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The Immunomodulatory Potential Role of Mesenchymal Stem Cells in Diseases of the Central Nervous System

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Abstract
Introduction: Several studies indicate the role of mesenchymal stem cells (MSCs) as an important tool in regenerative medicine associated with injuries that affect the central nervous system (CNS). The MSCs have the capacity to differentiate into cells of the embryonic tissue, such as the mesoderm. So, these cells can be found in a variety of tissues. Also, the MSCs can release immunomodulatory and neurotrophic factors performance as inflammation mediators operating in injured tissue regeneration. Furthermore, they can differentiate into neural-like cells in vitro. Thereby, because of the high immunomodulatory role of MSCs, this review sought to describe the main immunomodulatory mechanisms performed by MSCs in CNS recovery after tissue injury or neurodegenerative diseases. ***Methods:*** PubMed and ScienceDirect were searched between January 2011 to March 2021, and 43 articles met the criteria of the review. ***Results:*** This systematic review indicates that MSCs were used in vivo experimental multiple sclerosis, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, ischemic stroke, and traumatic brain injury. The treatment MSCs were usually from human origin, derived from bone marrow, and administered intravenously. ***Conclusion:*** It was shown that MSCs, independent from origin or administration pathway, can reduce inflammation and help in the recovery and preservation of injured neural tissue. Thus, the use of MSCs represents a potential therapeutic option in the treatment of neurological disorders mediated by inflammatory processes.

Introduction

The recovery of neurological functions and decline in neurodegeneration processes is based upon a population of somatic neural stem cells (NSCs) and progenitor cells able to differentiate in tissue-specific cell types [1–4]. Central nervous system (CNS)'s renewing occurs due to the presence in the adult brain of a population of NSCs with long-term self-renewal properties [5]. NSCs give rise to new neurons and glial cells throughout life. The in vitro neuroprotective effects of NSCs have been previously demonstrated. NSCs migrate to the injured areas acting as an anti-inflammatory and chaperone-like agent, inhibiting neuronal death [6]. However, NSCs are hard to isolate due to ethical (from fetal tissue) or methodological

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(from pluripotent stem cells) problems. Mesenchymal stem cells (MSCs) are obtained easily in therapeutic quantities. Similar to NSCs, these cells exert paracrine effects on damaged cells and microenvironments. Therefore, in recent years, they came to replace NSCs in regenerative medicine associated with lesions in the CNS [7]. Although MSCs are found in the CNS, they are commonly obtained from mesodermal tissue, as bone marrow and adipose tissue, from extraembryonic tissues, as umbilical cord blood and placenta, and also from the dental pulp from ectomesenchyme [8–10]. One of the in vitro characteristics of these cells is their capacity to differentiate into cells from the mesoderm (adipocytes, chondrocytes, osteoblasts, and myocytes) [11, 12]. Also, some authors showed MSC differentiation into the cells of the endodermal lineage (insulin-releasing cells and hepatocytes) [13] and the ectodermal lineage (neurons and astrocytes) [14].

MSCs come from different tissues, but they exhibit common characteristics when used in cell therapy. Several years ago, we believed that MSCs might differentiate into neural cells. However, currently, we know that in vivo this does not occur. That is why MSCs were also denominated medicinal signaling cells[15]. Similar to NSCs/precursors, MSCs act through the production and release of immunomodulatory and neurotrophic factors [7, 11, 16, 17]. In addition, MSCs can interact directly with immune system cells, like T and B lymphocytes, natural killer cells, macrophages, dendritic cells (DCs), neutrophils, and mast cells [11, 18, 19]. The cellular interactions and the release of several trophic factors make MSCs an important tool in clinical therapy. Moreover, their use in the treatment of CNS lesions or disease is possible because of their higher adaptive potential. Several clinical trials communicated on Clinictrials.gov, corroborating the properties of MSCs in the local and/or systemic anti-inflammatory actions.

The present review aims to describe if the immunomodulatory processes directed by MSCs may influence the neuroprotection and neuroregeneration of the CNS in diseases such as multiple sclerosis (MS), Parkinson's disease (PA), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) and neural tissue injuries such as ischemic stroke (IS) and traumatic brain injury (TBI) in experimental models in vivo.

Materials and Methods

Search Strategy

A systematic search was conducted from January 2011 to March 2021 using two databases (PubMed and ScienceDirect) and according to the PRISMA Checklist. The keywords were identified using Medical Subject Headings (MESH), being the terms of stem cells ("Stem Cell, Mesenchymal" OR "Mesenchymal Stem Cell"), of intervention therapy ("Immunomodulation" OR "Immunomodulatory Therapy") and cerebral ("Brain OR Brain injury" OR "Brain disease"). The studies were limited to articles whose objective was to investigate the action of MSCs on the brain of male/female rats or mice with lesions/diseases in the CNS.

Inclusion/Exclusion Criteria

All articles included in this systematic review should show the following criteria: (1) adult male or female rats/mice with CNS injuries/diseases; (2) the treated group with MSCs from the dental pulp, bone marrow, adipose tissue, umbilical cord, placenta, or Wharton's jelly; (3) control group with CNS lesions/diseases but without treatment with MSCs; (4) comparative studies, randomized controlled clinical trials, controlled clinical trials without randomization, self-controlled clinical trials with results of neuronal regeneration and immunomodulation; (5) articles published in English.

The exclusion criteria included: (1) young or elderly rats/mice; (2) animals without injuries/diseases in the CNS; (3) treatment without the use of MSCs in the treated group; (4) use of MSCs from other tissues; (5) treatment on the animals in the control group; (6) observational, descriptive studies, reviews, case reports, abstracts presented at congresses and conferences, study protocols, personal opinions, and book chapters; (7) it did not provide any description of the protocol used in the application and obtaining the MSCs; (8) there were no immunomodulatory results; (9) it did not include a control group; (10) MSCs' previous treatment in a conditioned medium; (11) it did not have neuroinflammatory results.

The study selection process was performed independently by two authors. First, we have evaluated the title, the abstracts' content, and the keywords for the eligible studies. Then, we analyzed the selected articles comparing the data collected to ensure the minimization of differences. If any remaining disagreement occurred, a third reviewer joined the discussion to reach a consensus. Finally, after the selection, we began the extraction of the contents of the articles' interests.

Data Collection and Extraction Process

The data extraction of each selected article was carried out by two examiners regarding the characteristics of the study (species, sex, age), disease (type of neurological disease and the method of inducing the disease), stem cells (lineage of MSCs, inoculation method, and time), primary and secondary results, and conclusion. In addition, we extracted the name of the principal author, the year of publication, the title, and the objectives of the study.

Results

Study Selection

The criteria for study selection are presented in Figure 1. A total of 968 studies were initially screened using the above search terms through the database search, PubMed and ScienceDirect. After authors checked titles and abstracts, 103 reviews, 1 conference abstract, 1 article in

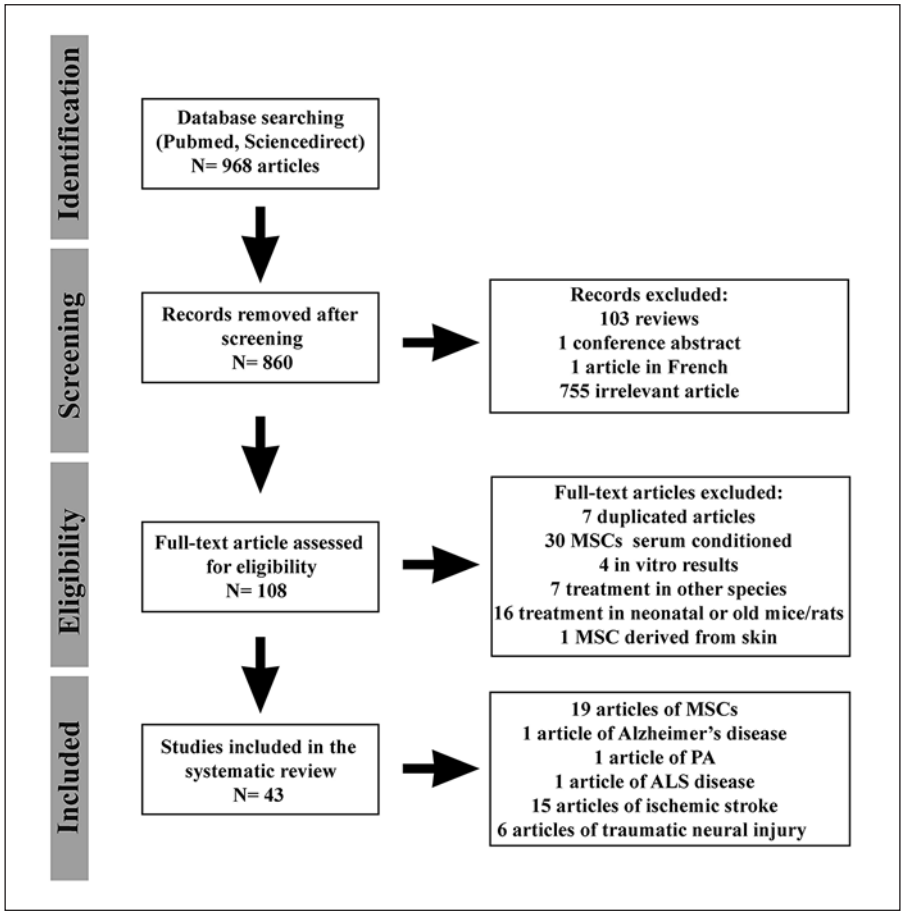

Fig. 1. Flow diagram of studies included through the systematic review process.

French, and 755 articles that were not related to the scope of this systematic review were removed. A total of 108 articles were retrieved for full-text screening. After screening, the authors excluded 7 duplicated articles, 30 articles with MSCs serum conditioned, 4 articles with results in vitro, 7 articles that not used rat or mice species, 16 articles with treatment in neonatal or old mice/rats, and 1 article with MSCs derived from the skin. In total, 43 articles met the criteria and were used in the analyses, including 19 articles on MS, 1 article on AD, 1 article on PA, 1 article on ALS disease, 15 articles on IS, and 6 articles on TBI.

Neurodegenerative Diseases

Multiple Sclerosis

For MS, 19 articles met our inclusion criteria. Of the total number of selected articles, three were performed on rats (15.8%) and sixteen on mice (84.2%), with the female gender as the most prevalent (57.9%). Among the species of mice used, we have twelve articles that used the C57BL/6 lineage (63.2%) and one article that used the SJL/J lineage (5.3%). The other mice articles used two species, one being C57BL/6 and BALB/C; Foxp3GFP and C57BL/6; C57BL/6 and NOD/Lt. Among the species of rats used, we have one article that used Wistar (5.3%), one article that used Lewis (5.3%), and one article that used Dark Agouti (5.3%). Regarding the type of MSCs used, we had seven articles with MSCs from the bone marrow (36.8%), five articles with MSCs from the adipose tissue (26.8%), three articles with MSCs from the placenta (15.8%), two articles with MSCs from embryonic cells (10.5%), and one article with MSCs from the dental pulp (5.3%) and Wharton's Jelly (5.3%), respectively. 68.4% MSCs came from human tissue, 21.1% from mice, and 10.5% from rats. The main inoculation mechanism was intravenous (31.6%), and intraperitoneal (26.3%). The inoculation time after experimental autoimmune encephalomyelitis (EAE)-MS model was 1st day (20.8%), third day (20.8%), 6th to 9th day (29.2%), 10th to 12th day (16.6%), 14th day (8.4%), and 30th day (4.2%) (online suppl. Table 1; see www.karger.com/doi/10.1159/000528036 for all online suppl. material).

Parkinson's Disease, Alzheimer's Disease, and Amyotrophic Lateral Sclerosis

Regarding neurodegenerative, progressive, and no cure diseases that affect the CNS, we have PA, AD, and ALS. For each of these diseases, we found one article that met the criteria of the review. The PA article used adult female Sprague-Dawley rats with cannula injection of MSCs from the human term placenta on the fourth day after stereotaxic surgery for 6-OHDA injection. For the Alzheimer's article, female and male transgenic rats were used, and MSCs derived from human term placenta were inoculated intravenously. The MSC inoculation time was not described in the selected article for AD. Finally, in the ALS article, male B6SJL-TgN transgenic mice were used in the disease model with injection into the cisterna lumbaris of human MSCs. Also, the MSC inoculation time was not described in the selected article (online suppl. Table 2).

Neural Tissue Injury

Ischemic Stroke

Of the 15 selected IS studies, four studies were performed in mice (26.6%) and eleven studies in rats (73.3%). Among the species, we have a study with Lewis's rats (6.6%), three studies with Wistar rats (26.6%), five studies with Sprague-Dawley rats (41.7%); one study with Balb/C mice (6.6%), one study with C57BL/6 mice (6.6%), and one study with CD1 mice (6.6%). Regarding gender, thirteen studies used males (86.6%), and two studies used females (13.3%). In all studies, the performing ischemia method was through the middle cerebral artery occlusion (MCAO) model. The occlusion time varied from 45 min to 180 min. One study did the occlusion for 45 min (8.3%), one study did the occlusion for 75 min (8.3%), three studies did the occlusion for 60 min (25%), six studies performed occlusion for 90 min (50%), and one study did the occlusion for 180 min (8.3%). Regarding the MSCs, one article obtained the dental pulp MSCs (6.6%), one article from the placenta (6.6%), two articles from the umbilical cord (13.3%), two articles on adipose tissue (13.3%), and nine articles on bone marrow (60%). The origin of MSCs was mainly human (71.4%), followed by rats (21.4%) and mice (7.1%). Finally, for the mechanism of MSCs inoculation, we have one article with intracranial inoculation (6.6%), one article with intraperitoneal inoculation (6.6%), two articles with local inoculation (13.3%), and eleven articles with intravascular inoculation (71.4%). The inoculation time after MCAO was 30 min (6.6%), 6 h (6.6%), 24 h (46.6%), 48 h (13.3%), 72 h (13.7%), 120 h (6.6%), and 168 h (6.6%) (online suppl. Table 3).

Traumatic Brain Lesion

In total, 6 articles on TBI met the criteria of our review. Among them, five were performed on rats (83.3%) and one on mice (16.7%), and all were performed on males. Among the species of rats are Sprague-Dawley (66.7%) and Wistar (16.7%), and C57BL/6 for mice (16.7%). Two types of neural injuries were selected, a TBI and an intracerebral hemorrhage injury (ICH). In TBI, the injuries were caused by impacting and neurochemically. In the ICH, the lesions were performed through the injection of collagenase. Regarding MSCs, five articles obtained the bone marrow MSCs (83.3%) and one article on adipose tissue (16.7%). The origin of MSCs was of humans (66.7%), and rats (33.3%). Finally, for the mechanism of MSCs inoculation, we have five articles with intravascular inoculation (83.3%) and one article with intracranial inoculation (16.7%). The inoculation time after injury ranged from 2 h to 72 h, being these 2 h (33.3%), 24 h (16.7%), 36 h (16.7%), 48 h (33.3%), and 72 h (16.7%) (online suppl. Table 4).

Discussion

Immunomodulation in Neurodegenerative Diseases

Multiple Sclerosis

MS is a progressive autoimmune disease that affects the CNS. It is characterized by demyelination plaques in various neural regions, leading to the formation of gliosis (glial scars) [20]. Although the exact cause of MS is still uncertain, around 2.5 million people worldwide have MS [21]. This disease has a more elevated incidence in women, between 18 and 55 years [22, 23]. Animal models have become one of the primary tools for the study of MS, being induced in different ways, including by the emulsion with Myelin Oligodendrocyte Peptide (MOG 35-55), a complete Freund adjuvant, and Mycobacterium tuberculosis [24], or with Pertussis Toxin [25, 26].

The main alteration observed in MS is the inflammatory demyelination of the CNS and the destruction of myelin leading to the formation of axonal lesions [27]. The axonal lesions occurred because of the development of autoantibodies that recognize the components of the myelin sheath, leading to microglial activation and macrophage recruitment [20]. The presence of autoantibodies occurs because of immunological dysregulation in innate and adaptive immune system mechanisms. The innate immune system responds by activating Toll-like receptors, leading to lymphocyte activation and cytokine production [27]. DCs and innate immune cells have the phe-

notype activated through the expression of the cell surface marker CD83. These cells migrate across the blood-brain barrier (BBB), differentiate in the CNS, and activate CD4+ T cells to differentiate into T-helper (Th) cells, where four phenotypes can be observed: Th1, Th2, Th17, and Treg [27–29]. The interaction between antigen-presenting cells and T lymphocytes (TCD4+ and TCD8+) is essential for the initiation of the acquired immune response since antigen-presenting cells secrete cytokines that modulate CD4+ T cells. In the presence of interleukin-12 (IL-12) or IL-23, CD4+ T cells differentiated, respectively, into Th1 helper cells or Th17 cells [29]. Consequently, the CD4+ Th cell phenotype is polarized leading to the expression of interleukins and secretion of specific cytokines [30, 31]. Cytokines produced by Th1 and Th17 cells are pro-inflammatory cytokines like interferon-gamma (IFN-γ), IL-2, and tumor necrosis factor-alpha (TNF-α). The Th1 and Th17 are sending to the CNS lead to the activation of macrophages, astrocytes, and microglia, resulting in axonal loss and demyelination. In parallel, Th2 cells secrete anti-inflammatory cytokines related to the regulation or suppression of immune responses [30–32]. Regarding CD8+ T cells, they also produce pro-inflammatory mediators like lymphotoxin and IL-17, and their presence in the CNS and cerebrospinal fluid corresponds with acute axonal damage [29].

Many studies have been demonstrated the neuroprotective role of MSCs from different tissues in the treatment of MS models, being the EAE the most common model. Clinically, it was observed in treatment with MSCs a delay in the onset of symptoms [26, 33], improvement in motor functions [20, 34], clinical signs [24–26, 35–42], and recovery/maintenance of body weight [37, 41, 42]. The most efficient clinical response was observed when MSCs were administered during the onset of disease relative to the disease peak and in untreated animals [24, 39, 41, 43]. However, animals treated at the peak of the disease also showed an improvement in clinical conditions, especially about the stage of the disease evolution compared to animals without treatment [44]. Parallel to the clinical findings, in the morphophysiological analysis, was observed a decrease in brain atrophy [20, 26, 34, 35], demyelination [20, 26, 33, 34, 39, 40, 42, 43, 45], and a smaller amount of inflammatory infiltrate [33–35, 37–44].

These morphophysiological findings are correlated with the improvement of clinical signs. The MSCs display a neuroprotective effect, contributing to axonal preservation and remyelination, seen by the presence of a newly formed myelin sheath [35, 44, 46]. Furthermore, MSCs play a neuroregenerative role as they differentiate into other cell types and secrete neurotrophic factors like brain-derived neurotrophic factor, ciliary neurotrophic factor, and transforming growth factor-beta (TGF-b) of anti-inflammatory cytokine. These neurotrophic factors induce axonal growth and cell survival while reducing microgliosis and astrocytosis [7, 26, 44, 47, 48]. The secretion of these neurotrophins also reduces inflammation and damage [7]. In addition to the morphophysiological findings and the release of neurotrophic factors, it was observed in animals treated an increase in myelin and neuronal growth markers. For myelin, there was increased immunostaining of the marker 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNPase) [34], myelin basic protein (MBP) [24, 25, 44], the protein proteolipid 1 (PLP1) [24], and Luxol Fast Blue (LFB) [48]. Regarding neuronal growth was observed an increase in the number of cells marked with a green fluorescent protein (GFP) [46] and growth-associated protein 43 (GAP-43) [44]. Furthermore, it was noted the presence of a higher total number of oligodendrocytes [45] and an increase in the expression of oligodendrocyte transcription factor (OLIG2) [48]. Finally, it was observed a reduction in microglial and astrocytic markers, such as ionized calcium-binding adapter molecule-1 (Iba-1) and glial fibrillary acidic protein (GFAP), respectively [24, 33, 34, 44, 48]. The presence of increased immunostaining of myelin, neuronal growth, and oligodendrocytes markers strengthens the neuroregenerative role of MSCs. While the lower immunostaining of microglia and astrocyte corroborates with the decreases in the inflammatory process.

Demyelinating injury associated with axonal damage is a hallmark of MS [49, 50]. The lesion causes alteration in the structure and components of the axonal membrane. The result is an impairment in the conduction of the nervous impulse or making them more excitable and active, originating the paroxysmal symptoms characteristic of the disease [51]. The onset of demyelination is a cascade in which oligodendrocyte apoptotic events are added to the activation of an initial microglia-mediated immune response and an adaptive immune response driven by the infiltration of autoreactive T cells into the CNS parenchyma [50–55]. In parallel, activation of astrocytes during demyelination contributes to leukocyte recruitment and survival in the CNS through the release of chemokines [56–58]. However, they can also attenuate inflammation and promote neuroprotection and injury repair through the release of brain-derived neurotrophic factor [59].

During the administration of MSCs, it is observed a neuroregenerative process and an immunomodulatory role in altering the expression of cytokines, pro-, and anti-inflammatory chemokines, and the presence of T-cell infiltrates in the CNS. Regarding pro-inflammatory cytokines and chemokines, it was observed a reduction in IFN-γ [34, 37, 38, 41, 42, 44], TNF-α [34, 42, 44, 48], IL-1β, IL-1, IL-6, IL-12, IL-17, and IL-18 [25, 33, 34, 37, 39, 41, 42], and also chemokine ligand 2 (CCL2), CCL9, CXCL1, CXCL5 [39], expression of nuclear factor-κB (NF-κB) and cyclooxygenase-2 (COX-2) [24, 40, 44]. The decrease of these inflammatory signals reduces the immune response of the individual. Conversely, studies have been describing an increase in anti-inflammatory cytokines like IL-4, IL-10 [20, 33, 37, 41, 44], and the TGF (TGF-β) [44, 46]. Moreover, concomitant with the reduction in pro-inflammatory cytokines and chemokines, there was a reduction in lymphocytic infiltrates, mainly CD4+ and CD8+ T cells, including Th1 and Th17 CD4+ subsets [20, 25, 33, 35, 37, 38, 41, 43].

Therefore, based on the articles included in this systematic review lead to MSCs, due to their neuroprotective and immunomodulatory properties, perform a beneficial modulatory role in the MS modifying the composition of cellular infiltrates and the release of regulatory factors of inflammation. Hence, the administration of MSCs contributed to myelin repair, to the preservation and activation of oligodendrocytes at the demyelination site, to the reduction of gliosis formation, and to the prevention of axonal degeneration, contributing to the improvement of MS clinical signs.

Analyzing the origin of MSCs and the inoculation path individually, the studies showed that regardless of the type of MSCs and the path of inoculation, the animals showed improvement in clinical signs with a decrease in the inflammatory infiltrates, preservation of myelin, and a reduction in pro-inflammatory cytokines, especially when inoculation is performed early in the disease. Regarding anti-inflammatory cytokines, no increase was described in articles that administered bone marrow-derived MSCs. However, treatment with MSCs from animals with EAE showed reduced efficacy when compared to MSCs from naive animals [39].

Parkinson's Disease

PD is a chronic progressive neurodegenerative disease of idiopathic etiology. It is described by the loss of neurons in the substantia nigra, the main dopamine-producing region. Dopamine is the neurotransmitter that acts to control movement and motor coordination. Initially, the primary symptoms of the disease are motor alterations like tremor, rigid muscles, bradykinesia (slowed movement), impaired posture and balance, loss of automatic movements, speech changes, and cognitive deficits. The cognitive deficits accelerate aging, enhancing the development of dementia [60]. In more advanced stages, there may be a loss of serotonergic and noradrenergic neurons, implying the appearance of other non-motor symptoms such as sleep disturbance, cognitive dysfunction, and psychiatric disorders [61, 62]. The progressive nature of PD implies a network of interactions between the vulnerability of dopaminergic neuron loss, genetic predisposition, and environmental factors. Once the neurodegenerative process begins, a series of secondary events cause neurochemical alterations [63, 64]. The neurodegeneration in PD may result from neuroinflammation mediated by microglial activation and increased pro-inflammatory cytokines like IL-1β, IL-6, IFN-γ, and TNF [64, 65]. In addition, the activation of T lymphocytes, the CD23 receptor for IgE, COX-2, the induced nitric oxide synthase (iNOS), the complement receptor (CR3), and the increased ferritin are involved in neuroinflammatory mechanisms, associated with the decrease of dopaminergic neurons [66]. There is evidence that several inflammatory cytokines, including TNF, IL-6, and IL-1β, increase in the brain of patients with PD, in parallel with an increase in microglial activation in the substantia nigra. Such alterations are associated with the participation of iNOS, which may contribute to the neurodegenerative process in PD. Given the alterations observed in patients with PD, studies have been using MSCs as a tool to reduce neuronal loss. Such studies with MSCs reported improvements in clinical symptoms and suppression of loss of dopaminergic neurons, resulting in an improvement in cognitive capacities and motor memory. Furthermore, the factors secreted by MSCs induce neurogenesis, neuroprotection of neurons, modulation of microglial activation, inhibition of apoptotic cells, inflammatory factors, and toxic molecules like α-synuclein. In addition, MSCs secrete TGF-β and IL-10, which are anti-inflammatory cytokines, providing a less neurotoxic environment [67]. Finally, MSCs secrete trophic factors, like glia-derived neurotrophic factor and neurturin, which exert neuroprotective effects and increase the survival of dopaminergic neurons [67]. Therefore, it is observed that MSCs in PD contribute to immunosuppression and neuroprotection against the loss of dopaminergic neurons, reducing the neurological changes associated with the disease.

Alzheimer's Disease

AD is a progressive degenerative neurological disease. It is the most principal cause of dementia, a general term for memory loss and other cognitive capacities [68, 69]. Although the cause is idiopathic, it is estimated that millions of people around the world have AD (International AD). In Brazil, the disease has a prevalence of 7.1% in individuals over 65 years of age, with a higher epidemiological prevalence in women [70, 71]. Usually, the first clinical sign is the difficulty in storing current information, loss of visuospatial skills, language, and executive functions [72–74]. The cholinergic hypothesis assumes that degeneration of cholinergic neurons in the frontal cortex region, in the medial septum, and the nucleus basalis of Meynert causes the appearance of dementia symptoms [75]. However, the hypothesis of hyperphosphorylation of the tau protein is responsible for the formation of neutrophil tangled. Physiologically the tau protein is important in neuronal homeostasis, being responsible for the aggregation of tubulin leading to the union of microtubules with components of the cytoskeleton. Its hyperphosphorylation is related to decreased cytoskeletal stability, contributing to a series of events that result in cell death because of the formation of intraneuronal lesions and neurofibrillary tangled [74, 76, 77]. The brain of AD patients has two striking features: extracellular deposition of β-amyloid (βA) protein, with the formation of senile plaques, and intracellular deposition of neurofibrillary tangled of hyperphosphorylated tau protein [74, 78]. Senile plaques are constituted of extracellular βA protein deposits that derive from the amyloid protein precursor. Amyloid protein precursor is part of the NOS, a family of proteins expressed by different cell types with unknown functions. But it has been suggested its functions are of neurotrophic and neuroprotective factors or the transport of vesicles along the axon [78]. In turn, βA is secreted by neuronal cells and can be found in the cerebrospinal fluid, blood, or deposited in cerebral capillaries, arterioles, and venules. They can also accumulate in some regions of the brain, like the cerebellum, striatum, and thalamus [79]. These molecular mechanisms associated with cellular alterations are responsible for the development of oxidative stress, culminating in the emergence of reactive oxygen species (ROS) and nitrogen species responsible for the production of apoptosis signals [72–74]. In turn, excess βA induces ROS production and depletion of endogenous antioxidant agents, which causes neuronal damage and death. The inflammatory response associated with the presence of senile plaques is considered secondary to βA accumulation and may be involved in neuronal damage and disease progression. Activation of glial cells (microglia and astrocytes) initiates an inflammatory response mediated by pro-inflammatory cytokines that activate the complement cascade with consequent cell damage [75, 78–80]. Overall, there is an increase in cytokines and chemokines, like IL-1β, IL-6, IL-8, TNF-α, TGF-β, and macrophage inflammatory protein-1α (MIP-1α) [81, 82]. Furthermore, the production of interleukins may be linked to the activation of microglia and astrocytes, leading to the secretion of pro-inflammatory molecules and amyloid. Hence, cytokines can affect the formation of βA, increasing its deposition and aggregation [83, 84]. Currently, treatment for AD is palliative, but studies have been using MSCs transplantation. Their immunomodulatory potential leads to a reduction in the expression of pro-inflammatory chemokines and cytokines [85]. In animal models of AD, a reduction in the number of βA plaques was observed in the cortex and the hippocampus. This decrease in βA was because of the increase in the number of residents and activated microglia with phagocytic activity around the plaques. Therefore, MSC assists in restoring the immune system and the number of microglia with phagocytic properties and modulates the immune state toward βA removal [86].

Regarding inflammatory cytokines was observed a reduction in IL-1, TNF-α, and an increase in the anti-inflammatory cytokine IL-10 and TGF-β. Increased levels of TGF-β mediate anti-inflammatory effects and are associated with a reduction in plaque numbers and βA levels. On the other hand, decreased levels of TGF-β are associated with increased neuronal death and microgliosis. In addition, TGF-β is believed to be associated with other immunosuppressive mechanisms involving regulatory T cells. Regulatory T cells play an immunosuppressive role. Thus, TGF-β released by AMSCs can induce microglia and regulatory T cells to exert a neuroprotective effect. Also, it was observed the increase in the levels of a β-degrading enzyme (IDE and metalloprotein MMP-9), an anti-inflammatory cytokine. Finally, clinically was observed an improvement in the memory of the animals treated with MSCs through the water maze test. These factors suggest the treatment with MSCs modulates the immune system in the brain by controlling the amount of microglia and Aβ, reversing AD pathology and functional recovery through immunomodulatory effects [86].

Amyotrophic Lateral Sclerosis

ALS is a progressive neurodegenerative neuromuscular disease that results in the loss of upper motor neurons (neurons that project from the cortex to the brainstem

and spinal cord) and lowers motor neurons (neurons that project from the brainstem or spinal cord to the muscle). The motor and extra motor symptoms are the most predominant clinical symptoms like weakness and progressive muscle atrophy. The symptoms progress to dysphagia and result in paralysis and death from respiratory failure [87, 88]. The etiology of ALS is idiopathic, but 10% of cases have a family history [89]. Of all cases of familial ALS, 20% have mutations in the gene that encodes the protein superoxide dismutase 1 (SOD-1). The SOD-1 gene mutation located on chromosome 21, important for neutralizing free radicals, promotes the activation of the oxidative cascade, producing oxidative stress and neuronal death by the apoptosis pathway [90]. The other 80% mutations were described in genes like ALS4, ANG, VAPB, FIG420, TDP43, FUS, and UBQLN2. So, even in familial cases, there is significant genetic heterogeneity and the involvement of several etiopathogenic mechanisms [89, 91]. After discovering the influence of these genes on familial ALS, a variety of hypotheses emerged to elucidate its pathophysiology. Among them the oxidative damage, accumulation of cell aggregates, mitochondrial dysfunction, failures in axonal transport, deficiency of trophic factors, inflammation, astroglial effects, and excitotoxicity promoted by glutamate [92–94]. The widely accepted hypothesis that triggers ALS is a failure in the reuptake of the synaptic cleft or a failure in the release of glutamate (the main excitatory neurotransmitter). The increased concentration of glutamate leads to the influx of calcium into the motor neuron, activating the signaling cascades that result in neuronal death because of excitotoxicity [95]. However, there is evidence that the clinical symptoms of ALS can be by altering the expression of vascular endothelial growth factor (VEGF), purine/pyrimidine endonuclease-DNA repairing enzyme (APEX), apolipoprotein E (Apo E), ciliary neurotrophic factor, and LIF.SOD [96]. The neuroinflammation process is a significant feature in the pathogenesis of ALS, in which it is possible to observe an increase in the systemic levels of inflammatory cytokines, such as TNF-α, IL-6, and IL-8 [97]. Simultaneously, there is also the action of the TCD4+ lymphocyte, which produces and releases pro-inflammatory cytokines like TNF-α and IL-17. The TCD8+ lymphocytes, also induce the motor neuron to apoptosis [98, 99]. Microglial and DC activations are also involved in the production of inflammatory cytokines such as IL-1, IL-6, and TNF [97]. Microglia also release monocyte chemoattractant protein-1 (MCP-1) responsible for monocyte infiltration through the BBB that contributes to motor neuron death [97, 100]. As the disease progresses, pro-inflammatory factors released into the environment promote astrocytic activation, leading to reduced neurotrophic factors (like TGF-B), downregulation of glutamate transporters (GLT1/EAAT2), and release of neurotoxic factors [100, 101]. Thus, to seek effective treatment for ALS, transplantation of MSCs has been used because of their potential to differentiate into various types of cells and their ability to survive and migrate. In animal models of ALS, MSC transplantation promotes immunomodulation by reducing the expression of cytokines and chemokines. Regarding pro-inflammatory cytokines, a decrease in the expression of IL-6 and TNF-α was observed associated with an increase in the amount of M2 macrophages [91]. Contrary, it was observed an increase in anti-inflammatory cytokines, like IL-13, IL-10, and VEGF; exerting a neuroprotective action. A decrease in the expression of microglial cells was also observed, which consequently decreases the monocyte infiltrates [102]. These findings demonstrate the beneficial effect of the administration of MSCs in the treatment of ALS since they produce an anti-inflammatory immunomodulatory effect, reducing inflammation and exerting neuroprotective effects.

Immunomodulation in Neural Tissue Injury

Ischemic Stroke

IS is one of the three types of strokes. It corresponds to the principal cause of morbidity and mortality worldwide [103]. The ischemia process occurs because of hypoperfusion of blood in an organ or tissue, which can be caused by partial or total obstruction of a blood vessel. About 80% of strokes are ischemic, in which blood clots block the blood flow in a cerebral artery [104, 105]. Animal models have been one of the main tools to study IS, with the model of MCAO the closest to human ISs. The MCAO model has been used in more than 40% of experiments with MSCs to analyze its neuroprotective effects [106].

The brain is extremely sensitive to reduced blood flow. Oxygen and glucose support are dependent on the blood flow rate, and the interruption of the supply severely affects brain function, causing biochemical or molecular changes, cell dysfunction, and/or death [103, 107, 108]. After a few minutes of vascular occlusion, a sequence of progressive pathophysiological events begins ("ischemic cascade") with the primary lesions. The mechanisms involved in the cascade are excitotoxicity, apoptosis, activation of glial cells, the release of free radicals, loss of BBB integrity, infiltration of leukocytes in the brain parenchyma, and production of inflammatory mediators [108–110]. The neural cells, because of the absence of oxygen, start to perform anaerobic respiration, reducing the pro-

duction of ATP. ATP reduction leads to dysfunction of ATP-dependent membrane transporters as the sodium and potassium (Na+/K+ ATPase) and calcium (Ca2+ ATPase) pumps. The accumulation of calcium in the cytoplasm activates hydrolase and cell depolarization, resulting in the release and accumulation of glutamate in the pre- and postsynaptic clefts. This phenomenon is called excitotoxicity and leading to neuronal death [111]. The excess of glutamate promotes the release of COX-2, contributing to the activation of microglia, astrocytes, and leukocyte infiltration [112–114]. The excitotoxicity process also produces a large amount of lactic acid, lowering the pH, and activating acid-sensitive ion channels, which are permeable to Ca2+. This process is called excitotoxicity [115]. Resulting from the ischemic cascade, tissue damage and cell death are observed. Tissue damage is irreversible, and disorderly cell death is directly related to the inflammatory process in the core of the lesion [116]. Furthermore, hypoxia induces the expression of p53 and proapoptotic genes of the Blc-2 protein family, like Bax and Bid. The Bax presence in the mitochondria causes changes in the membrane, releasing cytochrome into the cytosol, activating caspase-9, and forming the apoptosome complex. Subsequently, caspase-3 is activated via apoptotic protease activating factor (Apaf-1) corresponding to the intrinsic pathway [116, 117]. The extrinsic pathway activation occurs from receptors of the tumor necrosis factor family, the most common being TBFR1 and the first apoptotic signal. Consequently, caspase-8 (initiator) and caspase-3 (effector) activated lead to the cleavage of the Bid, resulting in increased mitochondrial permeability and release of cytochrome C [117]. Another possible mechanism of apoptosis present in ischemia is via endoplasmic reticulum signaling triggered by caspase-12. This pathway is activated by the accumulation of misfolded plasma reticulum proteins due to glucose deficiency, alterations in homeostasis and calcium, and oxidative stress [116, 117]. The inflammatory process begins and induces a secondary lesion, through the production of ROS and inflammatory mediators, like cytokines (IL-1, IL-6, TNF-a, and TGF-b), chemokines (MCP-1, CXCL12, and MMPs), and increased recruitment of mononuclear cells to the injury site [108, 109]. Once present, inflammation mediators activate microglia resulting in the release of more pro-inflammatory cytokines, and the induction of adhesion molecules (selectins, integrins) and immunoglobulins [112, 113]. Adhesion molecules mediate leukocyte adhesion to the vascular endothelium leading to their entry into the brain parenchyma [112, 113, 117]. With the increase in leukocytes, they release cytotoxic agents like MMPs, NO, and ROS, intensifying brain damage, cell death, and rupture of the extracellular matrix and the BBB [112].

Given the deleterious effects resulting from the ischemic process, several animal studies using the MCOA method have demonstrated the immunomodulatory properties of MSCs in IS [118, 119]. Regarding the primary lesion that occurs after the ischemic event, studies have reported a reduction in infarct volume [119–126] and brain water content [122, 127]. Among the mechanisms involved in the "ischemic cascade," such as apoptosis, activation of glial cells, and loss of the integrity of the BBB, such studies describe a modulation mediated by MSCs. Starting with apoptosis, the studies describe the prevention of neural apoptosis [126], observed by a reduction in TUNEL-positive cells and protein levels of c-Jun N-terminal kinase (JNK) [123]; and a reduction in the number of degenerating neurons, structurally preserved [123, 128]. Neural preservation was observed because of higher expression levels of NeuN in MSCs groups [128]. Regarding glial activation, it observed lower labeling of GFAP+ and Iba-1+ cells [121, 123, 126, 128–132] indicating less infiltration of glial cells, like astrocytes and microglia in the ischemic core and boundary zone regions. Finally, regarding the loss of BBB integrity, the findings demonstrate an increase in vessel density values, the number of endoglin-positive cells, and the placental growth factor (PIGF) in the core and ischemic core and boundary zone region [130]. Furthermore, VEGF showed an increased expression mainly in macrophages [130]. These factors indicate a positive modulation of MSCs in the recovery of the BBB, as well as in the reduction of neural damage present in the ischemic event. In parallel with the histological improvement, it was observed a better motor and neurological functional recovery, assessed by the rotarod test, and a shorter learning period assessed by the Morris Water Maze test [119, 121, 123, 126, 131]. Finally, about the secondary lesion resulting from the inflammatory process, studies with the administration of MSCs have shown an effective immunomodulatory effect. This was noted by the reduction of pro-inflammatory cytokines and the increase of anti-inflammatory cytokines. Among the pro-inflammatory cytokines and chemokines, there was a reduction in IL-1 [122], IL-6 [132], IL-17 [122, 124], IL-23 [122], TNF-a [119–122, 133, 134], NF-kB [120], IL-1α [132], IL-1b [119–121, 127, 132], IFN-γ [127, 133], MCP-1 [119, 129, 132], IL-8, COX-2 [129], C3 expression [124], CXCL1 [132], MIP-1α, and MIP-3α [132]. Regarding the anti-inflammatory cytokines and chemokine has described an increase in IL-4,

IL-5 [129], IL-10 [122, 128, 131], TGF-β [119, 128, 130], CD200 [128], and gene 6 protein (TSG-6) [124]. Concomitant to these findings are also described inhibition of the CD8+ cell infiltrate [119], and a decrease in Th17 [122]. Therefore, inoculation of MSCs suppresses immune propagation, reduces structural damage, and promotes functional improvement displaying a neuroprotective effect in the ischemic brain.

Traumatic Brain Lesion

TBI is the most common cause of death and disability in individuals under the age of 45 years in the world [135]. After the brain impact, a series of pathophysiological events begin for several days to weeks. Primary lesions after TBI are related to acceleration, rotation, and compression forces, promoting structural damage to the brain, BBB, and blood supply. The result is an intracranial hemorrhage, focal cerebral inflammation, and necrosis. Focal brain inflammation promotes secondary lesions as it exacerbates edema and promotes neuronal, glial, and endothelial cell death. The consequence is the presence of an inflammatory process, with edema formation, oxidative stress, and iron accumulation [135, 136]. After brain injury, there is an increase in the metabolic rate, which results in a rapid depletion of ATP leading to dysregulation in cellular ionic homeostasis. The low concentration of ATP promotes the activation of an anaerobic cascade causing an intracellular influx of sodium and calcium. The rise in the influx of sodium and calcium into the cell increases the influx of water, increasing cell volume (cytotoxic edema), and the uncontrolled depolarization of neurons, stimulating the release of excitatory neurotransmitters like aspartate and glutamate into the environment extracellular [136–138]. The high amount of intracellular calcium also leads to activation of tissue damage pathways, called the arachidonic acid cascade, which culminates in the activation of phospholipase A2 producing ROS [135, 136, 139]. Therefore, excitotoxicity and oxidative stress promote cells damage and apoptosis induction [138, 140–143]. However, apoptotic cell death represents only a percentage of neuronal deaths. The main mechanism of cell death is necrosis, increasing the inflammatory process [140]. Inflammation in a traumatic injury begins a few minutes after trauma and first activates microglial cells and astrocytes. Then, peripheral inflammatory cells like neutrophils and monocytes are recruited. The increased integrated activity of cytokines, chemokines, and vascular adhesion molecules amplifies the inflammatory response [144–146]. Among them, cytokines involved in this process are NF-kB, TNF, IL-1, IL-6, and IL-10 [144]. Chemokines, known for their role in leukocyte communication and migration, like IL-8, are responsible for the recruitment of neutrophils and have their expression increased after trauma [147]. The expression of COX is also notorious, like COX-1 and COX-2, responsible for the conversion of arachidonic acid into prostaglandins [148]. Adhesion molecules expressed by endothelial cells, such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), are essential for leukocyte migration, involving their rolling and adhesion. Such molecules are upregulated in traumatized brains [137]. Thus, given the damage to TBI added to inflammatory events, the use of MSCs promotes a less cytotoxic environment, secreting trophic factors and immunomodulatory molecules that modulate the inflammatory response after TBI [149–151]. In animal models of TBI and intracerebral hemorrhage (ICH), animals when treated with MSCs exhibit lower BBB permeability 24 h after infusion [152, 153]. The neurovascular protective action of MSCs is seen by the lower intensity of Evan's blue and reduced expression of matrix metallopeptidase-9 (MMP-9) [152]. The BBB is an essential component of the CNS, formed by endothelial cells, proteins, astrocytes, and pericytes, with the function of maintaining neural homeostasis [154, 155]. Because it is impermeable, it limits and regulates the exchange of substances between the blood and nervous tissue [156]. However, the dysfunction in BBB leads to ionic dysregulation, alteration of signaling homeostasis, the entry of immune cells and molecules into the CNS, microglial activation, neuronal dysfunction, and degeneration [156, 157]. The inflammatory response in the CNS is characterized by the presence of edema formation, greater infiltration of mononuclear cells, astrocytic, and glial cell activation and increased expression of pro-inflammatory cytokines and apoptotic markers [145, 158]. Treatment with MSCs contributed to the reduction of edema, glial cells, and mono- and polymorphonuclear infiltrates, particularly of macrophages, neutrophils, and CD8+ T lymphocytes [132, 152, 153, 159–161]. Reduction of activated astrocytes was observed only 24 h after MSC infusion [132]. Concerning astrocytic and glial markers, a lower expression of Iba-1 and GFAP was observed [152, 160]; as well as a reduction in apoptotic cells, seen by the decreased labeling of TUNEL-positive cells [152, 159].

In parallel, the administration of MSCs promotes immunomodulation in the CNS, altering the expression of pro- and anti-inflammatory cytokines and chemokines. Between the pro-inflammatory cytokines, it was observed a reduction of IFN-γ [152, 153, 159], TNF-α [152, 153,

159, 160], IL-1β, IL- 1α, IL-6, and IL-17 [132, 152, 159]. Regarding pro-inflammatory chemokines was observed a reduction in MCP-1, MIP-2) [132, 159], and chemokine ligand 5 (CCL5), CXCL1 [159]. In both cases, a reduction was seen between 24 h and 72 h after TBI, along with a reduction in the expression of NF-kB [152, 159] and OX-2 [153]. Opposite to what was observed with pro-inflammatory cytokines and chemokines, the articles described an increase in anti-inflammatory cytokines, in particular IL-10, TGF-β, and TNF-stimulated of TSG-6 [152, 159, 160]. No differences in IL-4 cytokine levels were described between control and MSC-treated groups [159]. These findings demonstrate the beneficial effect of administering MSCs during TBI since they produce an anti-inflammatory immunomodulatory effect, reduce acute inflammation, regarded by the reduction of circulating pro-inflammatory cytokines and chemokines within the period of 24 h–72 h, and show a neuroprotective effect, reducing edema and damage to BBB. Regarding the origin of MSCs and inoculation path, the selected articles preferably used MSCs from bone marrow with intravenous inoculation. One article inoculated cells locally using a Hamilton syringe and one article used MSCs from adipose tissue. However, no difference in results was observed in the other studies.

Conclusion

The present review strengthens the field by systematically investigating the relation between the inoculation of MSCs in injuries and neurodegenerative diseases of CNS. These cells display an immunomodulatory effect, promoting a decrease in the inflammatory process, better neural recovery, and preservation of brain tissue. Thus, we suggest the use of MSCs represents a potential therapeutic option for the treatment of neural diseases characterized by the presence of neurodegeneration, inflammation, and structural damage in the neural tissue.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Rodrigo de Andrade Rufino: responsible for concept/design, for screening of the articles, drafting of the manuscript, critical revision of the manuscript, and approval of the article.

Laís da Silva Pereira-Rufino: responsible for screening of the articles, drafting of the manuscript, critical revision of the manuscript, and approval of the article.

Thays Cristina Silva Vissoto: responsible for screening of the articles and drafting of the manuscript.

Irina Kerkis: contributed with critical revision of the manuscript.

Adriana da Costa Neves: contributed with critical revision of the manuscript.

Marcelo Cavenaghi Pereira da Silva: responsible for concept/design, critical revision of the manuscript, and approval of the article.

Data Availability Statement

All data are available, and they can be found in PubMed and ScienceDirect between January 2011 and March 2021. Further inquiries can be directed to the corresponding author.

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