Review Article

Therapeutic Effects of Mesenchymal Stem Cells for Parkinson's Disease

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Abstract

To appreciate the potential applications of stem cell technology in neurodegenerative diseases, including Parkinson's disease (PD), it is important to understand the characteristics of the various types of stem cells. These stem cells include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), embryonic stem (ES) cells, progenitor cells, and induced pluripotent stem cells (iPS). Among them, MSCs have several advantages over other counterparts. They are easily accessible and can be obtained from various tissues such as bone marrow, dental pulp, adipose tissue, amnion, placenta, umbilical cord and cord blood with avoiding ethical problems. Therefore, MSCs is attractive clinically because there are no related ethical and immunological concerns. Functional dopamine (DA) neurons can be efficiently induced from MSCs. Several studies, including our studies, have shown that MSCs can protect and/or stimulate regeneration in host-damaged DA neurons mainly through secretion of trophic factors and cytokines from MSCs. These results demonstrate the potential of MSCs derived from an autologous source for clinical applications for PD, although further studies are required. This review is focused on the potential of MSCs as a therapeutic cell source for PD.

ABBREVIATIONS

PD: Parkinson's Disease; MSCs: Mesenchymal Stem Cells; HSCs: Hematopoietic Stem Cells; ES: Embryonic Stem; iPS: Induced Pluripotent STem cells; DA: Dopamine; L-DOPA: L-dihydroxyphenylalanine; BMSCs: Bone Marrow MSCs; GFAP: Glial Fibrillary Acidic Protein; NICD: Notch1 Intracellular Domain; bFGF: Basic Fibroblast Growth Factor; CNTF: Ciliary Neurotrophic Factor; GDNF: Forskolin and Glial cell-line Derived Neurotrophic Factor; TH: Tyrosine Hydroxylase; DPSCs: Dental Pulp Stem Cells; DPCs: Dental Pulp Cells; SHEDs: Stem Cells from Human Exfoliated Deciduous Teeth; 6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; BDNF: Brain-Derived Neurotrophic Factor; NGF: Nerve Growth Factor; IGF-1: Insulin-like Growth Factor-1; NT-3: Neurotrophin-3

INTRODUCTION

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders. Its pathological characteristics include selective death of mesencephalic nigral dopamine (DA) neurons and the presence of intracytoplasmic inclusions (known as Lewy bodies) in the substantia nigra, which are consistently immunostained with an antibody against α-synuclein [1,2]. Although substitution of L-dihydroxyphenylalanine (L-DOPA or levodopa), a DA replacement therapy, is still considered the gold standard for patients with PD, this cannot delay the progression of loss of DA neurons in the substantia nigra. In addition, motor response oscillations and drug-induced abnormal involuntary movements develop in most patients with PD who receive L-DOPA therapy for more than 5 years [3-5]. On the other hand, an alternative approach for restoration of the damaged DA systems is transplantation of cells that synthesize DA. Allogeneic transplantation of the human fetal mesencephalon has provided proof-of-principle that cell therapy can work in patients with PD [6]. Replacement therapy, which uses the human fetal mesencephalon transplanted into the brain, showed some symptomatic relief [7,8]. However, this strategy using the human fetal mesencephalon involves ethical issues and problems in obtaining adequate numbers of DA neurons [1,9-11].

Stem cells have the capacity to proliferate and differentiate into multiple cellular lineages. There are different classifications of stem cells that reflect the range of possible cell types they can produce and the ways in which the stem cells are derived.

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These stem cells include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), embryonic stem (ES) cells, progenitor cells, and induced pluripotent stem cells (iPS) [10-12]. To appreciate the potential applications of stem cell technology in neurodegenerative diseases, it is important to understand the characteristics of the various available stem cell types and the potential impact of cellular therapies on disease mechanisms. Each stem cell type possesses certain qualities and advantages, and the rationale for utilizing each type depends on the desired applications and outcomes. Briefly, ES cells are undifferentiated pluripotent cells derived from the inner cell mass of blastocyst-stage embryos, which introduced a series of ethical problems in clinical application. To avoid such ethical problems are create histocompatibility, new technologies have enabled tissue cells to become iPS cells [13]. One characteristic of ES and iPS cells is their ability to form teratomas, which, in turn, is a major concern for future clinical application. MSCs are an alternative source of multipotent self-renewing cells. MSCs are derived from various adult and neonatal tissues, such as bone marrow, dental pulp, adipose tissue, amnion, placenta, umbilical cord and cord blood [14,15]. There are several evidences that MSCs can transdifferentiate into epithelial, endothelial, and neural cells [16-25]. Therefore, MSCs provide an accessible alternative to ES cells and potentially circumvent the need for immunosuppression in cellular therapies because they are derived from an autologous source. Unlike ES or iPS cells, MSCs have no ethical problems and have a low risk of forming teratoma, however, they are not completely free from malignancy potentials [13]. For cell transplantation therapy, MSCs have two major beneficial effects for PD: (1) differentiation to generate a broad spectrum of cells for the replacement of lost DA neurons and (2) a trophic effect that is mediated by the various types of trophic factors [26] (Figure 1). This review is focused on the potential of MSCs as a therapeutic cell source for PD.

Therapeutic potential of MSCs replacement therapies for PD

The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposes minimal criteria to define human MSC [27]. First, MSC must be plastic-adherent when maintained in standard culture conditions. Second, MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Third, MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro. MSCs can be retrieved from various adult tissues such as and neonatal tissues, such as bone marrow, dental pulp, adipose tissue, amnion, placenta, umbilical cord, and cord blood [14,15]. MSCs isolated from different tissues are quite versatile and can adopt morphological and phenotypic properties of neuronal cells under various culture conditions. MSCs are characterized by being able to differentiate along several lineages [16-25]. The majority of the protocols for MSCs neuronal induction utilize different combinations of chemicals, growth factors and signal molecules [28-36]. MSCs differentiate into DA neurons can be achieved through different protocols based on chemical induction, gene transfection, co-culturing and use of conditioned medium [21,37-44]. For instance, a system to specifically induce DA neurons from bone marrow MSCs (BMSCs) was reported [21], although undifferentiated BMSCs natively co-express several neuronal and glial markers, such as βIII-tubulin and glial fibrillary acidic protein (GFAP), respectively [45,46]. This system first generates postmitotic functional neuronal cells with a high efficiency without contamination by glial cells. The resulting neuronal cells are then further induced into DA neurons. The induction is achieved by lipofection method of plasmid vector containing a Notch1 intracellular domain (NICD) and G418 selection, followed by an administration of trophic factors such as basic fibroblast growth factor (bFGF), ciliary neurotrophic factor (CNTF), forskolin and glial cell-line derived neurotrophic factor (GDNF) [21,47]. The induced cells express the markers for DA neurons, such as tyrosine hydroxylase (TH), Nurr-1, Lmx1b, En1 and Pax3. In addition, the induced cells released DA into the culture media in response to high K^+ depolarizing stimuli. These findings suggest that functional DA neurons can be efficiently induced from BMSCs [26].
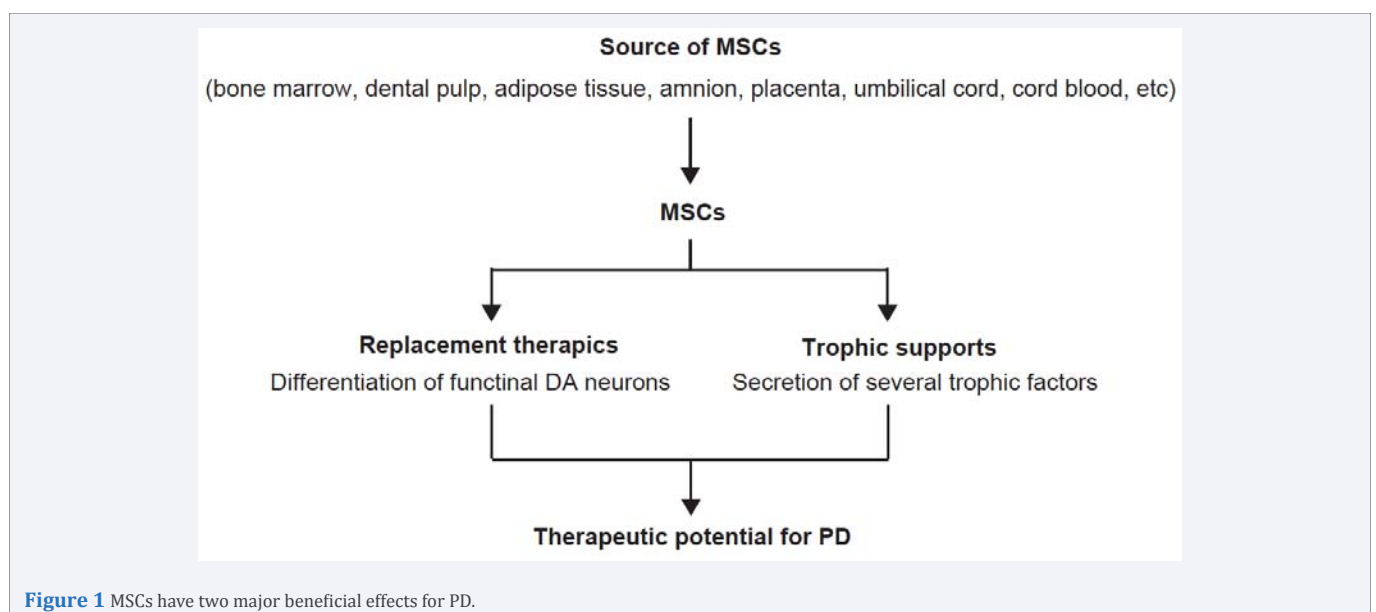

Figure 1 MSCs have two major beneficial effects for PD.

Recently, dental pulp stem cells (DPSCs) attract attention in the field of regenerative medicine. Dental pulp cells (DPCs) are obtained easily from adult teeth discard as medical waste and contain abundant DPSCs. Human adult DPSCs and stem cells from human exfoliated deciduous teeth (SHEDs) are self-renewing MSCs residing within the perivascular niche of the dental pulp [48,49]. They are thought to originate from the cranial neuronal crest, which expresses early markers for MSCs and neuroectodermal stem cells. Like BMSCs, DPSCs constitutively express neuronal and glial phenotypic markers even in an undifferentiated state. On exposure to embryonic midbrain cues (sonic hedgehog, bFGF and FGF8), DPSCs expressed mature neuronal markers and domapinergic neuronal markers, such as TH, En1, Nurr1, and Pix3, respectively [50]. In addition, induced DPSCs secreted DA constitutively and upon stimulation with potassium chloride and ATP [50]. Therefore, these findings indicate that MSCs, such as BMSCs and DPSCs, in the presence of embryonic midbrain cues show efficient propensity towards functional DA neurons in vitro condition.

In vivo condition, BMSCs have been proposed as potential cell sources for transplantation in PD since several studies in PD models have verified that BMSCs possess the capacity to protect and regenerate damaged DA neurons [16,51-60]. The PD models can be divided into those using environmental or synthetic neurotoxins and those using the in vivo expression of PD-related mutations discovered in human patients. In general, these neurotoxins, such as rotenone, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), are used to create PD models using rodents and non-human primates in the field of regenerative medicine. It has been reported that naïve murine BMSCs can differentiate into TH+ neurons and improve motor performance in MPTP-induced PD models [16]. In addition, BMSCs grafted into the striatum [51,54], intravenously [58], or intranasally [55] delivered BMSCs have a protective effect in 6-OHDA-induced PD models. Further, induced DA neurons from either rodent or human BMSCs were shown to exert neuroprotective effects against dopaminergic degeneration and to improve motor function in 6-OHDA-induced PD models [21]. Brain slice culture experiments demonstrated the production of DA in the grafted brains. Interestingly, no tumor formation was observed in the brain [21]. In general, unlike ES or iPS cells, BMSCs isolated from adult BM have a low risk forming tetatoma [13]. In addition, induced DA neurons from BMSCs that were differentiated using an optimized protocol had the potential to both regulate the risk of tumorigenesis and improve parkinsonian motor dysfunction [21]. Although no adverse effects have been reported, their long-term effect on tumorigenicity needs to be considered.

MSCs isolated from adipose tissue and umbilical cord have shown beneficial effects in PD models as well [61,62]. On the other hand, to date, DPSCs rescue dopaminergic neurons from 6-OHDA-induced apoptosis in vitro [63]. In addition, Engrafted SHEDs-derived cells having dopaminergic properties survived in the striatum of PD models, improved the DA level more efficiently than engrafted undifferentiated SHEDs, and promoted the recovery from neurological deficits [64].

Functional recovery following MSCs transplantation has been shown in several PD models. However, the underlying mechanisms are largely unknown. In summary, it is unlikely that either transdifferentiation of MSCs or MSCs replacement instead of damaged DA neurons is a major factor contributing to MSCs-induced functional recovery [65,66]. As above, MSCs can differentiate into neural phenotypes in vitro [16,18,19,21]. Cell fusion has recently been found to occur when BMSC are transplanted into various types of organs, including the brain [67]. Rather, several studies suggest that neuroprotective and restorative effects of MSCs in PD models are achieved mainly through secretion of trophic factors and cytokines, as described in the next section [65,66].

Therapeutic potential of MSCs trophic support

Previous studies showed that MSCs released trophic factors [21,66-72]. Previous studies also showed that a significant increase in the 6-OHDA-lesioned striatum of the MSCs-transplanted group compared with vehicle-treated control group [73,74]. A number of trophic factors have a protective effect on DA neurons in vitro and in vivo [69,75,76]. Briefly, GDNF, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), insulin-like growth factor-1 (IGF-1), neurotrophin-3 (NT-3), and bFGF have been reported to act on DA neurons in vitro and in vivo, making them potential therapeutic catalysts for PD. For instance, in animal models of PD, intraventricular injection of GDNF induces a long-term increase in the striatal DA content [77], although clinical trials using intraventricular injections of GDNF did not improve functional deficits in patients with PD and nigrostriatal function was not augmented [78]. Thus, intraventricular GDNF in humans appears to be the wrong method [79]. Therefore, Cell transplantation therapy is an alternative technique for providing trophic factors to DA neurons of the nigrostriatal pathway [80].

In addition, trophic factors, such as BDNF, GDNF, NGF, NT-3 and CNTF stimulate DA neuronal regeneration [81-85]. Therefore, it is presumable that trophic factors secreted from grafted MSCs and stimulated host cells are implicated in the therapeutic effects of MSCs in PD models [65]. However, the concept of cell differentiation and neurogenesis in the midbrain region still remains a controversial topic because conflicting findings have been obtained in previous studies [86-90]. Briefly, Zhao *et al.* suggest that DA neurons, the cell type lost in Parkinson's disease, are continuously generated in the adult substantia nigra pars compacta [91]. Using similar methodological procedures to label dividing cells, Frielingsdorf *et al.* showed that no evidence of new DA neurons in the substantia nigra, either in normal or 6-OHDA-lesioned hemi-Parkinsonian rodents, or even after growth factor treatment [88]. Therefore, we assume that transplantation of MSCs promote endogenous brain repair mechanisms, although there was no obvious evidence that progenitor cells in the substantia nigra can differentiate into DA neurons in the in vivo condition at present. Further studies are also needed to resolve the detailed mechanism of endogenous brain repair by stem cell transplantation.

Other protective effects of MSCs

The pathological characteristics of PD include selective death of mesencephalic nigral DA neurons and the presence of Lewy bodies in the substantia nigra [1,2]. We have reported that chronic

oral administration of rotenone caused specific nigrostriatal DA neurodegeneration in C57BL/6 mice [92,93]. Chronic exposure of rotenone produced some TH⁺ neurons, which induced a high level of cytoplasmic α-synuclein immunoreactivity in the substantia nigra [92,93]. Genetic studies led to the discovery of a small percentage of familial PD cases linked directly to genetic mutations, as well as gene duplications and triplications. The first gene associated with PD was α-synuclein (PARK1) [94]. Furthermore, duplication and triplications of α-synuclein are linked to an early onset familial PD (PARK4) [95]. These genetic studies suggest that excess increase of α-synuclein protein levels may represent a gain of toxic function. In our previous study, α-synuclein⁺/TH⁺ cells in the substantia nigra decreased on MSCs injection into the tail vein [66] (Figure 2). Although the exact mechanism remain unclear, neuroprotective effects of stem cells could involve a reduction in intracellular α-synuclein. The results suggest that MSCs transplantation may be a useful therapy for patients with PD as well as for those with other α-synucleinopathies such as multiple system atrophy and dementia with Lewy bodies.

Neuroinflammation has been described as an important participant in several neurodegenerative diseases including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis, and multiple system atrophy (MSA) [96,97]. McGeer *et al.* reported the presence of activated microglia and inflammatory macrophages as well as proinflammatory cytokines in SN postmorten samples from PD patients [98]. Activated microglia are also present in patients with early PD and they are correlated with the degree of DA neuronal loss [99]. Evidence supporting the inflammatory hypothesis of neurodegeneration comes from studies showing the expression of a bunch of inflammatory markers within the brain including specific proteins, pro-inflammatory cytokines

Figure 2 Intracellular expression of α-syn in TH⁺ neurons in the SNpc. Midbrain slices were immunostained with antibodies against α-syn and TH and the analyzed by laser scanning confocal microscopy. White arrowheads indicate α-syn⁺ and TH⁺ neurons. Semiquantitative analysis of α-syn⁺ / TH⁺ neurons in the SNpc. Each value is expressed as the mean SEM based on the number of TH⁺ neurons (n = 4-6 in each group).

** *P* < 0.01 vs. control mice; †† *P* < 0.01 vs. rotenone-treated mice. α-syn, α-synuclein; TH, tyrosine hydroxylase.

and markers of active glial cells [100]. Degenerative DA neurons caused by LPS or MPTP can be prevented by treatment of anti-inflammatry drugs sush as aspirin, dexamethasone, and the selective COX-2 inhibitor rofecoxib [65]. Several lines of evidence also indicated that anti-inflammatory responses by other clinical medicines such as simvastation, minocyclin, and memantine induced to reduce the inflammatory process and neuronal death by LPS [100-102]. Therefore, the involvement of inflammation and oxidative stress in PD pathophysiology suggests that anti-inflammatory and anti-oxidative stress effects of MSCs partially underlie their benefical effects. MSCs migrate to sites of inflammation and injured tissue. At these locations, MSCs repair the damaged region under conditions of inflammation and oxidative stress, by paracrine mechanisms where they stimulate endogenous stem cells and/or modulate the functions of immune cells, such as monocytes, macrophages, dendritic cells (DCs), and T and B cells as well as natural killer cells (NK). Although the exact mechanism of MSCs-mediated immunoregulation is not understood, the anti-inflammatory role of MSCs has been demonstrated in vitro and in vivo PD models [103]. Along with differentiational potency and trophic effects, the anti-inflammatory properties of MSCs could have therapeutic implications in the treatment of PD.

Clinical perspective

Although tremendous advancements have been made from preclinical (animal) studies using MSCs, substantial challenges are still to be overcome before MSC therapy can fulfill its promise in clinical applications for PD [104]. During clinical application of MSCs, the culture conditions must be tested and quality controls must be adapted. Although it is likely that multiple sources of MSCs will be used clinically in the future, the release criteria of the cell batch must be strict and must take into account the effectiveness of cellular product and the safety of the patient. Clinical application of MSCs requires a large number of cells for transplantation in accordance with Good Manufacturing Practice (GMP). To maximize the success of cellular replacement therapies for PD, there also are critical issues that involve biological, technical and surgical challenges such as: (1) anatomical location for cell administration; (2) Patient identification likely to respond to cellular replacement therapy; (3) Parameters for cell preparation and delivery to obtain optimal graft survival, including the optimal volume, dosage and format of cells; (4) Mechanisms for limiting host immunological responses to donor cells; (5) The optimimization of graft function, prevention of graft effects. Additional basic and preclinical research will provide a fuller understanding as to how to best apply MSCs to improve the symptom of PD. Such studies will greatly inform key points such as above-mentioned issues.

CONCLUSION

MSCs have several disadvantages relative to ES cells and iPS cells, such as insufficient numbers of stem cells, reduced proliferation and differentiation capacity with age in vitro and after stem cell transplantation in vivo [105,106]. However, MSCs can be obtained from patients with PD (for autologous transplantation) as well as from healthy donors (for allogeneic transplantation). MSCs are not burdened with the ethical issues associated with ES cells. Due to the focused loss of DA neurons,
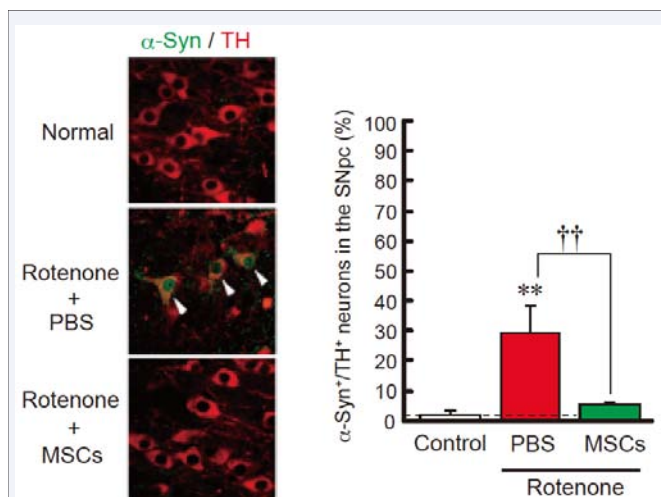
PD is particularly suitable for cell transplantation therapy. MSCs can be retrieved from various adult tissues. Functional DA neurons can be efficiently induced from MSCs. Several studies, including our studies, have shown that MSCs can protect and/ or stimulate regeneration in host-damaged DA neurons mainly through secretion of trophic factors and cytokines from MSCs. These results demonstrate the potential of MSCs derived from an autologous source for clinical applications for PD, although further studies are required.

ACKNOWLEDGEMENTS

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