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Mesenchymal stem cells for the treatment of neurodegenerative and psychiatric disorders

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that have the capacity to differentiate into all lineages of mesodermal origin, e.g., cartilage, bone, and adipocytes. MSCs have been identified at different stages of development, including adulthood, and in different tissues, such as bone marrow, adipose tissue and umbilical cord. Recent studies have shown that MSCs have the ability to migrate to injured sites. In this regard, an important characteristic of MSCs is their immunomodulatory and anti-inflammatory effects. For instance, there is evidence that MSCs can regulate the immune system by inhibiting proliferation of T and B cells. Clinical interest in the use of MSCs has increased considerably over the past few years, especially because of the ideal characteristics of these cells for regenerative medicine. Therapies with MSCs have shown promising results neurodegenerative diseases, in addition to regulating inflammation, they can promote other beneficial effects, such as neuronal growth, decrease free radicals, and reduce apoptosis. Notwithstanding, despite the vast amount of research into MSCs in neurodegenerative diseases, the mechanism of action of MSCs are still not completely clarified, hindering the development of effective treatments. Conversely, studies in models of psychiatric disorders are scarce, despite the promising results of MSCs therapies in this field as well.

Key words: Mesenchymal stem cells, treatment, neurodegenerative disease, psychiatric disorders.

INTRODUCTION

Mesenchymal stem cells were first described by Friedenstein as "colony forming units-fibroblastic" due to their ability to generate single cell-derived colonies (Friedenstein et al. 1976). Subsequently, authors have used different names to refer to these structures, and only in the 2000s did the committee of the International Society of Cytotherapy propose the name "multipotent mesenchymal stromal cells". Since then, authors have simply referred to them as

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mesenchymal stem cells (MSCs) (Dominici et al. 2006).

MSCs are multipotent progenitor cells that have the capacity to differentiating into all lineages of mesodermal origin, e.g., cartilage, bone, and adipocytes (Pittenger et al. 1999). Recent studies have shown that MSCs are also able to differentiate into cells from sources other than mesodermal, such as neurons and hepatocytes (Dezawa et al. 2004, Hermann et al. 2004, Perrier et al. 2004, Sato et al. 2005). MSCs have been identified at different stages of development, including adulthood, and in different tissues, such as bone marrow, adipose tissue, bone, lung, liver, teeth, skeletal muscle, amniotic fluid, umbilical cord, and cord blood (Campagnoli et al. 2001, da Silva Meirelles et al. 2006, Erices et al. 2000, Lee et al. 2004).

Three basic criteria have been established by the International Society of Cellular Therapy to determine whether *ex vivo* expanded cells could be considered MSCs; namely: 1) ability to adhere to plastic in cell culture; 2) capacity to differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*; and 3) expression of specific surface membrane molecules (CD73, CD90, CD105), simultaneous lack of expression of hematopoietic markers (CD14, CD34, CD45) and human leukocyte antigen DR (HLA-DR) (Dominici et al. 2006).

Due to their differentiation, self-renewal, and immune-suppressive abilities, MSCs have received increasing attention from investigators with regard to their potential use as cell therapy in different conditions, including ischemia, diabetes, and even neurological diseases (Drela et al. 2013, Ezquer et al. 2008, Honma et al. 2006, Horwitz et al. 1999, Phinney Prockop 2007). Therapies can consist of the implantation of exogenous cells to the injured site, or the release of trophic factors that will assist in the endogenous regeneration of the injured region (Sohni and Verfaillie 2013).

MIGRATION OF MSCs

Recent studies have shown that MSCs have the ability to migrate to injured sites (Chapel et al. 2003, Wang et al. 2002). MSCs migration mechanisms involve the expression of specific receptors to facilitate reaching the target site, adhering to and infiltrating the damaged organ or tissue. In this line, an important issue in MSCs therapy is the way that cells will reach the site of damage, a process denominated "homing." Therapy effectiveness depend directly on the cells' ability to produce trophic factors, such as growth factors and cytokines that will assist in the regeneration of endogenous cells. For this to occur, correct migration of cells to the injured tissue is of utmost importance. Important factors such as age, number of cell passages, number of cells, and the protocols used for cell delivery are crucial for the migration and homing processes to be successful (Ries et al. 2007, Rombouts and Ploemacher 2003).

So far, the gold standard delivery method in the administration of MSCs is intravenous infusion (Akiyama et al. 2002, Nomura et al. 2005). Notwithstanding, research continues to try to improve homing and migration, with the goal of increasing the number of MSCs capable of reaching the target site and consequently improving MSCs transplantation protocols for specific clinical applications (Cheng et al. 2008, Choi et al. 2010, Gerrits et al. 2010, Grayson et al. 2007, Maijenburg et al. 2011).

MSCs SECRETOME AND PARACRINE ACTIVITY

In addition to their differentiation potential and the migratory properties that enable tissue replacement (Mafi et al. 2011, Quevedo et al. 2009), MSCs have broad immunomodulatory properties (Aggarwal and Pittenger 2005, Menard and Tarte 2013) and paracrine activities (Mureli et al. 2013, Waszak et al. 2012). These characteristics have been associated with the therapeutic effects of MSCs and

have been investigated with a focus on potential clinical applications.

The MSCs secretome includes the molecules released by MSCs in response to injury that directly or indirectly promote repair, e.g., growth factors, cytokines, antioxidants, and extracellular matrix proteins (Chan and Lam 2013, Chen et al. 2008). Some conditions that lead to tissue damage, such as pro-inflammatory or hypoxic stimuli and exposure to apoptotic factors, increase the secretion of specific factors by MSCs, which act on angiogenesis, neurogenesis and regulate neural niche environment, mediating protection and repair processes (Chen et al. 2003, 2002, Rosova et al. 2008).

Evidence has suggested that MSCs have the potential to show paracrine activity even without direct cell contact. For instance, studies have demonstrated that MSCs conditioned medium was able to protect neurons from inflammation in the absence of engraftment, suggesting a neuroprotective effect through secretion of neurotrophic factors even at a distance from the damaged organ (Bai et al. 2012, Uccelli and Prockop 2010). Some of these factors with protective effects have been identified, namely: stem cell-secreted hepatocyte growth factor (HGF), fibroblast growth factor (FGF)-II, brain-derived neurotrophic factor (BDNF), and platelet-derived growth factor (PDGF)-AB (Bai et al. 2012, Constantin et al. 2009, Voulgari-Kokota et al. 2012). MSCs-secreted BDNF and nerve growth factor beta (β-NGF), for instance, have promoted cell resilience and neuritogenesis in co-culture experiments (Crigler et al. 2006). The characterization of MSCs conditioned media has pointed to insulin-like growth factor 1 (IGF-1), HGF, vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β) (Nakano et al. 2010), but other factors involved in the MSCs secretome remain to be identified.

MSCs can also secrete vesicles containing important molecules such as cytokines, in addition to isolated paracrine soluble factors. These vesicles act via paracrine or endocrine signaling, however, their composition and role remain to be established (Biancone et al. 2012, Camussi et al. 2013). Both the soluble factors and these vesicles seem to be essential to the paracrine activity associated with MSCs.

The paracrine effects of MSCs have been studied in different animal models of neurological disorders, e.g., stroke, Parkinson's, Alzheimer's, and Huntington's diseases, and amyotrophic lateral sclerosis, as will be discussed below. The paracrine activity of MSCs could also be related to the immunomodulatory properties of these cells – two functions acting together for brain protection and regeneration (Fig. 1).

MSCs SECRETOME AND IMMUNOMODULATION

An important characteristic of MSCs is their significant immunomodulatory and anti-inflammatory effects. For instance, evidence has shown that MSCs can regulate the immune system by inhibiting the proliferation of T and B cells (Duffy et al. 2011, Franquesa et al. 2012), natural killer (NK) cells (Di Nicola et al. 2002, Spaggiari et al. 2008) and neutrophil apoptosis (Raffaghello et al. 2008). Via this mechanism, MSCs influence the production and secretion of antibodies by B cells, cytokine secretion, and NK cytotoxicity (Aggarwal and Pittenger 2005, Spaggiari et al. 2008). MSCs have also been suggested to inhibit the differentiation of monocytes into dendritic cells and in addition to influencing the roles of these cells (Aggarwal and Pittenger 2005, Ivanova-Todorova et al. 2009).

The mechanisms responsible for the immunosuppressive effects of MSCs have been the focus of several studies, and cell-to-cell contact and soluble factors have been indicated as key elements in this area. Among soluble factors, the following have been highlighted: nitric oxide (Sato et al. 2007), indoleamine 2,3-dioxygenase (Meisel et al. 2004),

TGF-β1, HGF (Di Nicola et al. 2002), interleukin-10 (IL-10), prostaglandin E2 (pGe2) (Aggarwal and Pittenger 2005), heme oxygenase-1 (HO1), IL-6 (Kogler et al. 2005) and soluble HLA-G5 (Selmani et al. 2008). Several studies have suggested that MSCs inhibit inflammatory processes in different disease states (Lee et al. 2009a, Sanchez et al. 2011, van Koppen et al. 2012), contributing to the regeneration of damaged tissues, probably by modulating the immune response.

In summary, the paracrine and immunomodulatory factors present in the MSCs secretome seem to play important roles in establishing an appropriate tissue microenvironment to promote repair in damaged situations justifying research into the therapeutic potential of these cells.

MSCs SECRETOME: CLINICAL APPLICATION

Clinical interest in the use of MSCs has increased significantly over the past few years, especially because of the ideal characteristics of these cells for regenerative medicine. Specifically, MSCs can be obtained from tissues commonly present in clinical situations (e.g., bone marrow, adipose tissue, and umbilical cord blood), they can be expanded in culture for testing purposes and for clinical use, and have low immunogenicity, which is very useful for potential clinical applications (Le Blanc et al. 2003).

However, before MSCs can be used in regenerative medicine, it is essential to understand the biology of these cells and investigate the most appropriate ways to culture and handle them.

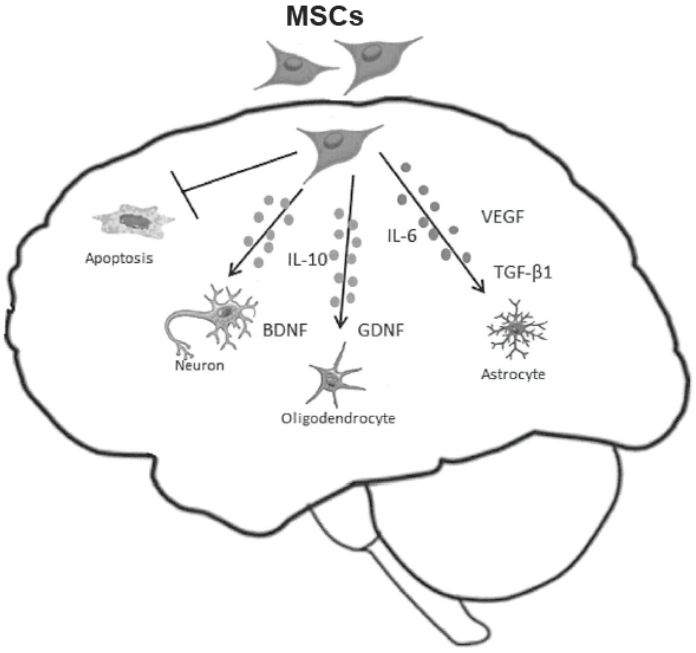

Figure 1 - Schematic figure to show the mechanism of action of MSCs in the CNS. The MSCs has been described to release neurotrophic factors and anti-inflammatories cytokines (BDNF, GDNF, VEGF, TGF-β1, IL-10, IL-6). These molecules act as an assistant in the nervous tissue regeneration through the activation of neurogenesis, neuroprotection, immunomodulation in astrocyte, oligodendrocyte and neuron. Furthermore can inactivating cell death through apoptosis.

In addition, it is important to know in detail the properties of the molecules secreted by MSCs, through the characterization of their secretome. In this sense, gene expression, proteomics, and metabolomics have been applied to investigate the potential therapeutic action of new and already known soluble factors secreted by MSCs.

MSCs APPLICATION IN NEURODEGENERATIVE DISEASES

Despite the vast amount of research into neurodegenerative diseases over the past few years, their etiology and pathophysiology are still not completely understood. Moreover, the complexity of these conditions pose difficulties to the development of effective treatments. Inflammation has been identified as a key factor in the pathophysiology of degenerative diseases affecting the central nervous system (CNS). In these pathologies, the primary insult evokes a local inflammation, with reactive astrogliosis, macrophage influx, and cell death generating tissue damage and glial scar formation (Drela et al. 2013). Therefore, immunomodulatory therapies may become a good therapeutic strategy in these cases.

MSCs therapies have shown promising results in neurodegenerative diseases. In addition to regulating inflammation, they can also promote other beneficial effects, such as neuronal growth, a decrease in free radical levels, and reduce apoptosis (Dharmasaroja 2009). Once again, application of MSCs therapies in these scenarios may help reduce all the adverse pathological events caused by neurodegenerative diseases (Table I).

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a devastating and the most common form of dementia, characterized by extracellular amyloid plaques, neurofibrillary tangles, and a progressive loss of neurons and synapses in different brain regions. Patients with AD present memory deficits and cognitive impairment (Ballard et al. 2011). To date, the treatment of AD is only palliative, and involves mainly drugs to increase cerebral acetylcholine levels. MSCs therapy seems to be a very attractive option in this condition (Drela et al. 2013).

Several studies have shown promising results with the use of MSCs in animal models of AD. One study in particular showed that bone marrow-derived MSCs injected intracerebral were effective in reducing accumulation of amyloid-β (Aβ) in the brain of an animal model of AD prepared via direct Aβ injection in the hippocampal dentate gyrus (Lee et al. 2010b). The same group showed that intracerebral transplantation of bone marrow-derived MSCs to amyloid precursor protein and presenilin in double transgenic mice ameliorated cognitive function. Furthermore, mice treated with MSCs showed a decrease in hyperphosphorylated tau protein levels (Lee et al. 2010b). In another study, Lee et al. (2010a) reported that intracerebral injection of human umbilical cord blood-derived MSCs in an acute model of AD, improved cognitive function, reduced levels of neuronal apoptosis, and decreased activation of astrocytes and microglia (Lee et al. 2010a). Injection intracerebral of bone marrow-derived MSCs has also been shown to improve learning and memory in a chemically and age-induced rat model of AD (Babaei et al. 2012). Kim et al. (2012) in turn, evaluated the mechanisms involved in Aβ degradation induced by MSCs. According to that author, soluble intracellular adhesion molecule-1 (sICAM-1) is released by human umbilical cord blood-derived MSCs and acts on microglial cells, inducing the expression of the Aβ-degrading enzyme (Kim et al. 2012).

Recently, one study showed that a single intracerebral injection of MSCs, decreased cerebral Aβ deposition compared with animals treated with phosphate buffered saline (PBS). The expression of dynamin 1 and synapsin 1, two proteins typically decreased in the brains of AD patients, were

increased in the brains of AD animals treated with MSCs (Bae et al. 2013).

Even though the results obtained with animal models have been encouraging, findings from clinical studies are not yet available.

PARKINSON'S DISEASE

Parkinson's disease (PD) is an extremely common neurodegenerative illness. This condition is characterized by the progressive loss of dopaminergic neurons in the substantia nigra and a severe decrease in striatal dopamine contents (Jenner 2008). The clinical symptoms of PD include tremor, muscle rigidity, bradykinesia, and postural instability. Existing pharmacological therapies and surgeries can improve clinical symptoms at early stages, but become less effective as the disease progresses (Glavaski-Joksimovic and Bohn 2013). Thus, it is clear that new therapeutic strategies are needed to decrease neuronal loss and slow progression of disease.

MSCs therapy has been considered in PD to replace lost neurons in the substantia nigra with healthy dopaminergic neurons and to avoid neuron loss (Huang et al. 2012). Over the past years, an increasing number of reports have described promising results of MSCs therapy in experimental models of PD. Animals treated with MSCs had the capacity to protect and decrease damage in dopaminergic neurons (Blandini et al. 2010, Danielyan et al. 2011, Li et al. 2001).

Improved behavior has been observed in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of PD after bone marrow-derived MSCs transplantation (Li et al. 2001). In addition, increased viability and migration of transplanted bone marrow-derived MSCs was observed in lost dopaminergic neurons after the administration of 6-hydroxydopamine (6-OHDA) in an animal model (Hellmann et al. 2006).

MSCs have also been used as a vector for gene delivery in a rat model of PD: cells were transfected with the gene coding for tyrosine hidroxylase (TH), which is the limiting-rate enzyme for dopamine synthesis. The authors reported successful transfer and expression of the TH gene in the rat striatum, as well as clinical improvement (Lu et al. 2005). Experimental studies have shown that MSCs conditioned medium promotes the survival of grafted xenogeneic dopaminergic neurons in affected mice (Shintani et al. 2007). Another study using MSCs intravenously showed a significant decrease in the loss of dopaminergic neurons in rats treated with MG-132, which causes a neurodegenerative disease similar to PD (Park et al. 2008). Furthermore, intravenous injection of MSCs reduced the loss of dopaminergic neurons in models of disease induced by injection of lipopolysaccharide (LPS) into the substantia nigra or by intraperitoneal injection of MPTP (Kim et al. 2009). In another study, treatment with MSCs and pretreatment with glial cell line-derived neurotrophic factor (GDNF) increased the proportion of TH-positive and dopamine-producing cells, resulting in clinical improvement in a 6-OHDA rat model of PD (Dezawa et al. 2004). Yet another study of the same group of authors showed that administration of dopaminergic neuron-like MSCs to the striatum, ameliorated motor function in parkinsonian macaques – a finding that was associated with restoration of the dopaminergic function (Hayashi et al. 2013). Finally, in the same line, intra-striatal injection of MSCs cultured in favorable conditions for neuronal differentiation has been shown to improve clinical symptoms in murine models of PD (Bouchez et al. 2008, Levy et al. 2008). One of the latter studies found comparable efficacy when using undifferentiated MSCs (Bouchez et al. 2008).

Other mechanisms of action of MSCs in PD refer to the immunomodulatory and anti-inflammatory effects of these cells. There is a

body of evidence suggesting that inflammation and microglial proliferation are involved in the pathophysiology of PD. One study has demonstrated that MSCs have the capacity to protect dopaminergic neurons from LPS-induced microglial activation and from the production of nitric oxide and tumor necrosis factor alpha (TNF-α) (Kim et al. 2009). Chao et al. (2009) observed that intravenous administration of mouse MSCs, protected dopaminergic neurons from MPTP toxicity and decreased microglial activation (Chao et al. 2009). Those studies reinforce the potential importance of the immunomodulatory effects of MSCs for the treatment of PD.

In humans, only one clinical trial has been conducted, consisting of seven PD patients aged between 22 and 62 years, followed up for a period that ranged from 10 to 36 months. The patients received a single dose of autologous bone marrow-derived MSCs transplanted to the subventricular zone using stereotaxic surgery. Three of the seven patients showed an improvement in symptoms, with a decrease in off/on periods measured using Unified Parkinson's Disease Rating Scale. Two patients also reported subjective improvement of symptoms and reduction in drug dosage (Venkataramana et al. 2010). Further investigation is necessary to confirm the efficacy of this therapy.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease that affects the CNS, characterized by recurrent episodes of axonal lesion and demyelination (Compston and Coles 2002, Hernandez-Pedro et al. 2013). MS is the most common cause of neurological disability in young adults (Chandran et al. 2008). Treatments currently available focus on the immune system, aiming to control the inflammatory process that leads to demyelination (Karussis and Kassis 2008). These therapies are only partially effective, as they are not capable of reversing neuronal damage. Because neurodegeneration is thought to be the cause of the gradual worsening observed in patients with MS, new approaches that promote neuronal repair are needed (Cohen 2013).

Over the last decade, several preclinical studies have demonstrated a great potential of MSCs in the treatment of MS (Gerdoni et al. 2007, Karussis et al. 2010, Zappia et al. 2005, Zhang et al. 2005). The most common animal model of MS is experimental autoimmune encephalomyelitis (EAE), in which immunization with neural antigens derived mainly from myelin, in combination with adjuvants, leads to demyelination, inflammation, and axonal damage in the CNS (Cohen 2013). Zappia et al. (2005) have shown that intravenous injection of MSCs in mice with chronic EAE leads to reduction of demyelination and CNS infiltration by inflammatory cells (Zappia et al. 2005). In that study, MSCs also improved the clinical severity of MS. MSCs were effective when administered at disease onset and peak, but not after disease stabilization. In a study conducted by Zhang et al. (2005), MSCs also caused significant functional improvement when injected intravenously in EAE mice, with some level of engraftment in the CNS. Demyelination significantly decreased, and BDNF cells significantly increased in treated mice, compared to controls (Zhang et al. 2005).

The immunomodulatory activity of MSCs is relevant for the treatment of MS, but it is important to keep in mind that the effects of MSCs are not limited to these properties. MSCs have been shown protect neurons even with very limited evidence of engraftment or transdifferentiation (Morando et al. 2012). MSCs can inhibit pathogenic myelin-specific antibodies, as shown in the study by Gerdoni et al. (2007), where a limited number of labeled MSCs were detected in the CNS of treated EAE mice (Bai et al. 2009, Gerdoni et al. 2007). Many other studies have demonstrated that these cells can modulate peripheral immune response to myelin

antigens. Bai et al. (2009) showed that treatment with human bone marrow-derived MSCs, reduced inflammatory T-cells and associated cytokines, and concomitantly increased IL-4-producing type 2 helper (Th2) cells and anti-inflammatory cytokines in treated EAE mice (Bai et al. 2009).

Based on the evidence provided by preclinical studies, a few clinical trials have attempted to demonstrate the safety and efficacy of MSCs in patients with MS (Bonab et al. 2012, Connick et al. 2012, Karussis et al. 2010, Yamout et al. 2010). All those studies were open-label and employed autologous MSCs. Bonab et al. (2012) studied 25 patients with progressive MS unresponsive to conventional treatment recruited to receive a single intrathecal injection of autologous bone marrow-derived MSCs. Therapeutic response was followed for 12 months, and the authors showed that the clinical course of the disease could be stabilized with no serious adverse effects (Bonab et al. 2012). Another recent clinical trial assessed the neuroprotective effects of intravenous MSCs on optic nerve function and reported improvement after MSCs injection (Connick et al. 2012).

Currently, there are a upcoming clinical trials registered in clinicaltrials.gov aiming to assess the efficacy of MSCs therapies in MS. Although this approach has shown promising results, larger randomized controlled clinical trials are needed to determine treatment feasibility and to elucidate the mechanisms by which this tool can be useful.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a mutation in the huntingtin (*htt*) gene. HD is characterized by neuronal cell loss leading to intellectual decline, movement disorders, and behavioral changes (Lin et al. 2011, Maucksch et al. 2013). The neuropathology of HD manifests in the progressive degeneration of striatal GABAergic neurons. Currently, there is no therapy available capable of interrupting disease progression (Lin et al. 2011, Maucksch et al. 2013).

There is a large interest in the use of MSCs to treat HD, and several preclinical studies have investigated the potential applications of this therapy in animal models. Lee et al. (2009b) showed that human adipose-derived MSCs transplanted into the ipsilateral striatal border of mice transgenic for HD, increased survival, attenuated the loss of striatal neurons, and reduced *htt* aggregates (Lee et al. 2009b). The same study also investigated the effects of human adipose-derived MSCs in cell culture. The authors demonstrated that the cells secreted multiple growth factors, e.g., BDNF, IGF-1, and NGF, among others.

A recent study investigated the effect of the extract of adipose-derived MSCs in a HD mouse model and in neuronal cells. Intraperitoneal injection of the extract improved performance in the rotarod test, used to evaluate motor coordination in rodents and especially sensitive to detect cerebellar dysfunction (Im et al. 2013, Shiotsuki et al. 2010) . Treatment also ameliorated atrophy and mutant *htt* aggregation in the striatum. Neuro2A neuroblastoma cells treated with the same extract showed increased expression of cAMP response element-binding protein (p-CREB) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α), which could modify HD progression (Im et al. 2013).

Another two studies have investigated the effects of human MSCs in different mouse models of HD (Lin et al. 2011, Snyder et al. 2010). Both studies demonstrated reduced striatal atrophy after intrastriatal transplantation of human MSCs, suggesting a neuroprotective effect associated with the neurotrophic factors secreted by these cells (Maucksch et al. 2013).

Results reported in studies with animal models are encouraging. However, further studies are required, especially clinical trials, to establish the

TABLE I
Summary of the main results using MSCs application in neurodegenerative and psychiatric diseases.

Disease	Model	Route of delivery	Main findings	References
Alzheimer's disease	Animal mode	Intracerebral	Reducing accumulation of amyloid-β (Aβ) in the hippocampal dentate gyrus	Lee et al. 2010b
	Animal model	Intracerebral	Improved cognitive function, reduced levels of neuronal apoptosis, and decreased activation of astrocytes and microglia	Lee et al. 2010a
	Animal model	Intracerebral	Improved learning and memory	Babaei et al. 2012
	Animal model	Intracerebral	Decreased cerebral Aβ deposition	Bae et al. 2013
Parkinson's disease	Animal model	Intracerebral	Increased viability and migration of dopaminergic neurons	Hellmann et al. 2006
	Animal model	Intracerebral	Increased expression of the TH gene in the rat striatum, as well as clinical improvement	Lu et al. 2005
	Animal model	Intravenous	Reduced the loss of dopaminergic neurons in models of disease induced by injection intraperitoneal of MPTP	Kim et al. 2009
	Animal model	Intravenous	Protected dopaminergic neurons from MPTP toxicity and decreased microglial activation	Chao et al. 2009
	Clinical trial	Intra-ventricular	Three of the seven patients showed an improvement in symptoms, with a decrease in off/on periods measured using Unified Parkinson's Disease Rating Scale	Venkataramana et al. 2010
Multiple sclerosis	Animal model	Intravenous	Reduction of demyelination and CNS infiltration by inflammatory cells and improved the clinical severity of MS	Zappia et al. 2005
	Animal model	Intravenous	Functional improvement with some level of engraftment in the CNS and decreased demyelination and increased BDNF	Zhang et al. 2005
	Animal model	Intravenous	Reduced inflammatory T-cells and associated cytokines, and concomitantly increased IL-4-producing type 2 helper (Th2) cells and anti-inflammatory cytokines	Bai et al. 2009
	Clinical trial	Intrathecal	Clinical course of the disease was stabilized with no serious adverse effects	Bonab et al. 2012
	Clinical trial	Intravenous	Improvement in visual acuity and visual evoked response latency	Connick et al. 2012
	Clinical trial	Intrathecal + Intravenous	Functional improvement	Karussis et al. 2010
Huntington's disease	Animal model	Intracerebral	Increased survival, attenuated the loss of striatal neurons, and reduced *htt* aggregates	Lee et al. 2009b
	Animal model	Intraperitoneal	Improved performance in the rotarod test, ameliorated atrophy and mutant *htt* aggregation in the striatum.	Im et al. 2013
	Animal model	Intracerebral	Demonstrated reduced striatal atrophy after intrastriatal transplantation of human MSCs, suggesting a neuroprotective effect associated with the neurotrophic factors secreted by these cells	Lin et al. 2011
Depression	Animal model	Intracerebral	Increased hippocampal neurogenesis and improved depressive behavior	Tfilin et al. 2010

safety and effectiveness of using MSCs in the treatment of HD.

MSCs APPLICATION IN PSYCHIATRIC DISORDERS

Over the past few years, many studies have focused on immunological abnormalities and the decrease of neurotrophic factors that characterize the pathophysiology of psychiatric disorders. Several studies have shown increased levels of pro-inflammatory cytokines, e.g., TNF-α, IL-6, and IL-2, as well as decreased levels of BDNF, an important neurotrophin for CNS, in severe mental illnesses, such as bipolar disorder, schizophrenia, and major depression (Asevedo et al. 2013, Kapczinski et al. 2011, Kunz et al. 2011, Patas et al. 2013). Furthermore, many studies have shown important cognitive impairment, neuroanatomical alterations and decreased neurogenesis in the hippocampus of patients with affective disorders (Caletti et al. 2013, Dranovsky and Hen 2006, Thomas et al. 2007, Torrent et al. 2010, Trivedi and Greer 2013).

In fact, despite the promising contributions of MSCs therapies in psychiatry, few studies have evaluated the effects of MSCs in models of psychiatric disorders. MSCs have the ability to promote neurogenesis and the survival and differentiation of neural cells by expressing neurotrophic factors, e.g., BDNF, NGF, and IGF. Moreover, as a result of their immunomodulatory properties, they can prevent apoptosis and decrease inflammation (Crigler et al. 2006, Yoo et al. 2008).

Tfilin et al. (2010) showed that treatment of an animal model of depression with MSCs, increased hippocampal neurogenesis and improved depressive behavior (Tfilin et al. 2010). Another study evidenced that intra-hippocampal transplantation of MSCs enhanced neurogenesis and did not impair behavioral functions in rats (Coquery et al. 2012). These results are promising and may lead to a novel modality for the treatment of psychiatric disorders. However, more studies are necessary to elucidate the precise mechanisms of action of MSCs in mental illness.

CONCLUSIONS

There are numerous preclinical studies using MSCs transplantation for diseases on the CNS that show promising results. These studies suggest that MSCs act through release of different neurotrophic factors, anti-inflammatories and antiapoptotic factors that can promote recover the injured area and prevent damage in neurodegenerative disorder. However, more clinical studies are necessary to understand the exact mechanism of action of MSCs in neurodegenerative disease and evaluate if the treatment with MSCs could cause side effects in patients. On the other hands, there are a few studies using the MSCs in psychiatric disease, but these studies have demonstrated promising results in depression and suggest that the MSCs can be a new strategy for the treatment of mental disorder. Future studies should be developed to evaluate the most effective routes of administration, dose and source of MSCs for each disease and their therapeutics effects. Thus, this new treatment may became an important therapeutic option for psychiatric patientes that do not respond to conventional treatment.

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RESUMO

Células tronco mesenquimais (CTMs) são células progenitoras multipotentes que têm a capacidade de se diferenciar em todas as linhagens de origem mesodérmica, como, cartilagem, ossos, e adipócitos. CTMs têm sido identificadas em diferentes fases do desenvolvimento, incluindo a idade adulta e em diferentes tecidos, tais como medula óssea, tecido adipose e cordão umbilical. Estudos recentes têm mostrado que as CTMs possuem a capacidade de migrar para locais de lesões. Nesse sentido, uma característica importante das CTMs são os seus efeitos imunomodulatórios e anti-inflamatórios. Por exemplo, há evidências que as CTMs podem regular o sistema imune por inibição da proliferação de células T e B. O interesse clínico no uso das CTMs tem aumentado consideravelmente nos últimos anos, especialmente devido às características ideais destas células para a medicina regenerativa. Terapias com CTMs têm mostrado resultados promissores em doenças neurodegenerativas, além de regular a inflamação, elas podem promover outros efeitos benéficos, tais como, crescimento neuronal, diminuição de radicais livres e reduzir a apoptose. No entanto, apesar de muitas pesquisas das CTMs em doenças neurodegenerativas, o mecanismo de ação das CTMs ainda não estão completamente esclarecidos, o que dificulta o desenvolvimento de tratamentos eficazes. Por outro lado, estudos em modelos de doenças psiquiátricas são escassos, apesar dos resultados promissores utilizando terapias com CTMs nesta área.

Palavras-chave: Células-tronco mesenquimais, tratamento, doença neurodegenerativa, transtornos psiquiátricos.

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