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Immunomodulatory Effects of Mesenchymal Stem Cells in Neurodegenerative Diseases

Amani A. Alrehaili[1*]

[1]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Taif University, PO Box 11099, Taif 21944, Saudi Arabia

[*]Corresponding Author: Amani A. Alrehaili[1*]

Abstract

Neurodegenerative diseases are chronic, life-threatening central nervous system disorders characterized by neuronal damage or apoptotic cell death. Even with the presently available therapies, these disorders are incurable. Regenerative medicine is the field of medicine that uses the ability of stem cells to repair damaged tissues and organs; thus, it refers to all procedures using stem cells that have been properly identified and harvested before being locally stimulated to multiply and differentiate for transplantation in the area of regeneration. Cell therapy is a feasible alternate approach, particularly the use of mesenchymal stem cells (MSCs), which are pluripotent stem cells that can self-renew and differentiate in multiple ways. MSCs are a dependable source of nerve cells for cell therapy or transplantation. The present review assessed the evidence for MSC treatments in neurodegenerative diseases with an emphasis on Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. Furthermore, the possible MSC modes of action were evaluated, and a few issues with MSC-based stem cell therapy were outlined. Overall, this review presented details on MSC treatments and how they might improve treatments for neurodegenerative diseases.

Keywords: Neurodegenerative disease; mesenchymal stem cells; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis

1. Introduction

Neurodegenerative diseases (NDs) are characterized by a progressive loss of neuronal integrity and performance or number of neurons in the brain or spinal cord. The main examples of

NDs include Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [1]. Most of the global population has NDs [2]. Age is the single most important risk factor for the occurrence of NDs; however, the majority of NDs are caused by genetic and environmental factors, leading to difficulty in the prediction of illness [3].

Although there have been massive attempts to determine treatments for NDs over the last few decades, effective medicines are limited. ND can be caused by several factors. First, various cellular and molecular processes have been associated with the pathogenesis of these diseases; moreover, the cause of neuronal death and the precise molecular mechanism involved in the progress of this disease remain unknown [4, 5]. Second, early detection is difficult due to the lack of effective biomarkers [6]. Third, progressive neurodegeneration often includes additional consequences, such as a chronic inflammatory process requiring modification in the treatment [7]. Finally, the blood–brain barrier is a significant obstruction to the successful treatment of NDs [4].

The present transplant procedures highlight the need to study biological regenerative potential in several medical specialties. Thus, it is important to improve the current state of knowledge in the medical field and the therapeutic application of cells in neural regeneration. Regenerative medicine is a field of medicine that uses the ability of stem cells to repair damaged tissues and organs [8]. It refers to all procedures using stem cells that have been properly identified and harvested before being locally stimulated to multiply and differentiate for transplantation in the area of regeneration [9].

Mesenchymal stem cells (MSCs) were first identified as bone-forming and multipotent adult stem cells in bone marrow in the 1960s [10]. In contrast to hematopoietic stem cells derived from bone marrow, MSCs can be extracted from several other sources, including the placenta, umbilical cord, adipose tissue, teeth, and menstrual fluid [11]. Based on their tendency to differentiate into mesodermal tissues, there has been a strong focus on the ability of MSC to regenerate. However, the findings of Bartholomew et al. (2002) revealed the novel properties of these progenitor cells; MSCs avoid T-cell detection and inhibit T-cell reactions to mitogens [13]. Moreover, their implications for many fields of medicine have been studied. MScs continued to be immunologically favored due to this range of activities, which later affected the lymphocytes (B and T), natural killer (NK) cells, and antigen-presenting cells [14]. Moreover, they avoid T-cell detection as they have limited numbers of major histocompatibility complex (MHC) class I proteins; rarely show MHC II; and lack CD40, CD40L, CD80, and CD86 molecules [15]. MHC has no control over its effects on immunocompetent cells, allowing allogeneic MSCs to be used without antigen matching with host human leukocyte antigens [16].

The present review assessed the evidence for MSC treatments in neurodegenerative diseases, with an emphasis on PD, AD, and ALS. Furthermore, the possible MSC modes of action were evaluated, and a few issues with MSC-based stem cell therapy were outlined.

2. Pathways of The Therapeutic Effect of MSCs In NDs

Although in vitro and in vivo data on the regenerative functions of MSCs are available, the pathways through which MSCs perform their immunoregulatory and regenerative actions are unknown; moreover, many mechanisms are involved.

2.1 Homing of MSCs

Stem cell homing refers to the ability of stem cells, either circulating or externally delivered, to identify and enter an environmental area. One of the greatest benefits of MSC-based treatment is its ability to preferentially identify damaged tissues [17]. A stem cell can transfer between nesting sites throughout its lifetime during both the embryonic growth stage and adulthood. There are two types of homing which are non-systemic homing and systemic homing. Non-systemic homing involves the local transplantation of MSCs at the target area, where they are then directed by a chemokine gradient to the site of injury. Whereas MSCs are injected or used endogenously into the bloodstream during systemic homing, where they go through number of steps to leave circulation and get to the site of injury [18].

2.2 MSC Migration and Homing Modes

2.2.1. Adhesion Molecules and MSCs Homing

One of the most important steps in homing is the mobility of MSCs in circulation and

transendothelial migration. MSCs migrate into circulation using the same mechanism as leukocytes by relying on adhesion molecules. Integrin blocking and knockout research studies have confirmed that MSC migration is affected by cell adhesion molecules (CAMs). Leukocytes can tether, roll, adhere, and transmigrate to the extravascular space with the help of CAMs expressed by MSCs, such as integrins, selectins, and chemokine receptors [19]. MSCs exhibit integrin receptors, such as α1-5, αv, β1, β3, and β4. VCAM-1, ICAM-1, ICAM-3, CD166 (ALCAM), and endoglin/CD105 are other CAMs expressed by MSCs [20].

2.2.2. Chemokines and Chemokine Receptors in MSCs Homing

Chemokines secreted by tissues and endothelium may stimulate ligands required for the adhesion, migration, chemotaxis, and preservation of MSCs in target tissues. In response to chemokine and chemokine receptor signaling prompted by inflamed tissues, MSCs move into these inflamed tissues [21]. MSCs have a broad spectrum of chemokines and chemokine receptors that are involved in MSC homing. MSCs also express chemokine receptors such as CCR1-CCR10 and CXCR1-CXCR6, which contribute to MSC migration [22]. The migration of MSCs to injured tissue is enhanced by CXCR1, CXCR2, CXCR4, interleukin (IL)-8, MIP-1, and monocyte chemoattractant protein-1 (MCP-1) [23].

2.2.3. Role of Metalloproteinases (MMPs) in MSCs Migration

MMPs degrade extracellular matrix proteins, letting MSCs differentiate, multiply, and migrate. They also promote angiogenesis. MSC motility and recruitment to injured tissues are promoted by the expression of CXCR4, MMP-2, and MT1-MMP [24].

2.2.4. Regulation of MSCs Homing (Cytokines and Growth Factors)

IL-6, platelet-derived growth factor (PDGF), PDGF receptor, placenta growth factor, vascular endothelial growth factor receptor 1, vascular endothelial growth factor 1, and insulin-like growth factor-1 play critical roles in MSC migration [25]. PDGF receptors are extensively expressed on the membrane of MSCs; PDGF promotes MSC motility [26]. According to transwell migration assays, PDGF is a more efficient MSC chemoattractant cytokine than stromal cell-derived factor-1 and MCP-1 [27, 28].

2.3. Paracrine Factors of MSCs in Regeneration and Repair

The level of growth factors and cytokines secreted by MSCs defines their therapeutic efficacy rather than their ability to differentiate into cardiac, vascular, or renal cells [29]. MSCs release many regulating and nourishing elements, including a significant number of growth factors, cytokines, and chemokines. These elements respond to stressful events, such as physiologic variation (oxygen deprivation or oxygen depletion), small molecular activation, and cytokine therapies [30].

Hepatocyte growth factor (HGF), a pleiotropic factor released by MSCs, is a key chemical growth factor. The pleiotropic effect is achieved by increasing the motility, replication, and durability of cells [31]. In the presence of variations in HGF concentration, MSC migration is associated with significant c-met expression in vitro. HGF helps in the migration of rat MSCs by stimulating Akt and focal adhesion kinase pathways [32]. During the analysis of the effects of MSCs on cardiac damage, paracrine stimuli showed pleiotropic effects during the repair and regeneration processes [33]. Secreted frizzled-related protein 2 (SFRP2) and hypoxia and Akt-induced stem cell factor are the main modulatory proteins that function in two distinct ways to increase cell regeneration in myocardial injury [34].

To prevent cardiac cell death, SFRP2 and hypoxia and Akt-induced stem cell factor regulate the Wnt3a apoptosis-inducing gene and PKCε. SFRP2 suppresses the proliferation of bone morphogenetic protein 1 and stem cell antigen 1 cardiac progenitor cells, reduces scarring, and stimulates cellular differentiation, along with showing its cytoprotective function. After SFRP2 attachment to Wnt6, the differentiation step promotes non-canonical Wnt/planar cell polarity signaling via the c-Jun N-terminal kinase (JNK) pathway [35].

This function is also exerted by the Abi3bp gene by promoting the c-Kit+ progenitor of differentiation in myocardial cells [36]. MSCs increase neuronal renewal, inhibit apoptosis, decrease free radical concentrations, encourage the generation of new synaptic connections from injured neurons by promoting axonal branching,

control neuroinflammatory processes, and enhance the proteasomal breakdown of ubiquitinated misfolded proteins [37]. Furthermore, mouse BM-MSCs provide neuroprotection by secreting prosaposin, a protein capable of recovering mature neurons from apoptosis [38].

2.4. Immunoregulation

MSC immunoregulation may be associated with interactions with T cells, B cells, and NK cells. MSCs can regulate immune cell activity by inhibiting T-cell stimulation and restricting antibody production by B cells and cytokines released by NK cells [39]. When cultured with allogeneic T and NK cells, MSCs can avoid detection and disintegration [40].

3. MSCs in The Treatment of NDs

3.1. Parkinson's Disease (PD)

PD is a chronic neurodegenerative condition characterized by the degeneration of dopaminergic neurons in the pars compacta and the accumulation of cytoplasm fibrillary aggregates (Lewy bodies) [41]. The current primary treatment for PD is pharmacological therapy comprising anticholinergics, dopaminergic agonists, and neuroprotectants [6]. According to the findings of Minakaki et al (2020), improperly accumulated α-synuclein in the neurons of patients with PD was identified and targeted as an antigen by immune cells; moreover, several inflammatory cytokines were increased in these patients [42]. The autophagy function is dysregulated in the brains of patients with PD and PD animal models, indicating that autophagy probably plays a role in the disease [43]. MSCs enhance α-syn elimination and modulate autophagy-lysosomal function in PD models [44]. In cell-based assays, the secretome of MSCs had multiple factors linked with autophagy regulation, particularly beclin-1, gamma-aminobutyric acid receptor-associated protein-like 1, and autophagy-related 12 [44]. MSCs have immunomodulatory properties as they can stimulate an inflammatory response when the immune system is suppressed and inhibit the inflammatory process when it is overactive [45]. MSC treatment improves anti-inflammatory cytokine production in the animal models of epilepsy and PD, including transforming growth factor-beta1 (TGF-β1), prostaglandin E2, HGF, indoleamine 2,3 dioxygenase, nitric oxide, IL-4, and IL-10, and decreases pro-inflammatory cytokine production, namely, IL-6, IL-1β, and tumor necrosis factor-alpha (TNF- α) in the brain and blood [46].

3.1.1. Clinical Studies of MSCs in The Treatment of PD

Wang et al. (2014) enrolled 15 patients with PD (stages 3–5 on the Hoehn and Yahr Scale scale) in a research protocol that included the transplantation of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and observed a significant reduction in the Unified Parkinson's Disease Rating Scale within a month of the intervention [47]. Comparable results were observed in a limited study conducted in 2016 on five PD patients who received intravenous infusions of allograft hUC-MSCs, with three of the five patients showing a reduction in disease severity after 3 months of UPDRS evaluation [48]. Boika et al. (2020) assessed the effectiveness of an autologous MSC transplant in 12 patients with PD. The efficiency of the therapy was evaluated between 1 and 3 months after the transplantation. UPDRS was used to assess the intensity of locomotor disturbances. A statistically considerable drop was observed in the degree of both locomotor and nonmotor symptoms in the study subjects over the post-transplant interval [49]. Three patients with PD received 5–6 autologous adipose MSC administrations in succession; UPDRS for all three patients showed a significant therapeutic response [50].

3.2. Alzheimer's Disease (AD)

AD is the most prevalent source of dementia in older adults and is characterized by amyloid plaques, neurofibrillary tangles, and neuronal death. AD is associated with progressive inflammatory processes in the cerebral cortex and hippocampus, comprising improper stimulation of microglia and astrocytes and invasion of peripheral immune cells [51].

MSCs may be a favorable treatment option for AD as they have immunomodulatory effects, protect and regenerate neurons, and inhibit apoptosis, along with showing antioxidative effects. Furthermore, MSCs decrease alpha-beta plaques, beta-secretase, and tau hyperphosphorylation; reverse microglial inflammation; and promote anti-inflammatory cytokines in AD [52]. It has been also demonstrated that MSCs enhancing neuroprotection and reducing proinflammatory cytokines [53].

MSC-derived neurotrophins promote regeneration and synaptic formation while modulating immunological cellular responses by increasing protective mediators, including IL-10, and decreasing inflammatory mediators, such as IL-1β and TNF- α. Moreover, it enhances microglial cell phagocytosis, improves neovascularization, prevents cell damage caused by Aβ and tau, reduces free radical formation and apoptotic cell destruction, modifies autophagy modes, and decreases plaque size [54].

3.2.1. Clinical Studies of MSCs in The Treatment of AD

In the Phase 1 clinical trial, human umbilical cord blood-derived MSCs were administered once to patients with mild-to-moderate AD. Of these patients, six received a high-dose infusion (6×10^6 cells/60 µL) and three received a low-dose infusion (3×10^6 cells/60 µL). The low dose was well tolerated during the 2-year follow-up with no apparent toxicity; however, it did not achieve the equivalent clinical usefulness as shown in animal trials [55]. According to Kim et al. (2015), although it may not be as accurate as conventional methods to identify solitary or scattered amyloid deposits in the brain, positron emission tomography may be the cause of this discrepancy between animal and human studies [55]. In animal studies, immunohistochemistry stains, enzyme-linked immunosorbent assay, and western blotting are used to determine various forms of amyloid deposits. One additional rationale for why it is difficult to reproduce data from the nervous system from preclinical studies could be the differences in their AD cellular environments. Furthermore, xenogeneic transplantation is used in preclinical experiments, whereas allogeneic transplantation is used in human clinical studies [56-58].

A phase 1/2a study completed in December 2019 assessed the tolerability, dosage, and toxicity and explored the efficacy of three successive intraventricular administrations of human umbilical cord blood-derived MSCs (NEUROSTEM®) compared with placebo at 4-week durations in patients with AD; the study's outcomes are yet to be published [56-58].

3.3. Amyotrophic Lateral Sclerosis (ALS)

ALS is the most common motor neuron disease; it is a life-threatening disorder with a 3-year median survival time after the development of symptoms. In ALS, there is degeneration of the upper motor neurons in the cortex and the lower motor neurons in the brainstem and spinal cord, causing gradual degenerative changes in the muscular system. Approximately 5%–10% of those diagnosed with ALS have a family history; it is inherited as an autosomal dominant disease [59].

TDP-43 proteinopathy is found in 97% of patients with ALS [60]. However, misfolded proteins in Cu-Zn superoxide dismutase type 1 and fused in sarcoma genes have been observed in some patients with ALS [61].

MSCs release substances that promote growth and trophic activity, which work to control both innate and adaptive immune functions. They can also alter the behavior of T lymphocytes and macrophages, two cell types involved in the neuropathology of ALS [62, 63]. Proinflammatory cytokines like interferon-γ and TNF- α can induce the expression of some immunomodulatory molecules in MSCs [64].

3.3.1. Clinical Studies of MSCs in The Treatment of ALS

The use of MSCs with significant therapeutic potential is important for successful treatment. MSCs have been used in various clinical trials involving patients with ALS, which are registered on www.clinicaltrials.gov.

The safety and reliability of intravenous and intrathecal injections of bone marrow-derived MSCs (BMMSCs) were validated in the NCT01759797 and NCT01771640 phase I clinical studies [65]. During the 12-month follow-up after MSC transplantation, no severe side effects or aberrant abnormalities were observed on the magnetic resonance images of the central nervous system. However, the forced vital capacity percentage and Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) scores of both patient groups were significantly lower, indicating that the disease was progressing [65]. Two consecutive intradural injections of BMMSCs were well tolerated by patients with ALS (study ID NCT01363401). During the 12-month follow-up period, only minor, temporary side effects, such as pyrexia, discomfort, and headaches, were observed, with no significant side effects [66]. The ALSFRS-R score decline lasted for 6 months after the initial MSC injection and did not worsen during the 6-month follow-up period. Furthermore, the cerebrospinal fluid

exhibited a relative increase in the levels of IL-10, TGF-1, TGF-2, TGF-3, and IL-6 after treatment, whereas the MCP-1 level decreased, indicating a favorable effect on the immunological reaction [68]. According to the phase 2 randomized trial (ID: NCT01363401), repeated intradural infusions of BMMSCs are tolerable and may have a therapeutic effect lasting for at least 6 months. Patients with ALS were randomly allocated into two subgroups: those receiving riluzole alone and those receiving two BMMSC injections along with riluzole. No considerable treatment-related side effects were noted. Between the start of the study and 4 and 6 months after the transplant, the ALSFRS-R scores of the MSC group changed less than those of the control group on average. Furthermore, the anti-inflammatory cytokine levels were higher than the pro-inflammatory cytokine levels in the CSF of the MSC-treated group. In those who responded well, TGF-1 and MCP-1 had a poor association. Long-term survival did not vary significantly between the two patient groups. The author then suggested that the proposed mode of action of BMMSCs was to facilitate the transition from pro- to anti-inflammatory conditions [67]. Interestingly, the NCT02881476 study showed the effectiveness of allogeneic MSCs derived from Wharton's jelly in patients with ALS [68]. Intrathecal injections of BMMSCs were found to be feasible and beneficial for some patients in a separate study (NCT02881489) [69].

4. Conclusion

MSCs have demonstrated therapeutic promise in several clinical contexts. MSCs show their effects by differentiating to specific cells or excreting various growth and trophic factors, including both glial tissues and axons, suggesting a promising therapeutic approach for tissue regeneration in NDs. They also have important clinical benefits in terms of immunomodulation, and neuroprotective properties, wherein they can effectively prevent immunological rejection and help improve the lives of patients. Both animal and human clinical trials have used MSCs derived from bone marrow, fat, umbilical cord, or placenta from allogeneic or autologous sources, and only minor side effects have been reported. Continuous research toward safer, more effective, and more feasible treatment will be required. To provide more effective treatment approaches for patients, the process of preparing MSCs, the mode of administration, and the optimal doses need to be improved. Understanding their mode of action in more depth will benefit the clinical application of MSCs and increase their prospective treatment efficacy.

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