Review Article

Stem Cell INVESTIGATION

Cell replacement therapy is the remedial solution for treating Parkinson's disease

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Abstract: The selective degeneration of dopaminergic (DA) neurons in Parkinson's disease (PD) has made an idol target for cell replacement therapies and other emerging surgical treatments. Certainly, by transplantation method, the therapeutic regimens such as human fetal ventral midbrain (hfVM) cells, human embryonic stem cells (hESCs), human neural stem/precursor/ progenitor cells (hNSCs/hNPCs), human mesenchymal stem cells (hMSCs), human induced neural stem cells (hiNSCs), and human induced pluripotent stem cells (hiPSCs) have been used into DA deficient striatum. In recent decades, surgical methods such as deep brain stimulation (DBS) and gene therapies have been used with the aim of treating PD. Though the technology has improved and many treating options arise, the permanent source for curing PD has not been identified yet. In this review, we examine how stem cell therapies have made advancement as a therapeutic source for PD when compared with surgical treatments.

Keywords: Cell replacement therapy (CRT); dopaminergic neurons (DA neurons); Parkinson's disease (PD); stem cell; surgical treatment

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Introduction

For complex progressive neurodegenerative disorder such as Parkinson's disease (PD), the modulation of the host immune response to the transplanted cells by means of immune suppressive treatments which will influence cell therapy against PD. The therapy which exists for the treatment of PD will treat symptoms but not the cause. There is no role in reversing the characteristic degeneration of PD by using current pharmacological treatments such as L-3,4-dihydroxy-phenylalanine (L-DOPA) and mono amine oxidase-B inhibitors, as well as advanced surgical interventions such as deep brain stimulation (DBS) (1). The regenerative-medicine researchers have worked on developing autologous stem cell–derived therapies and have found that mature cells could be coaxed back into stem cells in the decade. The potential source for regenerative medicine is the human pluripotent stem cells (hPSCs) which include hESCs, hiPSCs, human neural cells and mesenchymal cells. After transplantation into humans, the neuronal progenitors will contribute to behavioral recovery especially with PD patients (2). The current perspective is that using human fetal brain, human neural stem cell (NSC), and embryonic stem cells, dopamine neurons can be derived. The functional deficits of dopamine neurons will be improved by means of transplantation and also incur immune rejection as these cells are allergenic. Currently, L-DOPA (a dopamine precursor) and drugs (e.g., pramipexole and ropinirole) are used as the therapeutic target.

Additionally, the drug rasagiline, an inhibitor of

monoamine oxidase-type B, can delay disease progress. By taking the combination of these drugs, the dopaminergic function gets restored (3). Neuronal stem cells are an endogenous source for PD in neuronal replacement therapy. The impaired neurogenesis in PD can restore by means of providing a source of an endogenous repair (4). The gold standard of PD treatment is Levodopa. Hence it is more effective even in advanced stages. After 4–6 years of treatment, 40% of patients may develop dyskinesias and motor fluctuations. It depends on severity, duration, and dosage of the drug. Hence, it becomes refractory to the traditional oral treatment. Therefore, advanced therapeutics has been developed such as DBS, Continuous Subcutaneous Apomorphine Infusion (CSAI) and Levodopa-Carbidopa Intestinal Gel (LCIG). These therapeutic approaches will allow mimicking normal physiological condition. These must be performed with strict inclusion and exclusion criteria and also possible side effects must be accurately monitored (5). The possible side effects arise from the subthalamic nucleus (STN) and internal globus pallidus (GPi). On one hand, DBS improve verbal memory and also reduce anxiety and also investigated that more detrimental results are observed after DBS, attention impairment will occur (6). The aim of the review is to make a comparison of cell replacement therapy (CRT) and surgical treatment as a therapeutic application in PD and to suggest the best therapeutic strategy towards the treatment of PD.

Initiative in Parkinson's therapeutics

PD treatment has a choice for the physicians, for patients and families, and for the society. Without any change of patient experience, the emergence of new drugs and technologies has been expanded in the last few decades as a choice of treatment in curing PD. There is no therapy that has been a solution which can slow down the disease and transform the lives (7). In society, PD is an increasing burden and is the second most common neurodegenerative disorder in people who are above the age of 60. Cognitive deficits emerge in a significant proposition of patients (8). PD is a clinical syndrome since it is a multifunctional impairment and systemic involvement disease (9). At present, therapeutic approaches such as L-DOPA replacement therapy, DA agonist administration, and DBS intend to relieve PD motor symptoms (10) which are palliative and incompetent in counteracting PD progression. Till now, there is a lack of treatment for PD, which shows the shift to stem cell research recently has been a therapeutic way in curing PD. Stem cells are self-renewable and produce progenies as well as differentiating into multiple cell lineages (11).

By the proposal of stem cell research, many of the cell lineages have been employed for dopamine neurons derivation and differentiation for using as a disease modeling, drug screening, and CRT for PD. Currently, for DA neuron derivation, human fetal ventral midbrain (hfVM) cells, human neural stem/precursor/progenitor cells (hNSCs/hNPCs), hESCs, hMSCs, hiNSCs, and human-induced pluripotent stem cells (hiPSCs) (12,13) have been used as a restorative therapeutic regimens. Stem cell technologies have been a hope for the treatment of diverse brain diseases. The selective dopaminergic cell degeneration in PD uses novel cell replacement strategies to restore dopamine supply to the striatum. The recent upcoming research using embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) has unveiled in bringing stem cell technology to the clinic in the expected future in the form of disease modeling and stem cell therapy (7).

CRT

CRT is a promising avenue for treating neurodegenerative diseases. Due to physical and chemical barriers, the CNS is unable to regenerate its own neurons (14). Hence the research is focused on different forms of stem cells due to its pluripotent potential. Dopaminergic (DA) neurons can be created when the stem cells are differentiated under certain conditions. The produced neurons can be transplanted into PD patients which replace the dopamine levels and relieving from symptomatic effect. The renowned foundations such as Michael J. Fox Foundation and Parkinson's UK refer to stem cell therapy as a potential treatment. The usage of CRT in treating PD has been started in early 1990's (15). In 1994, a fetal ventral mesencephalic tissue from aborted fetuses which is rich in dopaminergic neuroblasts was transplanted into the striatum of two PD patients (16). This study showed that the neural transplantation was the right step in CRT since the transplanted DA neurons survived and re-innervated the striatum. Plenty of studies followed CRT which added as a treatment for PD (17). Similarly, there were certain limitations when using transplanted fetal tissue since a study showed that 14 patients who received the graft of fetal mesencephalic tissue suffered from graft-induced dyskinesias (18). The mechanism is still not clear but the side effects could be due to dopamine reaching over-sensitized receptors or due to the non-dopaminergic

portion of the graft. Though it has shown a promising effect it is not a viable model to treat PD.

Embryonic stem cells (ESCs)

ESCs have the potential to self-renew and give rise to three primary germ layers- ectoderm, mesoderm and endoderm under certain circumstances. The essential characteristics are needed when human ESCs (hESCs) are used. The features are:

(I) Stem cells should derivate from the pre-implantation or peri-implantation embryo;
(II) Undifferentiated proliferation for a prolong period, and;
(III) Developmental potential to form three embryonic germ layers even after prolonged culture (19).

It is said that hESCs provides a limitless supply of homogenous DA progenitors/precursor cells and neurons of specific neural lineages, hence the neural transplantation of hESCs restores DA dysfunction and modifies disease progression in PD which shows a promising therapeutic strategy in PD treatment. A study on hydroxydopamine (OHDA) lesioned rats showed the effects of transplanting a low dose of mouse ESCs produced functional DA neurons (20). Using positron emission tomography (PET) scans and quantitative measurements the rats showed a significant improvement of symptoms. But this study showed the side effects of tumor formation and graft failure. Additionally, a study published in Nature proved that the differentiation of ESCs into DA neurons *in vitro* before transplantation proved to be functional and it concluded that the tumor formation is an unacceptable one. Hence, further studies needed to understand the safety and efficacy of transplants (21). Differentiation of ESCs *in vitro* follows certain approaches. To prove this, several morphogenesis such as fibroblast growth factor (FGF), epidermal growth factor (EGF), sonic hedgehog (SHH) and glial cell-derived neurotrophic factor (GDNF) (22) are neurogenic stimulators which are needed for normal embryonic development and differentiation as well (23). The culture methods and differentiation protocol have been improving and succeeded in creating a scalable population of DA neurons (A9-type) specific to ventrolateral and caudal regions of the substantia nigra. Though there are aberrant innervations and graft-induced dyskinesias, animal models showed an evidence of increased fiber outgrowth which has seen improved outcomes. The hypothesis is that the genetic modification of these implanted neurons might limit the excessive outgrowth (3). From the above studies, the therapeutic use of ESCs and complications are clearly demonstrated. Earlier, from the fetal tissue implants the regenerating potential of lost DA neurons in PD patients shows how far is the CRT is an operational procedure in PD patients. ESCs are also limited and reveal complicated ethical questions.

NSCs

NSCs are capable of self-renewing and generating the nervous system phenotype in embryo and adult, in vivo, they are committed to forming the neural lineage differentiation, oligodendrocytes, and astrocytes (24). Due to the deficiency of NSCs in PD in the affected brain regions shows that NSCs are the appropriate candidate for CRT (24). Hence, by the replacement of NSCs into an impaired brain, either as endogenous NSCs, iNSCs, or stem cell-derived NSCs shows a possible therapeutic mean for PD.

The establishment of NSCs of multifarious origin, human neural precursor cells would be produced as an immense practical value for both neuroscientists and clinical neural transplantation trials (24). The evaluation of NSCs grafted PD models shows that NSCs combine into the nigrostriatal pathway and restores the projection of substantia nigra to striatum resume DA synthesis and release and relieve PD-like symptoms (25-27). It seems NSCs are the perfect therapeutic candidate for PD because it has a unique capacity to expand and differentiate into various neurons and glia. For the preparation of adult NSCs, protecting adult human CNS tissues is a difficult process in case of treating PD. For this reason, it is important, to establish human NSC lines for serving as an ideal alternative cellular source. In a rat model of Parkinsonism, human fetal NSCs transplanted and their survival, migration, proliferation and differentiation were documented (28,29). The human fetal NSCs provide a high yield of DA cells which standardizes the cell source in clinical testing. In a study on PD patient, NSCs of cortical and subcortical tissue samples were isolated and injected into the striatum. A long lasting improvement in was observed in Unified Parkinson's Disease Rating Scales scores (UPDRS) along with 33% increase in dopamine uptake in the implanted putamen (30). Adult NSCs from the subventricular zone (SVZ) found out to be a promising candidate for neurogenesis due to DA differentiation, migration into damaged areas of the brain and close proximity to the striatum.

MSCs

MSCs are multipotent cell lines arising from stromal structures of the bone marrow (31) other than adipose tissue (32), umbilical cord (33), dermis (34), and peripheral blood. The MSCs derived from peripheral blood may represent a new source of cells for autologous transplantation therapies in neurodegenerative disease. In PD, due to the loss of DA neurons, MSC is a suitable candidate for CRT. The two types of MSCs (naive MSC and neutrally-induced MSCs) are used as a promising therapy in PD. These two types of MSCs shown to cause a therapeutic effect in PD models by various groups in which both shows the survival of grafted cells, TH (tyrosine hydroxylase) expression and behavior recovery (35).

Additionally, genetically engineered MSCs have also demonstrated the therapeutic potential in PD treatment. Numerous studies showed that the growth factors such as GDNF, VEGF and neurturin, protects DA neurons in rodent and primate models (36-39). In short, the differentiation of MSCs into DA neurons achieved through various protocols based on chemical induction, gene transfection, co-culturing with glial, neuronal and neuronal stem cells and employment of conditioned medium (40).

hiPSC

Human iPSC is similar to hESCs, including the morphology, ability to self-renew, profiling gene expression and differentiate into three embryonic germ layers *in vitro* and *in vivo* (41). An important advantage of induced cell reprogramming is that the patients showing the sporadic or familial form of PD can possibly generate iPSC. The *in vitro* models have patient's genetic variants which are the cause for PD onset and progression. Furthermore, iPSC can further be differentiated into neurons, which would be an unlimited source of native phenotypes of cells involved in neuronal death in *in vitro* during neurodegeneration. The major issue in iPSC is that, due to aging factor, modeling PD using iPSC should be a major part in reproducing late-onset characteristics. iPSC was first used to model neurodevelopmental phenotypes and early-onset phenotypes (42-44). Studies with iPSC using familial and sporadic forms of PD patient have proved the pathophysiology of the late-onset neurodegenerative disorder. In addition to it, during disease progression, the phenotypes can be produced even when the inducible factors that cause cell stress, due to mitochondrial toxins (45), growth factor deficiency, or even modulated aging with induced expression of progerin (46). Stem cell grafts have been practiced in PD patients as well as in animal models. In 1995, fetal mesencephalic tissue from seven human embryos was grafted into the post-commissural putamen of a patient with PD. For up to 18 months this procedure was continued and through PET scans, fluorodopa uptake was increased after 6 and 12 months and this showed an improved neuronal function in the region of transplanted tissue. By using UPDRS test, the motor ability was analyzed (47). By performing the same trial, there were increases clinical benefits which withdraw L-DOPA treatment (48). Some studies showed a vice versa reaction (49,50). Kordower and colleagues (51) analyzed that after 14 years of the operation, a low UPDRS was observed in the first 10 years but there were some side effects such as gait and difficulty in balance. On post-mortem analysis, it was found that Lewy body-like structures in the brain made PD progression after the transplantation (51). The first study to produce PD-specific iPSC was observed in a sporadic case in 2008 (52). The following year, it was able to demonstrate PD-specific iPSC-derived differentiate towards DA by the Jaenisch group, however, there was no neurodegeneration or disease-related phenotypes were observed (53). Similarly, the Jaenisch group generated gene-free iPSC lines from skin fibroblasts of PD patients, and by *in vivo*, PD-specific iPSC-derived DAn survived and engrafted in rodent striatum. Recently, the coding gene for α-syn protein, SNCA using iPSC-specific PD have been generated (54,55). These cells showed an improvement in α-syn mRNA and protein levels (54) and when exposed to oxidative-stress inducers there was an increased vulnerability to cell death (55). Chung *et al.* observed that iPSC model with the rare missense A53T SNCA mutation found to show pathogenic phenotype in patient-derived neurons. In the context with α-syn toxicity, a connection between nitrosative and ER stress was observed. iPSC-derived DAn, with A53T SNCA mutation, enhanced basal ROS/RNS production with α-syn aggregation and altered mitochondrial machinery (45). Interestingly, Ryan *et al.* postulated that due to the complex interaction between environmental factors and gene expression MEF2-PGC1α pathway contributes to late-onset phenotypes in PD (56). When PD associated pesticides were added, oxidative/nitrosative stress was observed by inhibiting MEF2-PGC1α and inducing apoptosis (45).

Jiang and colleagues proved the transcription of monoamine oxidase, the spontaneous release of dopamine and significantly decreased dopamine uptake, susceptibility

to reactive oxygen species (57). The common mutation of LRRK2 gene G2019S in iPSC model was found to show the characteristic features of PD, such as accumulation of α-syn, increase in genes responsible for oxidative stress and susceptibility to hydrogen peroxide, displayed through caspase-3 activation (58). Another study created iPSC lines from seven patients with idiopathic PD and four patients with G2019S mutation in the LRRK2 gene (59). The results were found out to be with morphological alterations in PD-derived iPSC and also with an increase in apoptotic neurons for 2.5 months. Sporadic form of PD study revealed that DAn, after long-term culture, from idiopathic PD patients, showed an increased susceptibility to degeneration *in vitro* (59). In autophagic process, proteins may get altered at the lysosomal level through chaperone-mediated autophagy (CMA). In a study with iPSC-derived LRRK2 DAn, degradation of α-syn by CMA showed an increased co-localization of α-syn (60). The G2019S LRRK2 protein was more resistant to the CMA-mediated degradation resulted with α-syn accumulation (60). An important goal of the stem cell-based PD study is to create a new drug that could protect from neurodegenerative process. Patient-specific stem cell-based models help in creating new pharmacological strategies for designing personalized therapies. Forebrain neurons have been used to screen disease modifying drugs. A recent study investigated the signs of PD disease in patient-specific iPSC neurons to test the drug (61). In addition, high-throughput screening (HTS) was performed to identify the molecules that protect DAn from the toxic effect of pesticides.

It was observed that due to the interaction between environmental factors and gene expression the MEF2-PGC1α pathway contributes to the late-onset PD phenotypes (45). By using this HTS, a new drug isoxazole was identified that targets MEF2-PGC1α pathway. Hence, these findings prove that the use of iPSC technology as a therapeutic tool and the genetic forms of PD would remain in identifying in sporadic patients with uncertain genetic cause of the disease.

Pitfalls in CRT

As we discussed above, in ESCs, the use of fetal ventral mesencephalic tissue showed a rare proliferation and tumor formation. Similarly, in a study conducted in the striatum of parkinsonian rats with the transplantation of undifferentiated ESCs resulted in a spontaneous differentiation into DA neurons but 5–25 rats died due to teratoma formation (20). This study shows a risk of unregulated cell growth whereas, in NSCs, the transplantation showed limited capacity to differentiate into DA neurons (62). Another pitfall in PD is graft-induced dyskinesia were PD progression did not affect the grafted tissues after transplantation. By decreasing or removal of tumor formation and stem cell migration, the potential benefits of stem cell transplantation in Parkinson's patients should be recalculated for positive results.

The other negative outcomes are neurosurgical hemorrhage, postoperative infection, graft rejection and transplantation of infected cells which are associated with neurosurgery and transplantation medicine. The risk of neurological complications in NSCs due to stem cell migration to inappropriate regions of the brain leads to seizure - like symptoms or brain dysfunction which can be reduced by pre-differentiating NSCs before transplantation. The current research on stem cell transplantation has shown that ESCs provides a promise to relieve parkinsonian symptoms.

Though stem cell therapy has shown positive outcomes in cell-based studies and animal models, the clinical trials did not reveal any convincing results. The cause of this is due to mode of tissue engraftment, patient selection and level of immunosuppression (63). From the discussion, CRT research would benefit the society and it is a valuable treatment for PD as well as for other neurodegenerative disorders. Before moving to the treatment, institutional review boards should ensure for minimized risks so that benefit to risk ratio can be obtained. Hence the treatment with stem cell grafts in PD is a promising one and it should be made a practice for creating drugs in curing PD as well as other neurodegenerative diseases.

Other treatments

Surgical treatments

The patients with levodopa treatment experienced motor fluctuations and dyskinesia (64). The surgical management of PD patients is done with people who are experiencing motor fluctuations.

DBS

Stereotactic neurosurgery raised up due to which the effect of transplantation closed in the treatment of difficult movement disorders. In early 1990's stimulator devices were implanted which created lesions in selected nerve

nuclei which in turn caused a trigger in motor features of PD (65-67). DBS has many benefits such as improvements in the cardinal motor features of tremor, stiffness, and slowness when compared with their therapies. In spite of medication, DBS created stimulation in subthalamic nucleus (STN-DBS) (68). Though the surgical treatment is restricted to certain patients, by assessing the axial and gait symptoms progress despite surgery, then STN-DBS is not suggested as an effective therapy. The gait and axial symptoms relate to the progression of the disease (69), the brainstem pedunculopontine nucleus (PPN) have also been targeted in some studies. The outcome of PPN-DBS remains unidentified (70). The disease progression is unaltered and the nonmotor symptoms and cognitive symptoms were untouched in DBS in certain cases. Though disease modification has some effects on animal models (71), in human, DBS has slight or no impact as a cure in neurodegeneration (72). Hence, from the above data, it is said that DBS remains for specific symptoms. It is not an appropriate choice of treatment in PD.

Gene therapy

Gene therapy aims at treating disease by genetically modified cells either as functionally impaired directly or which are capable of relieving the symptoms. The modified genes can cause either increase or decrease gene expression or restore the gene products. As a therapeutic application, somatic cells are used in these cases. By using viral vectors and non-viral vectors, gene delivery can be made to the targeted cells. Using gene gun or electroporation methods, gene transfer can be made to CNS. In CNS, the most common method used for gene transfer is by using viral vectors (73). This approach is advantageous since the virus can able to transfer the genetic material to the targeted cells to withstand the gene expression. Viral vectors from wild-type viruses are engineered and the genetic information is removed and used as in *trans* for vector production. Hence, the vectors infect cells and transfer the genetic material into the nucleus. This aspect is critical since by replication with the host organism prevents the uncontrolled spreading of transgene delivery as it eliminates virus pathogenicity

In PD, the enzyme aromatic L-amino acid decarboxylase (AADC) is supplied surgically, by an adenoma-associated viral (AAV2) vector, to striatal neurons, were it converts L-DOPA (supplied exogenously by tablets) into DA which is necessary for neuromodulation (74). In contrast, lentiviral vector incorporates genes for three enzymes [guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1), TH, and AADC—marketed as ProSavinV], which supplies the molecular tools for manufacturing DA (75). The effect of this treatment is still unclear. Theoretically, gene therapies can avoid the fluctuating effects of oral medication and slow down the side effects which are inherent to DBS. The smooth delivery of subcutaneous apomorphine and intra-jejunal levodopa replace DA receptor stimulation, and reduces motor fluctuations and improve some aspects of nonmotor symptoms (76). Each of the technologies has some potential drawbacks. For instance, DuoDopa and apomorphine are expensive and poorly tolerated—either by device or drug side effects. In gene therapies, so for the ProSavin gene therapy, lack the control over DA production from the inserted gene and it leads to hyperdopaminergic side effects, which includes dyskinesia and behavioral problems, additionally, it has certain theoretical risks of inducing neurodegeneration in striatal cells (77).

Conclusions

PD is a progressive neurodegenerative disease and the exact mechanisms leading to DA neuronal death in PD are still unclear, though protein aggregation, mitochondrial dysfunction, oxidative stress, altered autophagy have been mentioned as mechanisms that contribute to this devastating neurodegenerative process. From past studies, it is known that the generation of reliable iPSC-based models recently has made an opening with crucial pathogenic mechanisms responsible for the initiation and progression of PD, and also made an impact in identifying novel drugs that may prevent or release from neurodegeneration in PD. Recent findings have optimized for the discovery of new targets for therapeutic intervention. When compared with surgical treatment, there is no single DBS or gene therapy technique that perfectly fits every patient seeking surgical treatment for PD. Based on clinical studies, altered therapies allows consideration of the complexity of the disease that might contribute to positive or negative DBS outcome. Till now, gene therapy has reached clinical trials on the basis of improving the treatments that target motor symptoms. Gene therapy is less effective when compared with CRT. From previous findings, it is evident that the use of CRT by stem cell approach would be an effective and permanent remedy in treating PD. Thus, CRT shows a promising therapy and a mainstream technology in PD and in other neurodegenerative disorders in which advanced research has to done in creating ways to tackle the disease.

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Footnote

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