

Stem Cell Therapy for Parkinson's disease: A Review

Vipul Gandhi, Sushil Burle, Satish Kosalge
Department of Pharmacy,
Hi-Tech College of Pharmacy,
Morwa, Chandrapur, Maharashtra, India
* vipul96gandhi@gmail.com

ABSTRACT

Some of the problems with unproductive relaxing treatments and insufficient repair aptitude in the central nervous system are most troubling problems for few neurological diseases. Providentially, the development of clinically relevant populations of stem cells has provided an opportunity to overcome the failure of endogenous repair systems and substitute new cells into the injured brain. However, there are still several existing difficulties in interpreting into clinical application. In this review, we mainly focus on the stem cell based therapies for Parkinson's disease and discuss the possible advantages and drawbacks. We hope this review may provide suggestions for viable policies to overcome the current technical and biological issues related to the application of stem cells in Parkinson's disease (Fu et al., 2015).

Keywords: Stem cells, Cell replacement therapy, Neurodegenerative disease, Parkinson's disease

INTRODUCTION

The Stem cells have the potential to develop into many different types of cells in the body. It mostly serves as a repair system for the body. This type of cells is of two type embryonic cells and adult cells. On a division, the stem cells have a potential while repairing it remains same or develop into another type of cell with more sophisticated functions it mostly develops as a muscle, brain or RBC cells.

The stem cells consist of many different types of cells it many modifies the embryonic and adult cell used to differentiate stem cells by the developmental stage of the animal from where this cells come. The adult stem cells more correctly termed as "**somatic**" stem cells meaning **from the body** mostly found in the fetus, umbilical cord blood, placenta, and infants. In the 3- to 5-day-old embryo, called a blastocyst, the inner cells give rise to the entire body of the organism, including all of the many specialized cell types and organs such as the heart, lung, skin, sperm, eggs and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease. In laboratory scientist and researchers are continuously working on various aspects of stem cell how they are different from other cells, there essential properties and what makes them different from specialized cell

types. Many new researchers are also using the stem cell for the screening of new Drugs moiety apart from this it also helpful for the development of model systems to study normal growth and identification of causes of birth defects (Canet et al., 2014)

CLASSIFICATION OF STEM CELLS (Canet et al., 2014)

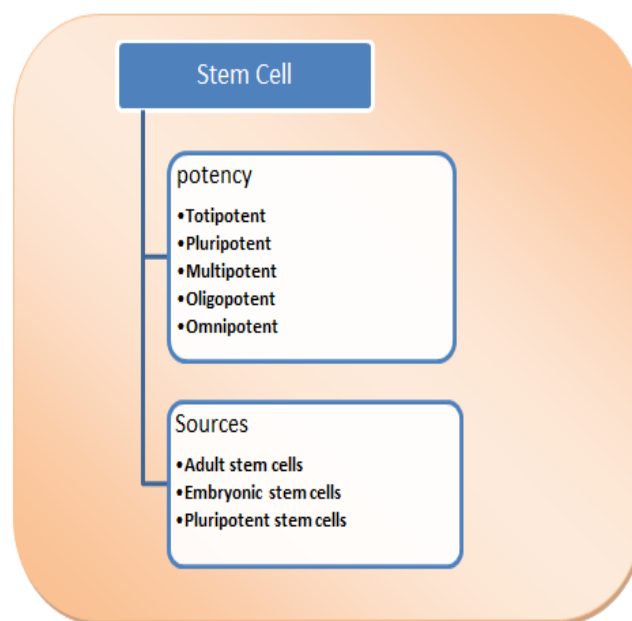


Fig.1. Classification of Stem Cell

ON THE BASIS OF POTENCY

The stem cell classification on the basis of potency:

Totipotent: These types of cells are having the ability to differentiate into all possible cell types. Examples are the zygote formed at egg fertilization and the first few cells that result from the division of the zygote.

Pluripotent: The ability to differentiate into almost all cell types. Examples include embryonic stem cells and cells that are derived from the mesoderm, endoderm, and ectoderm germ layers that are formed in the beginning stages of embryonic stem cell differentiation.

Multipotent: The ability to differentiate into a closely related family of cells. Examples include hematopoietic (adult) stem cells that can become red and white blood cells or platelets.

Oligopotent: The ability to differentiate into a few cells. Examples include (adult) lymphoid or myeloid stem cells.

Omnipotent: The ability to only produce cells of their own type, but have the property of self-renewal required to be labeled a stem cell. Examples include (adult) muscle stem cells.

ON THE BASIS OF SOURCES

The easiest way to categorize stem cells is by dividing them into two types: Early or embryonic and mature or adult. Early stem cells, often called embryonic stem cells, are found in the inner cell mass of a blastocyst after approximately five days of development.

Embryonic stem cells: Embryonic stem cells are self-replicating pluripotent cells that are potentially immortal. They are derived from embryos at a developmental stage before the time of implantation would normally occur in the uterus. The embryos from which human embryonic stem cells are derived are typically four or five days old and are a hollow microscopic ball of cells called the blastocyst.

Adult stem cells: Adult stem cells are undifferentiated totipotent or multipotent cells,

found throughout the body after embryonic development that multiplies by cell division to replenish dying cells and regenerate damaged tissues.

Pluripotent stem cells: nowadays the third type of stem cell, with properties similar to embryonic stem cells, has emerged. Scientists have engineered these induced pluripotent stem cells (iPSCs) by manipulating the expression of certain genes - 'reprogramming' somatic cells back to a pluripotent state.

WHAT IS PARKINSON'S DISEASE? (Choi, S. S et al., 2017) (Standaert D.G. et al., 2006)

Parkinson's disease is a type of disorder of movements that can affect the ability to perform common and daily activities. As this disease is linked to a wide range of symptoms, These symptoms are typically divided into; i) Motor symptoms and ii) Non-Motor symptoms.

The most common motor symptoms of Parkinson's disease are tremor (a form of rhythmic shaking), stiffness or rigidity of the muscles, and slowness of movement (bradykinesia). A person with Parkinson's disease may also have trouble with balance, posture, coordination, and walking. Common non-motor symptoms of Parkinson's disease are constipation, sleep problems, depression, anxiety, and fatigue (Sung et al., 2017).

CAUSES OF PARKINSONS DISEASES

Genetic Factors: Scientists have estimated that less than 10% of cases of Parkinson's disease are primarily due to genetic factors. The most usual genetic effect that triggers Parkinson's disease is a mutation in a gene called LRRK2. This defect is particularly found in families of North African or Jewish descent. Mutations in alpha-synuclein have been found to trigger Parkinsons disease, but these are very few. In most cases of Parkinson's disease, no primary genetic cause can be found.

Environmental Factors: Certain environmental effects, such as exposure to chemicals, pesticides or certain heavy metals and repeated head injuries, can increase the risk of Parkinson's disease. It may not affect in certain cases due to habituation of environment. However, the environmental factors

do influence the development of Parkinson's disease, perhaps particularly in people who also have a genetic susceptibility.

Other Factors: This factor includes age because of it most common in adults above the age of 50. Mostly the women are having more percentage than men. Parkinson's disease often seems to affect Caucasians more than African Americans or Asians. Now that you know a bit more about what Parkinson's disease actually is, the following chapter will provide greater detail about what to expect in terms of symptoms (Khan et al., 2013).

MOTOR AND RELATED SYMPTOMS OF PARKINSON'S DISEASE:

There are five primary motor symptoms of Parkinson's disease:

- Tremor

- Rigidity
- Bradykinesia (slow movement)
- Postural instability (balance problems)
- Walking/gait problems.

NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

- Disturbances in the Sense of Smell
- Sleep Problems
- Depression and anxiety
- Fatigue
- Mental processes
- Weight loss
- GIT related issues
- Lightheadedness
- Urinary issues
- Sexual concern
- Sweating
- Melanoma

STAGES OF PARKINSON'S DISEASE:

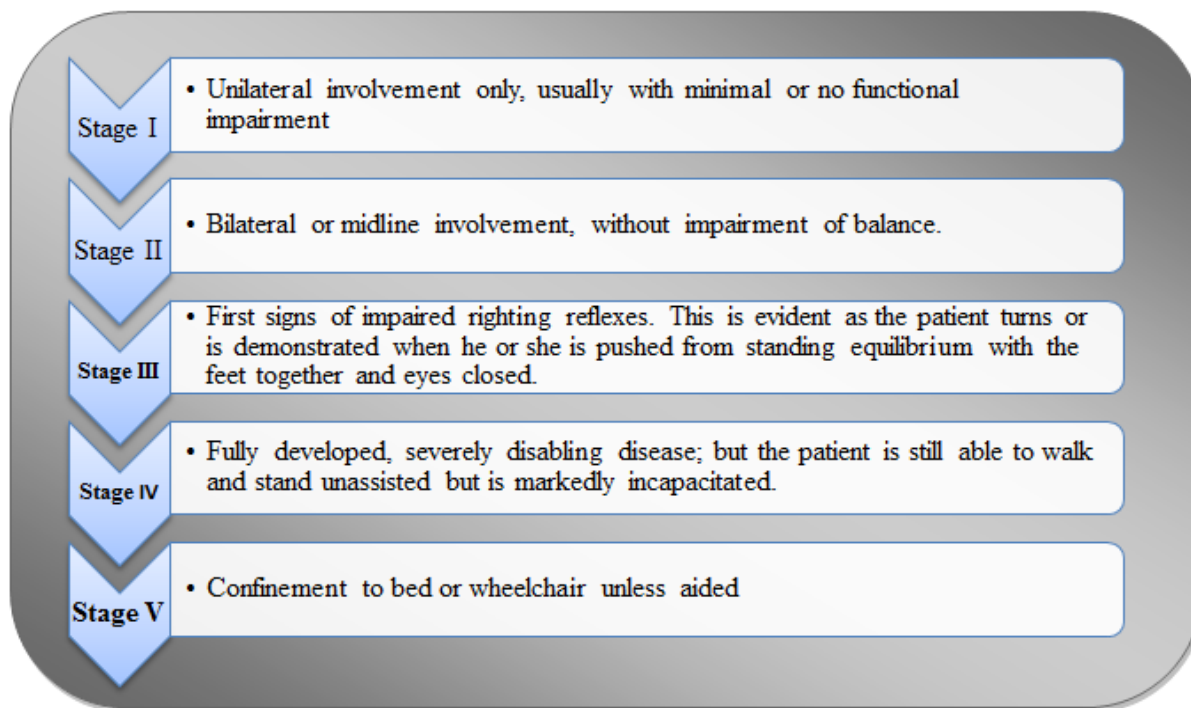


Fig.2. Stages of Parkinson's disease

PATHOPHYSIOLOGY

The characteristic pathological features of Parkinson's disease are a reduction in neurons of pigmented brainstem nuclei, along with the presence of eosinophilic inclusion bodies, called Lewy bodies,

in living cells. In Parkinson's disease, before the appearance of symptoms, there is a loss of over 80% of nigral neurons. The 'Braak hypothesis' has been proposed to account for the spread of pathology within the Parkinsonian brain and suggests that α -

synuclein may first accumulate in the lower brainstem and then gradually arises rostrally to affect critical brain regions including the substantia nigra and ultimately the cerebral cortex (Chen L. et al.,2005) Dopaminergic neurons are not only cells to die within the brainstem, but an excess of other nuclei and neurotransmitter systems are involved too. For example, cholinergic neurons within the pedunculopontine nucleus degenerate, providing potential clinicopathological correlates with postural instability, swallowing difficulty (dysphagia) and sleep disturbance (REM sleep behavioral disturbance). The involvement of this nucleus in Parkinson's disease may explain why dopaminergic therapy is relatively ineffective in treating these particular clinical problems. Within the striatum, changes occur within γ -aminobutyric acid-containing neurons, as a concern of nigrostriatal dopaminergic deficiency and also an anon-physiological dopaminergic replacement. These changes are thought to play a key role in mediating the development of involuntary movements (dyskinesias) which develop after a number of years of levodopa treatment. The loss of noradrenergic and serotonergic neurons within the locus coeruleus and the raphe nucleus, correspondingly, may provide a pathophysiological basis for depression, which is common in Parkinson's disease. (Shulman J.M. et al.,2011) (Chen L. et al.,2005)

STEM CELL THERAPY

The stem cell is the techniques most useful for cure of injury or treats the disease. This type of cell is having the ability to self-renew which offers significant potential for generation of tissue that can potentially replace diseased and damaged area in the body with minimum risk of rejection and side effects (Rusu, E. et al., 2016) The medical researcher anticipate that adult and embryonic stem cell will soon be able to treat cancer, diabetes, parkinsonism, Huntington's disease, etc. (Kalra and Tomar, 2014) (Rusu, E. et al., 2016)

TREATMENT OF PARKINSON'S BY STEM CELL THERAPY: (Lindvall and Kokaia 2006; Lindvall et al. 1987; Weil, R. et al., 2016)

Parkinson's disease (PD) is the second most common neurodegenerative disorder, which affect 1 % of the population worldwide after the period of 65 years of

age. The typical symptoms of Parkinson's disease are bradykinesia, rigidity and resting tremor. The main pathological features are extensive loss of dopamine neurons in the Substantia Nigra pars compacta and the accumulations of cytoplasmic eosinophilic inclusions, Lewy bodies. The cause of degenerated nigrostriatal dopaminergic neurons is unknown. Presently the therapy given to Parkinson's patients include levodopa, monoamine oxidase inhibitors, dopaminergic agonists, and deep brain stimulation. Normally, the effectiveness of oral medications starts to wear off after a period of 5 years. Moreover, these treatments cannot repair the damaged dopaminergic striatal projections; therefore, restorative approaches should be considered in order to improve the therapeutic action. Since Parkinson's disease patients display selective degeneration of SN dopaminergic neurons, cell replacement therapies which can produce functional dopaminergic neurons may be a valuable therapeutic tactic. To achieve a successful cell-based therapy in Parkinson's disease, some criteria for cell transplantation are generally suggested (Lindvall and Kokaia 2006; Lindvall et al. 1987).

- The cells should possess the molecular, morphological and electrophysiological properties of dopaminergic neurons in substantia nigra;
- The therapy should enable 100,000 or more DA neurons to survive long-term in human putamen;
- The grafted cells should re-establish a dense terminal network throughout the striatum to functionally integrate into host neural circuitries. Here we review the progress of stem cell therapies and discuss the major problems encountered in Parkinson's disease.

Graft (Implantation):

The content of graft is the serious issue when performing the transplantation. It is presently unknown whether symptomatic relief would be best achieved by implanting of DA neurons or a graft containing a portion of glial cells. During embryonic development, several studies support the necessary role of astrocytes in neural differentiation, implying that glial cells are important for fate determination

of precursors during implantation. So, mesencephalic tissues consisting glial cells were most often used in previous studies. Another key issue in performing grafts for PD treatment is that implanting the most suitable subtype of DA neurons is also critical for the result of transplantation. DA rich-ventral mesencephalic grafts contain two types of DA neuron progenitors, containing A9 Substantia Nigra neurons and A10 dopamine neurons of the Ventral Tegmental Area. The A9 subtype DA neurons only sends innervated axons into the striatum in rats suggesting that mesencephalic grafts with more A9 subtype DA neurons would be more beneficial for PD treatment. In the late 1980s, clinicians transplanted human embryonic or fetal ventral mesencephalic tissues into PD patients, but the results were varied. In Madrazo and Lindvall's open-label trials, PD patients showed improvement of Unified Parkinson's Disease Rating Scale (UPDRS) after receiving fetal DA neuron graft. Yet, the results from two double-blind trials funded by the National Institutes of Health (NIH) in the 1990s showed no major effects. Even more, several side-effects have been shown in PD patients who received these transplantations. The results of these two open-label and double-blind trials raise critical issues regarding ethical considerations and may enhance controversy which can dissuade the potential use of transplants for PD.

ES cell derived DA neurons ES cells are one important source that has been used to differentiate into DA neurons in the laboratory. DA neurons derived from rodents and humans have been shown to survive and function after transplantation into the striatum of PD rats (Kim et al. 2002). Furthermore, the uptake of [18F]-DOPA also increased 14 weeks after transplantation, suggesting exogenous ES cell-derived DA neurons could offer the functional recovery of DA neurons. Until now, ES cells are still the most promising source to differentiate into DA neurons (Kim et al. 2002); however, the efficiency to differentiate into DA neurons and the existence rate of these neurons after transplantation is still low. For example, prior reports showed less than 300 tyrosine hydroxylase (TH)-positive neurons survived after transplanting 100,000–400,000 ES cells into the striatum. Therefore a critical issue that must be resolved to enhance recovery after transplantation

in PD is an improvement of the differentiation and survival rate (Bergman and Deuschl, 2002)

iPSC-derived DA neurons: (Nguyen, H.N., et al., 2011) (Fu, M.-H et al., 2015) (Cooper, O et al., 2012) Subsequently, the iPSC technique was recognized in 2006, another cell source to generate DA neurons was provided. At first, in 2008, the DA neurons were made from mouse into the striatum of a rat Parkinson's disease model, thereby easing the symptoms of Parkinson's disease. In 2010, DA neurons differentiated from iPSCs of Parkinson's disease patients were transplanted into Parkinson's disease transgenic rats, and these neurons survived for some months and further eased the symptoms of Parkinson's disease. These transplanted cells did not display α -synuclein positive inserts bodies in hosts, signifying that in Parkinson's disease patients may be a viable option. However, several reports have mentioned patient-derived iPSCs are still more vulnerable to Parkinson's disease because of mutations or epigenetic markers in cells. Furthermore, the risk of tumor formation still needs to be reduced before the medical application can be understood. Since the method of iPSC production was only developed a few years ago, further optimization may overcome these problems. (Nguyen, H.N., et al., 2011)

NSCs and NSC derived DA neurons: NSCs (Neural stem cells) are multipotent stem cells that are defined as "neurally" designed cells and retain their regional specificity. Therefore, NPCs that are derived from chiefly DA (dopamine) vicinity, such as ventral mesencephalon (VM), should be the most suitable source of DA neurons. Several reports have shown the potential skill of NSCs to differentiate into DA neurons, and also established the advances of symptoms in Parkinson's disease models after transplantation of NSC-derived DA neurons. Furthermore, overexpression of different genetic factor, such as Lmx1a, glial cell line-derived neurotrophic factor (GDNF), Brn4 and TH, in NSCs has improved the valuable effects of NSC-derived DA neurons. In animal studies, NSC-derived DA neurons overexpressing Nurr1, a critical factor involved in DA requirement and survival, has led to functional improvement in rats treated with 6-hydroxydopamine (6-OHDA), a toxic-induced

Parkinson's disease model. However, the survival rate of TH positive neurons after a replacement was less than 4.3 %. The auxiliary of NSCs from SVZ boosted the recovery of Parkinson's disease symptoms, but the survival rate of these cells was still low. Therefore, the most important matter that must be overcome in order to achieve NSC relocation is to increase the cell number and existence rate of transplanted cells. (Nguyen, H.N., et al., 2011)

IMMUNE RESPONSE

Although the brain is considered as an immune-privileged site, the host immune system still responds to the grafts. The interaction between implantation and the endogenous immune system affects the survival of grafted cells. In several clinical trials, transplantation without adequate immune-suppression may have led to poor outcomes, while transplantation with an immune-suppressant, such as cyclosporine, azathioprine, and prednisolone, produced better effects (Lindvall et al. 1987). Unfortunately, patient symptoms worsened after withdrawal of immune-suppression, and postmortem showed grafts were surrounded by activated microglia and immune reactivity. These results imply that immune reactions exert a negative effect during transplantation, and it would be necessary to use an immunosuppressant in combination with grafting; however, further studies are still needed to determine the optimal immunosuppressant and the period of treatment. (de la Fuente-Fernandez, R et al., 1998)

MAJOR DISPUTES AFTER GRAFTS:

Depending on the reports of several cell-based studies in both animals and humans, there are two major apprehensions related to grafts.

Graft Induced Dyskinesia (GID) (Fu, M.-H et al., 2015)

The occurrence of dyskinesia after transplantation was first reported by Defer et al. (1996), but did not obtain much courtesy till Freed's trial in 2001. They described the development of "graft persuaded dyskinesia (GID)" in 15 % of transplanted patients 1 year after transplantation. This surprising symptom reached 56 % in Olanow's study. It is speculated that the number of grafted cells used in the surgery-controlled clinical trials was less than those of other

more successful studies (Lindvall et al. 1987). Furthermore, immune-suppression may be also an important aspect since dyskinesia did not develop till immunosuppression withdrawal in several reports. The other possible dispute is that other varied grafts were originated in ventral putamen, containing serotonergic neurons. These grafts led to islands of reinnervation and abnormal production of DA. Hence, transplanting a sufficient number of cells having a pure population of DA neurons in basal ganglion with immunosuppression is suggested to avoid the progress of GID.

Grafts affected by PD process: Indications that PD pathology may propagate from host to grafts is emerging. The presence of LBs and Lewy neurites in grafted DA neurons were generally observed 11–16 years after human fetal mesencephalic transplantation however, α -syncline staining is generally not detectable in adults younger than 20-year. These observations imply that PD pathology can be transferred from host to graft. The exact reasons for this negative outcome remain unresolved. A recent report showed that fetal cell transplantation in two PD patients remains highly functional even 15–18 years after surgery. Therefore, although the spread of PD pathology may occur after transplantation, the period of beneficial effects from transplantation is still longer than that of current medications, suggesting stem cells still could be a potential clinical therapy (Rana, 2011).

MECHANISMS OF STEM CELL THERAPY IN PARKINSON'S DISEASE

The mechanism is classified in two ways it includes: Direct Repair Pathway. 2. Indirect Repair Pathway

1. Direct repair pathway:

It includes supplementing endogenous neurogenesis, DA neuron differentiation, DA release, striatum reinnervation and neural trails integration.

2. Indirect repair system through trophic factors:

Stem cells express various neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), cerebral dopamine neurotrophic factor (CDNF), nerve growth factor (NGF), or glial-derived neurotrophic factor (GDNF), and facilitate DA neuronal differentiation and maintenance. These passerby effects are mainly likely to result from

grafts comprised of NSCs and MSCs. However, it is still hard to distinguish clearly which pathway shows a dominant role, and, as a result, it is generally assumed that both direct and indirect pathways contribute to the beneficial effects after transplantation. (Kim, J.H. et al., 2002)

Treatment Efficacy from Patient Perspective:

We need to detect the outcome measures that are meaningful not only to investigators and clinicians but also to patients and for that we will work in partnership with end users in order to safeguard our key outcomes which are related to patient perspective. As a mean, we will early on establish a “user board”. An ultimate challenge is also to explicitly identify/develop tools that imitate real-life challenges (e.g. outdoor mobility) in standardized settings to certify that potential treatment effects translate into “real-world” settings. Pilot tests are then needed well advance of a clinical trial in order to determine the acceptability, probability, and reliability of such assessments. Toobin-depth investigate the patient viewpoint, qualitative methods (e.g. interviews) will be used as a complement to quantitative methods that include both unbiased measures and patient-reported outcomes measures. Taken together, our measurements will hit the difficulty of health condition such as PD by covering both functions, activities of importance in daily life and participation, i.e. “involvement in life situations”. (Lindvall and Kokaia 2006; Lindvall et al. 1987).

CONFLICT OF INTEREST: Authors have no conflict of Interest.

CONCLUSION

From the above theories, it has been concluded that there is still no perfect treatment for Parkinson's disease has been developing yet. However, the outcomes from the clinical trials have not been proven consistent or convincing. This may be due to a combination of factors, such as patient selection, amount and mode of tissue engraftment and the level of immune-suppression. Moreover, another side effect to be considered is GID. Fortunately, grafted tissues were unaffected by PD progression within 10 years after transplantation, so the treatment of PD with stem cell grafts is still a favorable direction. The major advantage of this strategy is the restorative and trophic abilities of the grafted cells which reach far away from drugs prescribed in a recent practice.

Another thing is the regeneration of dopaminergic neurons and the maintenance of dopamine homeostasis which are important for successfully treating this disease as the patients with PD are greatly affected by the loss of dopaminergic neuron. However, the major problem to developing therapeutic strategies for neurodegenerative diseases is the brain complexity. Due to the reason that the transplanted stem cells can redevelop neurons and glia in an optimal microenvironment and produce neuroprotective molecules, the stem cell therapy has great potential to treat PD as well as other neurodegenerative diseases.

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