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REVIEW ARTICLE

Clinical potential and current progress of mesenchymal stem cells for Parkinson's disease: a systematic review

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Abstract

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease characterized by severe dyskinesia due to a progressive loss of dopaminergic neurons along the nigro-striatal pathway. The current focus of treatment is to relieve symptoms through administration of levodopa, such as L-3,4-dihydroxy phenylalanine replacement therapy, dopaminergic agonist administration, functional neurosurgery, and gene therapy, rather than preventing dopaminergic neuronal damage. Hence, the application and development of neuroprotective/disease modification strategies is absolutely necessary. Currently, stem cell therapy has been considered for PD treatment. As for the stem cells, mesenchymal stem cells (MSCs) seem to be the most promising. In this review, we analyze the mechanisms of action of MSCs in Parkinson's disease, including growth factor secretion, exocytosis, and attenuation of neuroinflammation. To determine efficacy and protect patients from possible adverse effects, ongoing rigorous and controlled studies of MSC treatment will be critical.

Keywords Mesenchymal stem cells · Secretome · Parkinson's disease · Dopaminergic neurons

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease associated with aging, second only to Alzheimer's disease (AD), the most common dyskinesia disease. The prevalence of the elderly over 65 years old is 2%. Parkinson's clinical manifestations are resting tremor, rigidity, dyskinesia, and postural instability. PD lesions mainly occur in the substantia nigra (SN) striatum pathway, with SN dopaminergic neuron degeneration and Lewy bodies (LBs) as the main pathological features. LBs are unique intracytoplasmic inclusions containing a variety of cellular proteins. Synaptic nucleoprotein (α-synuclein, α-syn) is the main component of LBs [1, 2]. In recent years, PD hotspots have mainly focused on the mechanism of action of α-syn. A-syn is a characteristic marker of various types of PD, and its aggregation is closely related to the pathogenesis of PD [3]. It has been reported that oligomerization or aggregation of α-syn overexpression and aggregation has toxic effects on cells, which can cause mitochondrial dysfunction and apoptosis and lead to the death of dopaminergic neurons [4–6]. However, the current specific PD system is still unclear. Currently available therapies are pharmacotherapy (including levodopa, DAergic receptor agonists, monoamine oxidase B (MAO-B) inhibitors, cathecol-O-methyltransferase (COMT) inhibitors), functional neurosurgery, such as pallidotomy surgery, deep brain stimulation (DBS), and gene therapy. Traditional medicine treatment can only improve the symptoms, but it is easy to form resistance and it cannot control disease progression. There is a risk of intracranial hemorrhage, facial paralysis, and speech impairment for surgical treatment. DBS may also lead to dysarthria and paresthesia [7]. Therefore, a new treatment is based on stem cell (SC) therapy to replace degenerative nerve cells.

Stem cell treatment of nerve transplantation has shown some promise to combat PD [8–10]. Embryonic stem cells (ESCs) are pluripotent cells derived from the interior of the blastosphere. Although promising, their application in research and treatment has generated ethical concerns. Mesenchymal stem cells (MSCs) are multipotent stromal cells that are obtained from obtained from different tissues, such as bone marrow, adipose tissue, umbilical blood, and dental pulp

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[11]. The advantages of MSCs over ESCs are, for example, from patients, no risk of immune response, low risk of tumor formation, and no ethical issues. Both ESCs and MSCs can produce neural precursors (NPs), a promising therapeutic strategy for neurological diseases because they can differentiate into mature neurons, functional astrocytes, and oligodendrocytes. In summary, their genetic stability, lack of tumorigenicity, and ethical dilemma make them ideal tools for treating Parkinson's disease [12].

Among the stem cells, MSCs appear to have the greatest potential because of their characteristics to secrete neurotrophic factors and to differentiate to DAergic neurons. In fact, MSCs not only produce different molecules, which play a key role in neuroprotective, immunomodulatory, chemotactic, and angiogenic effects, but also stimulate the differentiation of host stem cells. MSCs for the first time were reported in the bone marrow, and until now, they have been isolated from various tissues, such as adipose tissue, umbilical cord, endometrium, dental tissues, and amniotic fluid. The initial studies claimed that the transplantation and differentiation capacity of MSCs was the primary responsible mechanism for their therapeutic effects. However, recent studies have raised concerns about bioactive molecules or neurotrophic factors produced by MSCs, generally referred to as the secretome [13, 14]. In this group of factors/molecules released by MSC, we can list the soluble proteins (such as chemokines, cytokines, and growth factors), lipids, and the extracellular vesicles to promote cell survival and differentiation, protect cells from oxidative stress, protect neurons from death, or even modulate inflammatory processes [13, 15, 16].

Although growth factors and cytokines are related to cell secretions, studies have also shown that MSCs seem to be able to secrete a large number of micro-vesicles or nano-vesicles, just like exosomes [17–19]. Although its mechanism has not yet been elucidated, several authors believe that this structure has important characteristics, such as the transfer of proteins and genetic material (e.g., mRNAs, miRNAs) to other cells [20–22]. Given the evidence, some authors believe that MSC secretome may be the main reason for their ability to produce immune regulation and regeneration at damaged areas in addition to cell to cell interaction [23–25].

Moreover, the secretome of stem cell administration may have several merits compare with stem cell transplantation directly from a clinical perspective in terms of manufacturing, storage, handling, and lack of immunosuppression-based adjuvant therapies [14]. For instance, the use of secretome can significantly reduce the time and cost of culturing stem cells and it can be stored for a long time without loss of product efficacy and quality [26, 27]. In addition, the secretome avoids potential problems associated with cell transplantation, including the number of cells available for transplantation and their postoperative survival, tumorigenicity, infection transmission, and immune compatibility [28].

The purpose of this article is to review the application of mesenchymal stem cells in the treatment of Parkinson's disease. For that, studies should focus on several key points to enable the translation of this strategy from bench to the bedside in the future days.

Properties and sources of MSCs

MSCs differentiate into not only mesodermal cells but also endoderm and ectoderm-derived elements, including neurons and glial cells. MSCs are readily isolated from bone marrow with the ability to immunomodulate and repair tissue. MSCs may differentiate into neuron-like cells and secrete a variety of growth factors and chemokines. Although the exact mechanism of MSC induction therapy for PD has not yet been fully understood, it is likely that it includes neurogenesis and revascularization, anti-apoptotic, immunomodulatory, and anti-inflammatory effects [17, 29, 30]. Given the ability to migrate and engraft at sites of inflammation and injury, most of the effects are exerted by their paracrine expression of neurotrophic factors and cytokines [31].

MSCs have the following advantages: easy to isolate, great proliferative potential, not easy to age; isolated from different tissue sources; immune suppression; secrete a variety of biological factors, such as fibroblast growth factor (FGF), brain source neurotrophic factor (BDNF), forskolin, and retinoic acid (RA) [13, 29, 32, 33]; and source of autologous transplantation is safety. These features make MSCs more convincing for the treatment of neurodegenerative diseases of the central nervous system.

It is well known that the origin of MSCs is not only limited to the fetal tissues but also found in other adult organs. The widely reported bone marrow (BM)-derived MSCs are the most common. In addition, MSCs may also be derived from umbilical cord blood, adipose tissue, peripheral blood, amniotic fluid, dental pulp, endometrium, neural progenitor cells, retinal progenitor cells, skin, synovium, and aortic tunica media. MSCs from these sources exhibit certain characteristics, such as adherent, multidirectional differentiation, and expression of CD markers and pluripotency genes. Obviously, postnatal organs and tissues serve as a good source of bone marrow-derived MSCs; however, each derived stem cell has varying degrees of differentiation potential and expression of stem cell-associated markers. Therefore, comparative analysis of different sources of MSC efficacy has been confirmed in various studies. Comparing various porcine-derived MSC from the same or different hosts, it has been found that not all sources have the same mesenchymal character. MSCs from different sources have their own advantages and

disadvantages: collection of bone marrow-derived MSCs requires an invasive procedure; the amount of cells isolated is low; and other sources of MSCs have been used over the past decade to assess their potential neuroprotection and regeneration. Among all MSC types, adipose-derived MSCs can be obtained by liposuction. In fact, adipose tissue is highly vascularized and appears to be abundant in MSCs. Several research reports that the adipose tissue may contain 500 times MSCs than the bone marrow [34, 35]. However, there is growing evidence that mesenchymal stem cells harvested from the human umbilical cord (UC-MSCs) are a vital source of human autologous and allogeneic therapeutic cells. Human UC-MSCs are multipotent, primitive, have low risk of immune rejection, and highly proliferative cells with significant immunomodulatory capacity [36–38].

Routes of MSC administration

Mesenchymal stem cell transplantation included the following: (a) stereotaxic injection into the striatum, substantia nigra, or ventricle; (b) injection into the vein or arteries, the migration of bone marrow stromal stem cells to impaired tissue with blood flow; (c) the subsequent intranasal injection, followed by migration to the substantia nigra and striatum, prevents reduction of DA in the brain injury area. Different injection routes have their own merits and demerits. A summary of the advantages and disadvantages of different routes of administration in PD is provided in Table 1. In future studies, the optimal dosage and the administration way will be better defined to obtain functional improvements.

Clinical study of stem cells for Parkinson's disease

Clinically, it has been reported that MSCs are used to treat cardiac, respiratory, and digestive diseases, such as myocardial infarction (MI), acute respiratory distress syndrome, and gastrointestinal cancer [39–41]. So far, only two cases reported the treatment of PD. Li et al. [42] recently reported two PD patients who underwent transplantation of fetal mesencephalic dopaminergic neurons, wherein the neurons survived for more than 10 years, but later found that transplant donor neurons exhibited alpha-synuclein-positive Lewy body, suggesting the pathological process can spread to transplanted stem cells. On the other hand, when autologous BM-derived MSCs were transplanted into the sublateral ventricular zone (SVZ) through stereotaxic surgery, the results showed that three of seven patients have performed a great improvement in the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr (H&Y), and Schwab and England (S&E) scores. Besides, two patients have significantly decreased the dosages of PD medicine. These results have shown that the treatment appears to be safe without serious adverse events that occurred after transplantation in seven patients with PD over a period of 12–36 months. Not only that, but imaging with MRI indicates that there were no parenchymal changes or evidence of tumor formation at the end of the follow-up period [43]. Therefore, the current research on PD mainly focuses on animal models (Table 2).

Safety and effectiveness assessment for MSCs in Parkinson's disease

MSCs have been used in several methods for the treatment of regenerative cell therapy, as well as in the treatment of Parkinson's disease. MSCs for cell therapy have been shown to be safe and effective, but the challenges need to be solved before widespread application in the clinical setting. Preclinical trials of stem cell therapy should demonstrate that these cells (1) are able to survive in large numbers after transplantation, (2) can effectively regenerate nerves in the nigrostriatal tract, (3) have the ability to promote axon growth and release of DA, and (4) cause behavioral improvement in PD animal models [16]. Serious adverse events were defined as diseases and events requiring hospitalization or surgery-induced death. Asymptomatic bleeding along the needle track during surgery is considered an adverse event, but not a serious adverse event.

Feng Yin et al. reported that human retinal pigment epithelial (hRPE) cells were implanted in PD post-commissural putamen with stereotactic operation in 12 patients with PD. Surgical procedures are well tolerated by patients, and there is no significant postoperative inflammatory response. Three days after the surgery, MRI examination showed no serious adverse reactions, such as bleeding and edema. At 3 months after the treatment, the primary measurements of 11 patients showed improvement, especially in the UPDRS score in the "off" periods. Positron emission tomography (PET) showed a trend toward increased dopamine (DA) release in the first 6 months [44]. In this study, the over-expressions of Bcl-2 and P53 in the transplanted corpus striatum indicated that tumorigenesis was absent in PD rats after long-term human umbilical cord MSC treatment. Besides, no tumor-like formations (duct-like structures, irregular nests, malignant cell infiltration, or specific ultrastructural organization) were observed based on the HE stain of the corpus striatum [45]. Bernardo et al. have reported that human BMSCs can be cultured in vitro for long periods of time without losing their phenotypic, characteristic morphological and functional properties. In addition, MSCs were continuously propagated in the culture medium for up to 44 weeks, maintaining normal karyotype, and no expression of telomere maintenance mechanism was shown [46]. Weiss and his co-workers reported that transplantation of undifferentiated human UC-MSCs into the

brain of non-immunosuppressed semi-Parkinson's disease rats improves apomorphine-induced rotation. In addition, there was no tumor or host immune rejection in normal rats transplanted with UC-MSCs [47]. Besides, Shetty et al. showed that undifferentiated UC-MSCs could improve the behavior of PD rats, but differentiated UC-MSCs showed prominent effects in these animals, and the symptoms improved gradually after 12 weeks. Interestingly, both differentiated and undifferentiated MSC types did not have immune rejection in the rat brain, and no tumorigenesis was observed in vivo [48]. MSCs differentiate and express DAergic neurons in vivo and in vitro animal model of specific markers tyrosine hydroxylase (TH) survival of at least 4 months, and with no tumor, chromosomal abnormalities, or immune rejection and other adverse effects [10].

Schwerk and his colleagues evaluated the early- and long-term efficacy of AD-MSC transplantation in 6-OHDA-induced PD models. DAergic neuron variation in SN was not affected by AD-MSC administration, and TH^+ AD-MSCs were not observed three days after transplantation, indicating MSCs did not differentiate into DAergic neurons. Compared with non-transplanted animals, substantial increase in neurogenesis in the subventricular zone (SVZ) suggests that MSCs have some benefits in the repairment of Parkinson's disease, which is due to the release of neurotrophic factors and neurogenic effects. Nevertheless, MSCs can reduce DAergic degeneration of SN at 6 months after transplantation because of high TH levels in the brain of transplanted animals. MSCs increase neurogenesis in hippocampus and SVZ, and neonatal neurons survive at least six months. Given that olfactory disappearance and memory loss are one of the major non-motor symptoms in PD, transplanting MSCs can exert beneficial effects. When MSCs were located, most of them were at the site of injection and the surrounding environment 3 days after transplantation, and the rest showed endothelial phenotypes around the blood vessels or S100b and BDNF in the subarachnoid space. Six months after the transplantation, MSCs are located in SN and subarachnoid and express pericytes and endothelial markers [49]. Recent studies have shown that combining choroid plexus conditioned medium with retinoic acid (RA) induces DAergic neuronal differentiation of UC-MSCs, such as TH and dopamine transporter (DAT) expression. In addition, transplantation of these differentiated UC-MSCs into striatum improved apomorphine (APO)-induced rotation and maintained DAergic phenotypes in vivo in 6-OHPA diseased rats [32]. In fact, some studies report that DA neurons derived from BMSCs, ASCs, and Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) are transplanted into the corpus striatum of both primate and rodents models of PD, improved motor symptoms of PD models due to long-term survival, and increased the levels of DAergic markers, such as TH, MAP-2, Tuj1, DAPI, and nestin.

In the animal model of PD, undifferentiated and differentiated MSCs can significantly improve the motor behavior, but differentiated MSCs are more effective in the treatment of PD [48, 50]. In the treatment of PD, TH-expressing neural progenitor cells are counted in a mixed population of DAergic neurons to predict the activity of the relevant organism after transplantation. Chen et al. observed that behavioral improvement and protection of the striatum were associated with increased TH^+ cells in substantia nigra (SN) [51]. Li and his colleagues showed that BMSCs from donor adult mice were transplanted to the striatum after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. MPTP-injured mice with MSC intrastriatal transplantation exhibit significant

Table 1 Advantages and disadvantages of different routes of administration in PD

Routes of administration	Advantages	Disadvantages
Stereotaxic injection	1. Accurate positioning, short operating time, small surgical trauma 2. Patients under local anesthesia can withstand the surgery 3. All stem cells can be concentrated to the lesion and surrounding area to work rapidly and directly	1. Implanted stem cells may be eliminated by microglia and macrophages 2. Local stem cells are prone to overcrowding, which is not conducive to the differentiation of stem cells 3. There is still a risk of puncture bleeding, which many patients are unwilling to accept
Intravenous injection	1. Small trauma, easy to be accepted by the patients 2. Avoid damaging normal brain tissue 3. Can be transplanted multiple times.	1. It need long-term migration from the peripheral vein into the brain, and finally the number of cells into the brain is very limited 2. Increasing the number of transplanted cells would raise the cost of treatment.
Intranasal injection	1. Ease of self-administration and induction of mucosal as well as systemic immunity 2. The nasal cavity's easily accessible, rich vascular plexus permits topically administered drugs to rapidly achieve effective blood levels	Lung and systemic side effects.

Table 2 Summary of key clinical trials related to stem cells in ClinicalTrials.gov

Title	Status	Interventions	Outcome measures	Study designs	Phase	Study start	Locations
Autologous Mesenchymal Stem Cell Transplant for Parkinson's Disease	Suspended	Procedure: autologous Bone marrow derived stem cells transplant	Improvement in clinical condition of the patient assessed using UPDRS and Time Tests	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment		July 2009	Jaslok Hospital And Research Centre, Mumbai, Maharashtra, India
A Study To Evaluate the Safety and Efficacy of Human Neural Stem Cells for Parkinson's Disease Patient	Enrolling by invitation	Biological: human neural stem cell	1. The change of UPDRS score from baseline motor function index; 2. Non-motor function score: a. cognitive function b. smell c. fatigue d. emotion e. non-motor symptoms f. autonomic symptoms g. the quality of life 3. Immunological index; 4. Imaging index; 5. Blood routine examination; 6. Biochemical routine examination; 7. Safety index	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 2 Phase 3	April 15, 2017	Department of Neurology, Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
Mesenchymal Stem Cells Transplantation to Patients With Parkinson's Disease	Unknown status	Biological: bone marrow derived mesenchymal stem cells	Number of participants with adverse events; Effect assessment	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1 Phase 2	October 2011	Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, Guangdong, China
Parkinsonian Brain Repair Using Human Stem Cells	Active, not recruiting	Drug: Human Stem Cells	Safety as Measured by the Number and Severity of Adverse Events; F-DOPA uptake; Raclopride uptake; DTBZ uptake; Barona Demographic Equation; North American Adult Reading Test (NAART); Wechsler Test of Adult Reading (WTAR); Wide Range Achievement Test (WRAT); Mattis Dementia Rating Scale (DRS); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); Efficacy as measured by UPDRS; and 42 more	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1	May 2014	Hospital Angeles del Pedregal, Mexico City, Mexico
Allogeneic Bone Marrow-Derived Mesenchymal Stem Cell Therapy for Idiopathic Parkinson's Disease	Recruiting	Biological: Allogeneic bone marrow-derived MSCs	Safety of allogeneic MSC therapy in patients with PD as indicated by the presence of adverse events that are confirmed to be related to the therapy; Change in motor function as assessed by UPDRS score; Change in motor function as assessed by Timed-Up-and-Go (TUG); Change in disability as measured by the Modified H & Y Scale; functional connectivity between substantia nigra and dorsal striatum as assessed by resting state functional magnetic resonance imaging fMRI; perfusion as assessed by arterial spin-labeled (ASL) perfusion MRI; structural connectivity as assessed by diffusion-weighted MRI for diffusion tensor image (DTI) analysis;	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1 Phase 2	November 1, 2017	The University of Texas Health Science Center at Houston, Houston, Texas, United States

Table 2 (continued)

Title	Status	Interventions	Outcome measures	Study designs	Phase	Study start	Locations
			volume of subcortical structures as assessed by T1- and T2- weighted MRI with Fluid Attenuated Inversion Recovery; cortical thickness as assessed by T1- and T2-weighted MRI with Fluid Attenuated Inversion Recovery; and 7 more				
Molecular Analysis of Human Neural Stem Cells	Enrolling by invitation	Procedure: Harvesting of neural stem cells	Neuronal differentiation into dopaminergic neurons	Case-Only; Time Perspective: Prospective	Early Phase 1	June 2011	Los Angeles Neurosurgical Institute, Los Angeles, California, United States
Transplantation of Neural Stem Cell-Derived Neurons for Parkinson's Disease	Not yet recruiting	Biological: Intracerebral microinjections	Motor UPDRS	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1 Phase 2	February 2018	–
Using [18F]FDOPA PET/CT to Monitor the Effectiveness of Fetal Dopaminergic Grafts in Parkinson Disease Patients	Recruiting	Drug: [18F]FDOPA PET/CT	Differences (assessed by standard uptake values (SUV)) between pre and post-surgical nigrostriatal uptake of [18F]FDOPA	Case-Control; Time Perspective: Prospective	–	October 2016	University Of Saskatchewan, Saskatoon, Saskatchewan, Canada
Study to Assess the Safety and Effects of Autologous Adipose-Derived SVF Cells in Patients With Parkinson's Disease	Withdrawn	Harvesting and Implantation of Adipose-Derived Stem Cells	UPDRS; Modified H & Y Scale; England Activities of Daily Living Scale; Number of participants with adverse events; Reduction of Parkinson's medications; Improvement in subjective symptoms: facial expression, gait, and freezing	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	–	May 2014	Ageless Regenerative Institute LLC, Aventura, Florida, United States
A Study to Evaluate the Safety of Neural Stem Cells in Patients With Parkinson's Disease	Recruiting	Biological: ISC-hpNSC The study will enroll 4 patients for cell injection at each of three different doses. A total of 12 patients with moderate to severe PD will be treated. Each patient receives a single dose. The main objective of the study is to evaluate the safety of the cell transplantation.	Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, related TEAEs, severe TEAEs; Change in UPDRS score from baseline; Proportion of patients with improvement defined as any reduction in UPDRS motor score	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1	March 2016	Dept of Neurology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia
Safety and Efficacy Study of Human ESC-derived Neural Precursor Cells in the Treatment of Parkinson's Disease	Recruiting	Biological: NPC transplantation; Drug: Levodopa	Incidence of treatment-emergent adverse events (TEAEs), severe TEAEs as assessed by head MRI and blood examination; Change in UPDRS score from baseline; Change in DAT scan from baseline; Change in H & Y Scale from baseline	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Phase 1 Phase 2	May 2017	The first affiliated hospital of Zhengzhou university, Zhengzhou, Henan, China
Outcomes Data of Adipose Stem Cells to Treat Parkinson's Disease	Active, not recruiting	–	Change from Baseline Over the Course of a 12 Month Period as Measured by the Parkinson's Disease Quality of Life Questionnaire (PDQUALIF);	Cohort; Time Perspective: Prospective	–	July 2014	StemGenex, La Jolla, California, United States
Rajavtihi Neuronal Adult Stem Cells Project	Unknown status	Other: Progenitor Stem Cell Culture	–	Intervention Model: Single Group Assignment; Masking: None (Open Label); Primary Purpose: Basic Science	Phase 2	July 2009	Rajavithi Hospital, Bangkok, Thailand
Hereditary Parkinson s Disease Natural History Protocol	Completed	–	The primary objective of this study is to genetically define the combination of autosomal recessive genetic defects linked to EOPD and characterize their	Case-Control; Time Perspective: Cross-Sectional	–	July 28, 2015	National Institutes of Health Clinical Center, 9000 Rockville Pike, Bethesda, Maryland, United States

Table 2 (continued)

Title	Status	Interventions	Outcome measures	Study designs	Phase	Study start	Locations
			composite molecular and physiologic effect on cellular homeostasis and response to dopamine; The secondary objective is to evaluate whether these composite of these genetic defects and their effects on cellular quality control correlate to age of onset and disease penetrance in EOPD subjects.				
Neurologic Stem Cell Treatment Study	Recruiting	Procedure: Intravenous BMSC; Procedure: Intranasal BMSC	Activities of Daily Living (ADL); Neurologic Functioning	Allocation: Non-Randomized; Intervention Model: Parallel Assignment; Masking: None (Open Label); Primary Purpose: Treatment	–	June 2016	The Healing Institute, Margate, Florida, United States; Al Zahra Hospital, Dubai, United Arab Emirates
Autologous Stem/Stromal Cells in Neurological Disorders and Disease	Recruiting	Procedure: Microcannula Harvest Adipose; Device: Centricyte 1000; Procedure: Sterile Normal Saline Infusion	Number of participant with adverse events (AE) or severe adverse events (SAE)|Neurological Function; Neurological Tested Functions; MRI	Allocation: Non-Randomized; Intervention Model: Single Group Assignment; Masking: None (Open Label); Primary Purpose: Treatment	–	December 29, 2017	Global Alliance for Regenerative Medicine-USA, Stevensville, Montana, United States|GARM, Roatan, Hn, Honduras
Development of iPSC From Donated Somatic Cells of Patients With Neurological Diseases	Recruiting	–	–	Observational Model: Case-Control; Time Perspective: Prospective	–	April 2009	Hadassah Ein Kerem, Jerusalem, Israel
Safety and Clinical Outcomes Study: SVF Deployment for Orthopedic, Neurologic, Urologic, and Cardio-pulmonary Conditions	Recruiting	Procedure: Administration of autologous adipose derived SVF	Number of participants with adverse events; Changes in the Oswestry Disability Index; Changes in the Neck Disability Index; Changes in Koos Physical Function Shortform; Changes in Hoos Physical Function Shortform; Changes in the DASH questionnaire; Changes in the Visual Analog Pain Score; Changes in the Aqol-4; Changes in the O'leary-Sant IC Questionnaire; Changes in PUF Symptom Scale; Changes in the IIEF Questionnaire; EHGS Grading Score measuring change in hardness score	Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	–	March 2012	California Stem Cell Treatment Center, Rancho Mirage, California, United States

UPDRS, Unified Parkinson's Disease Reting Scale; F-DOPA, L-3,4-dihydroxy-6-(18)F-fluorophenylalanine; DTBZ, [18F]9-fluoropropyl-(+)-dihydrotetrabenazine; H&Y Scale, Hoehn and Yahr Scale; EOPD, Early-Onset Parkinson Disease; ISC, induced stem cells; hpNSC, human parthenogenetic neural stem cells; iPSC, induced pluripotent stem cells

improvement on the rotarod test ($P < 0.05$) at day 35. In addition, MSC survived in the transplanted area and expressed TH for at least 4 weeks after intracerebral transplantation [52]. In addition to their ability to induce survival and repair of DA neurons, BMSCs have immunomodulatory and anti-inflammatory characteristics as well. Neuroinflammation is defined as the negative contribution of non-neuronal cells (such as immune cells, glial cells) to neurodegenerative diseases. Although all the details have not yet been resolved, the mechanism by which activated microglia, astrocytes, and T cells can interact with each other to increase neuronal death is clear. In this study, Danielyan and her colleagues recently demonstrated that intranasal delivery of MSCs to the brains of unilaterally 6-OHDA–lesioned rats and intranasal application of MSCs increased TH level in the lesioned ipsilateral striatum and substantia nigra and prevented any decrease of the dopamine level in the damaged area [29]. Furthermore, substantial and significant improvement of motor function in PD animal models has also been observed. These neuroprotective and functional restorations of the DAergic system are indirectly related to increased BDNF levels in injured hemispheres and the ability of BMSCs to modulate host immune responses and play a strong anti-inflammatory activity. In fact, MSCs are known to regulate inflammatory cell responses through reducing the expression of pro-inflammatory cytokines, for instance, interleukin 1β (IL-1β), IL-2, IL-6, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor (TNF) [29, 53]. Moreover, IL-6, IL-10, transforming growth factor-β, and anti-inflammatory cytokines secreted by BMSCs are also connected with the protection of DAergic neurons in the substantia nigra. Furthermore, recent reports show that MSCs secrete miRNA-containing microvesicles and exosomes that mediate intercellular communication and act as repair agents, besides soluble growth factors and cytokines [17, 54, 55]. On the other hand, Xin et al. have showed that exosomes secreted by BMSCs mediate the microRNA 133b (miR-133b) transfer to astrocytes and neurons in vitro [56].

From the previously referred studies, it is easy to draw a conclusion that MSCs are able to secrete a wide spectrum of elements with strong immunomodulatory properties, inhibit apoptosis, enhance angiogenesis, and promote neuronal survival and differentiation.

Potential mechanism of MSCs in the treatment of PD animal models

Although great progress has been made in the treatment of various neurological diseases, such as cerebral infarction, brain injury, spinal cord injury, and neurodegenerative diseases, the exact mechanism by which MSCs play a beneficial role in Parkinson's disease is still being studied. However, many different mechanisms may play a role that may be contributed just as follows: (1) secrete important neurotrophic growth factors, such as vascular endothelial growth factor (VEGF), brain-derived nerve trophic factor (BDNF), interleukin-6, and glial cell line-derived neurotrophic factor (GDNF), cystatin C, new glial derived proteins, galectin-1, and pigment epithelium-derived factor [16, 57, 58]; (2) strongly modulate the immune system via direct cell to cell interactions and can aid wound healing [58]; (3) improve neuronal health by donating their mitochondria [59, 60]; (4) affect the DAergic neurons through prostaglandin E2 and its signaling pathway [61]; and (5) release dopamine by depolarizing potassium channels [62].

Conclusions and future perspectives

As a promising method of treatment, stem cell therapies have become at the forefront of the field of PD research, especially in the area of MSCs. On the one hand, MSCs can be easily harvested and proliferated without using other supporting cells. On the other hand, MSCs have no ethical and immune rejection problems compared with ESC, which is due to the lack of major histocompatibility complex III (MHC-III). Unfortunately, the observed numbers of MSC-derived neurons and glial cells are quite small and do not restore normal cellular structure, although some in vivo studies have demonstrated that MSCs can differentiate into neuronal cells upon transplantation [63–65]. Therefore, how to generate adequate and specific neuronal or glial subtypes suitable for cell transplantation in future studies is an ideal outcome.

MSC appears to be promising in PD cell therapy. MSC transplantation from different origins has shown an improvement in PD symptoms after transplantation into animal models. At least some of the improvement seems to depend on neurotrophins that protect DAergic neurons from damage and stimulate neurogenesis. Whereas, some evidence suggests that neuronal differentiation of MSCs may be more effective in the treatment of PD. Given that BM-MSCs are the first isolated MSCs, it is not surprising that they are most used in experimental models, but AD-MSCs and UC-MSCs may exhibit the advantage of easier separation and a greater number of MSCs. However, additional studies are needed to elucidate which MSC sources to use, which routes of administration, and their safety and possible contraindications. Before being applied to the body, adequate preclinical testing is needed to reduce clinical limitations and achieve satisfactory results. As with ESCs and NSCs, the safety issues associated with tumor formation, immune rejection, and biodistribution-related toxicity should also be addressed in order to translate MSCs into the ultimate choice for PD therapy. We are convinced that, although MSC research is still in its infancy, the MSC still has a great deal of hope for patients with PD.

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Compliance with ethical standards

Conflict of interests The authors have declared that no conflict of interests exists.

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