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Stem Cell Applications in Parkinson's Disease

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Abstract

Parkinson's disease (PD), characterized by the loss of dopaminergic neurons in the substantia nigra, is one of the most common neurodegenerative disorders in elderly people. However, few effective therapies are available for neurodegenerative diseases, including PD. Stem cell therapies have been studied as potentially effective treatment options for neurodegenerative diseases through mechanisms of neuronal regeneration and substitution. Stem cells can migrate into injured regions and produce new neurons and glia, as well as neuroprotective molecules to improve neuron survival in the region. The survival and integration of these transplanted stem cells is an important issue for the success of stem cell therapy in neurodegenerative disease. Recent research in animals shows the promise of stem cell transplantation as a powerful treatment for Parkinson's disease, among other neurodegenerative diseases, in the near future.

Keywords: Parkinson's disease; Stem cells; Neurodegeneration

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders causing behavioral deficits in elderly people. PD occurs at a rate of 8~18 per 100,000 people and the PD incident rate increases with age, affecting more than 1% population over the age of 60 years old and ~4% of those over the age of 80 [1,2]. PD is characterized by the loss of A9 neurons in the substantia nigra, which provide dopaminergic innervation to the striatum. Few therapies for PD are available at present, and these generally have unfortunate side effects [3]. The hallmarks of PD are the formation of protein aggregates (Lewy bodies) containing α-synuclein and ubiquitin in the cytoplasm and axon, ultimately motor symptoms resulting from loss of dopaminergic neurons and these hallmarks [4,5]. PD includes various motor symptoms, such as tremor, bradykinesia, rigidity, postural instability, and altered gait pattern, as well as non-motor symptoms, such as cognitive impairment and bladder dysfunction [6-9]. The administration of L-dihydroxyphenylalanine (L-DOPA), a precursor of dopamine, is an effective treatment of PD; however, long-term use of L-DOPA produces negative side effects [10]. Stem cells have been useful for various neurodegenerative diseases, such as Alzheimer's disease and PD [10,11].

Stem cell therapy is a promising alternative approach for PD treatment. Stem cells have the ability to renew themselves, and those with pluripotent properties can differentiate into multiple types of cells during embryonic and adult neurogenesis [2,3]. Thus, stem cells possess the properties necessary for regeneration and replacement of neurons and glia in neurodegenerative disease. Here, we review cell therapies for treatment of PD.

Stem Cell Therapy

Neurons and glia can be derived from various stem cell sources such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs). There is no cure for PD, but stem cell-based cell replacement therapy, such as dopaminergic neuron implantation, provides new hope for treatment of PD [12]. Important areas for improvement in stem cell therapy include enhancing cell graft targeting, migration and density [13].

Human neural stem cells overexpressing both tyrosine hydroxylase (TH) and GTP cyclohydrolase 1 (GTPCH1; F3.TH.GTPCH cells) transplanted in rat PD models showed neuroprotective effects in dopaminergic cell regeneration and behavior improvement [14]. Replacing lost dopaminergic neurons is important for treatment of PD, and neurons with the electrophysiological and behavioral properties of dopaminergic cells have been differentiated from ESCs [15]. Some studies have reported that neurons differentiated from ESCs have therapeutic effects for PD, including improvement of motor behaviors in a rodent PD model [16,17].

Recently, rat MSCs were transplanted into substantia nigra in a PD rat model induced by 6-hydroxydopamine. This procedure improved abnormal behavior and demonstrated survival and differentiation of transplanted MSCs [18]. Adipose tissue-derived MSCs can migrate in the substantia nigra and not only maintain dopamine levels but also generate neurons in hippocampal and subventricular regions [19].

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Implanted rhesus monkey adipose-derived mesenchymal stromal cells survived for 4 months and improved behavioral symptoms in MPTP-lesioned rhesus monkeys [20].

IPSCs are an important stem cell source developed by Shinya Yamanaka. When protein-based reprogrammed-iPSCs were differentiated into dopamine neurons and transplanted into rodent PD models, improvement of motor functions was observed [21]. iPSCs may represent an ideal therapeutic cellular source for PD therapy because they overcome the problem of immune rejection. In another primate study, iPSC-derived dopaminergic neurons from cynomolgus monkey were transplanted into a PD monkey model. One monkey showed long-term survival for 2 years and behavioral improvement without any immunosuppression intervention [22]. Thus, autologous transplantation of stem cells may have beneficial clinical application. Some limitations remain to be solved, however, such as age-related mitochondrial DNA mutations that reduce the therapeutic potential of iPSCs via defects in the respiratory process [23].

The survival and integration of stem cells have become important issues in recent research of stem cell therapy. To improve the survival of transplanted dopaminergic neurons for PD treatment, Jiang and colleagues manipulated dopaminergic neuron-like cells to overexpress the H2AX gene, an H2A histone family gene, to manage DNA repair and cell apoptosis. These manipulated cells were more resistant to DNA damage and subsequent apoptosis after induction of cell death by ultraviolet irradiation and 1-methyl-4-phenylpyridinium (MPP+) treatment [24]. In another study, iPSC-derived dopaminergic neurons were transplanted into striatum of PD model rats along with estradiol-2-benzoate, which activated integrin α5β1 and resulted in the integration of grafted dopaminergic neurons [25]. Thus, administration of estradiol and dopaminergic neurons may eventually be used as an advanced therapeutic tool to treat PD.

Bladder dysfunction is a complication of PD, and many patients with neurological diseases and spinal cord injury suffer from bladder dysfunction [10]. Improvement of bladder dysfunction by stem cell therapy was observed in experiments in spinal cord injury animal models [26]. Treating complications such as bladder dysfunction is important for improving the patient's quality of life. Stem cells provide hope as treatment strategies for these complications of neurological disease.

Conclusion

Because patients with PD are greatly affected by dopaminergic neuron loss, the regeneration of dopaminergic neurons and the maintenance of dopamine homeostasis are important for successfully treating this disease. However, brain complexity is a major obstacle to developing therapeutic strategies for neurodegenerative diseases. Because transplanted stem cells can regenerate neurons and glia in an optimal microenvironment and produce neuroprotective molecules, stem cell therapy has great potential to treat PD as well as other neurodegenerative diseases. iPSCs, in particular, are an excellent stem cell source for application of autologous cell therapy. Recent research has made significant advances in improving the survival and integration of transplanted stem cells; however stem cell therapy is still in infant status for PD treatment. We still have the limitation of stem cell therapy from immune rejection, tumorigenesis and low efficiency which comes from unknown factor to prevent functional innervation of stem cell such as age-relative mitochondrial DNA mutation. Therefore, further improvement is needed to enhance the therapeutic effects of stem cells. Future research should also focus on the development of screening systems for determining the quality of transplanted stem cells and enhancing their efficiency.

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