A Review on the Potential of Stem Cells in Traumatic Brain Injury Treatment

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Abstract

Traumatic Brain Injury (TBI) is characterized by trauma to the head, resulting in serious damage. Currently, there are no curative treatments for TBI. Rather, treatments are aimed at mitigating progression. Due to the number of individuals affected by this condition, novel therapeutic strategies are essential. Administration of stem cells (SCs) has been proposed as a treatment for TBI as it consists of neuroprotective properties. SCs can differentiate into any cell and proliferate. Neuronal SCs preserve structural and functional plasticity, which allows for restoration and integration of neural cells in the affected area. Mesenchymal SCs have anti-inflammatory and immunomodulatory properties and can selectively translocate to the affected site to develop into cells that enhance motion function. Studies conducted on the effect of SCs in TBI treatment have shown positive preclinical outcomes. Therefore, the efficiency of using SC in the management of TBI should be further investigated as a novel treatment option.

Traumatic Brain Injury (TBI) is caused by an external assault to the head, resulting in dysfunction of brain processes, and every year it affects over 50 million individuals worldwide.[1,2] TBI can damage neural cells, causing serious cognitive, physical, and emotional complications, as well as temporary or permanent impairment.[3,4] The Glasgow Coma Scale is the primary clinical tool used to classify the severity of TBI as mild, moderate, and severe.[3]

TBI can be categorized as primary and secondary injuries. Primary injuries refer to the initial mechanical force, often damaging neural cells, brain tissue, and the blood-brain barrier.[1] Secondary injuries refer to the cellular damages that follow the primary injury, leading to cytotoxic cascades due to toxins released during primary injury, and the overall worsening of the primary injury.[2] TBI causes acute cell death, leading microglial cells to move towards the damage site and release inflammatory cytokines, resulting in inflammation.[5] Secondary injuries can physically and cognitively affect an individual for years.[1] The damaged region of the brain inflicts stress upon the organ, making it difficult to maintain cognitive functions.[2] This significantly interferes with an individual's quality of life.

At present, there are no effective and standardized treatments for TBI which entirely reverse the damage inflicted by the trauma.[3] Treatment is focused on mitigating progression, also known as secondary damage, and vary according to severity of the injury.[3] Some examples include head elevation, hyperventilation, and hyperosmolar therapy to reduce intracranial pressure, therapeutic cooling to reduce oxidative injury, and surgical interventions (bilateral decompressive craniotomy).[6] In recent years, scientists have taken interest in the use of stem cells (SCs) in the

treatment of TBI and have proposed SC administration as a valuable tool in repairing damaged areas of the brain due to their neuroprotective properties (Figure 1).[6]

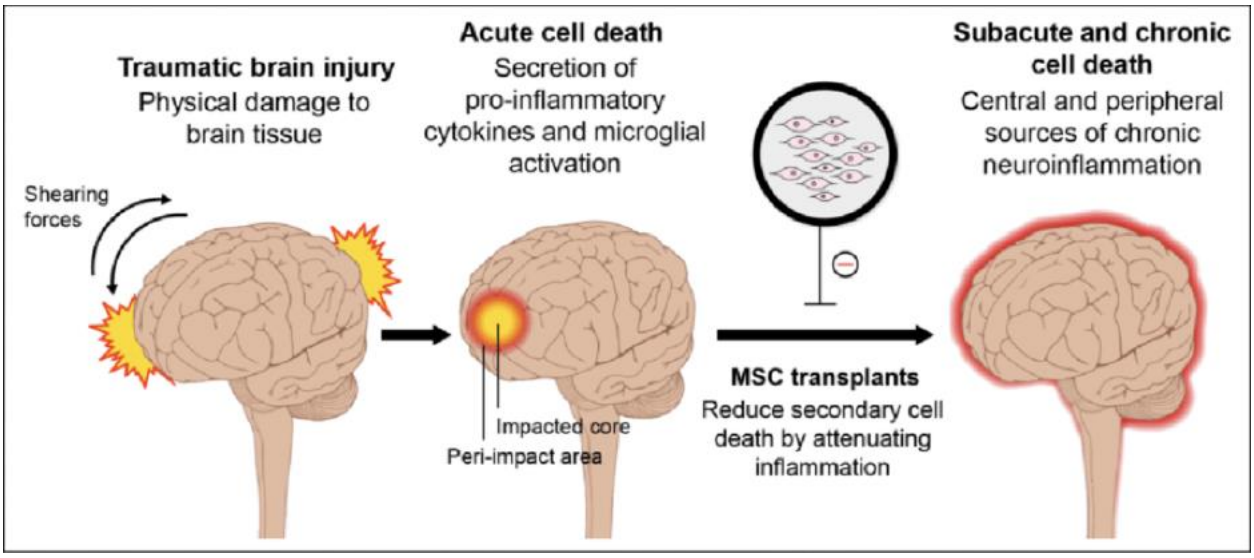

Figure 1: A schematic diagram showcasing the treatment of MSC transplant. Once TBI is inflicted due to external force (primary injury), brain tissue is damaged. Next, acute cell death leads to the release of inflammatory cytokines, causing inflammation at impact site (secondary injury). MSC transplant may decrease secondary cell death by reducing neuroinflammation.[7]

SC are unspecialized cells that originate from a single cell and can differentiate into any cell within an organism and proliferate.[8] Neuronal SCs (NSCs) are derived from neural tissue, and are obtained from either the central nervous system, or the peripheral nervous system. They can then differentiate into all cell types, including oligodendrocytes and astrocytes.[9] They release cytokines and neurotropic factors, and studies show that NSCs release chemicals that preserve structural and functional plasticity, which aids in the restoration and integration of neural cells at the damaged area.[3] Mesenchymal SCs (MSC) are multipoint stromal cells derived from various areas, including bone marrow, umbilical cord, placenta, and oral cavity.[3] MSC can differentiate

into cell type, including osteoblasts, adipocytes, and chondrocytes.[3] They exhibit anti-inflammatory and immunomodulatory properties through the release of neurotrophic factors and growth factors, and recruitment of local stem cells to replace damaged ones.[3] Interestingly, MSCs can selectively move towards the site of damage, and then develop into neurons and astrocytes which can improve motion function.[10] There is also evidence suggesting that through paracellular pathways, MSCs may have the ability to cross the blood-brain barrier, making it an appealing therapeutic approach.[11]

There are two routes of administration of SCs: intravenous and local infusion. The intravenous administration is non-invasive, however very few SCs reach the target site.[3] Local infusion consists of SC administration through the use of stereotaxic injections, which is an invasive approach however it allows for SC to be injected directly into the target injury site.

There are few studies that demonstrate the effects of SCs for TBI treatment, however they exhibit positive preclinical outcomes and safety is well-established for further exploration of this treatment.[7] Lee et al. demonstrated that human NSCs transplant in mice affected by intracerebral hemorrhage resulted in reduced edema and lower neurological impairment due to the anti-inflammatory capabilities of NSCs.[12] Another study conducted by Haus et al. showed that human NSC implantation into immunodeficient rodents with TBI restored cognitive function, and NSCs were able to differentiate into mature cell types.[13] A study conducted by Wang et al. demonstrated that transplantation of MSC of the umbilical cord improved neurological function of individuals with TBI sequelae.[4] Guo S. et al. implanted bone-marrow MSCs into TBI-affected mice, and results showed improved angiogenesis and neurological function.[14] Furthermore, the

transplant mitigated the impairment of memory and learning ability, decreasing TBI-induced apoptotic injury, and enhanced production of micro vessels in brain tissues.[14]

Considering the size of affected population and lack of satisfactory treatments for TBI, development of innovative therapeutic strategies is of utmost importance. SC therapy, specifically, implantation of NSC and MSC, may satisfy the compelling need for effective treatment. As seen in this review, the clinical studies conducted on the role of SCs in TBI treatment show promising potential, however the possibility of immunological rejection and the longevity of SCs is not determined.[13] Therefore, further studies must be conducted to investigate the safety and efficacy of stem cell therapy in TBI treatment, and the long-term effects of this treatment.

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