Stem Cell Therapy for Traumatic Brain Injury

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Abstract

Traumatic brain injury is a prevalent issue in the world, and recent development of stem cell therapy has led to advancements in the treatment of this disease. Using endogenous neural progenitor cells, as well as transplantation of exogenous stem cell therapy can assist in the promotion of cognitive and motor skills by increasing neural stem cell proliferation. Exogenous therapy can be used to further induce endogenous therapy, all while repairing the damaged tissue and maintaining the homeostatic balance of the cells within the body. Molecules like curcumin-loaded niosome nanoparticles can assist in the promotion of the neural stem cells and will further improve the regeneration of injured cells in the brain. Pediatric brain injury differs from adult traumatic brain injury, with differences in the treatment and overall process of the incorporation of the neural stem cells, but using exogenous and endogenous therapy in similar ways can yield proliferation and development in neurons, preserving the cognitive functions of the child.

Introduction

After an object violently hits the head or pierces the skull, entering the tissue, immediate impact on the brain can cause traumatic brain injury. Traumatic brain injury occurs when a sudden trauma causes damage to the brain. Depending on the severity of the traumatic experience, mild traumatic brain injury can occur, which affects the brain cells temporarily. However, more severe brain injury can result in long-term complications and death.

Severe brain injury can be categorized into two different types of injury. Primary injury occurs when there is damage to the brain tissue, neurons, glial cells, endothelial cells, and the blood-brain barrier. The harm from the initial impact of an object exclusively causes primary injury. Secondary injury follows primary injury, where the damage causes injured cells to release several toxic, forming a cytotoxic cascade. The formation of cascades the initial, primary brain damage and further increases the risk of lasting neurodegenerative and inflammatory diseases.

Early research has shown that after traumatic brain injury, little can be done to reverse the initial trauma, leading to harmful effects. Arising disabilities that may occur can affect cognitive functions like thinking and memory, sensory processive, communication, and behavior changes including spontaneous outbursts and depression. More uncommon consequences can include unresponsive or vegetative state. Additionally, traumatic brain injury can affect different people differently, depending on the level of brain development and severity of brain injury. Childhood traumatic brain injuries can result in permanent disabilities and reduced quality of life from effects of visuomotor and cognitive impairment.

Recent development in scientific and technological advancements have allowed researchers to explore the therapeutic potential of stem cells following traumatic brain injury on different scales. Experiments have illustrated how intravenous stem cell treatment can enhance functional recovery following damage to parts of the brain. Stem cell therapy illustrates an anti-inflammatory approach to identify injured tissue and repair the damaged cells, speeding up internal recovery and decreasing the likelihood of permanent cognitive disabilities.

Stem Cells

Stem Cells are cells found in the body that are responsible for the specialized function generated by all other cells within the body. To do this, stem cells divide to form daughter cells that can then be specialized for different uses in the body. Stem cells are also incredibly important in providing renewable resources for studying normal development of diseases, and testing drugs and therapies. In addition, stem cells have been found to have potent anti-inflammatory effects. Young stem cells have a regulatory influence on the body and can be utilized in big cell quantity transplantation. They can also lessen the immune reaction that the body is unable to control on its own. Stem cells are able to perform this reaction by regulating how the immune system repressseds pathological responses, but maintains the integrity of fighting off diseases. Rejection of transplantation is then minized because the stem cells are capable of repressing the immune response that prevents the rejection. Many different types of stem cells can be found in the body, including mesenchymal stem cells, found in bone marrow that are important for repairing tissues, such as cartilage, and neural stem cells, cells of the nervous system that make up neurons and glial cells.

Mesenchymal Stem Cells (MSCs) can be vital in differentiating neural tissue and creating neuronal cells. Directional differentiation into mesenchymal and non-mesenchymal tissues is an important capability of mesenchymal stem cells. By differentiating the tissue, they may encourage the repair of injured tissues by reducing inflammation, secreting trophic factors, and enlisting local progenitor cells to replenish missing tissue cells. MSCs focus on only neural tissue that is separated and can increase the maintenance and care of that specific tissue. MSCs can decrease the expression of inflammatory proteins, leading

to anti-inflammation and decreasing edemas and aneurysms. MSCs can also prevent the body from overproducing and using T-cells. T-cells are lymphatic cells vital in fighting infections but can also result in the body attacking its own cells, causing autoimmune disorders. The overproduction of T-cells in the body can signal cancer or other infections the body is trying to fight and the presence of Mesenchymal cells ensure that T-cells are only overproduced when there is a real threat to the body. The impact of MSCs occurs without weakening the patient's natural immune system or making them susceptible to illness, due to a decrease of T-cells. Mesenchymal Stem Cells are important in the regulation of damaged neural tissue.

Neural Stem cells (NSC) are self-renewing stem cells that can develop further into oligodendrocytes, glial cells, and neurons. NSC transplantation could be a successful, long-term therapy for neurological rehabilitation following brain damage. The proliferation, differentiation, and other activities of NSCs might be improved by the transfection of growth-promoting genes into NSCs. Neural stem cells are sensitive to change, and can travel through the nervous system to find different sites of injury and improve recovery.
While Mesenchymal Stem Cells and Neural Stem Cells are the two primary stem cells, many different stem cells exist in the body that exist in smaller quantities. Induced pluripotent stem cells are important in self-renewing cells and are also utilized for differentiation and specialization. They are also useful in restoring brain function immediately following injury. Endothelial Progenitor Cells are recruited to the site of endothelial tissue, and can be critical in endothelial healing following brain trauma. They can help retain the integrity of the white matter, lessen the capillary damage, and control the local angiogenesis, or the process where new blood vessels form from pre-existing vessels.

Endogenous Neural Progenitor Cells Therapy

Endogenous Neural progenitor Cell therapy refers to endogenous restoration of damaged cells via mature neural regeneration. The movement of new neuronal cells to the area of damaged tissue is guided in order to maintain long-term survival of the harmed tissue. Endogenous Cell Therapy in response to traumatic brain injury has shown elevated cell proliferation levels in subventricular zones and in the hippocampus of more severely injured animals. Using rodent models, research concluded that injury-induced endogenous neurogenic stem cell therapy is directly correlated with cognitive functional recovery.

In order to perform endogenous neural progenitor cells therapy different nurophins must be active for support. Metformin is a drug shown to mobilize endogenous progenitors in the hippocampus following traumatic brain injury. Metformin was initially used to manage diabetes by mimicking a binding protein to regulate glucose production. This same binding protein, called CREP, can be mimicked in a kinase pathway responsible for recruiting endogenous neural progenitors in different zones of the brain, called subgranular zone and subventricular zone. Metformin can mimic the CREP binding protein and activate the protein kinase pathway, stimulating endogenous neurogenesis.

One method of endogenous neural progenitor cell therapy is by using oligodendrocyte progenitor cells. These cells can differentiate into oligodendrocytes in the developing and mature brain, and are primarily utilized for the development of myelination and myelin plasticity. Oligodendrocyte progenitor cells are also important in maintaining a homeostatic balance of cells in the brain throughout life. When tissue is damaged, demyelination occurs, resulting in oligodendrocyte progenitor cells becoming reactive to produce oligodendrocytes. The new oligodendrocyte can structurally change, proliferate, and migrate to the site of injury in order to repair and increase the rate of wound closure.

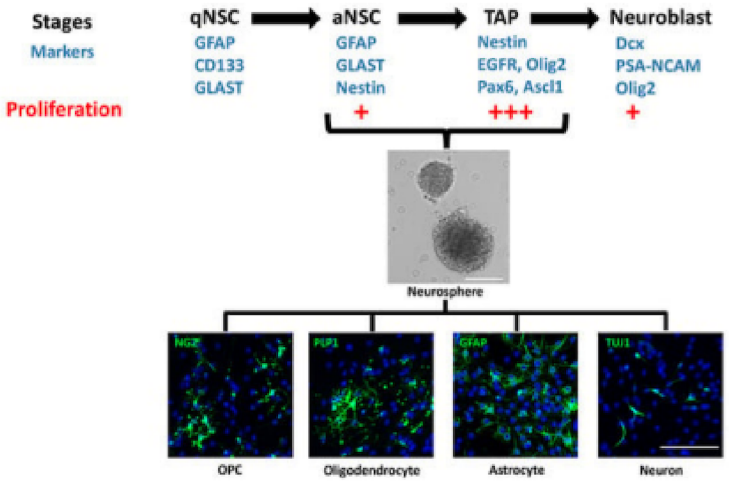

Figure 1. The figure shows the stages of neural stem cells and the level of proliferation. Only activated NSCs and transit-amplifying progenitors grow as neurospheres and differentiate into the oligodendroglial, astroglial, and neuronal lineages in vitro. Endogenous Neural Progenitor Cells Therapy increases the proliferation of the different daughter cells.

Exogenous Stem Cell Therapy

Exogenous stem cell therapy works by migrating exogenous stem cells towards damaged brain tissue, which then participate in the repair of damaged brain tissue by further differentiation to replace damaged cells, while releasing anti-inflammatory factors and growth factors, thereby significantly improving neurological function. Exogenous stem cell transplantation has accelerated immature neuronal development in damaged areas, allowing for potential treatment for post-traumatic brain injury regeneration by increasing development of new neurons that are not inherently damaged. Transplanted cells can replace the damaged neural cells with new, viable cells and also provide neurotrophic support to reestablish and stabilize the damaged brain tissue.

Given the limited supply of endogenous neurogenic stem cells, exogenous stem cell supplementation to the injured brain tissue by neural transplantation is a promising therapy for post-traumatic brain injury regeneration. In addition to being able to replace the destroyed neural cells, the transplanted cells will also provide neurotrophic support in the aim of reestablishing and stabilizing the destroyed brain

tissue. Mesenchymal stem cell transplantation, as well as neurotrophic factors derived from MSCs have driven endogenous neurogenesis. Neural stem cells can also secrete neurotrophic factors that can drive endogenous neurogenesis. There is a greater proliferative cell response with exogenous NSC transplantation. These findings demonstrate how exogenous stem cell therapy can upregulate endogenous stem cell therapy, which further increases rates of repairing injured tissue from traumatic brain injury.

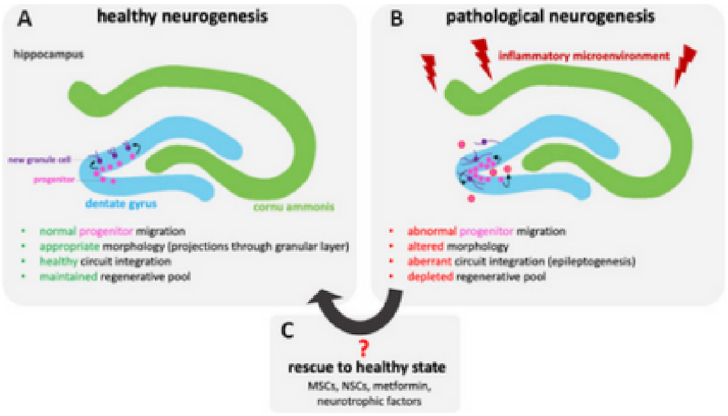

Figure 2. The difference before and after traumatic brain injury, showing healthy and pathological hippocampal neurogenesis. Part A demonstrates hippocampal neurogenesis in healthy tissue. Part B shows injured tissue and the depletion of the regenerative pool, along with abnormal progenitor migration and different structures. Part C illustrates exogenous stem cell therapy through transplantation and how neurogenesis is shown to be restored.

Nanoparticle Therapy

Simply using endogenous and exogenous cell therapy may not be enough to fully restore the functions of the damaged tissue to their full capacity, but combining the neural stem cells with nanoparticles loaded with curcumin noisome can be used to improve brain inflammatory responses associated with traumatic brain injury. Neural stem cells from the brain can be accompanied with curcumin-loaded niosome nanoparticles to improve functional recovery by decreasing the severity of the impact of damage to a pathway in the body referred to as TLR4-NF-kB. The curcumin-loaded niosome nanoparticles show decreases in neuroinflammation after injury because of inhibition of stress oxidatives and down-regulating the pathway.

Pediatric Therapy

Traumatic brain injury (TBI) is prevalent in the pediatric population as it is the leading cause of death and disability in children. Characterizing the activity of neural stem cells and neural progenitors in the immature brain in response to injury can help in the understanding of brain injury pathology and the development of therapeutic targets for pediatric TBI. The location, type, and population density of neural stem cells (NSCs) are developmentally regulated. Adult and pediatric brains display different responses to stem cell therapy. Both neonatal and pediatric traumatic brain injury result in a large increase in proliferating glial fibrillary acidic protein (GFAP)-positive cells, indicating increased astrocytic proliferation and astrogliosis, which in turn leads to inflammation and further damage.

The main focus in pediatric therapy following traumatic brain injury is highlighting the anti-inflammatory effects, while also enhancing the long-term survival and integration of the stem cells. Mesenchymal stromal cells may help in tissue repair and regeneration, are activated by neonatal HI and go to the site of the wounded tissue from the peripheral circulation. Between 3 and 7 days after neonatal HI, stem cell factor expression rises in the periventricular, corpus callosum, and hippocampal regions. In the injured brain, neural stem cells' capacity for self-renewal and natural propensity to differentiate into neurons and glial cells may help to promote regeneration and neurogenesis.

Conclusion

The recent advances in stem cell therapy in managing the treatment of traumatic brain injury have been improved using endogenous neural progenitor cells and exogeneous stem cell transplantation. The development of stem cell therapy increases cognitive and motor skills and directly increases the repairment of cells in damaged tissue. Stem cell therapy has been used to treat adults and children alike, with assistance from different particles to further enhance treatment. More research should be conducted on the effects of stem cell transplantations in different regions of the brain, along with different damage levels of the injury site. Many researchers believe the exploration of stem cell therapy is a growing avenue for the improvement of regeneration and healing of damage sites that were once believed to be unrepairable.

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