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Application of mesenchymal stem cells for the treatment of traumatic brain injury and neurodegenerative diseases

Abstract

Despite the prevalence of traumatic brain injuries (TBIs) and neurodegenerative diseases, there is still a lack of effective and efficient therapeutic treatment options. TBI triggers an innate immune response and releases inflammatory molecules, creating a hostile environment that inhibits repair and regeneration. TBI has also been linked to a higher risk of suffering from neurodegenerative diseases, such as Parkinson's, Alzheimer's and Huntington's disease in later years. Novel stem cell research has provided a treatment option that overcomes existing barriers and can be used in regenerative medicine. Mesenchymal stem cells (MSC) are of particular interest due to their easy obtainability, homing potentials, multipotent differentiation, and immunomodulatory aptitudes. The challenges of this cell therapy and future prospects are discussed as well. This review aims to comprehensively study the potential of mesenchymal stem cells in regenerative medicine for treatment of traumatic brain injuries and neurodegenerative diseases.

Keywords: mesenchymal stem cell, traumatic brain injury (TBI), neurodegenerative disease, neurogenesis, neurons, central nervous system, treatment

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Kennedy Jordahl, Vincent S Gallicchio
Department of Biological Sciences, College of Science, Clemson University, USA

Correspondence: Dr. Vincent S. Gallicchio, Department of Biological Sciences, College of Science, Clemson University, Clemson, SC 29636 USA, Email vsgal@clemson.edu

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Abbreviations: AD, Alzheimer's disease; AT-MSC, Adipose tissue derived mesenchymal stem cell; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; BM-MSC, Bone marrow derived mesenchymal stem cell; CNS, Central Nervous System; DAI, Diffuse axonal injury; EC, Endothelial cells; EGF, Epidermal growth factor; FGF-2, Fibroblast growth factor-2; GDNF, Glial cell line-derived neurotrophic factor; GFAP, Glial fibrillary acidic protein; HD, Huntington's disease; I.a., Intraarterial; IL, Interleukin; I.v., Intravenous; MAP-2, Microtubule-associated protein 2; MCP-1, Monocyte chemoattractant protein-1; MSC, Mesenchymal stem cell; NF-H, Neurofilament heavy chain; NGF, Nerve growth factor; NT-3, Neurotrophin-3; PD, Parkinson's disease; SDF-1, Stromal cell-derived factor-1; TBI, Traumatic brain injury; TH, Tyrosine hydroxylase; UC-MSC, Umbilical cord derived mesenchymal stem cell; VEGF, Vascular endothelial growth factor

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death worldwide, and is a major contributor to long-term disability.[1] According to the Center for Disease Control and Prevention, approximately 1.7 million people suffer from TBI each year in the United States.[2] While 80% of TBIs are considered mild head injuries, moderate to severe TBIs are primary causes of induced death and disability. Adolescents aged 15 to 19 years old and older adults aged 65 years or older are the most likely to maintain a TBI and progression of a neurodegenerative disease. In recent years, the intensive care and management of TBI and neurodegenerative disease patients have significantly improved.[3] However, even under the best circumstances, there is 36% mortality for acute TBI; 15% severe disability; 20% moderate disability; and 25% complete recovery.[4]

TBIs are inflicted via external sources. These external sources can include direct incidences such as collision, crash, or jolt to the head; or indirect incidences such as whiplash. In both cases, the normal structure and function of the brain is disrupted. Following the trauma inflicted on the brain, a cascade of events occurs, this includes the primary injury and a secondary injury consisting of several pathophysiological mechanisms. The duality of the human body's innate inflammatory response to injury has protective and regenerative properties, yet also, destructive and inhibiting properties that make healing more difficult. This inability to regenerate neurons can be the onset neurological disease as well as inhibit pre-existing neurological impairment from being treated. The continuation of the body's deleterious inflammatory response to TBI has been linked to neurodegenerative diseases. Neurodegenerative diseases are characterized by the loss of functional neurons in a debilitating and progressive manner, which can affect memory and physical capabilities. In fact, if neuronal death caused by TBIs continues to progress, the patient may be at higher risk of suffering from neurodegenerative disease in later years, such as Parkinson's, Alzheimer's, and Huntington's disease.[5-7] The loss of neuron functionality caused by brain injury was previously thought to be irreversible.[8,9] Encouragingly, however, the current view is that the central nervous system consists of a variety of mechanisms allowing recovery. In fact, neurogenesis and angiogenesis in humans have confirmed to occur in a few areas of the brain.

While the primary impact of brain injury cannot be reversed, several leading stem cell therapy options may be useful in preventing secondary injuries and neurodegeneration. Of particular interest is the use of mesenchymal stem cells (MSCs) due to their ease of isolation, multipotent differentiation capabilities, tissue repair, homing potentials, ability to cross the blood-brain barrier (BBB), and immunomodulatory properties. Arguably the most important property of MSCs is their secretome. Trophic factors secreted by MSCs such as cytokines and growth factors, as well as neural protein expression, are predominantly responsible for the beneficial effects of this cell therapy.[10] While MSCs can be found in almost all adult tissues types throughout the body [11], MSCs from adipose tissue,[12,13] bone marrow, and umbilical cord tissue[14] have shown great success in neural differentiation. All of these aspects make MSCs a promising prospect in regenerative medicine. Overall, this research review aims

to comprehensively study the properties of MSC's and their potential applications in regenerative medicine for treatment of TBIs and neurodegenerative diseases.

Discussion

Pathophysiology of TBI

Traumatic brain injury (TBI) is caused by external forces such as a jolt or blow to the head. The effects of TBI can be separated into external and internal consequences. Externally, the skull which protects the brain could be damaged; potential outcomes are hematoma, hemorrhagic contusion, herniation, and midline shifts of the brain. Internally, the complex BBB may be compromised by allowing immune cells to migrate into the central nervous system.[15] Normally, the BBB balances ion concentrations (Ca++, Na+, and K+), regulates what flows in and out of the brain, as well as protecting against foreign elements circulating in the bloodstream. The primary stage is the initial, physical injury to the neurons, glial cells, nerve fibers, and the BBB.[16,17] This initial impact can cause local inflammation that exacerbates damage by spreading inflammation to surrounding neurons, ischemia (reduction of oxygen and glucose supply to cells), anaerobic respiration, lactic acid accumulation, loss of functioning ion pumps, and several cytotoxic effects; these consequences lead to further neuronal death.[18-20] The secondary stage initiates another cascade of events resulting in enlarged astrocytes that creates a barrier that surrounds the injured area. This physical barrier is called the glial scar which has both beneficial and inhibitory effects. This barrier protects the neurons still intact by isolating the site of injury and preventing inflammation from spreading to surrounding areas of the brain. However, this isolation slows the rate of macrophages entering the damaged area, prevents the regrowth of neurons, and inhibits the repair of the BBB and full recovery of functionality.[21-23]

There is ongoing research aiming to find ways to reduce neurological damage and detrimental inflammatory processes, but a strong focus has been on the use of MSCs. It is also important to understand that the severity of TBI can affect the patient's inflammatory response and thus treatment options. The severity and mechanism of injury is assessed to determine the extent of injury. Specifically, the Glasgow Coma Scale, a test ranging from 3-15 points, is used to assess a patient's consciousness level. For instance, a score of 13-15 is classified as mild TBI; a score of 9-12 is classified as moderate TBI; a score of 8 and below is classified as severe TBI.[24]

TBI and neurodegenerative diseases

Neurodegenerative diseases are characterized by the loss of functional neurons in a debilitating and progressive manner, which can affect memory and physical capabilities. A history of TBI has been linked to induce long-term neurodegenerative diseases.[5-7] After TBI, diffuse axonal injury (DAI) is one of the most common neuropathological consequences; DAI results in vulnerable white matter axons.[25-27] Interestingly, in vitro and in vivo studies have found that myelinated axons are more tolerant to mechanical stress compared to unmyelinated axons.[28-30] The cascade of events seen in TBI pathophysiology is similar to the progression of neurodegeneration. Following trauma, inflammation intensifies; neuronal swelling occurs; and cytoskeletal failure and disconnection ultimately lead to Wallerian degeneration.[31,32] Wallerian degeneration is the innate immune response to traumatic nerve injury.[33] Neuron and axonal degeneration can have a role in the development of these diseases in both the acute and chronic phases following injury.[34-36] However, the risk of developing a neurodegenerative disease is partially dependent on the severity of the TBI. For instance, mild TBI without loss of consciousness does not necessarily correlate to enhanced risk of Parkinson's (PD), Alzheimer's (AD) or Huntington's disease (HD).[37,38] However, some TBI cases can lead to an earlier onset age of PD, AD, and HD.[39-41] The cause of PD symptoms is due to the loss of dopamine (DA) neurons, and thus DA neurotransmitters. While there are existing drugs that provide symptomatic relief to patients, there are no current treatments that attenuate disease progression. The overlap in neuropathology of TBI and neurodegenerative diseases suggest potential similar mechanisms. Thus, the trophic and immunomodulatory properties exhibited by MSCs may be applied to treat both TBI and neurodegenerative diseases.

MSCs and their properties

Vocabulary

Stem cells are undifferentiated cells capable of self-renewal and proliferation that produce progeny cells which can then differentiate into various cell types. Stem cells are immature progenitor cells that divide via asymmetric mitosis, giving them self-renewal and differentiation capabilities. Asymmetric mitosis yields two daughter cells; one daughter cell is identical to the stem cell, while the second daughter cell is able to differentiate into a more mature cell.[42] There are several types of stem cells, but this review primarily focuses on MSCs. The International Society for Cellular Therapy has proposed criteria for the scientific community to accept to standardize the identification of MSCs.[43] MSCs are classified as heterogeneous multipotent stromal cells, meaning they are derived from embryonic cells that can differentiate into cells of the ectoderm, mesoderm and endoderm.[44] Ectodermal tissue includes neurons; mesodermal tissue includes adipocytes, osteocytes, and chondrocytes; endodermal tissue includes endothelial cells (EC).[45] As the definition of MSCs states, MSCs are distinguished by particular surface markers. MSCs must be positive for CD105, CD73, and CD90, and negative for CD34, CD45, CD14, CD11b, CD7α, CD19, and HLA-DR surface molecules.[46-48]

While MSCs are named stem cells, there has been an ongoing debate as to whether they actually qualify as stem cells; the accuracy of this title depends on the context of which they are being studied.[49] In vitro, MSCs have demonstrated their ability to proliferate, regenerate, and give rise to different progeny of ectodermal, mesodermal, and endodermal tissue descent. In vivo studies have also shown successful survival and differentiation into neurons and astrocytes, leading to improved motor function 50. However, there are ongoing studies determining whether the phenotype of these stem cells may vary between in vitro and in vivo environments due to changing chemical and physical conditions.[51] This discussion is noteworthy to ensure research findings are not taken out of context. Yet, the science community has generally accepted MSCs as stem cells.[51]

MSC Sources

MSCs were originally isolated from bone marrow[52] but are also fetal and adult tissue of adipose tissue,[13] placenta,[53] lung,[54] umbilical cord,[55] synovial membrane,[56] dental pulp,[57] and many others. The properties of MSCs may vary depending on the source they are obtained from, cell culture conditions, and isolation procedures. In fact, variation has even been found in MSCs obtained from the same patient between isolations.[42,58] Some studies found that autologous MSCs differ from those obtained from healthy patients and can ultimately affect the efficacy of treatment.[59] Due to this, it is important to understand how these differences can affect MSC behavior when applied to clinical trials. Several studies aim to understand the properties of MSCs

derived from bone marrow (BM-MSC), umbilical cord (UC-MSC), and adipose tissue (AT-MSC).

UC-MSCs generally have the highest proliferation rate regardless of the cell culture condition used.[60,61] In comparison, AT-MSCs have a moderate proliferation rate and BM-MSCs have the lowest proliferation rate.[62-64] However, BM-MSCs are most sufficient in maintaining their abundant secretion of trophic and proangiogenic factors independent of cell culture condition; AT-MSCs are the only producers of collagen I, II, and III; and UC-MSCs have the highest secretion of cytokines which attract inflammatory cells.[62-65] The production of collagen by AT-MSCs enhance the retention, survival, and brain metabolism of cells in rat TBI models.[66] UC-MSCs also reduced expression on inflammatory cytokines including IL-1α, IL-6, and IL-8.[61] Differentiated cells can also influence levels of secreted cytokines, growth factors, proangiogenic factors, and proteins. For instance, without any stimulation, BM-MSCs already express neural proteins before differentiation even occurs. In particular, immature neuronal proteins such as Nestin and Tuj-1 were innately expressed; after exposure to a neuronal induction medium, mature neuronal proteins such as TH, MAP-2, and GFAP were significantly more expressed. This mature neuronal protein expression supports the differentiation capability of BM-MSCs into neurons and glial cells.[67] In addition, co-culturing BM-MSCs with astrocytes or Schwann cells further encourages differentiation into neurons and glial cells.[68] The trophic factors secreted by UC-MSCs differentiate microglia and macrophages to remodel the brain thus leading to significant improvement in neurological functioning.[69] UC-MSCs are also promising candidates for stem cell therapy as they are easily obtained, have a lower risk of rejection after transplantation, and no ethical controversy.[70] AT-MSCs are also easily isolated MSC derivatives and are capable of differentiating into neurons, endothelial-derived cells, and Schwann cells.[68] The neuroprotective properties of AT-MSCs are due to the release of growth factors, such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). These subtle differences between MSC derived sources are critical to be aware of as they influence the final properties and efficacy when administered to patients.

Administration of MSCs to Site of Injury

The route of administration must be taken into consideration as it determines how many MSCs successful engraft to the site of injury. Three major methods of MSC delivery include intracranial,[71] intraarterial (i.a.)[72] and intravenous (i.v.) infusion.[73] Other methods that have been used include intranasal,[74-76] intrathecal,[77] and intracisternal.[78] Intracranial injection provides a direct route for MSCs and shows the advantage of reducing the number of stem cells used but is also the most invasive. Knowing that the TBI and neurodegenerative diseases may not be localized, it could be deduced that systemic administration would have beneficial results. Both i.a. and i.v. administration have shown functional neural recovery in animal models,[79-81] but the optimal administrational route has yet to be agreed on. Each method comes with advantages and disadvantages, for example, i.v. delivery can be used in broad distributions, large volumes, and is minimally invasive;[82] however, it is contradictory whether or not this method allows enough MSCs to reach the site of injury as most cells accumulate in the lungs, spleen, and liver.[73,83-85] On the contrary, the entrapped MSCs can then release micro vesicles and immunomodulatory factors that influence the healing process and state of the patient.[83] The i.a. method seems to direct the majority of injected MSCs to the brain, especially when injected through the carotid arteries.[84,86] However, there have been highly variable results using the i.a. route since precapillary entrapment can occur during i.a. infusion as well, but to a lesser degree than i.v. administration. Additionally, the i.a. route increased the risk of cerebral lesions after a stroke, which might limit the role of i.a. administration of MSCs.[87] Overall, the best route of administration has not been established as each method has advantages and disadvantages. Yet, the method of administration should be well-selected to treat TBI and neurodegeneration. While the delivery method is critical to consider, the survival of transplanted MSCs after transplantation is also crucial. Novel methods and mechanisms have been suggested to precondition stem cells in vitro in hopes of increasing the retention rates in vivo. Poor MSC survival in vivo has been linked to anoikis (type of programmed cell death), potential immune rejection, and oxidative damage mediating apoptosis.[85]

The dose quantity is critical to consider in the administration process as well. One study showed that an increased number of MSCs administered does not show increased therapeutic effect in the brain injury animal model. Another study used autologous MSCs in hopes of increasing engraftment success after transplantation. A does of 107-109 cells were directly administered to the site of injury followed by a dose of 108-1010 cells via i.v. infusion. There were no major adverse effects with exception of one patient who experienced two epilepsy episodes in the first two months.[88] The window of efficacy must be considered as well. One study done by Tian and others implanted MSCs via lumbar puncture into 97 patients, with 24 patients being in a permanent vegetative state.[89] The time of MSC administration varied between patients, but the overall finding was that the sooner MSCs are implanted to the time of injury, the more effective the treatment responses are likely to be.

Homing potentials

While the underlying mechanisms are unclear, MSCs contain a migratory capacity, allowing them to home to sites of injury;[47,90] this property is crucial especially when MSCs are administered systemically. In other words, MSCs have the ability to recognize injured areas in otherwise healthy tissue. This homing potential of MSCs is influenced by chemokines, growth factors, and their ability to adhere to injured endothelium via vascular cell adhesion molecules.[91] Since MSCs may express a variety of chemokine receptors, the homing affinity could depend on the type of tissue.[92] One of the major pathways involved in MSC migration is the METR/HIF-1/CXCR4 pathway.[93] This pathway proceeds to decrease the number of peripheral leukocytes infiltrating the BBB; upregulates anti-inflammatory cytokines and downregulates proinflammatory cytokines; reduces the proinflammatory cytokine cascade; and ultimately slows and prevents the loss of neuronal cells. The chemo attractants involved in the enhancement of MSC homing to the brain are monocyte chemoattractant protein-1 (MCP-1) and stromal cell-derived factor-1 (SDF-1). Interestingly, the expression of these chemo attractants is dependent upon region and time. For instance, a study conducted by Lee and colleagues found that MCP-1 and SDF-1 directed i.v. infused MSCs to the cortex one day after injury or to the striatum in subsequent days.[94]

Ability to cross blood-brain barrier

The blood-brain barrier (BBB) is a dynamic system critical to the central nervous system that separates peripheral blood from neural tissue. These blood vessels strictly regulate the movement of ions and molecules between the blood and brain. ECs in the BBB are predominantly responsible for its functions and interactions.[95] Thus, understanding the normal function and structure of this barrier is important when studying how it functions under variable conditions,

such as disease or inflammation. MSCs exhibit leukocyte-like homing capabilities that enable them to interact with and cross the BBB. The BBB is naturally held together by tight junctions; it has been suggested that MSCs, similar to leukocytes, alter the properties of the tight junctions allowing them to infiltrate the brain.[96] There are many mechanisms involved in ensuring this crossing is successful.[97] MSCs utilize adhesion molecules (VCAM-1/VLA-4 and β1 integrin) to exit the bloodstream and adhere to the endothelium. MSCs then integrate into host tissue via the plasma podia.[97] Once in the brain, several studies support that MSCs already possess the ability to cross the BBB via paracellular pathways.[96-99] For instance, AT-MSCs administered intravenously were successful in crossing the BBB in mice with AD.[100,101] Successful MSC engraftment also displayed positive results in animal models with HD[102,103] and PD.[104-106] MSCs were observed to actively cross the BBB, but the alteration to the vasculature and inflammation post-injury may allow the passive movement and accumulation in the brain via entrapment.[107] TBI and neurodegenerative diseases break the impermeability of the BBB, allowing immune cells to enter the site of injury and trigger the release of inflammatory mediators.[108,109] This ability to cross the BBB is appealing for the treatment of TBI and neurodegenerative diseases.

MSC differentiation

The multipotent differentiation capabilities of MSCs make this cell therapy promising for regenerative treatment. Differentiation into neuroectoderm is of particular interest here. During development, the neuroectoderm lies immediately above the notochord and gives rise to the entire nervous system; this includes the neural precursor cells, neural tube, brain, spinal cord, neurons, glial cells, and neural crest cells.[110] It has been confirmed that MSCs injected into the CNS migrate throughout the brain and adopt morphological and phenotypic characteristics of neurons and astrocytes (sub-type of glial cells).[111-114] The numerous methods to promote neural cell differentiation is not well distinguished as they are inconsistent. However, it is suggested that expression of certain agents, neuronal proteins, secretion of growth factors, and environmental conditions play a role in neuronal differentiation of MSCs.[110]

While MSC derivatives have an innate ability to differentiate, agents are generally used to induce neural differentiation in vitro. Such agents include compounds that increase intracellular cyclic AMP levels, retinoic acid, growth factors, antioxidants, a demethylating agent, and noggin (a physiological neural inducer); these agents collectively induce MSCs to adopt neuron-like morphologies and phenotypes as well as express several neuronal proteins.[115] Neuronal proteins expressed included nestin, glial fibrillary acidic protein (GFAP), neurofilament heavy chain (NF-H), and B-III tubulin.[116,117] Other studies have proposed methods to direct MSCs to differentiate into specific neuronal subtypes via expression of tyrosine hydroxylase,[118-120] glutamate receptors,[121] Schwann cell markers,[122] glutamate transporters,[123] inward rectifying potassium channels,[124] synaptic vesicle proteins,[125,126] and neurotrophic receptors.[127] Environmental conditions have also been suggested to play a part in influencing the differentiation of MSCs into neuroectoderm. For instance, MSC differentiation may require a toxic environment.[128,129] A toxic environment could include exposure to detergents, high pH, and molarity sodium chloride induced a neuron-like phenotype in MSCs.[130]

One concern over the fact that so many agents can influence differentiation of MSCs is that cell fate decisions in development are generally controlled by one master regulatory gene.[131] Additionally, many of these processes are reversible. Thus, additional studies should be done to better understand if neural protein induction of MSCs alone constitutes functional differentiation and commitment into neuroectoderm in vivo, or whether they are just temporary behaviors in vitro.

Immunomodulatory Properties

Upon impact of injury or mechanism of neurodegeneration, the body activates its innate inflammatory response. Due to the homing potentials of MSCs, they are able to migrate to the site of injury and utilize their immunomodulatory properties to decrease inflammation. This reaction is crucial as excessive inflammation in the brain causes drastic degeneration of the central nervous system.[132,133] Furthermore, these kinds of injury activate microglia and astrocytes, which are primary sources of inflammatory cytokines, such as IL-1α, IL-1β, IL-6, TNF-α, and TNF-β.[109,134] If this cascade is not interrupted, the BBB is likely to be damaged, and be exacerbated as lymphocytes and monocytes continue to migrate to the site of injury.[135,136] Thus, the main immunological cells involved include microglia, astrocytes, lymphocytes, and macrophages.[137,138] MSCs modulate inflammation by upregulating anti-inflammatory signaling and deregulating pro-inflammatory signaling. MSCs also use direct cell-to-cell interactions and paracrine factor secretions to interfere with different pathways of the immune response.[139-142] For instance, MSCs have shown significant immunomodulatory effects such as inhibiting the proliferation of T cells, B cells, and natural killer cells.[143-146] Inflammation can also be modulated by MSC inhibition of interleukin six (IL-6) and IL1-□, pro-inflammatory signals, and enhancing IL-10, an anti-inflammatory signal.[68,147] BM-MSCs exhibit anti-inflammatory effects by promoting the differentiation of lymphocytes. This modulatory behavior slows the inflammatory response cascade and as a result halts the progression of secondary brain injuries after impact. Therefore, MSCs may be a very promising treatment option to combat these detrimental events as they promote neurogenesis and endogenous repair.

Neurogenesis and tissue regeneration

Previously, it was thought that neurons were unable to regenerate, but stem cell research has revealed new potentials in the past two decades. Neuron development was generally understood to only occur during specific developmental periods. However, other studies have shown otherwise. Successful neurogenesis has been reported in the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricle during the postnatal and adult stages.[148-150] In order for MSCs to carry out neurogenesis and their tissue repair function, inflammation must be regulated as they secrete growth factors to maintain homeostasis. The trophic secretions of MSCs act as signaling molecules that induce functional tissue recovery by inhibiting apoptosis;[151,152] promoting neurogenesis,[153-155] angiogenesis,[156-158] and synaptogenesis;[153-155] and supporting the survival and proliferation of endogenous cells.[149,159-161] The significance of cytokine and adhesion molecule production by MSCs is well established to regulate hematopoiesis. Specifically, VEGF, BDNF, GDNF, and NGF, FGF-2, EGF, (NT-3) are leading factors in repairing lesioned areas.[162-164] GDNF promotes growth and nourishment to neurons lost in PD, particularly dopamine neurons. These chemokines may act indirectly by activating nearby astrocytes, which then promote neurogenesis.[165] Further studies revealed that MSCs encode proteins that regulate angiogenesis, wound repair, immunity, defense, and neural activities.[166] Interestingly, many of these proteins are expressed by subpopulations of cells; this complex composition explains the broad therapeutic applications of MSCs. As explained previously, MSCs are found in almost all adult human tissue; however, bone marrow is one of the most promising sources. One explanation for

this is because bone and marrow are innervated by nervous tissue which is why BM-MSCs express several regulatory neuronal proteins including neurotrophins, neurite-inducing factors, and neuropeptides. These factors are understood to assist in guiding innervation to repair injured tissue as well as maintaining existing healthy tissue.[167-169] This behavior validates this approach for therapeutic treatment of TBI and neurodegenerative diseases.

Challenges and future prospects

While there are many promising qualities of MSCs in the treatment of TBIs and neurodegenerative diseases, there are many challenges that may affect actually applying this science in a clinical setting. For instance, more information is needed to understand how MSCs target specific tissues;[170] their potential correlation with tumors;[171-174] and the window of efficacy. The trophic factors of MSCs are capable of tissue regeneration, but the precise mechanisms and pathways need to be further understood. For instance, the secretory factors of MSCs are clearly beneficial in regenerative healing, but it should be distinguished whether these secretory factors can be used independently or if actual MSCs are necessary for regenerative treatment. With respect to concerns over the correlation to tumors, they may be prevented by use of MSC-derived exosomes.[175] With respect to the window of efficacy, MSC treatment is generally more effective when implemented close to the date of injury.[176] Yet, the challenge of understanding the effect of time on efficacy still needs to be overcome in patients receiving this treatment past the ideal window of care. In addition, there is a lack of standard parameters to measure the effectiveness of this therapy between MSC harvest location, TBI severity, and quantity of MSCs. Controls are also difficult to employ, placebo effects are abundant, and the cost of trials are great.

While the barriers mentioned above are significant, there is hope in the fact of knowing that similar problems have been encountered in previous novel treatments and have since been overcome. This objective may be accomplished by the combined efforts of hematologists and researchers around the world by creating a comprehensive website that presents all collected data of MSCs administered to patients.[140] Another aspect to consider is the necessity for a standardized cell injection strategy as repeated injections of MSCs have shown beneficial outcomes by providing continuous stimulation for repair.[177-182] There are two aspects that are the most striking in MSC treatment applications. First, few if any adverse effects have been well-documented in patients who received this treatment. Second, while many underlying mechanisms of this treatment are unclear, MSCs have resulted in drastic improvements in large scale animal models and some patients. Ultimately, the use of MSCs for the treatment of TBI and neurodegenerative disease is quite promising.

Conclusion

The use of MSCs for the treatment of TBI and neurodegenerative diseases has attracted substantial interest by the science community in the last two decades. While homing and differentiation capabilities of MSCs were the original attraction for therapeutic treatments, their release of paracrine molecules seem most promising due to the secretion of growth factors and anti-inflammatory effects. Both in vitro and in vivo experiments support trophic factors secreted by MSCs to modulate inflammation and create a more favorable environment for successful neurogenesis and tissue repair for TBI and neurodegenerative disease applications. More phase II/phase III trials are urgently needed to combat the challenges of this treatment and they should follow the guidelines proposed by the International Society for Stem Cell Research. Ultimately, the wide applications of MSCs provide hope to finding an effective and efficient therapeutic treatment option for TBIs and neurodegenerative diseases.

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