New perspectives for mesenchymal stromal cells as an adjuvant therapy for infectious disease-associated encephalopathies

https://doi.org/10.4103/1673-5374.314292

Date of submission: November 11, 2020

Date of decision: December 29, 2020

Date of acceptance: February 24, 2021

Date of web publication: June 7, 2021

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Abstract

Knowledge of the mechanisms that trigger infection-related encephalopathies is still very limited and cell therapies are one of the most promising alternatives for neurodegenerative diseases, and its application in infectious diseases can be of great relevance. Mesenchymal stromal cells are cells with great immunomodulatory potential; therefore, their use in clinical and preclinical studies in a variety of diseases, including central nervous system diseases, increased in the last decade. Mesenchymal stromal cells can exert their beneficial effects through several mechanisms, such as direct cell contact, through surface receptors, and also through paracrine or endocrine mechanisms. The paracrine mechanism is widely accepted by the scientific community and involves the release of soluble factors, which include cytokines, chemokines and trophic factors, and extracellular vesicles. This mini review discusses mesenchymal stromal cells mechanisms of action in neurological disorders, the neuroinflammatory process that takes place in the brain as a result of peripheral inflammation and changes in the brain's cellular scenario as a common factor in central nervous system diseases, and mesenchymal stromal cells therapy in encephalopathies. Mesenchymal stromal cells have been shown to act in neuroinflammation processes, leading to improved survival and mitigating behavioral damage. More recently, these cells have been tested in preclinical models of infectious diseases-associated encephalopathies (e.g., cerebral malaria and sepsis associated encephalopathy) and have shown satisfactory results.

Key Words: behavior; cell therapy; cognition; encephalopathy; malaria; mesenchymal stromal cell; sepsis

Introduction

Mesenchymal stromal cells (MSCs) are a heterogeneous population of cells with immunomodulatory and regenerative properties, which support their therapeutic use. MSCs are multipotent cells that show a capacity to self-renew and differentiate into cells with mesenchymal origins (osteoblasts, adipocytes and chondroblasts). In addition, MSCs are characterized as plastic-adherent when maintained in standard culture conditions, present specific surface antigen expression, such as CD105, CD73 and CD90, and lack expression for markers of differentiation or further lineage commitment (e.g., CD45, CD34, CD14, CD19) (Dominici et al., 2006). They can be found in several tissues including adipose tissue, bone marrow, Wharton jelly, and dental pulp. According to their tissue of origin, MSCs may differ widely in their transcriptomic signatures, differentiation potential, and biological functions (Hass et al., 2011). Due to their accessibility, relative ease of handling and ability to replicate *in vitro* while maintaining their biological immunomodulatory properties, they are commonly used as therapy in pre-clinical research.

MSCs might exert their beneficial effects through several mechanisms, such as direct cell contact and in a paracrine/endocrine mechanism with the release of soluble factors. Direct cell contact communication may occur with the participation of connexins forming gap junctional intercellular communication, allowing the passage of small molecules, especially microRNAs, in order to regulate the target cell (Lim et al., 2011). The paracrine mechanism of action promotes a regenerative environment in order to restore immunological homeostasis through the release of several mediators, such as immunosuppressive molecules, growth factors, metabolites, chemokines and complement system components.

MSCs and its secretome are able to modulate the innate and adaptive immune responses (Shi et al., 2018). Within the innate immune system, MSCs are able to regulate macrophages, neutrophils, mast cells, myeloid-derived suppressor cells, dendritic cells and natural killer cells. MSCs have the ability to inhibit macrophages, monocytes and neutrophils infiltration into injury sites in a tumor necrosis factor-inducible gene 6 protein-dependent pathway in acute lung injury (Wang et al., 2018), corneal injury (Song et al., 2018) and colitis (Sala et al., 2015). In addition, MSCs can

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Funding: *This work was supported by the Brazilian Council for Scientific and Technological Development (grant number 406110/2016-6) and Inova Fiocruz/Oswaldo Cruz Foundation (grant number VPPCB-008-FIO-18-2-56-30; to TMG).*

How to cite this article: *Lima MN, Barbosa-Silva MC, Maron-Gutierrez T (2022) New perspectives for mesenchymal stromal cells as an adjuvant therapy for infectious disease-associated encephalopathies. Neural Regen Res 17(1):48-52.*

promote macrophage polarization from pro-inflammatory phenotype toward an anti-inflammatory phenotype releasing immunosuppressive molecules, such as prostaglandin E2 (Vasandan et al., 2016), tumor necrosis factor-inducible gene 6 protein (Mittal et al., 2016; Wang et al., 2018), lactate (Selleri et al., 2016) and kynurenic acid (Wang et al., 2018).

Considering that MSC influences innate immune response, it is reasonable to presume that these cells may exert indirect effects in the adaptive immune response. By keeping macrophages, monocytes and dendritic cells in an immature (or anti-inflammatory) state, MSCs prevent effector T cells activation and promotes the generation of regulatory T cells (Ma et al., 2014). Moreover, there are also direct effects on T cells specially mediated by immunosuppressive factors, such as nitric oxide, indoleamine 2,3-dioxygenase (Su et al., 2014), prostaglandin E2 (Aggarwal and Pittenger, 2005), heme oxygenase 1 (Chabannes et al., 2007), leukemia inhibitory factor (Cao et al., 2011), programmed cell death 1 ligand 1 (Augello et al., 2005), and galectins (Sioud et al., 2010). In a direct way, MSC can suppress cytotoxic $CD8^+$ T cells activation, T helper 1 and T helper 17 cells differentiation and finally promote $CD4^+CD25^+FOXP3^+$ T cells activation and differentiation (Groh et al., 2005; Hsu et al., 2013).

Thus, MSCs ability to modulate the immune system by releasing cytokines and chemokines inducing an anti-inflammatory environment and promoting regeneration is an important mechanism of action. However, their immunosuppressive activity is not constitutive and must be induced by the environment to which they are exposed. This idea can affect their clinical therapeutic applications and the timing of administration might play a crucial role in therapy effectiveness (Martin et al., 2019).

Search Strategy and Selection Criteria

Studies cited in this review published from 1993 to 2020 were searched in the PubMed database using the following keywords: mesenchymal stromal cells, neuroinflammation, encephalopathies, infectious disease, and neurodegeneration.

Mesenchymal Stromal Cell Mechanisms in Neurological Disorders

The spectrum of conditions for MSC therapeutical use is vast and has already been reported in lung diseases, cardiovascular, graft-host diseases, neural disorders (e.g., stroke and spinal cord injury) and neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases) (Shi et al., 2018). Considering just mesenchymal stem cell therapy, neurological disorders represent one of the most common causes for ongoing clinical trials. At the moment, there are 256 studies listed at www.clinicaltrials.gov.

The mechanisms by which MSCs exert their therapeutic effects in central nervous system (CNS) disorders are not completely clear and seem to be diverse. As aforementioned, MSCs present limited differentiation capacity and it is controversial if they are able to differentiate into ectodermal cells (including neurons). However, in most cases MSCs are not expected to exert their beneficial effects through differentiating and incorporating themselves into neuronal networks. MSCs secrete a panel of growth factors, including neurotrophic growth factors, important for neuronal survival, neurogenesis, and synaptic plasticity, such as brain-derived neurotrophic factor (BDNF), glial cell derived neurotrophic factor, and vascular endothelial growth factor. MSC therapeutic properties in the CNS are probably mediated by these molecules (Shi et al., 2018).

Several studies have shown the efficacy of neurotrophins in reducing neurological deficits and improving neurological recovery (Kitagawa et al., 1998; Schabitz et al., 2000; Takeshima et al., 2011; Sherman et al., 2019). Thus, one of the MSC's mechanisms of action and their therapeutic properties in the CNS could be mediated by these growth factors (Shi et al., 2018). When transplanted into the striata, human MSCs that were genetically engineered to overexpress BDNF decreased striatal atrophy and reduced anxiety-like behavior in a murine experimental model of Huntington's disease. In addition, MSC therapy (with and without BDNF overexpression) increased neurogenesis-like activity and mean lifespan (Pollock et al., 2016). BDNF is an important neurotrophin and is able to regulate neuronal survival, development, plasticity and neurite outgrowth guidance (Baydyuk and Xu, 2014). BDNF exert its effects by binding and activating specific tropomyosin-related kinase (Trk) receptors in neurons, triggering several intracellular signaling cascades, such as, (1) phospholipase C γ pathway, leading to diacylglycerol production and increasing intracellular calcium resulting in Ca^{2+}/calmodulin-dependent protein kinases and protein kinase C activation; (2) Phosphoinositide 3-kinase pathway, leading to AKT activation pathway, mediating anti-apoptotic effects; and (3) mitogen-activated protein/extracellular signal-regulated kinases pathway, which is involved in in the regulation of several cellular functions and protein translation (Cruz and Cruz, 2007; Segal, 2003).

Neuroinflammation as a Common Feature in Encephalopathies

Neuroinflammation is a common feature of CNS disorders and comprises an inflammatory process that occurs in the CNS due to mediators released from brain-resident and blood-derived immune cells. This proinflammatory environment leads to molecular and cellular changes in brain homeostasis. Microglial cells change their morphology and phenotype, increasing the release of proinflammatory cytokines and chemokines. Astrocytes become hypertrophic with increased expression of intermediate filament protein expression (e.g., glial fibrillary acidic protein) and modified secretome. Activated astrocytes present impairments in their role as supportive cells, especially in the regulation of neurotransmitter concentration at the synaptic cleft, which may result in glutamate toxicity and aberrant neurotransmission, thus affecting neuronal cells (**Figure 1**).

In the presence of inflammatory mediators, neurotoxicity and changes in neurotransmitter systems are also mediated by increased activity of indoleamine 2,3-dioxygenase, an enzyme involved in tryptophan-serotonin availability through the activation of the glutamatergic system and expressed in microglial cells. It is believed that these changes in brain homeostasis lead to cognitive and behavioral consequences, such as learning deficits, memory loss, anxiety- and depression-like behaviors (**Figure 1**). Considering that neuroinflammation is a key factor in several CNS disorders, mitigating neuroinflammation can be pivotal in the treatment of CNS disorders.

Rationale for Using Mesenchymal Stromal Cells Therapy in Encephalopathies

Encephalopathies are defined as brain dysfunctions and can present an extensive spectrum of symptoms and altered mental status due to a local (within the CNS) or systemic insult. The pathophysiology of encephalopathies is complex and involves particularities depending on the primary cause of insult. Encephalopathies can be primarily caused by systemic etiologies, such as metabolic syndromes (e.g., obesity and diabetes), infectious diseases (e.g., sepsis, influenza and malaria), or by neurological etiologies, such as cerebral vascular diseases, trauma, neurodegenerative diseases (e.g., Alzheimer's, Parkinson's and Huntington's diseases) and autoimmune conditions (e.g., autoimmune encephalitis,

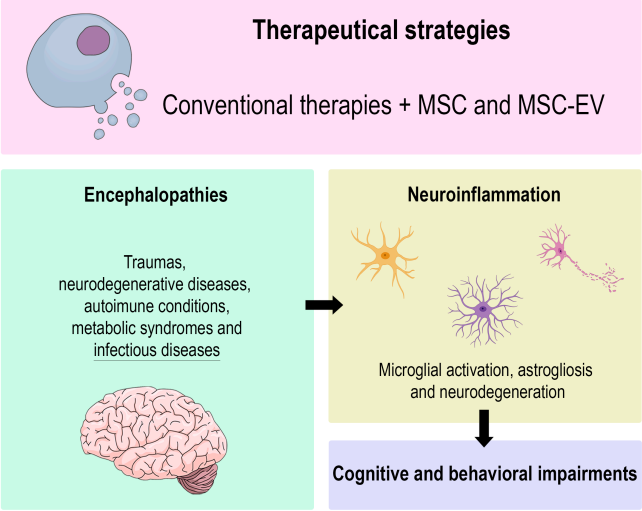

Figure 1 | **Adjuvant MSC therapy as a therapeutic strategy for encephalopathies.**
Adjuvant therapy with MSC and MSC-EV seems to be an efficient therapeutic approach to treat encephalopathies, including those caused by infections. For this therapeutic strategy, MSCs or MSC-EVs are used concurrent with traditional therapy in order to treat secondary effects caused by encephalopathies. Encephalopathies have different causes, lead to changes in brain function and have neuroinflammation as a common feature. When brain homeostasis is disturbed, glial cells become reactive and neurodegenerative processes might occur. These changes in the cellular and molecular scenario result in cognitive and behavioral impairments that can be prevented or reversed with MSC therapy. MSC: Mesenchymal stromal cells; MSC-EV: mesenchymal stromal cell-extracellular vesicle. Figures were created with BioRender.com and MindTheGraph.

multiple sclerosis) (Erkkinen and Berkowitz, 2019) (**Figure 1**). Clinical outcomes may include memory loss, subtle personality changes, dementia, seizures, coma, or death. Many cases of encephalopathies can be prevented by avoiding their primary cause and early treatment can mitigate or halt their symptoms resulting in a good recovery rate. However, if not treated, chronic encephalopathies may lead to permanent long-term consequences leading to neurodegenerative conditions, reducing quality of life and lifespan. Therefore, it is important to have appropriate treatments for the primary cause of encephalopathies as well as for their consequences. The large diversity of primary causes is a major challenge in developing a single therapy for encephalopathies. In addition, most treatments available focus on the primary causes of the disease and not on their neurological consequences.

As aforementioned, neuroinflammation seems to be a shared feature between encephalopathies from different etiologies and is strongly associated with behavioral long-term consequences. In this context, MSCs are promising candidates for this task. Huntington's disease is a rare neurodegenerative disease of the CNS characterized by general brain shrinkage/reduction and striatum degeneration, psychomotor deficits, cognitive decline and psychiatric symptoms such as depression, psychosis and obsessive-compulsive disorder. Bone marrow-derived MSCs transplanted in a murine model of Huntington's disease increased animal survival, striatum volume and reduced impairment of motor function, analyzed using the rotarod test. This study also showed that bone marrow-derived MSCs can survive, differentiate and integrate into the striatum after transplantation (Lin et al., 2011). Nakano and colleagues demonstrated that intracerebroventricular administration of MSCs improves cognitive impairment in rodent Alzheimer's experimental model. The beneficial effects were related with exosomal miR-146a secreted by MSCs in the cerebrospinal fluid, that can be absorbed by astrocytes decreasing NF-κB in these cells (Nakano et al., 2020).

Another important application of MSC therapy is in neurological complications caused by metabolic dysfunctions. There is a cross talk between the brain and the immune system, and cognitive and behavioral impairments have already been observed in obesity and diabetes. Diabetes is a multifaceted metabolic disorder that leads to systemic inflammation (Hotamisligil et al., 1993; Shoelson et al., 2006). As discussed before, systemic inflammation can result in neuroinflammatory and neurodegeneration processes. Diabetic patients demonstrate cognitive decline and a tendency to develop Alzheimer's disease (Ott et al., 1999; Teixeira et al., 2020). In an animal model of diabetes, intravenous therapy with MSCs improved learning and memory impairment in diabetic mice, analyzed by the Morris water maze test, and these results are associated with the secretome of these cells, more specifically with secreted extracellular vesicles (EVs) (Nakano et al., 2016).

Mesenchymal Stromal Cells as an Adjuvant Therapy for Infectious Disease-Associated Encephalopathies

Infectious disease-associated encephalopathies are neurological complications that can occur even without the pathogen infecting the CNS, and lead to cognitive and behavioral consequences including sickness behavior, memory loss, cognitive impairment, anxiety, depression and in some most severe cases, delirium, seizures and coma.

Recently, our group and others reported the use of MSC treatment in experimental models of sepsis-associated encephalopathy. We observed that a single dose of intravenously administered MSCs was able to modulate inflammatory mediators systemically and in the brain, preserve blood brain barrier integrity, decrease astrogliosis and improve spatial and aversive memories and anxiety-like behavior. In addition, *in vitro* experiments with astrocytes stimulated with lipopolysaccharide and treated with conditioned media from MSCs reduced astrogliosis, suggesting a paracrine mechanism of action (Silva et al., 2020). Akhondzadeh and colleagues observed that rodents that received MSC injection or CMMSC presented better memory retrieval and attenuation in the phosphorylated form of calcium/calmodulin-dependent protein kinase type II-α, which is inversely involved in regulating memory processes in the hippocampus compared with the cecal ligation and puncture group (Akhondzadeh et al., 2020).

Souza and colleagues were the first to evaluate the effects of MSCs in experimental cerebral malaria, a severe parasitic disease which leads to damage in brain microvasculature. Increased phagocytic neutrophil content in the brain was observed, however, they did not observe through histological staining differences between MSC treated and non-treated mice (Souza et al., 2015). We observed that a single dose of MSCs as adjuvant therapy protected against vascular damage and BBB disruption, and improved depression-like behavior in mice infected with *Plasmodium Berghei* ANKA (Lima et al., 2020). Similar to our previous study in sepsis, we observed that MSC secretome protected endothelial cells stimulated with heme (a molecule related to parasite metabolism) from cell damage/death by reducing the release of lactate dehydrogenase (Lima et al., 2020). Considering the beneficial results of MSC administration in sepsis-associated encephalopathy and cerebral malaria, MSC therapy in other infectious neurological complications has a great potential to modulate acute changes and improve neurologic conditions.

It is known that viral infections (e.g., influenza virus, human immunodeficiency virus, and more recently SARS-CoV-2 virus) lead to neuroinflammation and CNS consequences. Nevertheless, to date, there is no specific treatment or

approach to treat CNS damage. Neurological complications in patients with SARS-CoV-2 infection have been reported, including encephalopathies with delirium or psychosis, inflammatory CNS syndromes including encephalitis, acute disseminated encephalomyelitis, with the presence of hemorrhage, necrosis, and myelitis (Paterson et al., 2020). Cell-based therapies have been quite extensively studied for potential applicability in SARS-CoV-2 infection, especially given the short time since the onset of the pandemic. MSC transplantation caused no adverse effect, symptoms were improved, and the plasma levels of pro- and anti-inflammatory mediators were modulated after MSC therapy (Leng et al., 2020).

Despite the promising results and although MSCs present low immunogenicity, in some cases, MSC administration may evoke an immune response in the host. Moreover, once injected, these cells are considered short lived and only exert their effects for 48–72 hours (Eggenhofer et al., 2012). Since one of the main mechanisms of action of MSCs is through their paracrine anti-inflammatory and immune modulation capacity to repair tissue damage, a promising alternative is the use of their secretome, which comprises bioactive mediators, such as cytokines, chemokines, growth factors, and EVs (Eleuteri and Fierabracci, 2019; Staff et al., 2019)

MSC-EV appear to have the same therapeutic potential and provide an efficient delivery for soluble factors and microRNAs (Eleuteri and Fierabracci, 2019). In the last years emerging evidence shows that EVs are able to transfer miRNA and mRNA in order to reprogram/regulate target cells (Ratajczak et al., 2006). The transfer of interleukin-10 mRNA from EV-MSC to injured tubular cells was reported, and this transferred mRNA was efficiently translated into the corresponding protein (Ragni et al., 2017). Besides RNAs, EVs also carry enzymes which can be released and exert beneficial effects. Using an *in vitro* model for Alzheimer´s disease, MSC-EV protected neurons against oxidative stress through the release of catalase (de Godoy et al., 2018).

In addition, EV-based therapies have been shown to be safer than their parent cell, with a lower risk of embolism. EVs are more stable and the outcomes could be potentially more reproducible than MSCs, as they are not influenced by the individual microenvironment. Cell-based and cell-free therapies present challenges such as standardization of tissue origin and culture conditions, harvesting and purity of EVs, dosing, route and timing of administration (Gorabi et al., 2019; Maron-Gutierrez and Rocco, 2020). In most cases, the use of allogeneic cells and EVs is preferable compared to the use of autologous cells and EVs due to rapid patient deterioration, short time for harvesting and culture conditions.

Summary

MSCs have been shown to modulate neuroinflammation. Studies show that MSC therapy combined with conventional therapies are effective in mitigating long-term effects induced by neuroinflammation, such as cognitive and behavioral impairments. The secretome of these cells, which includes growth factors, cytokines, chemokines and extracellular vesicles carrying genetic material, are involved in the protective effects described. Therefore, an interesting approach is to use MSCs or MSC-EVs as adjuvant therapy for infectious disease-associated encephalopathies.

Author contributions: *All authors made substantial contributions and participated in drafting the manuscript and revising it critically; all authors gave final approval of the final manuscript.*
Conflicts of interest: *The authors declare that they have no competing interests.*
Financial support: *This work was supported by the Brazilian Council for Scientific and Technological Development (grant number 406110/2016-6) and Inova Fiocruz/Oswaldo Cruz Foundation (grant number VPPCB-008-FIO-18-2-56-30; to TMG).*
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Open peer reviewers: *Ramesh Periasamy, Universitat Bern, Switzerland; Catarina O. Miranda, University of Coimbra, Portugal.*
Additional file: *Open peer review reports 1 and 2.*

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P-Reviewers: Periasamy R, Miranda CO; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y