Review Article
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Medical Journal of the Islamic Republic of Iran (MJIRI)
Iran University of Medical Sciences

Stem cell-based approach for the treatment of Parkinson's disease

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Received: 22 May 2013 Accepted: 21 April 2014 Published: 28 January 2015

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative brain disorder which is around 1.5 times more common in men than in women. Currently, drug medications, surgery, and lifestyle changes are common approaches to PD, while all of them focused on reducing the symptoms. Therefore, regenerative medicine based on stem cell (SC) therapies has raised a promising hope. Various types of SCs have been used in basic and experimental studies relevant to PD, including embryonic pluripotential stem cells, mesenchymal (MSCs) and induced pluripotent SCs (iPSCs). MSCs have several advantages over other counterparts. They are easily accessible which can be obtained from various tissues such as bone marrow, adipose tissue, peripheral blood, etc. with avoiding ethical problems. Therefore, MSCs is attractive clinically because there are no related ethical and immunological concerns . Further studies are needed to answer some crucial questions about the different issues in SC therapy. Accordingly, SC-based therapy for PD also needed more complementary evaluation in both basic and clinical study areas.

Keywords: Cellular therapy, Neurodegenerative diseases, Parkinson's disease, Stem cell.

Cite this article as: Goodarzi P, Aghayan H.R, Larijani B, Soleimani M, Dehpour A.R, Sahebjam M, Ghaderi F, Arjmand B. Stem cell-based approach for the treatment of Parkinson's disease. *Med J Islam Repub Iran* 2015 (28 January). Vol. 29:168.

Introduction

Parkinson's disease (PD) is the first or second most common neurodegenerative brain disorder after Alzheimer's disease that affects the control of body movements (1, 2). First time PD was formally described in "An Essay on the Shaking Palsy," published in 1817 by a London physician named James Parkinson (3). It is resulted from the degeneration of dopamine-producing nerve cells in the substantia nigra, a region in the mesencephalon that controls movement. This degeneration results in a reduction of a neurotransmitter called dopamine in the brain which is necessary for regulating of body movement. Clinical signs of PD appear when about 70% of the dopamine-producing neurons are damaged. Symptoms of PD include slow physical movements (bradykinesia), shaking (tremor), muscle stiffness (rigidity) and postural instability (impaired balance and coordination), and pain (4-7). PD is about 1.5 times more common in men than in women, and its prevalence increases with age. It affects about 1%–2% of the

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population over 70 years of age (8). The causes of PD are still unknown, however a number of researchers believe that it develops in response to a combination of certain genetic and non-genetic factors (9).

Current treatments for Parkinson's disease

There is currently no cure for PD thus; several treatments have focused on relieving the symptoms (10). Accordingly, current treatments include the use of oral preparations of L-3,4-dihydroxyphenylalanine (L-DOPA) and dopamine receptor agonists, apomorphine in more serious cases, continuous intestinal infusion of L-DOPA, and deep brain stimulation (DBS) in subthalamic nucleus and globus pallidus by using surgically implanted electrodes (11). Therefore, pharmacological treatments are based on the uptake of levodopa (L-DOPA) and inhibition of dopamine degrading by using dopamine agonists and also dopamine degrading enzymes inhibitors. Today, dopamine receptor agonists are used as the first choice to delay the starting of L-DOPA. Furthermore, they will be useful in advanced stage of PD as adjunct therapy with L-DOPA. Their mechanism of action is stimulation of presynaptic and postsynaptic dopamine receptors. Levodopa as a known medication for PD treatment has been used to relieve the effects of dopamine deficiency. Unfortunately, its therapeutic effect is reduced after around 3-5 years (8, 12-15). As well, there are some other medications that are used for PD for instance; Bromocriptine, Pramipexole, Ropinirole, anticholinergic medications (e.g., Benztropine), monoamine oxidase B inhibitors (MAO-B-I), Amantadine, and DBS which stimulates the part of brain affected by PD (16, 17). MAO-B-I can stabilize the dopamine levels in the synaptic cleft. Selegiline and Rasagiline are two irreversible MAO-B inhibitors that catalyse the oxidative deamination of active amines and cause prolonged dopamine activity (18). Also, here are some other types of Levodopa degradation inhibitors such as catechol-O-methyl transferase (COMT) inhibitors (19). All of these treatments have some considerable side effects such as wearing off phenomena, motor fluctuation, and abnormal movements as dyskinesia. On the other hand, DBS as a surgical treatment has some serious limitations. It is costly and generally considered for late stage disease without dementia. Furthermore, it can produce cognitive disorders, which may be permanent (8). As current therapeutic approaches for PD only provide symptomatic relief with serious limitations therefore, some alternative treatments such as regenerative medicine and stem cells (SCs) therapy are necessary (20-22). There are several types of (stem) cells that have been investigated as potential candidates for cellular therapy in various neurological disorders such as spinal cord injury, multiple sclerosis, stroke, and PD, including embryonic pluripotential SCs, fetal or adult SCs (hematopoietic and mesenchymal SCs), iPSCs from different sources, and human fetal ventral mesencephalic (hfVM) tissue that contains nigral dopaminergic cells (23-29). Different types of stem cells have been investigated for treatment of PD with specific advantages and disadvantages (Table 1). The purpose of this review is to describe various sources of SCs that are candidate for treatment of PD.

Embryonic stem cells (ESCs)

These are "pluripotent cells" derived from the inner cell mass of a blastocyst (2, 32) and can differentiate into any type of cell in the body for instance, nigral dopaminergic neurons (33-35). On the other hand, human ESCs are a source of dopamine neurons for transplantation in PD (36, 37). It has been demonstrated that, embryonic pluripotential stem cells-derived dopaminergic neurons generate functional recovery after transplantation into the striatum of PD in animal models (38). However, there are some serious concerns about the use of these cells for treatment of PD or other neurodegenerative diseases. Tumor formation is one of the most important adverse effects which can

Table 1. Advantages and disadvantages of stem cell types used in Parkinson's disease (11, 26, 30, 31)

Type of stem cell	Advantages	Disadvantages
Embryonic stem cell (ESCs)	(a) Highly proliferative/pluripotent (b) Able to form all three germ layer (c) Generate dopaminergic neurons (d) Transplantation survival/some degree of functional recovery	(a) Risk of tumor formation (b) Ethical issues (c) Genomic instability
Induced pluripotent stem cells (iPSCs)	(a) Unlimited PD patient-specific cells/autologous transplantation (b) Transplantation survival/some degree of functional recovery (c) Minimized immune reactions and ethical issues	(a) Risk of tumor formation (b) In autologous transplantation risk of susceptibility to the original pathology of the patient
Mesenchymal stem cells (MSCs)	(a) Improve motor performance in mice (b) No reported adverse effects in humans (c) A realistic cell source for regenerative medicine (d) Easily accessible from different tissues	(a) Modest clinical improvement in humans
Fetal brain neural stem cells (fNSCs)	(a) Lower risk of tumor formation and immune rejection in comparison with ESCs (b) Ability to differentiate into neurons, astrocytes, oligodendrocytes, and dopamine neurons	(a) Limited differentiation in vivo (b) Partial effect in PD-like symptoms (C) Risk of GIDs (d) Ethical issues (e) Histocompatibility concerns (f) limited supply

be avoided by cell sorting, prolonged differentiation and subsequently exhaustion in vitro before transplantation (11, 39-42). Several animal studies have shown a mild to moderate improvement in PD symptoms after transplantation of ESCs or neural stem cells differentiated from embryonic pluripotential stem cells (38, 43-45).

Mesenchymal stem cells (MSCs)

MSCs are multipotent cells which can be commonly isolated from bone marrow. Bone marrow-derived mesenchymal stem cells (BMSCs) are the most well studied MSCs. Additionally, there are some other MSCs sources, such as umbilical cord, dermis, adipose tissue, peripheral blood, etc. (29, 31, 46-48). They have potentially self–renewal property with differentiation capacity into a variety of cells such as osteoblasts, chondrocytes, myocytes, adipocytes, fibroblasts, neurons, and also dopaminergic neurons (48-50). MSCs can protect injured tissues to generate a wide spectrum of cells, for instance, dopamine neurons, which can renew damaged or lost cells in PD (31, 51, 52). Although, it has been demonstrated that embryonic pluripotential stem cells and neural stem cells (NSCs) are considerable candidates for transplantation therapy in neurodegenerative diseases (53), there are some limitations on using of them such as potential problems of cell regulation, ethical issues, and probability of tumorigenicity. Accordingly, several studies showed that MSCs have a high therapeutic potential against neurological diseases, without the mentioned limitations. In addition, MSCs are readily accessible, isolated and expanded easily with no risk of rejection (54). MSCs have low immunogenic properties due to the lack of MHC-II (55). Furthermore, they have protective effects on dopaminergic neurons loss in animal models and human (56-64). Some experimental studies elucidated that MSCs are potentially useful as vectors for treating a variety of central nervous system disorders (65). These findings also revealed MSCs ability to transdifferentiate into special neurons which is a substantial factor for treating neurodegenerative disorders. Some clinical transplantation trials are performed by using MSCs for treatment of PD. For instance, autologous BMSCs were used in a clinical trial in which patients followed for up to 36 months after transplantation. This trial

showed partial improvement with no tumor formation or other side effects. Although MSCs have been promising candidate for treatment of PD, more clinical studies are needed regarding MSC transplantation and its safety and efficacy (31).

Induced pluripotent stem cells (iPSCs)

iPSCs are usually derived from adult somatic cells, such as fibroblasts by overexpressing self-renewal and pluripotency factors (Oct4, Sox2, Klf4, and Myc) (66, 67). Besides pluripotency and self-renewal properties, iPSCs have some advantages as a source for cell-replacement therapies. For instance, the opportunity to obtain the reprogrammed cells directly from the patients, thus potentially reducing the risk of transmissible infections and immune reactions following cellular therapy (68). Rather, using iPSCs in basic and clinical researches has no ethical limitations. In other words, for treatment of PD, patients own somatic cells can be differentiated into a pluripotent state to produce dopaminergic neurons which could be transplanted into the patient's brain (69, 70). iPSCs are counterparts of embryonic pluripotential stem cells in morphology, proliferation, surface antigens, and ability to differentiate into three germ layer cells (71). Several basic and clinical investigations elucidated promising role of iPSCs in regenerating dopaminergic neurons as the underlying factor in treatment of PD. Transplantation of these cells into the striatum ameliorated PD symptoms (10, 11, 31, 72, 73). Although, the use of iPSCs has various advantages, the risk for tumor formation is a serious obstacle to use these cells in clinical transplantation trials. Accordingly, it is needed to minimize this risk and the probability of genetic mutations before translating iPSCs related basic science into clinical setting in PD (11, 74, 75).

Other tissue sources

Different tissues were used for treatment of PD including; carotid body, sympathetic ganglion neurons, and adrenal medulla. Carotid body is located in the bifurcation of common carotid artery and has some dopaminergic cells as an alternative treatment in PD (76-78). Likewise, sympathetic ganglion tissue from cervical and thoracic sympathetic trunk can be implanted into the striatum in PD (79). In addition, adrenal medullary tissue as a source of dopaminergic neurons is another choice for treatment of PD with limited benefits (80).

Conclusion

Current treatments and medications of PD try to relieve motor symptoms by providing dopamine substitutes or dopamine receptors agonists and also in advanced PD patients, apomorphine, continuous intestinal administration of L-Dopa, and DBS (19, 81). Although these treatments have some effects on controlling symptoms, their adverse effects are considerable. Additionally, they cannot replace or regenerate the lost dopaminergic neurons. While, cellular therapy using stem cells extracted from different sources such as, hfVM tissue can provide dopaminergic neurons regeneration, replacement, and reinnervation and also symptomatic relief lasting for several years following transplantation in some cases that were able to withdraw from L-DOPA therapy (11, 18, 19, 26, 82). Therefore, it is the time to apply a novel and more effective treatment for PD by cellular therapy and regenerative medicine. Nowadays, stem cell therapy has turned into an attractive field of science for researchers and consequently stem cells have been optimized to use for treatment of various neurological disorders based on their potential to differentiate into neural cells. In particular, these cells could be induced to generate dopaminergic neurons for an effective treatment of PD (31). Although, there are no good-established inclusion criteria for patient selection, several clinical trials have introduced criteria to include the PD patients in their trials (83). For instance, some studies have included patients with at least 2 features of PD (tremor, rigidity, or bradykinesia), good response to L-dopa, and intact

higher mental functions (84) and also a minimum of 7 years of treatment, the presence of intractable problems (more advanced stages), taking L-dopa for several years and established L-dopa induced dyskinesia (8). In addition, more precise inclusion criteria have been introduced in some ongoing clinical trials. For instance, a clinical trial has described the inclusion criteria as below;

- Males and females aged 18-80 years.
- Current diagnosis of PD with motor complications according to standard criteria.
- Responsiveness to dopa agonists.
- Stage 2.5, 3 & 4 based-on HOEHN & YAHR staging.
- Stable medications for 60 days prior to the surgery.
- No gross atrophy or any other pathology of brain in MRI.
- Montgomery-Asberg Rating Scale (MADRS) less than 19 for depression.
- No significant cognitive impairment (MMSE > 21) (85).

Obviously, better realizing the underlying basic and cellular mechanisms of PD could help scientists to explicate safe and efficient stem cell-based approaches to overcome side effects such as uncontrolled differentiation and growth which can induce tumor formation. Although, it is elucidated that dopaminergic neurons generated from stem cells can be the best candidate for treatment of PD, It is needed to understand more about the basic etiology of PD, also dopaminergic cell differentiation, regeneration, and function. MSCs have several advantages over embryonic pluripotential stem cells. iPSCs, and neural stem cells, for example, they can be obtained from patients for auto even allo-transplantation (31). Moreover, MSCs are easily accessible that can be obtained from different types of tissues such as bone marrow, adipose tissue, peripheral blood, etc. with no ethical problems (86). Accordingly, it seems that MSCs are the ideal candidate and maybe ready to translate from the basic and experimental researches to the clinical transplantation trials in various diseases including, neurological disorders and PD. On the other hand, embryonic pluripotential stem cells, iPSCs, and also fetal stem cells have some valuable properties in comparison with adult MSCs for instance, pluripotency and self-renewal capacity, which introduce them as a considerable source for research and future cellular therapies. Of course, various ethical problems and safety concerns (e.g. tumorigenesis), are needed to overcome by performing further investigations in both fields (11). Generally, against the promising clinical potential of (stem) cell based therapies, there are also potential risks. Some of the considerable risks of stem cell based therapies include; 1) transplantation site reactions, 2) immune response to the transplanted cells, 3) biodistribution/ectopic grafting, 4) unintended differentiation into another cell type, 5) tumorigenicity, and 6) lack of functional characteristics (30). As it has been described, there are various cell or stem cell sources that have been used for treatment of PD, but the most successful clinical trials have applied hfVM tissue to treat PD (26). Therefore, we are trying to explain more details of the characteristics, complications, and different aspects of this treatment in comparison with other types of cellular therapies. Following implantation of hfVM tissue, survival of grafted dopaminergic neurons, has been shown in the PD patients' brain striatum using positron emission tomography (PET), and histopathological methods (86, 87). Dopaminergic grafts can be functionally integrated into neural circuitries in brain (87). Additionally, it has been demonstrated that, afferent and efferent synaptic connections can be established between grafted and host neurons. Long-term survival of the implanted grafts have been reported several years (more than 10 years) after transplantation (86,88) with acceptable function and restoring dopamine release in the PD patient's brain (87). Alternatively, following stem cell transplantation, dopamine restoring could be provided

by two different paths; 1) in vitro pre-differentiation of stem cells toward dopaminergic neurons prior to transplantation, 2) In vivo differentiation toward dopaminergic neurons after implantation into the PD patient's brain (86). Consequently, HfVM tissue transplantation has some complications such as producing Lewy bodies after transplantation and graft-induced dyskinesias (GID) (26, 87). Furthermore, there were lack of homogeneity of effects in initial clinical trials and also they caused GID as a considerable adverse event in a subgroup of patients (11). Accordingly, the most serious complication after hfVM tissue transplantation is GIDs which can be treated with DBS in the globus pallidus (87). Various studies showed that GIDs are caused by the hfVM graft-derived serotonergic hyperinnervation. These investigations supported some evidence-based strategies for avoiding GIDs following treatment of PD using hfVM tissue or stem cells. As the hfVM tissue contains both dopaminergic and serotonergic cells, thus minimizing the serotonergic portion of the graft is seriously suggested to reduce occurrence of GIDs. On the other hand, during processing and preparation of dopaminergic neurons from different sources of stem cells, depletion of serotonergic neurons should be considered as a rule. In addition, stem cell expansion and long-term storage of the grafts before transplantation could reduce the dopaminergic/non-dopaminergic ratio, thus avoiding cell manipulation or long term storage, could help investigators to decrease the incidence of GIDs. An alternative treatment of GIDs is the systemic administration of serotonin 1A agonists, which can reduce transmitter release from serotonergic neurons (11,87). It also should be noted that, non-motor symptoms such as dementia is not effectively treated by using current medications and DBS (87). Likewise, some patients who received the dopaminergic grafts still suffered from nonmotor symptoms including depression, dementia, visual hallucinations, and sleep disorders. Therefore, cellular therapy for PD needs additional transplantation of serotonergic neurons to relieve nonmotor symptoms (88). There are various trials that have been performed in the mentioned arena using stem cells or hfVM tissue grafts. In some of them the grafts or cells have been implanted unilaterally (84) and in others bilaterally (83, 86, 88, 89) in different parts of the brain such as putamen (86, 88, 89), sublateral ventricular zone (83, 84), and caudate nucleus (88). Additionally, in these trials, the number of transplanted stem cells was 1-2 million cells/Kg of body weight (83,88). Eventually, results of experimental studies suggest future (stem) cell-based approaches to PD, while there are remained several fundamental questions about the stem cells' mechanism of action, adverse effects, the best cell source for dopaminergic neurons, as well ethical and safety concerns particularly about embryonic pluripotential stem cells and iPSCs (11, 86). Therefore, stem cell-based therapies for PD are still in its infancy and performing more experimental researches as well clinical trials is crucial for advancement of knowledge in this arena (86).

Acknowledgements

The authors would like to acknowledge Seyed Hassan Emami-Razavi, Abbas Norouzi-Javidan, Fereshteh Mohamadi-Jahani, Hanieh Rostamabadi, and Maryam Kavousi for their considerable assistance.

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