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Stem-cell Therapy for Parkinson's Disease

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Abstract

Parkinson's disease (PD) is one of the most common aging-related neurodegenerative disorders and is characterized by the loss of dopaminergic neurons in the substantia nigra. However, few effective therapies exist, in part due to the complexity of the central nervous system. Because the loss of dopaminergic neurons is a hallmark of PD, stem cells may have therapeutic potential in PD due to their regenerative and substitution properties. Transplanted stem cells can migrate and generate new neurons and glial cells in disease lesions in vivo. Engrafted stem cells and explants can also produce and secrete neuroprotective molecules, such as neurotrophic factors, to improve neuron survival. Therefore, stem cells have powerful therapeutic potential to regenerated opaminergic neurons in PD patients. In this minireview, we discuss the therapeutic utility of stem cell types in PD.

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List of Abbreviations

PD : Parkinson's disease, LRRK2 : leucine-rich repeat kinase 2, PINK1 : PTEN-induced kinase 1, GBA : Glucocerebrosidase, L-DOPA : L-dihydroxyphenyl alanine, GTPCH1 : GTP cyclohydrolase 1, MSCs : Mesenchymal stem cells, 6-OHDA : 6-hydroxydopamine, MPTP : 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, ESCs : Embryonic stem cells, iPSCs : Induced pluripotent stem cells, pNSCs : Human parthenogenetic neural stem cells

Introduction

Parkinson's disease (PD) is one of the most common aging-related neurodegenerative and neurobehavioral disorders and is characterized by the loss of dopaminergic neurons in the substantia nigra and the formation of α-synuclein-containing Lewy bodies [1]. PD is also characterized by motor symptoms due to the loss of dopaminergic neurons. There are few effective therapies for AD available at present, and those available are limited to treating symptoms only [2].

Stem cell therapy is an alternative approach for PD treatment. Stem cells are self-renewing, multipotent progenitors that can differentiate intomultiple types of cells during embryonic and adult neurogenesis [3].They also have properties related to neuronal regeneration and replacement in neurodegenerative diseases. Stem cell transplantation is a powerful therapeutic tool that has been studied for the treatment of various human neurological diseases, such as Alzheimer's disease and PD [2, 4]. In this review, we review stem cell therapiesfor the treatment of PD.

Symptoms of Parkinson's Disease

PD was first reported as a clinical syndrome by James Parkinson in 1817 [3].PD is a progressive disease closely related to agein individuals older than 60 years [5]. PD is characterized by theloss of dopaminergic neurons and Lewy bodies, insoluble protein aggregates containing α-synuclein and an observed loss of motivation, resting tremors, postural instability, bradykinesia, and rigidity [3,6].

Non-motor symptoms of PD include depression [7], olfactory defects [8], anhedonia [9], sleep disturbances [10], and cognitive dysfunction [11]. These non-motor symptoms often develop along withthe motor symptoms of PD [12]. The motor symptoms are caused by a loss of dopaminergic neurons in the substantia nigra [13]. Most of PD is sporadic and related to multiple factors, such as age and mutations in genes, such as α-synuclein, leucine-rich repeat kinase 2 (LRRK2), PTEN-induced kinase 1 (PINK1), glucocerebrosidase (GBA), Parkin, and DJ-1 [14-18].

One effective treatment for PD is the administration of L-dihydroxyphenyl alanine (L-DOPA), but L-DOPA is limited in its duration for use because of its side effects [2]. Thus, stem cell therapy may be a useful alternative for PD treatment.

Stem-cell Based Therapy

Stem cells are a beneficial tool for various neurodegenerative diseasesand have the therapeutic effect of regeneration and substitution of cells and tissues.Therapies using stem cells may be the most promising strategies for the treatment of several neurodegenerative diseases [4]. In order to realize the beneficial effects of stem cell therapy for PD, implanted stem cells should be integrated into host neural tissues to recover function of dopaminergic neurons.Transplantation of human neural stem cellsover-expressing both tyrosine hydroxylase (TH) and GTP cyclohydrolase 1 (GTPCH1) (F3.TH.GTPCH)was shown to produce a neuroprotective effect against dopaminergic cell depletion and to improve behavioral symptoms in rat PD model [19].

Mesenchymal stem cells (MSCs)are also therapeutic cell sources for neurodegenerative diseases. Adipose-derived MSCs were transplanted in a 6-hydroxydopamine (6-OHDA)-lesioned model. Transplanted

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MSCs localized in the substantia nigra and the arachnoid mater and not only protected dopamine levels but also increased neurogenesis in hippocampal and subventricular regions [20]. In another study, rhesus monkey adipose mesenchymal stromal cells were differentiated into cells of the neuronal phenotype in the presence of LMX1A and Neurturin and implanted into the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine(MPTP)-lesioned rhesus monkeys. The implanted cells survived for 4 months and improved behavioral symptoms [21].

Dopaminergic neurons were first differentiated from mouse embryonic stem cells(ESCs) in 2002. These dopaminergic neurons showed electrophysiological and behavioral properties of midbrain neurons [22].Some studies using ESCs have reported that neurons differentiated from ESCs have therapeutic effects in PD and were able to improve PD motor syndromes in a rodent model of PD [23,24].

Methods

Dopaminergic neurons also can be differentiated from induced pluripotent stem cells(iPSCs). iPSC-derived dopaminergic neurons were transplanted into the striatum of a6-OHDA-lesioned hemi-parkinsonian rat model. Estradiol-2-benzoate has been shown to facilitate the integration of grafted dopaminergic neurons via the activation of integrin α5β1 [25]. Double administration of estradiol and dopaminergic neurons may provide an advanced therapeutic tool for treating PD. In another study,mesenchymal stem cells derived from fetal liver were transplanted into the striatum of 6-OHDA-induced mouse models. Grafted cells integrated into the host striatum and improved parkinsonian symptoms [26].

Transplantation of these cells was shown to improve PD symptoms in arat model in another report [27]. In another study, iPSCs were reprogrammed with protein-based reprogramming and differentiated into functional dopamine neurons. These cells improved motor symptoms in a rodent PD model [28]. iPSCs may provide an ideal therapeutic cellular source for treating PD because they escape problems associated with immune rejection.

iPSCs derived from cynomolgus monkeys were differentiated into dopaminergic neurons and transplanted into a PD monkey model. One out of three monkeys who received the cells showed long-term (2-year) survival and functional motor improvement without any immunosuppression [29]. Autologous transplantation of stem cells may thus potentially provide a benefit in clinical application.

Clinical Studies in PD

Alternatively, human parthenogenetic neural stem cells (hpNSCs) derived from unfertilized oocytes escape ethical problems and represent an unlimited cellular supply. When these cells were transplanted into rodent and primate models of PD, they were engrafted successfully and produced higher levels of dopamine in the striatum without any adverse events [30]. Currently, the use of hpNSCs is in Phase I clinical trials for PD.

MSCs have been injected by infusion into the cerebral arteries of five patients with progressive supranuclear palsy, a rare and severe form of Parkinsonism, and followed for 1 year in a PhaseI clinical study. Four out of five patients showed clinical stabilization of their motor function for at least 6 months [31].

Future Prospects

The loss of dopaminergic neurons followed by the breakdown of dopamine homeostasis is a hallmark of PD. Thus, the regeneration of dopaminergic neurons and the maintenance of dopamine homeostasis are important therapeutic goals in PD. Regenerated dopaminergic neurons can generate an optimal microenvironment for dopaminergic neuron survival and dopamine maintenance. Transplanted stem cells can also produce many neuroprotective molecules to assist neural cell survival. Stem cell therapy thus has promisefor improvingnot only PD but also other neurodegenerative diseases, such as Alzheimer's disease. iPSCs represent an excellent and unlimited source that could be usedin autologous cell therapy. However, in a recent report, age-related mitochondrial DNA mutations were shown to generate some defects in respiratory function of iPSCs, which could limit their therapeutic potential [32]. In the future, studies should focus on producing the optimal stem cell for applicability in clinical trials as well as a determination system for examining the quality of transplanted stem cells.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

The authors substantially contributed to the acquisition and interpretation of the data and drafting the manuscript.

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