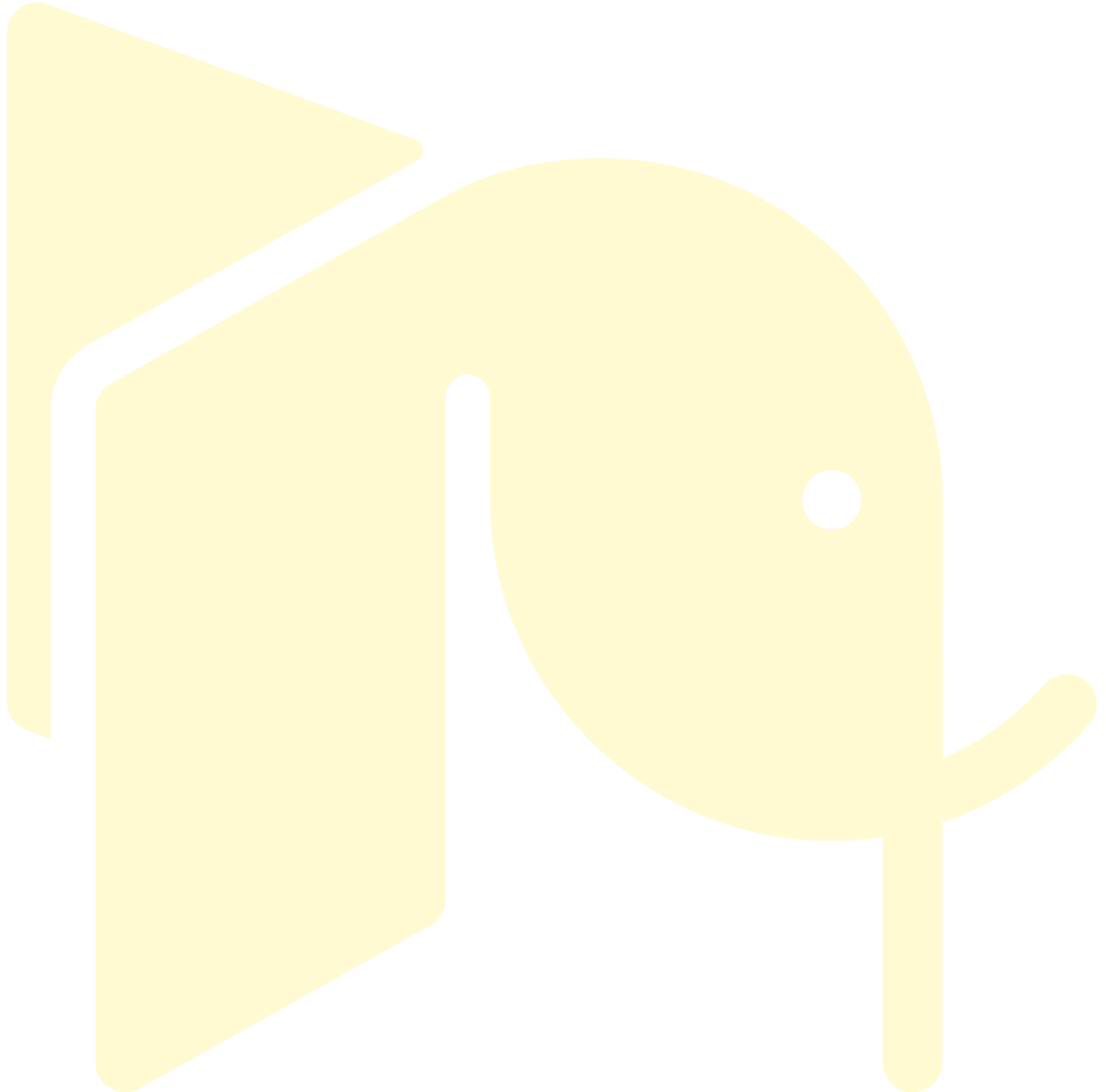


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Clinical and Experimental Cell Therapy in Parkinson's Disease

By Keun-A Chang and Seonghan Kim

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Abstract

Parkinson's disease (PD), a chronic neurodegenerative disorder, is characterized as a movement disorder with resting tremor, dyskinesia, gait disturbance, etc. The main pathology is based on the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain. These motor symptoms can be treated by dopaminergic drugs, but over time, the drug's effect has less efficacy, and side effects develop such as involuntary movements. As there is no gold standard long-term treatment for this condition, there is a strong need to develop new drugs and therapies. The clinical and experimental findings of successful intrastriatal transplantation of fetal mesencephalic dopaminergic neurons into the brains of patients with PD have been well established. The development of human stem cell technology including embryonic stem (ES) cells or induced pluripotent stem (iPS) cells opened a new field called clinical cell therapy, especially for PD. In this chapter, we cover the scientific progress of the clinical and experimental trials of cell therapy for patients with PD. It also contains the recent advances in the clinical application of stem cells including neural stem cells, mesencephalic stem cell, ESC, and iPS cells and unsolved problems in the clinical setting. The combination of gene therapy and gene-manipulated stem cell application in PD therapy will be the most discussed in this area.

Keywords

Parkinson's disease

neurodegenerative disorder

dopaminergic neuron

stem cell

cell therapy

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1. Introduction

The principal pathological features of Parkinson's disease (PD) is the progressive degeneration of dopaminergic (DA) neurons located in the substantia nigra in the midbrain and their projections to the striatum, leading to a major loss of striatal dopamine that controls motor functions []. The degeneration of DA neurons in many patients with PD also results in non-motor symptoms, such as mood problems and cognitive impairment []. The etiology of PD remains unknown in the vast majority of cases, and there are no disease-modifying treatments in the clinic. Characteristic motor symptoms, including rigidity, hypokinesia, tremor, and postural instability, can be treated effectively with the DA precursor L-dopa, DA agonists, monoamine oxidase-B inhibitors, and Catechol-O-methyl transferase inhibitors that reduce the breakdown of DA. The current pharmacologic treatments, including L-dopa, mostly target symptoms only. However, the effect of these drugs decreases over time, and patients may acquire side effects such as motor disturbances along with behavioral and neuropsychiatric problems. Deep brain

stimulation (DBS), in the subthalamic nucleus or globus pallidus, has been introduced as an advanced surgical intervention that works electrically to enhance the motor output. However, none of these treatments reverse the progress of DA neuron degeneration. A new treatment is cell transplantation therapy to replace lost DA neurons and accompanied tissues in PD []. Treating PD with cell transplantation began over three decades ago []. Cell transplantation trials for DA cell replacement and restoration used a variety of different catecholaminergic cells, but the beneficial effect was minimal []. So, there have been many efforts to find an available source of nigral DA cells for grafting, including DA neurons from different species [] and various types of stem cells. Neurorestorative approaches to PD, based on stem cell technology, have been improved to make a large number of nigral DA cells from a stem cell source safe. With two main features (i) the ability of self-renewal and (ii) the capacity to differentiate into specialized cell types, stem cell therapy is in the spotlight for PD treatment, and new studies are being developed recently. The advanced trials of stem cell-based DA cell production have also opened the possibility of developing novel reprogramming strategies []. In this chapter, we discuss how stem cells are currently used in research and are translated into clinical trial for the future treatment of PD.

2. Advent of cell transplantation for treatment of Parkinson's disease

The fundamental principle of cell replacement therapy is simple. The strategy is to restore brain function by replacing dead cells with new healthy cells through intracerebral transplantation. Until the late 1970s, it was believed that repairing the central nervous system might never be possible and then experimental trials showed that intracerebral grafts of fetal mesencephalic DA-rich tissue in rats could ameliorate the symptoms of experimental PD [,]. These preclinical data raised the possibility of transplantation therapy for patients with PD using a human fetal mesencephalic tissue. Although there was much enthusiasm for human cell transplantation, the translation into clinical practice was hindered by three main issues. First, there are practical problems of collecting enough human fetal tissue and identifying the ventral mesencephalon, containing the dopaminergic neurons to graft into the brain of patients with PD. Second, there are ethical problems regarding whether it is morally justified to use human fetal tissues derived from dead, aborted human fetuses. Finally, there were inconsistent results of trials and development of graft-induced dyskinesias in some patients [,]. The initial clinical transplantations in patients with PD were not performed with human fetal tissue. Backlund and Lindval performed pioneering work to implant autologous adrenal medulla cells into the striatum of patients with PD as a local catecholamine source [,]. However, there were adverse effects and low efficacy that led researchers to abandon this method. Clinical trials continued until the early 2000s. Even though there were some reports of improvements, overall there was no significant change in treated patients as compared to controls [-].

Clinical cell therapy for PD now has renewed interest due to recent scientific advances in the development of a method for producing dopaminergic neurons from stem cells and reprogrammed cells. In addition to human fetal mesencephalic tissue, human embryonic stem (ES) cells and human-induced pluripotent stem (iPS) cells are being planned for clinical application. These new cell sources have the potential to prepare dopaminergic neurons in large numbers for cell transplantation therapy for PD []. Local factors within the microenvironment of transplanted neural stem cells affect the fate of the transplanted cells, long-term survival, proliferation, and differentiation []. Further studies for cell delivery route, cell dose, and patient selection are also required and need to be evaluated in greater depth to establish Backlund pre-conditional evaluation system for the successful clinical application of cell-based therapies [].

3. Application of stem cells in Parkinson's disease

There are several types of stem cells that are under consideration for therapeutic purposes, including embryonic stem cells (ES cells), neural stem cells (NSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs).

3.1. Embryonic stem (ES) cells

ES cells are pluripotent cells which are derived from the inner cell mass (ICM) of blastocysts. The indefinite self-renewal ability and plasticity of ES cells allows for *in vitro* generation of an unlimited number of distinct cell types []. In neuronal systems, previous studies have found that functional neurons, astrocytes, and oligodendrocytes could be derived from ES cells *in vitro* [,]. Therefore, ES cells are believed to be able to generate specialized cells to replace damaged tissue in patients suffering from various degenerative diseases [].

ES cells are one of the promising sources that might differentiate into DA neurons. Rodent and human ES cell-derived DA neurons have been shown to repair brain circuitry and restore cerebral function after transplantation into the striatum of rats with PD [,]. Primate ES cell-derived DA neurons were successfully placed into the putamen of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-lesioned monkeys []. In that study, 14 weeks after transplantation, the uptake of [¹⁸F]-DOPA increased, suggesting the functional recovery of ES cell-derived DA neurons. However, the differentiation rate and the survival rate of these neurons after transplantation are still low [,]; less than 300 tyrosine hydroxylase (TH)-positive cells survived after transplantation of $1 \sim 4 \times 10^5$ ES cells into the striatum [,]. Furthermore, residual undifferentiated ES cells may potentially cause tumors, especially teratomas []. Ethical and political concerns regarding ES cell origin are another major limitation. Isolating ICM from blastocysts destroys embryos and increases moral concerns []. Therefore, non-ES cells have become the focus for cell-based therapies.

3.2. Neural stem cells (NSCs)

NSCs are multipotent stem cells that are isolated from either fetal brains or specific regions in adult brains []. In the adult brain, neural stem cells have been found in two major niches: the subgranular zone (SGZ) in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles []. NSCs might differentiate into neurons, astrocytes, and oligodendrocytes []. Due to the specific lineage restriction of NSCs, the risk of potential tumor formation is reduced, and NSCs retain their regional specificity [].

Recent reports have shown the potential ability of NSCs to differentiate into DA neurons [,]. Overexpression of several genes, such as Brn4, TH, glial cell line-derived neurotrophic factor (GDNF), and Lmx1a, may contribute to the maturation and survival of differentiated DA neurons from NSCs [-]. Transplantation of NSC-derived DA neurons or NSC-derived DA neurons overexpressing Wnt5a or Nurrl has led to functional improvement in animal models of PD [,]. However, the survival rate for TH-positive DA neurons after transplantation was very low, less than 4.3%, and the transfection of Wnt5a into NSCs increased 10-fold over TH-positive DA neurons []. The transplantation of NSCs from SVZ improved the symptoms of PD, but the survival rate of these cells was still low [,]. Therefore, new methods to increase the cell number and survival rate of transplanted cells must be developed for successful NSC transplantation.

3.3. Mesenchymal stem cells (MSCs)

MSCs are typically defined as multipotent stromal cells that can differentiate into all cells of mesodermal origin []. MSCs are commonly sourced from the bone marrow, but there has been successful isolation of MSCs from the adipose tissue, umbilical cord blood, amniotic fluid, and synovial membranes []. MSCs have several advantages; first, these cells are easily collected from patients' own tissue. Second, ethical concerns for MSCs are decreased because they can be retrieved from adult tissues or umbilical cord blood donations. Third, MSCs are an immunologically favorable source for transplantation. MSCs have a property of immunomodulation to suppress inflammation and downregulate pathogenic immune responses to limit graft-versus-host disease []. This characteristic would be an important benefit for use in transplantation.

3.3.1. Bone marrow MSCs (BMSCs)

Bone marrow is the most common source of MSCs. Important features of BMSCs are that they are a resource with easy access for harvesting, and they have the ability to migrate into the brain across the blood-brain barrier []. This important advantage suggests the possibility that MSC transplantation may be applicable with noninvasive and peripheral delivery tools. Several reports promote the possible potentials of neuronal differentiation of BMSCs [-]. Although these results support the therapeutic potential of BMSCs for treating neurological disease, their rate of differentiation into neuronal cells is low, and these cells can be maintained for a few passages []. However, only 0.8% of grafted cells expressed TH immunoreactivity []. Transfection with Notch1 intracellular domain (NICD), basic fibroblast growth factor (bFGF), forskolin, ciliary neurotrophic factor (CNTF), or GDNF increased the proportion of tyrosine hydroxylase-positive and dopamine-producing cells []. In a clinical trial, advanced patients with PD unilaterally transplanted with bFGF-treated BMSCs in the SVZ showed clinical improvement after 12–18 months of follow-up without being teratogenic [].

However, this result suggests that while BMSCs may be a good source for patient health and harvesting safely, their low differentiation rate limits the potency of BMSCs for transplantation.

3.3.2. Umbilical cord blood (UCB) cells

UCB cells are MSCs that are derived from umbilical cord blood attached to the placenta. The amount of cells that could be collected from cord blood is limited after delivery. However, UCB cells have many potencies for transplantation such as easy expandability and tolerance to human leukocyte antigen (HLA) disparities, which significantly decrease the risk of immune rejection [].

Although several reports showed that UCB cells could be differentiated into neuronal and glial cells [,], the differentiation potential of UCB cells is similar to that of BMSCs. To induce neuronal differentiation of UCB, UCB cells were cultured with sonic hedgehog (SHH) and fibroblast growth factor-8 (FGF-8), increasing the neuronal differentiation to 12.7%. However, transplantation of both undifferentiated MSCs and differentiated UCBs improved the symptoms of PD in 6-OHDA PD models [,].

3.3.3. Adipose-derived stem cells (ASCs)

ASC has an advantage due to easy access to adipose tissue and abundance with proliferation and differentiation potential []. ASCs have a high proliferation capacity *in vitro* and differentiate into cells with several neuronal and glial characteristics []. The implantation of human ASCs leads to no adverse side effects such as tumorigenicity, chromosomal abnormalities, or immune rejection []. In an *in vitro* study, the LIM homeobox transcription factor 1, alpha (LMX1A)- and neurturin (NTN)-infected ASCs showed a dopaminergic differentiation by secreting the dopamine [].

The therapeutic efficacy of ASCs has been assessed in various animal models with PD. The ASCs were intravenously injected into the tail vein of a PD mouse model induced by 6-hydroxydopamine (6-OHDA) []. After the injection of ASC, the behavioral performances were significantly improved, and dopaminergic neurons were rescued []. In a rotenone-induced PD rat model, transplantation with ASCs increased the serum level of BDNF and the brain levels of dopamine and TH []. This study suggests that ASC transplantation might be advantageous due to their immunomodulatory, anti-inflammatory, and neurotrophic effects. A recent study found that the transplantation of neuronal-primed ASCs derived from rhesus monkey tissue combined with adenovirus containing NTN and TH improved PD behavior including tremor recovery and motility in MPTP-lesioned hemi-parkinsonian rhesus monkeys []. In postmortem analysis, combined transplanted ASCs with NTN and TH could replace lost neurons and reconstruct the nigrostriatal pathway in the brain []. Overall, this study underscores that transplanted ASCs may have therapeutic potential for PD.

3.4. Induced pluripotent stem cells (iPSCs)

iPSCs were recently focused one as a potential cell source to repair neuronal networks in various neurological diseases. Since iPSCs are derived from adult tissues, complicated ethical issues and the risk of immune rejection can be avoided when used as a substrate for transplantation. For the production of iPSCs, retroviral transduction of four transcription factors Oct3/4, Sox2, Klf4, and c-Myc were needed []. Since c-Myc is well defined as an oncogene, and Oct4 and Sox2 are also overexpressed or activated in various types of cancer, reactivation of these genes increases the risk of tumor formation [-]. Therefore, one major weakness of the iPSC is an increased risk of tumor formation.

In a recent report, disease-specific iPSC derived from patients suffering from PD showed disease-specific cellular pathological phenotypes, such as abnormal pathological α -synuclein protein and accumulation and alterations in autophagy []. The use of iPSC in patients suffering from sporadic or genetic forms of PD can offer a PD iPSC-based model for drug discovery, earlier diagnosis and development of individualized treatment in the preclinical phase of the disease [].

DA neurons generated from mouse iPSCs were first transplanted into the striatum of a rat PD model, improving the symptoms of PD [,]. DA neurons differentiated from iPSCs of patients with PD were transplanted into the striatum of a PD transgenic rat, and these neurons survived for several months and further improved the symptoms of PD []. Most importantly, these transplanted cells did not display signs of teratoma formation in the grafts [].

4. Challenging points

The trials of cell transplantation to treat PD were first tested three decades ago []. Despite long time basic and clinical studies, there still is no cure of dopaminergic cell therapy for PD. Since the first trial of cell transplantation with autologous adrenal medulla cells into the striatum of patients with PD, cell sources of implants have been developed into fetal mesencephalic tissue, which was rich in dopaminergic neurons [,]. However, the minimal beneficial effects of transplantation, lack of efficacy, and occurrence of troublesome graft-induced dyskinesia (GID) have halted the clinical application of cell therapy for a while [, ,]. The translational trial of fetal ventral mesencephalon (fVM) has raised arguments about ethical decisions to use human fetal tissue. In addition, collecting enough fetal tissue to graft has been a problem in practical aspects and not promising for PD therapy due to their low efficacy.

The development of human stem cell technology including human embryonic stem (hES) cells or induced pluripotent stem cells (iPSCs) opens a new era to the field of clinical cell therapy, especially for PD in the restoration and replacement of degenerated dopaminergic neurons and DA neural circuit. Scientists are investigating which stem cells (e.g., embryonic, neural stem cells, mesenchymal stem cells, induced pluripotent stem cells, umbilical cord blood cells, etc.) are best for developing a potential therapy for PD. Translating animal model results into human trials requires controlling many factors including the type of stem cells, culture conditions, the protocols for injecting cells into the brain, and the method of activation into DA neuronal differentiation. Although stem cells have the best potential to become a future treatment for PD, there are some challenging points to overcome before application into human trials.

Point 1: Ethical issue regarding their origin

ES cells are inner cell mass (ICM) of blastocyst-derived pluripotent cells. For the isolation of ICM, it is inevitable to destroy early embryos, which leads to a moral concern []. This moral concern has been overcome by the ability to harvest adult stem cells and iPSCs. Thus, the number of basic and clinical studies has been increased. Therefore, this inherent ethical issue needs to be solved before launching the practical application of hES cells in PD cell therapy. This is very complicated due to multiple concerns such as regional, religious, and social interests. That is why scientists keep trying to find a common ground for future research. Since the iPSCs may be derived directly from adult tissues, complicated ethical issues may be avoided when they are used as a potential cell source for cell therapy.

Point 2: Development of large numbers of dopaminergic neurons in standardized preparations

It is estimated that for successful implantation into the human brain, the number of dopaminergic neurons needed will be >100,000. The overexpression of transcription factors involved in DA neuron development has been used in hES cell-derived DA neurons in culture. *Lmx1A*, *Nurr1*, and *Pitx3* have been shown to expand the number of DA neurons in culture [,]. GSK3 β inhibitor and FGF8 also showed reliable production of DA neurons []. iPSCs can be produced as patient-specific cells potentially used for transplantation. However, the reprogrammed dopaminergic neurons are still incomplete regarding their functional efficacy. The majority of generated neurons were glutaminergic and GABAergic. Several recent studies developed neuronal subtype-specific transcription factors that are involved in the direct conversion process into DA neurons [,].

Point 3: Risk of tumor formation

The tumorigenicity of stem cell-derived cells should be assessed, and all cell types in the implants must be identified. The high capacity of self-renewing and pluripotency of ES cells increases the risk of tumor formation, especially teratoma []. The major drawback of the iPSCs is also tumor formation because of the reactivation of *c-Myc*, one of the major oncogenes []. With a modified reprogramming protocol that eliminates *c-Myc*, it can reduce the tumorigenicity and also significantly decrease iPSC formation []. Recently, poly(ADP-ribose) polymerase I (ParpI) reported significantly decreased tumor formation in iPSC production [], but the teratoma formation after transplantation could not be completely excluded []. However, these trials are promising regarding the potential to overcome major drawbacks before clinical use. Tumor formation also reduces the efficacy of stem cell production in these patients. To generate better-defined stem cell populations free from tumor cells, fluorescence-activated cell sorting (FACS) and/or magnetic-activated cell sorting (MACS) techniques can be applied. The sorter can select transplantable safe stem cells, and thus deplete tumor cells simultaneously [,].

Point 4: Improvement of efficacy of the graft

After reviewing all of the previous points, cell potency of stem cell-derived dopaminergic neurons must be analyzed and compared to fetal dopaminergic neurons before application in patients. This comparison can be considered as the gold standard and can be used to estimate the number of cells to be implanted. The growth capacity of the dopaminergic neurons needs to be analyzed to determine the distribution of implants required to reinnervate human striatum. The recovery after cell therapy also depends on patient selection. For successful transplantation, it will be advantageous if patients are in an early stage of the disease.

5. Perspectives

Stem cells are unique in that they can self-renew and differentiate into specialized cell types, especially all neural lineage cells. These two key features have drawn the interest to develop and apply these cells in basic and translational research for cell therapy strategies. Despite three decades of DA neuron cell replacement research, transplantation of DA neurons into striatum has not yet been established as a competitive therapy for patients with PD. However, there have been several scientific advances in clinical trials. The grafted neurons survive over time, and neuronal growth with functional connections in adult human brain has been established for potential clinical applications. Dopaminergic innervation by cell replacement therapy shows major relief of motor symptoms. However, the patients developed non-motor symptoms such as anxiety, mood fluctuations, and sleep problems and were detected with a progressive loss of serotonergic neurons that occur concomitantly with the graft-induced dopaminergic regeneration. There are still significant challenges for the successful clinical application of stem cells as a treatment for PD. The issue regarding the risk for tumorigenicity and graft-induced dyskinesias should be assessed seriously. In this evaluation, the determination of identity of all cell types in the implants will be essential. Theoretically, cell sorting can eliminate tumor-forming cells and serotonergic neurons to improve the safety of cell transplantation. Combined with recent development in stem cell fields, cell-replacement strategy provides optimistic options. Human ES and iPSC-derived DA neurons are in development for clinical applications. With these new sources of cells, there will be a great development of clinically competitive cell therapy for patients with PD. Many challenges still remain for successful clinical trials; many research groups provide scientific progress and significant clinical advances in these fields.

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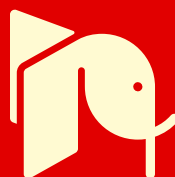
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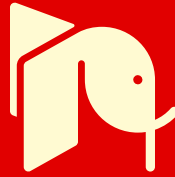


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