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REVIEW ARTICLE

Mechanism of Mesenchymal Stem Cells as a Multitarget Disease-Modifying Therapy for Parkinson's Disease

Aziz Unnisa[1], Kamal Dua[2] and Mohammad Amjad Kamal[3,4,5,6,*]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Hail, Hail, Kingdom Saudi Arabia;* [2]*Graduate School of Health, University of Technology Sydney, NSW 2007, Australia;* [3]*Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, China;* [4]*King Fahd Medical Research Center, King Abdulaziz University, Saudi Arabia;* [5]*Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Bangladesh;* [6]*Enzymoics, 7 Peterlee Place, Hebersham, NSW 2770; Novel Global Community Educational Foundation, Australia*

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Abstract: Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, affecting the basal nuclei, causing impairment of motor and cognitive functions. Loss of dopaminergic (DAergic) neurons or their degeneration and the aggregation of Lewy bodies is the hallmark of this disease. The medications used to treat PD relieve the symptoms and maintain quality of life, but currently, there is no cure. There is a need for the development of therapies that can cease or perhaps reverse neurodegeneration effectively. With the rapid advancements in cell replacement therapy techniques, medical professionals are trying to find a cure by which restoration of dopamine neurotransmitters can occur. Researchers have started focusing on cell-based therapies using mesenchymal stem cells (MSCs) due to their abundance in the body, the ability of proliferation, and immunomodulation. Here we review the MSC-based treatment in Parkinson's disease and the various mechanisms it repairs DAergic neurons in parkinsonian patients.

Keywords: Parkinson's disease, dopaminergic neurons, stem cell, therapy, mesenchymal stem cells.

1. INTRODUCTION

Parkinson's disease (PD) is the second most common progressive neurodegenerative disease and the most prevalent form of primary Parkinsonism. Approximately 1% of people over the age of 50 and around 2.5 % of people over 70 are affected by PD. Men have a 2.0 percent lifetime risk of developing PD, while women have a 1.3 percent lifetime risk [1]. Familial PD is genetically inherited in either an autosomal dominant or recessive fashion, while sporadic (idiopathic) PD is thought to arise due to interaction between genetics and environment. Alpha-synuclein (aSyn), phosphatase and tensing homolog-induced Kinase 1 (PINK1), Glucocerebrosidase (GBA), Parkin RBR E3 ubiquitin-protein ligase (PARK2), Vacuolar protein sorting-associated protein 35 (VPS35), Leucine-rich repeat Kinase 2 (LRRK2), and Parkinson protein 7 (PARK7) have been identified as causal genes for familial PD. These genes, along with some specific metabolites and biomarkers linked to PD, have been utilized to determine possible early detection strategies for the disease [2].

PD's motor and non-motor symptoms result from the loss or damage to striatal DAergic and non-DAergic neurons [3]. The appearance of bradykinesia, rigidity, loss of postural reflexes, and rest tremor is the most frequently encountered motor symptoms. However, clinical manifestations such as neuro-ophthalmological disorders, bulbar dysfunction, and respiratory abnormalities can also be recognized as the disease progresses. The fact that most motor symptoms respond to DAergic medication is one of the primary indicators that can help differentiate PD from other parkinsonian illnesses, hence disease identification [4]. Hyposmia, constipation, rapid eye movement (REM) behaviour disorder, depression, and olfactory impairment are other nonmotor symptoms [5]. Moreover, disturbances in odour, sleep, mood, and gastrointestinal function may signal the onset of Parkinson's disease or associated synucleinopathies. They may occur five or more years before these neurodegenerative diseases manifest [6]. Parkinson's disease has been linked to several risk factors and genetic mutations. Oxidative stress, the generation of free radicals, and various environmental pollutants are risk factors for the disease. Some studies demonstrate genetic links to PD, with several gene mutations being identified. Intriguingly, there is an inverse link between cigarette smoking, caffeine use, and the chance of acquiring PD [7].

The drugs which attenuate the pathology of α-synuclein or show favourable activity on other processes involved in PD can be used to treat PD successfully. Drug repurposing (using existing medications for a new indication) has sparked a lot of interest, as it could result in an

*Address correspondence to this author at the Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, China; E-mail: rrs.usa.au@gmail.com

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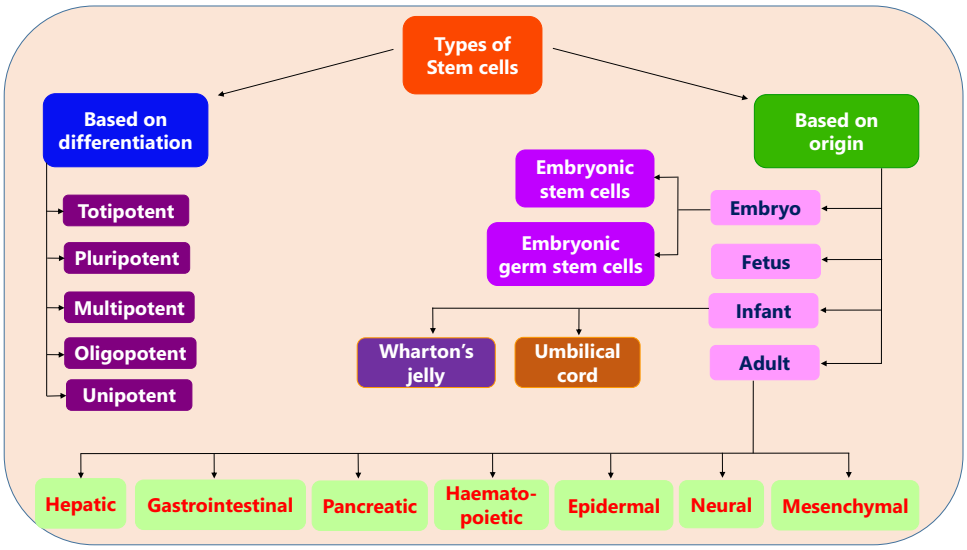

Fig. (1). Classification of stem cells. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

accelerated path to the clinic, provided that safety, as well as pharmacokinetic studies, is already established [8]. Currently, pharmacological therapies and surgery are unable to fix the problem effectively. Treatment by restoring DAergic neurotransmitters in individuals with PD using DAergic neurons and cell transplantation is being investigated, which has been made possible by the discovery of cell replacement therapy [9]. The concept behind clinical trials of cell therapy in PD patients is that restoring striatal DAergic transmission with transplanted DAergic neurons would result in clinical improvement, even if the condition is chronic and damages other regions of the brain and neuronal systems [10].

2. PD AS A CANDIDATE FOR STEM CELL THERAPY

The progressive death of neurons in the nervous system is referred to as neurodegeneration. Recent research suggests that neurons lose their regular structures and functions even before their death, implying that simply withholding these neurons from dying is not likely to be a successful treatment technique. As a result, stem cell therapy appears to be the most successful treatment option [11]. In 1979, prenatal rat DAergic neurons were transplanted to ameliorate motor impairments in a PD model of rats with good graft survival and axonal outgrowth. This study proved that cell therapy could restore deficiencies caused by minor brain tissue damage [12]—a procedure for converting Bone marrow-derived MSC (BM-MSCs) into Neurotrophic factors-secreting cells (NTFSCs) that release Brain-derived neurotrophic factors (BNDF) and Glial cell line-derived neurotrophic factors (GDNF) has been established. In a PD cellular model, the NTF-SC conditioned medium provides significant protection, and grafting of the NTF-SCs into a rat model after impairment led to the relocation of the transplanted cells to the affected site and restoration of the impaired DAergic nerve terminal system in the striatum [13].

3. TYPES OF STEM CELLS

The classification of stem cells based on their differentiation and origin is shown in Fig. (**1**).

4. DIFFERENT TYPES OF MSCS

MSCs derived from different sources were found to have certain similarities, such as identical surface markers and some differences. Hence it is crucial to collate these similarities and differences to determine which one is best suited for cell therapy. Furthermore, for stemness-related genes, BM-MSCs and Adipose tissue-derived MSC (AD-MSCs) had a remarkably similar transcriptional profile. Surface antigen expression, differentiation ability, and immunosuppressive activity were identical in Umbilical cord-derived stem cells (UC-MSCs), BM-MSCs, and AD-MSCs, but UC-MSCs exhibited a higher proliferation rate than the others and the lowest expression of senescence markers. AD-MSCs, on the other hand, had the shortest culture time and the lowest proliferation rate. Other studies have found that ADMSCs had a more substantial proliferation potential than BM-MSCs and a higher expression of neural markers in differentiated AD-MSCs. The secretion levels of certain factors like Vascular endothelial growth factors (VEGF), Transforming growth factors-β 1 (TGFβ1) were considerably higher in BM-MSCs than those of AD-MSCs.

Furthermore, UCMSCs had a higher rate of proliferation than Dental pulp-derived MSC (DP-MSCs), while DP-MSCs had a lower incidence of apoptosis and senescence, and their cell shape was maintained following subculture. Furthermore, compared with BM-MSCs, DP-MSCs and stem cells derived from human exfoliated deciduous teeth (SHEDs) demonstrated a better differentiating capability for neurogenesis [14]. Human endometrium-derived stem cells (hEDSCs) are a new source of cell therapy in PD treatment. They seem to be widely available and collected by a simple, safe, and painless method like Pap smears. After being injected into the striatum, the cells can implant into the striatum of (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) MPTP-exposed monkeys, relocate to the substantia nigra, and autonomously develop into DAergic neuron-like cells [15]. The sources and functions of MSCs are depicted in Fig. (**2**).

4.1. Bone-Marrow Derived MSCs

Due to their relative efficiency and safety, the lack of immunological complications with autografts, and the

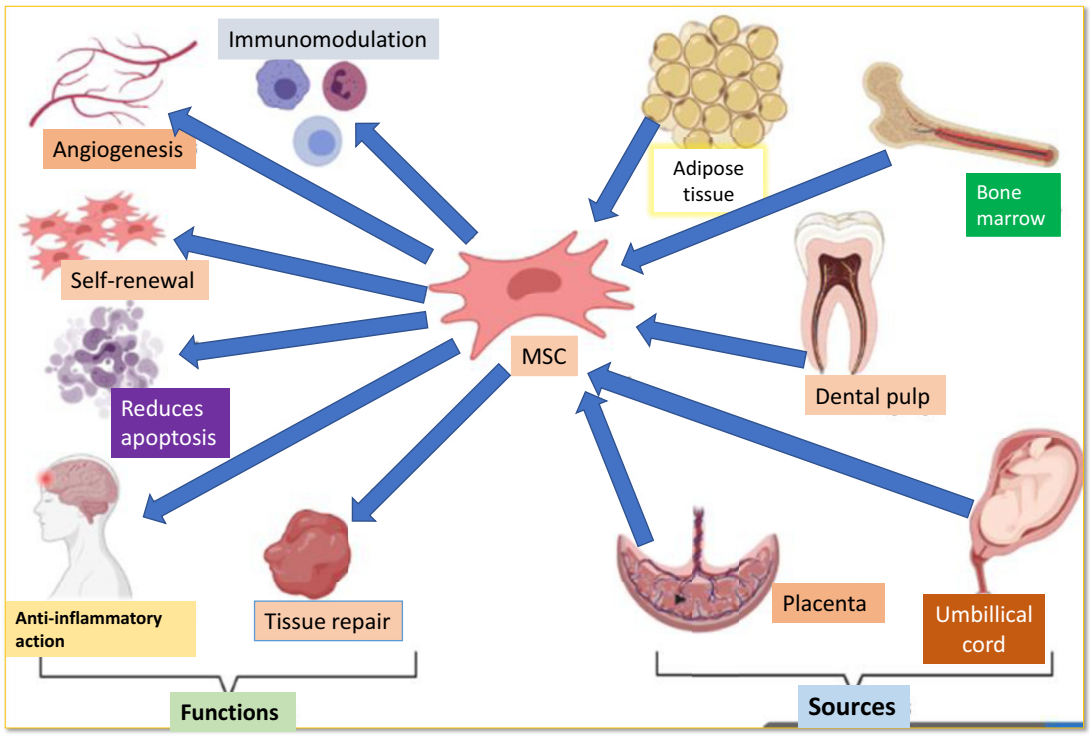

Fig. (2). Sources and functions of MSC. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

absence of religious and legal obstacles, adult bone marrow-derived cells, especially MSC (BM-MSCs), have gained enormous interest in PD research. Due to the tissue-repair capabilities and "homing" ability of these cells to the damaged site, studies have highlighted the transplantation of BM-MSC as a viable method for treating neurological diseases [16]. BM-MSCs are the most well-studied of the various types of MSCs. *In vitro*, BMSCs can be cultured as plastic adherent cells from bone marrow samples. The main advantage of BM-MSCs is that they are widely obtainable through aspiration of the patient's bone marrow, so they can be used for both auto- and allotransplantation without raising ethical concerns. The ability of BM-MSCs to release cytotrophic mediators, including Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and NGF-3; neurturin and Glial-derived neurotrophic factor (GDNF) is well recognized. Neurogenesis, neuroprotection, neuronal survival, and differentiation are all dependent on these neurotrophic substances [17].

BMMSC were shown to have positive benefits on PD patients and exhibited differentiation into DAergic neurons, with a detectable amount of Dopamine in the differentiated cells' culture media. Furthermore, three months after transplanting, PD rat models showed considerable per cent improvement. This demonstrates that BM-MSC can differentiate into DAergic precursors and offer many of their features, resulting in behavioural improvements in the hemiparkinsonian rat after transplantation in an animal model. Trzaska *et al.* [18] confirmed these findings, demonstrating that adult MSC has DAergic characteristics [19]. Lately, a clinical trial in advanced PD patients involving unilateral transplantation of autologous BM-MSC into the sublateral ventricular zone demonstrated significant clinical improvement with no side effects like tumour formation at 12 months [20].

4.2. Dental Tissue-Derived MSC

Many biological features of dental pulp stem cells (DPSC) are similar to those of MSC, such as bone marrow MSC (BM-MSC), adipose tissue-derived stem cells (ADSC), and umbilical cord MSCs (UCMSC); however, there are some differences in their proliferative capacity, differentiation, immunomodulatory effect, secretome characteristics, and secretory capacity [21]. DPSC are stem cells derived from ectoderm that emerge from migrating neural crest cells and have a high degree of plasticity [22]. DPSC release several substances that are important for neuronal survival, proliferation, and differentiation. Dental pulp conditioned medium (DPCM) included various neurotrophic factors, including neurotrophin-3 (NT-3) and nerve growth factor (NGF), which led to neuroprotective action against neurodegenerative disorders. The use of DPSC may be beneficial to people with PD. Exosomes generated by DPSC protect midbrain neurons against 6-hydroxydopamine (6OHDA) induced apoptosis, while neurotrophic factors including NGF and GDNF protect midbrain neurons from 6-OHDA *in vitro* [23].

DPSCs were transplanted intrathecally into the MPTP-induced old-age mouse model of PD, which favored behavioral recovery, repaired DAergic functions, and lessened MPTP-induced damage by minimizing the release of pro-inflammatory factors such as IL-1α, IL-1β, IL6, IL8, and tumor necrosis factor TNF-α and increased expression of anti-inflammatory factors like TNF-β, IL2, and IL4. In an *in vitro* model of PD, DPSC displayed neuro-immunomodulatory action by minimizing MPTP-induced impairments associated with Reactive oxygen species (ROS), DNA damage, and nitric oxide release [24].In Parkinsonian mice, the therapeutic efficacy of SHED was investigated. According to the researchers, SHED possessed DAergic differentia-

tion capacities, and SHED transplantation into the striatum of Parkinsonian rats reduced their behavioral abnormalities. When compared to SHED, DPSC have better neuronal plasticity toward DAergic neurons [25].

4.3. Adipose Tissue-Derived MSC

Adipose-derived stem cells were identified as MSCs in adipose tissue for the first time in 2001, and adipose tissue has been studied as a cell source for tissue engineering and in regenerative medicine since then [26]. They have a surface antigen marker profile and differentiation capacity similar to BM-MSC, in addition to being more heterogeneous [27]. ADMSC have a comprehensive immune regulatory function, making them ideal candidates for cellular treatment [28]. They can be cultured *ex vivo* in a short amount of time, but their 'stemness,' which is defined by their ability to proliferate and differentiate, declines over time [29]. They discovered that ADMSC have properties similar to those of BM-MSCs. Similar to BMSC, adipose tissue contains stem cells [30]. Even though ADMSC and BMMSC are pretty comparable, it has been noted that ADMSC is not entirely identical to BMMSC [31].

4.4. Umbilical Cord-Derived MSCs

The UC of a human being is a potential source of MSC. UC-MSC have demonstrated the ability to differentiate into three germ layers, aggregate in damaged tissue or inflammatory sites, stimulate tissue repair, and influence immune response, in addition to their obvious benefits, such as a painless collecting technique and rapid self-renewal [32]. Fast cell multiplication and high proliferative fitness at UC-MSC harvesting allow for the preparation of larger batches that can be stored for future administration [33]. UC-MSCs are less immunogenic and have a more decisive immunosuppressive action [34].

The umbilical cord and adipose tissues offer significant advantages over BM-MSC. The umbilical cord is derived from postnatal tissue discarded after delivery, making cell collection for donors less invasive. Adipose tissue, which may be retrieved readily through liposuction, has a substantial number of MSC. Because of their potential to differentiate into other cell types and proliferate, UC-MSC and AD-MSC are viable sources for cell-based therapies [35].

4.5. Placenta Derived MSC

The placenta is a stable and abundant source of fetal MSCs. These cells have the potential to differentiate into several cell types and possess immunological features [36]. Placenta-derived MSC (P-MSC) is a homogenous group of cells with strong homing and cellular lineage priming capabilities, as well as a high proliferation rate [37]. Amniotic fluid-derived MSC (AF-MSC) is a type of P-MSCs. Second-trimester amniotic fluid (AF) has been identified as a novel and rich source of foetal MSC that can be used in clinical applications [38]. In terms of developmental phases, AF-MSC is beneficial, but the invasiveness of the collecting procedures—amniocentesis and fetal infections—are problematic [39]. Because of their differentiation potential, *in vitro* culture aspects, absence of tumorigenic potential, and ethical problems, AF-MSC has a lot of potential for clinical applications [40].

The applications of MSC obtained from different sources are listed in Table **1**.

5. ROLE OF MSC IN THE TREATMENT OF PD

MSC are multipotent progenitor cells that have already been extensively used to treat bone diseases, autoimmune and inflammatory disorders, spinal cord injuries, severe pneumonia, myocardial infarction, allotransplant rejection, extensive burns, degenerative conditions, and severe chronic wounds [75]. MSCs can be differentiated into dopamine neurons, which would assist in the functional recovery of the lost neurons in people with PD. MSC participate in tissue repair and regeneration by activating various mechanisms once they have been mobilized to the damaged site. In several studies, pleiotropic effects of MSC have been revealed, offering them considerable therapeutic potential [76].

MSC can self-renewal and differentiate into various mesenchymal cells like adipocytes, tenocytes, osteoblasts, skeletal myocytes, chondrocytes, and visceral mesoderm cells. Furthermore, several investigations have revealed that MSCs can develop into neuron-like cells of ectodermal and endodermal origin, hepatocytes, and cardiomyocytes, in addition to the mesodermal lineage [77].

- Because of their broad availability in the body, proliferative capacity, and immunomodulatory characteristics, MSC has gained enormous attention from researchers interested in PD. MSC have various pathways that are responsible for their therapeutic potential. Protective neurotrophic factors, growth factors such as vascular endothelial growth factors (VEGF), insulin-like growth factor 1 (IGF-1), hepatocyte growth factors (HGF), brain-derived neurotrophic factors (BNDF), transforming growth factors-β (TGF-β), beta-nerve growth factors (β-NGF), glial cell-derived neurotrophic factors and fibroblast growth factor 2 (FGF-2), anti-apoptotic factors, and cytokines are secreted by MSCs at the injured site. MSCs could aid repair in this way by producing anti-inflammatory cytokines like interleukin (IL)-10 and TGF-β39, as well as inhibiting pro-inflammatory cytokines like tumour necrosis factor-α, interferon-gamma (IFN- γ), and IL-1 β, found in PD patient's brain.
- Through their paracrine signalling and multipotency, MSC also regulates hematopoiesis and facilitates tissue regeneration.
- MSC can differentiate into a neural lineage, which includes DAergic neuron precursors.
- Because of the crucial role of damaged mitochondria in the neurodegeneration of DAergic neurons, recent studies demonstrating that MSC can transport mitochondria to the injured site indicate another potential mechanism that could prove to be advantageous in PD therapy.
- There is no risk of neoplastic transformation with MSC therapy, and it is safe [78].
- Autophagic dysfunction due to lack of autophagolysosome generation may be linked to DAergic cell death in PD models treated with neurotoxin. However, MSC therapy enhanced autophagolysosome production and suppressed α-syn expression, possibly increasing DAergic neuron survival against environmental neurotoxins [79].

Table 1. Different sources of MSC and their applications.

Source	Differential Potential	Clinical Applications	References
Bone marrow	[1] Adipose cells [2] Embryonic tissue [3] Astrocytic glial cells [4] Cardiac muscle cells [5] Osteoblasts [6] Cartilage cells [7] Hepatocytes [8] Stromal cells [9] Myocytes [10] Neural cells [11] Mesangial cells	➢ Therapeutic potential against PD pathophysiology *via* multi-mechanistic actions. ➢ Chronic ischemic stroke ➢ Spinal cord injury ➢ Diabetes mellitus type 1 ➢ Cirrhosis in rats ➢ Treatment of the radiation-induced gastrointestinal syndrome ➢ Hematological malignancy ➢ Organ repair ➢ Regeneration of tissue-engineered urinary bladder and prevention of fibrosis ➢ Treatment of intrauterine adhesions in a rat	[41-49]
Adipose tissue	➢ Adipose cells ➢ Bone cells ➢ Cartilage cells ➢ Muscle cells	➢ Repopulate cardiac muscles after a heart attack ➢ Myocardium restoration ➢ Bone regeneration ➢ Nerve system rebuilding ➢ Skin reconstruction ➢ Cartilage repair ➢ Liver reconstruction ➢ Enhance radiotherapy effects on hepatocellular carcinoma. ➢ Osteoarthritis ➢ Promotes wound healing ➢ Stroke	[50-56]
Dental pulp	➢ Odontoblasts ➢ Osteoblasts ➢ Adipocytes ➢ Chondrocytes ➢ Neurogenic cells ➢ Myogenic cells	➢ Irreversible pulpitis ➢ Treat alveolar bone defects in human ➢ Regenerate periodontal tissues and bone damage ➢ Formation of blood vessels in the myogenic lineage ➢ Genetic disorders ➢ Endodontic regeneration	[57-62]
Amniotic fluid and placenta	AF-MSCs: ➢ Neural stem cells ➢ Adipocytes ➢ Osteoblasts ➢ Chondrocytes ➢ Hepatocytes P-MSCs: ➢ Pancreatic cells	AF-MSCs: ➢ Spinal cord injuries and demyelinating diseases ➢ Neuronal regenerative therapy ➢ Cancer treatment ➢ Improve ovarian function by resisting DNA damage ➢ Hyperoxic lung injury ➢ Ischemic heart injury ➢ Tubular necrosis of kidney and acute bladder injury P-MSCs: ➢ Cardiac diseases, ulcers, bone repair ➢ Autoimmune disorders ➢ Bronchopulmonary dysplasia	[63-69]
Birth derived tissue	UC-MSCs: ➢ Adipocytes ➢ Chondrocytes WJ-MSCs: ➢ DAergic neurons ➢ Chondrocytes	UC-MSCs: ➢ Musculoskeletal diseases ➢ Spinal cord injury ➢ APP and presenilin (PS1) double-transgenic mice ➢ Improve anticancer effects ➢ Cartilage regenration WJ-MSCs: ➢ Kidney injury, lung injury, orthopedic injury, and cancer therapy ➢ Wound healing and hair growth	[44, 56, 70-74]

Abbreviations: AF-MSCs = Amniotic fluid-derived MSCs, WJ-MSCs = Wharton's jelly derived MS.

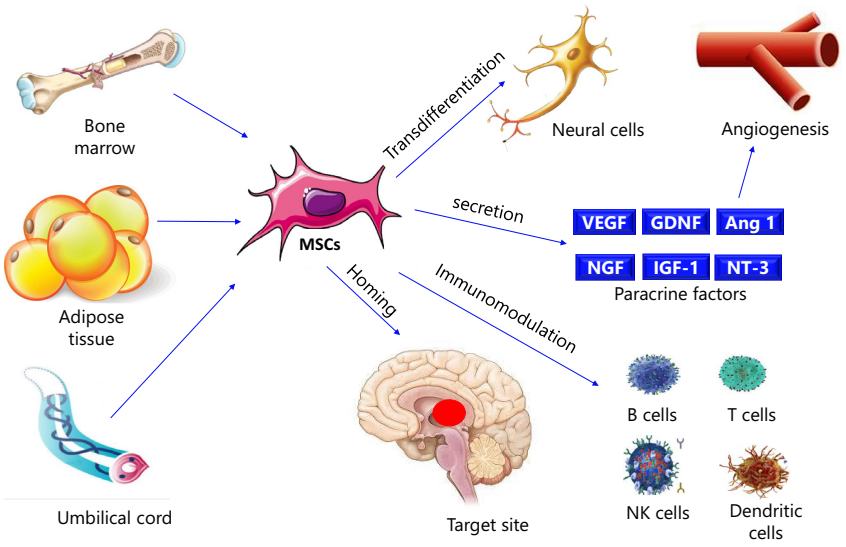

Fig. (3). Mechanisms of MSC in PD. VEGF: Vascular endothelial growth factor; GDNF: Glial cell line-derived neurotrophic factor; Ang 1: Angiopoietin 1; NGF: Nerve growth factor; IGF-1: Insulin-like growth factor 1; NT-3: Neurotrophin-3; NK cells: Natural killer cells. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

According to studies, the immune system can identify and destroy abnormally accumulated α-synuclein in the brain of PD patients as an antigen. Multiple inflammatory cytokines are increased in the patients. MSC's role in cell migration and immunological modulation would become highly significant in treating various disorders. Under certain culture conditions, MSC can also develop into neuron-like cells. Motor function was greatly improved, and trabecular meshwork MSC could differentiate into DAergic neurons, according to the findings [80]. Fig. (**3**) shows the mechanisms of MSC in PD.

6. DOSAGE AND TIMING OF MSC TREATMENT

MSC treatment dose and timing are issues that need to be resolved and confirmed for translational applications. Dosing for a particular disease entity may be determined by the potency and efficacy of the MSC preparation, as well as the disease's condition and phenotype. A single dose of MSC was employed in the *in vivo* asthma experiment, and it had a significant influence on the murine model of both acute and chronic illness. This holds for the other *in vivo* models as well. In clinical trials, multiple infusions were required to assist or cause clinical improvement using MSCs in Crohn's disease, osteogenesis imperfecta, and acute steroid-refractory graft versus host disease (GvHD) [81].

7. ROUTES OF ADMINISTRATION

The following procedures are included in mesenchymal stem cell transplantation: (a) stereotaxic injection, (b) intravenous injection, (c) subsequent intranasal injection [82].

8. INDUCTION AND TRANSPLANTATION OF DAERGIC NEURONS

MSC can be extracted from various embryonic and adult organs, including bone marrow and adipose tissue. BM-MSC has the potential to develop into a variety of cell types. The quantity of colony-forming unit of fibroblast (CFU-F) is measured to estimate the extent of proliferation of the mesenchymal stem cell [83].

8.1. Induction

It was reported that BM-MSC might be used to precisely generate dopamine neurons. This technique forms postmitotic functioning neuronal cells with high efficiency while avoiding glial cell contamination. The developed neuronal cells are then converted into dopamine neurons. The insertion of the Notch1 intracellular domain (NICD) causes the induction. After cytokine stimulation (basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), and forskolin (FSK), MSC becomes like neural progenitor cells (NPCs), displaying NPC markers. GDNF causes neurons to develop into dopamine neurons tyrosine hydroxylase (TH), which are beneficial in the PD model [84].

8.2. Transplantation

Induced dopamine neurons were transplanted into the striatum of a PD model rat from either rodent or human BM-MSC. The synthesis of dopamine in the transplanted brains was demonstrated in brain slice culture experiments. MSC promoted neurogenesis (progenitor cells), decreased inflammation, gliosis, and death signals, and elevated neuronal plasticity (neurorescue) with more remarkable cell survival (and an elevated striatal dopamine level). There was no evidence of tumour formation in the brain, indicating that DAergic neurons produced from BM-MSC cannot form tumors [85].

9. POSSIBLE MECHANISMS INVOLVED IN MSC-EVOKED REPAIR OF DAERGIC NEURONS

Multivariate mechanisms are involved in a successful MSC therapy. Exogenous and endogenous factors work together in a variety of ways to assist recovery. The external factors are fundamental to stem cells (SCs) and through

which the injected cells alter the underlying microenvironment and even integrate into the host neuronal networks. The endogenous factors are associated with the host's response to the introduction of SCs and the impact this has on SC behavior and survival [86].

MSC has two main effects: a trophic effect mediated by the numerous types of trophic factors and cytokines secreted by MSCs, and differentiation to form a wide range of cells to restore lost cells. They can inhibit the growth and activation of immune system cells. These interactions can occur either directly (*i.e.*, cell-cell interaction) or indirectly (*via* soluble factors) [87]. MSC can regulate the immune system by being engulfed by antigen-presenting cells. According to a recent study, the consequent display of MSC antigens by antigen-presenting cells (APCs) leads to a series of anti-inflammatory actions, thus enhancing the therapeutic process outcome [88].

9.1. Trans-differentiation and Fusion

The underlying mechanisms remain unclear, even though functional recovery after MSC transplantation has been found in various animal models of neurodegenerative disorder. MSC obtained from multiple tissues are incredibly adaptable, and under different culture conditions, they can adopt the morphological and phenotypic traits of neuronal cells. Co-culture with glial, neuronal, and neuronal stem cells, as well as astrocyte or neuronal conditioned media, can improve MSC's ability to differentiate into neurons. Overexpression of genes including Noggin, brain-derived neurotrophic factor (BDNF), and Notch intracellular domain (NICD), which are essential for neural development and function, can also accelerate MSC neural transdifferentiation. Similarly, diverse techniques based on chemical induction, gene transfection, co-culturing, and conditioned media can be used to convert MSC into DAergic neurons [89].

9.2. Secretion of Paracrine Factors

MSC have been found to secrete a variety of growth factors and cytokines, including BDNF, nerve growth factor (NGF), glial-cell-line-derived neurotrophic factor (GDNF), fibroblast growth factor 2 and 8 (FGF2 and FGF8), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), ciliary neurotrophic factor (CNTF), and stromal cell-derived factor-1(SDF-1). GDNF, BDNF, basic fibroblast growth factor (bFGF), and CNTF, among other growth factors produced by MSC, have neurotrophic and neuroprotective effects on DAergic neurons. Thus, growth factors released by transplanted MSC and activated host cells are likely to be involved in MSC's therapeutic benefits in many animal PD models [81].

9.3. Interaction with Host Cells

Transplanted MSC has been shown to influence endogenous neural stem cells (NSC), glial cells, and blood vessels *via* the release of paracrine factors, which aids in neuronal tissue repair and functional recovery, in addition to their effects on host DAergic neurons. Endogenous neuronal stem cells were induced to proliferate, migrate, and differentiate when human MSC was transplanted into the mouse hippocampus. Recent studies have also shown that transplantation of the intrahippocampal and intracerebroventricular MSC promotes neurogenesis. MSC' ability to enhance endothelial cell proliferation and angiogenesis is a crucial characteristic of their regenerative activities. Angiogenic factors such as VEGF, FGF, HGF, Stromal cell-derived factor-1 (SDF1), Angiopoietin-1 (Ang-1), Angiopoietin-2 (Ang-2), and matrix metalloproteinase-1 may mediate the MSC action on blood vessels [90].

9.4. Immunomodulation and Anti-inflammatory Effects of MSC

The role of inflammation in the etiology of PD suggests that MSC's immunomodulatory and anti-inflammatory actions may contribute to their therapeutic effects following transplantation in PD animal models. Several lines of evidence imply that MSC plays a dual role in the immune system: suppressing or activating immunological responses. Allogeneic MSC transplantation into a rat model of PD has been shown to elicit a cellular immune response. MSC, on the other hand, can inhibit immune cells such as B lymphocytes, T lymphocytes, dendritic cells, and natural killer (NK) cells [89]. Experimental investigations of ischemic heart disease and autoimmune disorders show that MSCs protect tissue by acting as anti-inflammatory mediators. MSC, on the other hand, can reduce inflammatory responses through a variety of mechanisms. MSC anti-inflammatory effects include a) expression of an Interleukine-1 (IL-1) receptor antagonist, b) release of anti-TNFα, c) secretion of PGE2, which changes macrophages to a phenotype that releases Interleukine-10 (IL-10), and d) expression of stanniocalcin-1, which minimizes ROS [91].

9.5. Homing

The exact mechanisms by which MSCs move and reside within tissues are still unknown. The cells tether and roll against the endothelium in the first step, causing the cells to decelerate in the blood flow. The cells are activated by G-protein-coupled receptors in the second step, which is succeeded by an integrin-mediated, activation-dependent arrest in the third step. Finally, in the fourth step, the cells transmigrate through the endothelium and the underlying basement membrane [92]. Several factors influence the therapeutic efficacy of MSC homing. Culture conditions, passage count, donor age, delivery method, and host receptivity are crucial factors [87].

10. PRECLINICAL STUDIES

Li and colleagues were among the first to investigate MSC's therapeutic benefits in PD models in 2001. PD was induced in adult male mice by giving MPTP hydrochloride for a week (intraperitoneally). Undifferentiated BM-MSC were stereotaxically injected intrastriatal into the mice after this week. The motor behavior of animals was assessed with the help of a rotarod test, a month following transplantation. Their brains were removed for immunohistochemistry examination. MSCs infused intrastriatally survive and improve functional recovery, according to the results [93]. Riecke *et al.* performed a meta-analysis in 2015 that evaluated the impact of MSC treatment on behavioral impairment in PD models. MSC may be explored for clinical studies in the treatment of early-stage PD, according to the results [94].

Table 2. Clinical trials of MSC in PD [97].

Title	Study Type	Study Design	No. of Participants	Route of Administration	Outcome Measures	Clinicaltrials.gov ID
To Study the Safety and Efficacy of Bone Marrow-Derived MSC Transplant in PD	Interventional	Single group assignment	5	Cerebral	Improvement in the clinical condition of the patient assessed using UPDRS (UNIFIED PARKINSON'S DISEASE RATING SCALE) and Time Tests.	NCT00976430
Phase I/II Trial of Autologous Bone Marrow-Derived MSC to Patients With PD.	Interventional	Single group assignment	20	Intravenous	Number of participants who experienced adverse effects	NCT01446614
Autologous Mesenchymal Stem Cell Therapy in Progressive Supranuclear Palsy: a Randomized, Double-blind, Controlled Clinical Trial	Interventional	Randomized	25	Arterial	Incidence of adverse effects	NCT01824121
Pilot Phase I Study of Allogeneic Bone Marrow-Derived **MSC** Therapy for Idiopathic **PD**	Interventional	Non-randomized	20	Intravenous	safety of allogeneic MSC therapy in patients with iPD as indicated by the presence of adverse events that are confirmed to be related to the therapy	NCT02611167
Safety and Efficacy Investigation of Patients With **PD** by Transplantation of Umbilical Cord Derived **MSC**	Interventional	Single group assignment	20	Intravenous	Changes of the Unified Parkinson's Disease Rating Scale (UPDRS)	NCT03550183
A Safety and Efficacy Study of the Effects of **MSC** (MSCs) Differentiated Into Neural **Stem Cells** (NSCs) on the Motor and Non-motor Symptoms in People With **PD** (PD).	Interventional	Randomized	10	Intrathecal and intravenous	Incidence of Treatment-Emergent Adverse Events (TAEAs) as a result of the injection	NCT03684122
Allogeneic Bone Marrow-derived **MSC** as a **Disease**-modifying Therapy for Idiopathic **PD**: Phase IIa Double-blind Randomized Placebo-Controlled Trial	Interventional	Randomized	45	Not defined	Safest number of effective doses of MSC as measured by the Part III of the Movement Disorder Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) scale	NCT04506073

One more study investigated the impact of human umbilical cord-derived MSC (hUC-MSC) on the MPTP-induced PD model. This hUC-MSC was previously stimulated by curcumin, a pigment that possesses anti-apoptotic and anti-inflammatory properties. In comparison to the control group, the supernatant of PC12 cells after hUC-MSC injection contained relatively low levels of NO and proinflammatory cytokines, but more differentiated DAergic neurons. These cells were discovered to represent a possible approach for promoting DAergic neuronal cell multiplication and differentiation [95]. In a PD model, AD-MSC had persistent anti-inflammatory and neurogenic effects, as well as improving cognitive function [96].

11. CLINICAL TRIALS

Dopamine replacement medication (L-DOPA or levodopa) is the primary treatment for PD in humans; however, it has side effects and the drawback that it fails to cease the advancement of DAergic neuronal loss in the substantia nigra. In search of an approach for DAergic neuron regeneration, the positive outcomes achieved from treating experimental PD models with MSC in humans highlighted the potential of adopting this strategy [97]. Clinical trials using MSCs as a therapeutic agent are being carried out due to their low immunogenicity, lack of teratoma risk and ethical issue, and low likelihood of tumorigenicity after transplantation into the human body [98]. However, none are success-

ful. Clinical trials focusing on MSC-mediated therapy for PD, currently set time from diagnosis and age as the primary inclusion criteria. The primary outcome measures for evaluating MSC therapy effectiveness differ in various studies as can be noted from Table **2**, while progress has lately been made in proposing a worldwide agreement of PD51 outcome measures. Furthermore, scales such as the Hoehn and Yahr scale, the Unified PD Rating Scale (UPDRS), and the non-motor symptoms questionnaire (NMS-Quest), *etc.*, are used not only to recruit individuals but also to track their clinical progress [79].

12. LIMITATIONS

Even though MSC transplantation has been a successful therapy for PD treatment, this is primarily owing to their trophic effects that are not long-lasting. Furthermore, intravenous infusion of MSCs at a higher concentration has been documented to produce pulmonary thrombosis [99]. As a result, from the standpoint of cell-based treatment, stereotaxic transplantation of MSC-derived DAergic neurons directly into the striatum of the patients is preferred. Since plasmid incorporation is required for DAergic neuron production utilizing NICD transfection, additional long-term research is required to assure tumour growth and effectiveness of modified MSCs.

MSCs are a diverse group of stem cells since they are frequently obtained from mesenchymal tissues as adherent cells [100]. MSC population might be infected by these adhering cells, especially early in the growth process. Following subcultures, the cells appear to cluster on general MSCs, with other cells being overlooked; however, MSCs are still not a single homogenous cell type. As a result, the concept of MSCs is still unclear, and there is a need to discover a distinct molecular marker that is uniquely expressed by MSCs. Because of all these factors, the differentiation of MSCs into DAergic neurons is still a mystery. MSCs do display trilineage differentiation, although the differentiation ratio is often low, and hence a subgroup of MSCs is believed to be linked to differentiation. The prospect for MSCs to be used to treat PD would be considerably enhanced if the cells accountable for differentiating into DAergic neurons are identified.

Despite the abovementioned limitations, MSC therapy remains a therapeutic reality, because MSCs can be effectively cultivated in the laboratory to obtain the required therapeutic scale and are freely available cells with minimal moral issues. Since they are already routinely employed in clinical conditions such as myocardial infarction and osteoarthritis, MSCs have a proven record in these settings. Moreover, they may be procured readily from patients, marrow banks, as well as through autologous transplantation, which may reduce the risk of rejection.

CONCLUSION AND FUTURE PROSPECTS

PD is a debilitating, degenerative condition for which there is presently no cure. The substantia nigra pars compacta, which characterized pathologically by persistent degeneration of DAergic neurons. PD can be treated in a variety of ways, including medication therapy and surgery. However, there is currently no effective treatment for PD. Through multi-mechanistic techniques, the current study highlighted MSCs' ability to ameliorate PD pathogenesis (immunomodulatory, anti-inflammatory, and anti-apoptotic effects as well as neurotrophic and neurogenic potentials). These encouraging findings pave the path for clinical trials of MSCs in treating neurodegenerative disorders, especially PD. Although these cells have been widely regarded as safe, future research should focus on constant monitoring and long-term follow-up to avoid the chance of tumor growth after MSC therapy. Previous clinical trial data should influence future paths, emphasizing the critical necessity for a systematic approach to finding optimal combinations of circumstances to develop reliable and effective treatment designs for PD.

LIST OF ABBREVIATIONS

6-OHDA	=	6-Hydroxydopamine
AD-MSC	=	Adipose Tissue-derived mesenchymal Stem Cells
AF-MSC	=	Amniotic Fluid-derived Mesenchymal Stem Cells
Ang-1	=	Angiopoietin-1
Ang-2	=	Angiopoietin-2
APCs	=	Antigen-presenting Cells
aSyn	=	Alpha-synuclein
bFGF	=	Basic Fibroblast Growth Factor
BM-MSC	=	Bone Marrow-derived Mesenchymal Stem Cells
BNDF	=	Brain-derived Neurotrophic Factors
CFU-F	=	Colony-forming Unit of Fibroblast
CNTF	=	Ciliary Neurotrophic Factor
DAergic	=	Dopaminergic
DP-MSC	=	Dental Pulp Derived Mesenchymal Stem Cells
DPCM	=	Dental Pulp Conditioned Medium
FGF-2	=	Fibroblast Growth Factor 2
FSK	=	Forskolin
GBA	=	Glucocerebrosidase
GDNF	=	Glial Cell Line-derived Neurotrophic Factors
GvHD	=	Graft Versus Human Disease
hEDSC	=	Human Endometrium-derived Stem Cells
HGF	=	Hepatocyte Growth Factors
IGF-1	=	Insulin-like Growth Factor 1
IL	=	Interleukine
LRRK2	=	Leucine-rich Repeat Kinase 2
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSCs	=	Mesenchymal Stem Cells
NGF	=	Nerve Growth Factor
NICD	=	Notch1 Intracellular Domain

NK cells = Natural Killer Cells

NPCs = Neural Progenitor Cells

NT-3 = Neurotrophin-3

NTFSC = Neurotrophic Factors-secreting Cells

P-MSC = Placenta Derived Mesenchymal Stem Cells

PARK2 = Parkin RBR E3 Ubiquitin-protein Ligase

PARK7 = Parkinson Protein 7

PD = Parkinson's Disease

PDGF = Platelet-derived Growth Factor

PINK1 = Phosphatase and Tensing Homolog-induced Kinase 1

REM = Rapid Eye Movement

ROS = Reactive Oxygen Species

SDF-1 = Stromal Cell-derived Factor-1

SHED = Stem Cells Derived From Human Exfoliated Deciduous Teeth

TGF-β = Transforming Growth Factors-β

TNF = Tumour Necrosis Factor

UC-MSC = Umbilical Cord-derived Stem Cells

VEGF = Vascular Endothelial Growth Factors

VPS35 = Vacuolar Protein Sorting-associated Protein 35

WJ-MSC = Wharton's Jelly Derived Mesenchymal Stem Cells

β-NGF = Beta-nerve Growth Factors

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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