the functional recovery of damaged animals after traumatic brain injury.[83] Another study used a traumatic rodent model to evaluate the anti-inflammatory and immunoregulatory properties of mesenchymal stem cells. When compared to the control group, neurological function was improved in the treatment groups from 3 to 28 days. Mesenchymal stem cell therapy significantly decreased the amount of microglia or macrophages, neutrophils, CD3 lymphocytes, apoptotic cells in the damaged cortex, and proinflammatory cytokines.[81] The main challenge of using mesenchymal stem cells for traumatic brain injury treatment is the long-term possibility of brain malignancy development because of the mesenchymal stromal cell's ability to antitumor response suppression.[84]

In a recent study, seven traumatic brain injury patients were given a mesenchymal stem cells transplant during a cranial operation and then administered a second dose intravenously. At the end of the 6-month follow-up period, patients exhibited better neurological function with no signs of toxicity.[85]

Human Umbilical Cord-Derived Mesenchymal Stem Cells

Recent studies revealed that the administration of exosomes-derived human umbilical cord mesenchymal stem improves sensorimotor function and spatial learning activities in rat models following brain injuries. Furthermore, the applications of these cells extensively decreased proinflammatory cytokine expression via inhibiting the NF-κB signaling pathway, reduced neuronal apoptosis, reduced inflammation, and increased neural regeneration ability in the injured cortex of rats following the injuries.[86] Human umbilical cord-derived mesenchymal stem cells have better anti-inflammatory activity that may prevent and decrease secondary brain injury caused by the immediate discharge of inflammatory factors following traumatic brain injury.[87] In traumatic brain injury rat models, the transplantation of umbilical cord-derived mesenchymal stem cells triggers the trans-differentiation of T-helper 17 into T regulatory, which in turn repairs neurological deficits and improves learning and memory function.[88]

Induced Pluripotent Stem Cells

To see the therapeutic effects of transplanted induced pluripotent stem cells compared to that of embryonic stem cells, Wang et al demonstrated animal models of ischemia and three different treatment options, which consist of pluripotent stem cells, embryonic stem cells, and phosphate-buffered saline for the control. The rodents were given an injection into the left lateral ventricle of the brain. Embryonic stem cell treatment group rodents showed a significant improvement in glucose metabolism within two-week period. However, 1 month following treatment, neuroimaging tests were done and

it was revealed that both pluripotent stem cell and embryonic stem cell treatment groups had improved neurologic scores as compared to the control group, suggesting that the treatment groups showed better recovery of their cognitive function. Further investigation indicated that the implanted cells survived and traveled to the area of injury. Finally, the investigator of this study concluded that induced pluripotent stem cells may be a better option than embryonic stem cells.[57] Different studies showed that induced pluripotent stem cells improved motor and cognitive function in the host mouse brain tissue, and these cells migrate the injured brain areas from the injection site.[89,90] Until now, there are limited studies on induced pluripotent stem cell therapy for brain injuries. This is because of the difficulty of obtaining induced pluripotent stem cells, high therapy costs, and technique limitations.

Conclusion and Prospects

In preclinical and clinical trials, advanced progress has been made in stem cell-based therapy for traumatic brain injury patients. Various studies reported the therapeutic effect of stem cells for regenerating damaged brain tissue. However, because of the complexity and variability of brain injuries, post-traumatic brain injury neuronal regeneration and repair remain a long-term goal. There are numerous unresolved challenges for successful stem cell treatment. For endogenous restoration via mature neural regeneration, methods guiding the movement of new neuronal cells to the area of damaged tissue and maintaining long-term survival are very important. In stem cell therapy, the inherent features of transplanted cells and the local host micro-environment influences the fate of grafted cells, an appropriate cell source, and a host environment, which are required for effective transplantation. Therefore, these problems should be solved in preclinical traumatic brain injury trials before stem cell-based treatments could be used in the clinic. The therapeutic application of neural stem cell treatment, whether via manipulation of endogenous or implantation of exogenous neural stem cells, is a method that has been shown in multiple studies to have substantial potential to increase brain function recovery in persons suffering from traumatic brain injury-related disability. However, further studies need to be done on the therapeutic application of stem cells for traumatic brain injury due to our poor understanding of possible consequences, unknown ethical issues, routes of administration, and the use of mixed treatment.

Disclosure

All authors declared no conflicts of interest for this study.

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