DOI: 10.5137/1019-5149.JTN.20829-17.1
Received: 22.05.2017 / Accepted: 16.07.2017
Published Online: 15.09.2017

Review

The Research Progress of Mesenchymal Stem Cells in the Treatment of Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity in children and adults throughout the world. It is urgent to ameliorate TBI damage and reduce the disability and case-fatality rate. Stem cell therapy is another medical revolution after drug and surgical medication. Mesenchymal stem cells (MSCs) are a class of cells with significant self-renewal and multi-lineage differentiation properties. They are favorable for the treatment of various diseases and injuries. It could be envisioned that MSCs transplantation may be a promising treatment for TBI. Currently, stem cell therapy has shown promising effects in the treatment of many diseases. In this article, we will review the characteristics of MSCs, MSCs for neuronal function restoration, the properties of immune-modulatory of MSCs, and the anti-apoptotic effects of MSCs, the angiogenesis effect of MSCs, and the safety issues in MSCs therapy in TBI.

KEYWORDS: Angiogenesis, Anti-apoptosis, Immunomodulatory, Mesenchymal stem cell, Umbilical cord, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) results from external forces, the consequence of direct impact, rapid acceleration or deceleration, a penetrating object, or blast waves from an explosion (38). According to the pathology, TBI involves primary injury and secondary injury. Primary injury occurs at the initial phase of trauma; the rapid deformation of brain tissue gave rise to focal contusion, haematomas, vascular damage and axonal injury, evolved membranolysis, cellular content efflux, hemodynamics disturbance and neuronal necrosis (41). Secondary injury comes after the primary injury, and causes a complex series of cellular and biochemical processes (51). Electronic, including blood brain barrier (BBB) disruption, excitatory amino acid (EAA) release, free-radical generation, calcium-mediated damage, gene activation, mitochondrial dysfunction, and inflammatory responses, and elicits an arrangement disorder, apoptosis and even loss of nerve cells (53).

The pathomechanism of TBI is unequivocal, but there are no effective strategies to reduce the loss of neurons, inhibiting apoptosis and increasing neurogenesis. TBI not only tortures numerous patients by permanent disability and cognitive dysfunction (5,33), it also imposes a heavy economic burden on their families and society (2,76). With rapid development of stem cells, many scientists and medical researchers are pinning their hopes on stem cell technology, and stem cells may be a prominent medication for TBI.

METHOD

A PubMed search was performed, using the phrase "Mesenchymal stem cells and Traumatic brain injury," for all years up to 2017. The references of systematic reviews were examined for additional sources. These articles were reviewed based on immunomodulatory properties, angiogenesis, anti-apoptosis, neuronal function restoration of the injured nervous system, and security analysis. Eighty-five articles were chosen for this review.

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REVIEW

Mesenchymal stem cells (MSCs) are a class of cells with significant self-renewal and multi-lineage differentiation properties, and can be harvested from bone marrow, adipose tissue, skin, umbilical cord blood, umbilical cord and peripheral blood as well as other organs. MSCs can be defined by the expression of surface molecular epitopes (CD73, CD90, CD105), and the lack of several surface markers (CD34, CD45, CD19, CD11b). MSCs express intermediate levels of human leukocyte antigen (HLA) major histocompatibility complex class I (MHC-I) molecules and negligibly low levels of HLA class II (HLA-II) and Fas ligand (30); they do not express the co-stimulatory molecules B7-1, B7-2, CD40, or CD40L. Promisingly, the hypoallergenic state of MSCs makes them difficult to be recognized by HLA incompatible receptors. Preclinical studies have shown that MSCs derived from bone marrow have therapeutic potential for treating a number of acute limb ischemia disease (75), myocardial ischemia (63,82), myocardial infarction (11), and cerebral hemorrhage. Furthermore, MSCs have also been reported to alleviate neurodegenerative diseases (22,26,54). A new class of cells with self-renewal and multi-lineage differentiation properties collected from neonatal umbilical cord tissue was named as umbilical cord derived mesenchymal stem cell (UCMSC) (10,34,77) andcould be incubated to differentiate into neuron-like cells, and express nestin, neuron-specific enolase (NSE), neurofilament (NF), glial fibrillary acidic protein (GFAP). Umbilical cord mesenchymal stem cellx (UCMSC) may be an ideal source due to the accessibility, painless procedures to donors, promising sources for cell therapy and lower risk of viral contamination.

To date, there are no efficient strategies aimed to alleviate neuron loss and promote nerve regeneration. Stem cells may have this potential. Some studies have shown that this might be due to the migration and homing (23) and differentiation into neuronal cells (14,52,61). However, increasing research suggests that the therapeutic results of MSCs might be due to the trophic factors and anti-apoptosis proteins to modulate host micro-environment (42) rather than replacing the damaged cell (58), and according to studies, the therapeutic effects of MSCs on TBI is mainly reflected in restoring neural function, reducing apoptosis, regulating immune response or immunosuppressive effects, and promoting angiogenesis (21), while preclinical research suggests that it is remarkable for MSCs transplanted in neurodegenerative disorder and spinal cord injury including TBI and cerebral infraction (25,70).

MSCs could be differentiated into neurons and glial cells and could ameliorate extracellular microenvironment, promote axonal regeneration and suppress cell apoptosis by expressing neurotrophic factors in vivo. And MSCs could make up the lesion area so as to inhibit the excessive proliferation of glial cells. Kopen et al. (27) found MSCs can migrate throughout the forebrain and cerebellum without disruption to the brain architecture. Some MSCs in the striatum and the molecular layer of the hippocampus expressed GFAP, and therefore, differentiated into mature astrocytes. In addition, neurofilament positive donor cells were found in the reticular formation of the brain stem, suggesting that MSCs also may have differentiated into neurons. Brazelton et al.(9) injected GFP-expressing bone marrow-derived cells into mouse by tail vein, the results revealed that hundreds of marrow-derived cells in brain sections expressed neurons makers (NeuN, 200-kilodalton neurofilament, and class III β-tubulin). Similarly, Mezey et al.(44) found transplanted bone marrow MSCs could migrate into the brain and differentiated into cells that expressed NSE. Zhao et al.(84) found that the Wnt3a protein secreted by MSCs recapitulates part of the neuroprotective and neurogenic effects, they can promote the restoration of neurocognitive function. These results indicate that the potential therapeutic mechanism, at least in part to the release of soluble factors after intravenous MSC administration.

Some kinds of crucial endogenous protective factors were founded, including neurotrophic factors, gangliosides (57), heat shock proteins (HSP), adenosine, magnesium et al. They could moderate the secondary neuronal injury, promote axonal regeneration and repair the damaged neurons in vivo and in vitro. However, most of neurotrophic factors cannot pass through the blood brain barrier, but MSCs could reduce blood brain barrier permeability, increase neuronal survival, and improve neurocognition (43,62,66).

MSCs express intermediate levels of human leukocyte antigen (HLA) major histocompatibility complex (MHC) class I molecules and negligibly low levels of HLA class II and Fas ligand, they do not express the co-stimulatory molecules B7-1, B7-2, CD40, or CD40L. Consequently, MSCs present low immunogenicity and immune regulatory properties or immunosuppressive properties. They can escape recognition by heterogeneous T lymphocyte. MSCs up-regulated MHC-II expression affected by interferon-γ (INF-γ), whereas the inhibition of MSCs was not dependent on MHC, which contribute to the low immunogenicity of MSCs (39), and lay the foundation for MSCs cell therapy in clinical application. Tse et al. (65) confirmed that MSCs could not stimulate allogeneic T cells or peripheral blood mononuclear cells in mixed culture system, which indicated that USMSCs may not express MHC-land and MHC-II. Weiss et al.(72) transplanted porcine umbilical cord MSCs into rats' brain without immunosuppressant, the result showed that MSCs migrated into rats' brain and expressed porcine nerve cells marker, reflected that MSCs can escape from host immune system attacking.

TBI induces a strong inflammatory response characterized by recruitment of peripheral leukocytes into the brain parenchyma and activation of endogenous immune cells (55,85). Neutrophil, monocytes and lymphocytes around the brain directly affect the survival and death of neural cells (20,35,55,85). In addition, activated microglial cells migrate to the injured tissue, and releasing the cytokines, chemokines, active oxygen, nitric oxide, proteases and other cytotoxicity substances may aggravate neuronal death (15,35). However, immune cells and inflammatory mediators may also play neuroprotective roles in TBI (46). For example, T lymphocytes may play a role in promoting repair in late brain injury (4,8). Proinflammatory cytokines interleukin-1 (IL-1), interleukin-6

(IL-6) and tumor necrosis factor-α (TNF-α) have both beneficial and detrimental effects on nerve cells (20,66,74). Microglia also can clear necrotic debris in brain tissue, promote the re-modeling of brain cells, and exert neuroprotective effects in some specific conditions (3,7,85). It is indicated that the inflammatory reaction caused by TBI is a crucial factor in secondary brain injury, and it may be effective and protective for a series of pathological process by anti-inflammatory or immune regulatory treatment. MSCs can affect immune cells proliferation, differentiation, activation and inflammatory cytokine secretion by cells interaction and secretion of soluble immune regulatory factors and inhibit the proliferation of T cells and microglia, regulate dendritic cells, monocytes and macrophages and natural killer (NK) cells secrete cytokines (16,42,47,49). Moreover, MSCs harvested from umbilical cord, pancreas, skeletal muscle and placenta present the same effects as bone marrow derived. But the exact mechanism in inflammation and immunosuppression is not clear. MSCs could induce peripheral immune tolerance and migrate to the damaged tissue, could inhibit pro-inflammatory cytokines release and promote the damaged cells survival (67), and MSCs achieved remarkable therapeutic effects in the treatment of acute lung injury (13,45), myocardial infarction (1), acute renal failure (56), cerebral ischemia (59) and Alzheimer's disease (31). It found that MSCs have inflammatory regulatory functions. One of the studies confirmed that UCMSCs have anti-inflammatory effects in the rat stroke model (68). Another study reported that neural stem cells of intravenous injected in the acute phase of stroke can interact with the peripheral inflammatory system to regulate and ameliorate congenital encephalitis (32). These studies demonstrate the feasibility of using MSCs transplantation to reduce cerebral tissue inflammation and regulate immune responses (83). TBI induced brain inflammatory response and MSCs play a role of regulating inflammatory, which is indicating the possibility of reducing the inflammatory response.

Apoptosis could be trigged by many intrinsic and extrinsic signals. The possible mechanisms of traumatic brain cell apoptosis involved in the increase of free radicals, the activation of the transcription signal and the gene expression (36). At present, varieties of related genes or factors have been found, such as bcl-2, c-my c, p53, ICE and fas. Recent studies have found that, the expression of bcl-2 and bcl-x protein in the CA3 area of stroke side hippocampus decreased significantly 6 hours after injury, while the expression of bax did not change significantly. Bcl-2 gene family participated in the apoptosis of neuronal cells after brain injury. The expression of different members of the gene family was involved in the apoptosis of neural cells (37). As reported, MSCs present anti-apoptotic effect. MSCs could up-regulate the expression of anti-apoptotic protein bcl-2 and promote angiogenesis of infarcted region by activating the PI3K/Akt signal pathway.

In the acute phase of cerebral ischemia reperfusion injury, MSCs could reduce apoptosis and significantly improve neural function after cerebral ischemia by promoting survivin apoptosis protein and suppressing Caspase-3 apoptosis protein expression in rats. In renal ischemia reperfusion injury model, MSCs could also inhibit the apoptosis of renal tubular epithelial cells by down-regulate the expression of bax of bcl-2 family (28,64,79). Recently our studies further confirmed the effects of regulating apoptosis.

After TBI, the degeneration and necrosis of nerve cells caused by ischemia and hypoxia lead to neurological deficits. Marshall (40) found that 90% of patients died in TBI had ischemic changes, and ischemia was the main mechanism of secondary damage. Neovascularization in the peripheral tissue of brain injury is the major prerequisite for improving blood circulation and the basis of synaptic communication and functional reconstruction (50). Accordingly, it is very important to restore the blood supply of ischemic region as soon as possible. Angiogenesis processes consist of angiogenesis, vasculogenesis and mature capillary networks formed by the original vascular shear remodeling. Numerous of cytokines were released after cerebral ischemia; they could, but limitedly, trigger angiogenesis so as to reduce the damage caused by cerebral ischemia. Angiogenesis treated by MSCs transplantation has got a research focus throughout the world. MSCs showed highly proliferate, differentiate, plasticity, rapidly amplify properties, and chemotaxis to injured tissue. They could differentiate into endothelial cells, vascular smooth muscle cell, and Schwann cells with hypoxic conditions, furthermore, and MSCs could secrete cytokines through autocrine and paracrine mechanism, including vascular endothelial growth factor, stromal cell derived factor-1, monocyte chemo-attractant protein, neurotrophic factor, etc., which contribute to promote angiogenesis (6,69).

The exact mechanisms of MSCs promote angiogenesis is not clear yet, most studies suggest that the differentiation of MSCs has an intimate relativity with its microenvironment. After ischemia or injury, it may be the variety of factors in the microenvironment of lesion tissue promotes MSCs differentiate into cells or tissues which the environment needed (17). As speculation, it may work by the following mechanisms: MSCs are integrated into the damaged vessels after transplantation to participate in the formation of ischemic tissue and provide endothelial cells for neovascularization (60,73). On the other hand, MSCs secret a variety of cytokines and growth factors through paracrine, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), hepatocyte growth factor, hypoxia-inducible factor-1α (HIF-1α), interleukin-8 (IL-8), interleukin-6 (IL-6) and TNF-α, to induce microvascular generation, stimulate peripheral mature endothelial cells proliferation and migration, improve the microenvironment of ischemic tissue to participate in angiogenesis (12,24,29,71). Zhang et al. (81) demonstrated that exosomes from human umbilical cord mesenchymal stem cells (UC-MSC-Ex) could promote cutaneous wound healings. Further, they proved UC-MSC-Ex could promote endothelial cells proliferation, migration and tube formation *in-vivo* and *in-vitro*. They found that UC-MSC-Ex could also repair a severe second-degree skin injury through delivering Wnt and activating Wnt/b-catenin signal pathway to promote angiogenesis. Studies have shown that angiogenesis plays an important role in initiating and promoting nerve regeneration after injury. It would be helpful, if restoring the structure and function of endothelial cells and promote the formation of new

blood vessels in brain injury ischemia as soon as possible, to improve brain tissue metabolism, promote penumbra damaged neurons repair (19), induce neurogenesis, accelerate toxic products clearance, deliver oxygen and nutrients to provide a livable microenvironment for the survival, migration and differentiation of implanted cells (80).

The clinical safety of MSCs has been concerned by both doctors and patients. If the MSCs for therapy were used unsafely or improperly, they might result in some side effects, even get a tumor or cancer. Irregular MSCs therapy contains potential danger. It is necessary to evaluate the systematic safety before treatment. There have been tremendous researches about MSCs, we suggest that numerous preliminary clinical trial on cell biological research and standardization of MSCs are indispensable, especially the clinical safety research. Meanwhile, government should formulate a series of regulations and standards to regulate stem cell therapy.

DISCUSSION

Accumulating evidences reported that MSCs transplantation have achieved remarkable effects for the treatment of cerebral infarction, cerebral hemorrhage, neuronal degeneration disease and spinal cord injury (26,48). The therapeutic effects of MSCs on central nervous system injury seem to have been confirmed, but its therapeutic mechanism for brain injury is not yet clear. The original intent of stem cell transplantation in the treatment of central nervous system injury is cell replacement therapy, namely stem cells can differentiate into mature neurons and glial cells to replace damaged neural cells owing to the ability of proliferation and differentiation. Experiment showed (78) the neurological function of MSCs treatment group was significantly improved one week after MSCs transplantation. In such a short time, MSCs apparently cannot differentiate into mature functional neurons, even cannot integrate into the host structure and participate in complex neural networks. Furthermore, Hasan et al. suggest that only a small percentage of intravenously injected MSCs reached brain after being filtered by the lung tissue (18). We suggest that MSCs repair damaged tissue by 'bystander effect'. The transplanted stem cells secrete trophic factors, anti-inflammatory factors and other bioactive molecules that interact with injured and/or normal body.

CONCLUSION

We suggest MSCs repair damaged tissue in TBI contains the 'bystander effect'. MSCs could be guided by the chemotaxis, inflammatory substance and could migrate to the lesion area, and preferentially release the nutritional factors and play the role of anti-apoptosis. Stem cell therapy is another medical revolution after drug and surgical medication. The research of MSCs developed rapidly from basic research to clinical application; scientists in the field of stem cells should seize the technical commanding point with the continuous development of science and technology in stem cell.

ACKNOWLEDGEMENT

Our study received support from the Natural Science Foundation of China (81401295), the natural Science Fund project in Tianjin (NO. 16JCYBJC27600).

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