# Cell based therapies in Parkinson's Disease

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**ABSTRACT**

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is characterized by bradykinesia, hypokinesia/akinesia, rigidity, tremor, and postural instability, caused by dopaminergic (DA) striatal denervation. The prevalence of PD increases from 50 years of age with steep rise after age 60 years. Current treatment of PD relies heavily on replacing lost dopamine either with its precursor L-dopa or dopamine agonists (ropinirole, pramipexole, bromocriptine, lisuride etc). Other pharmacological measures like catechol-O-methyltrasferase (COMT) inhibitors like entacopone, telcapone and monoamine oxidase B (MAO-B) inhibitors like selegiline and rasagiline are also useful, while L-dopa remains the gold standard in the treatment of PD. Emerging therapies are focusing on cell based therapeutics derived from various sources.

**KEYWORDS :** Parkinson's Disease, Stem Cells, PD Treatment, Cell Based Therapy

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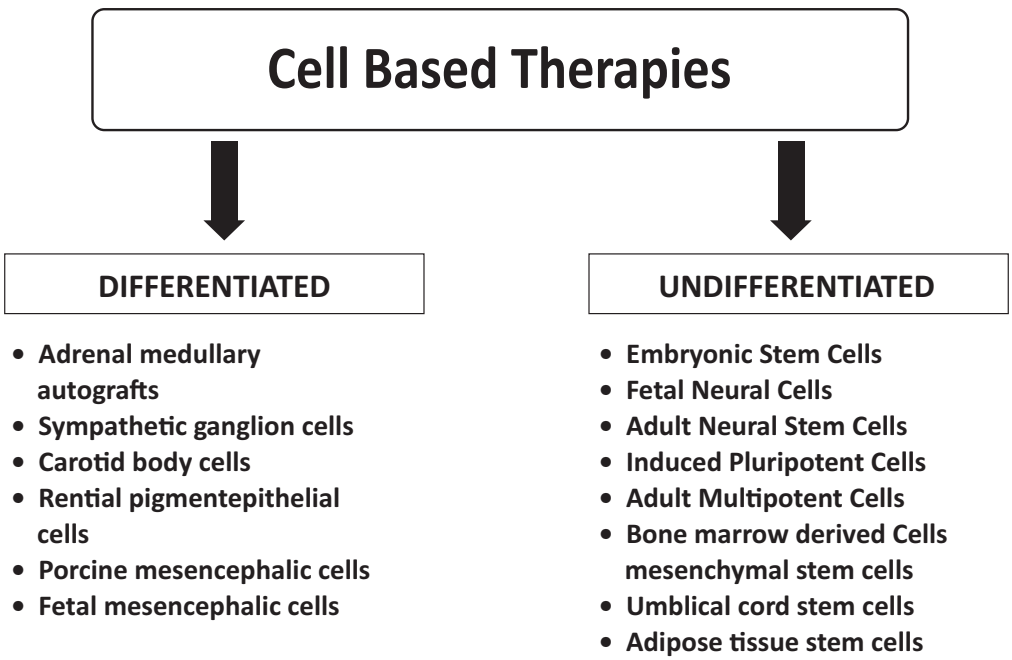
doi : 10.5214/ans.0972.7531.1118209

## Introduction

Community-based studies have shown prevalence of PD to range from 40 to 328 per 100,000 and incidence around 5-7 per 100,000 per year.[1-3] The neuropathological hallmark of PD is loss of neuromelanin containing DA neurons in substantia nigra pars compacta (SNc)[4] with loss of dopamine resulting in the motor symptoms. Microscopically, SNc shows neuronal loss, gliosis, and presence of cytoplasmic inclusion bodies called Lewy Bodies which are rich in hyperphosphorylated neurofilament proteins, lipids, iron, ubiquitin, and alpha-synuclein in the surviving neurons.[5] The progressive accumulation of $\alpha$-synuclein positive Lewy bodies follows a caudo-rostral pattern starting from lower brain stem and ascending to neocortex.[6] By the time motor symptoms of PD appear, approximately 60% of nigral DA neurons and 80% of striatal dopamine are depleted. $^{18}$F-dopa (F-DOPA) positron emission tomography (PET) studies have shown the onset of disease to predate motor manifestations by approximately 4.5 years.[7] Although, the etiology of PD is rather uncertain, large amount of evidence implicates genetic factors along with environmental factors to be responsible in the causation of PD.[8,9]

Current treatment of PD relies heavily on replacing lost dopamine either with its precursor L-dopa or dopamine agonists (ropinirole, pramipexole, bromocriptine, lisuride etc). Other pharmacological measures like catechol-O-methyltrasferase (COMT) inhibitors like entacopone, telcapone and monoamine oxidase B (MAO-B) inhibitors like selegiline and rasagiline are also useful, while L-dopa remains the gold standard in the treatment of PD. Though very effective in controlling motor symptoms of PD, long term use of L-dopa is associated with motor fluctuations and dyskinesias. Further, these medications do not control non motor symptoms and also fail to improve some motor symptoms like falls and freezing.[10] Surgical management by deep brain stimulation (DBS) of subthalamic nuclei (STN)



or globus pallidus pars interna (Gpi) has emerged as an effective tool for patients who have disabling motor fluctuations and dyskinesia but have shown good response to L-dopa therapy. A comprehensive meta-analysis of DBS studies has shown consistent motor improvements and about 60% reduction in dyskinesias.[11] However, DBS does not provide any additional benefit to signs and symptoms unresponsive to DA therapy.[10]

Cell based therapy with an aim to transplant/implant differentiated or undifferentiated cells to replace lost neurons has been used as a therapeutic approach since 1987. The success of cell based therapy for the treatment of PD is based on the fact that the predominant symptoms of PD are dependent on the dysfunction or loss of the DA neurons in a focal area of brain that is the nigrostriatal system. Cell based therapy can be defined as a class of therapy consisting of implantation of cells rich in dopamine that could replace DA neurons which have degenerated in PD and can restore DA function in a more physiologic manner as compared to oral replacement therapies.[12] The strategies use cells rich in dopamine, autologous or heterologous; allogenic or zoonotic; fetal/embryonic or adult cells. Whereas, the primary site of DA cell loss is SNc, the striatum is the major target of DA innervations, the common outflow site and its size makes it the preferred target for cell implantation. The placement of cells in striatum is considered necessary for extensive reinnervation though it may limit the functionality of the graft. Cells used in cell based therapies can be divided into undifferentiated cells which have a capacity for proliferation and cells which are pre-differentiated and cannot proliferate after transplantation. In this article, we review various cell based strategies which have been explored as treatment option for PD.

### Adrenal medullary autografts

Autologous grafts of adrenal medullary tissue were proposed for transplantation in PD with the rationale that autotransplants would be immunologically compatible and devoid of the risk of disease transfer between donor and host. The successful transfer of catecholamine-secreting cells into the rat anterior chamber of eye was first achieved by Olson and colleagues in 1970s.[13] Transplantation of adrenal tissue in 6-hydroxy-dopamine (6-OHDA) rat model[14] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primates showed limited cell survival.[15] The first adrenal transplant in human patients was done by Backlund in 1985[16] and later by Madarazo in 1987.[17] Two patients with PD received adrenal medullary autografts in caudate nucleus with significant clinical improvement.[17] Following these successful experiments, a multi center study including 19 patients showed significant decrease in mean "off" time and increase in mean "on" time though in contrast to observations of Madarazo, the dose of anti Parkinson medications could not be lowered. The authors cautioned against wide spread use of this measure outside of research centers.[18] However, improvement in these patients lasted only 18 months and was maximal at 6 months.[19] Post mortem of a patient after 16 years of transplantation showed poor survival of adrenal medullary transplants.[20]

### Autologous sympathetic ganglion and carotid body cells transplant

Use of other autologous source of catecholamine secreting cells in PD has also been explored. Autonomic sympathetic ganglion cells obtained from superior cervical ganglion and cultured for 2, 4 or 6 weeks were transplanted in striatum of 6-OHDA lesioned rats.[21] Rats receiving 2 or 4 weeks cultures showed improvement in rotational behavior and cell survival. A trial of transplantation of autonomic sympathetic ganglion in 35 PD patients showed improvement in bradykinesia and gait disturbances without any improvement in tremor or rigidity in half the patients.[22] No serious adverse effects were reported. Release of dopamine from transplanted sympathetic cells was believed to be the mechanism responsible for improvement.

Carotid body cells, also rich in dopamine have been considered candidate of cell based therapy in PD. Striatal grafts of carotid body cells have shown improvement in motor behavior in rats and monkey models of PD.[23,24] A trial of 13 patients who received bilateral implantation of carotid body cell aggregates into striatum showed clinical improvement in 10 patients.[25] Mean improvement in UPDRS score was 23% at 6 months, however, after 3 years, only 3 patients showed improvement. No "off" period dyskineisas were reported. There was a non significant improvement in F-DOPA PET uptake in these patients. The authors concluded that the positive effects of the carotid body grafts were mediated by release of trophic factors, rather than increased striatal DA as predicted.

### Porcine Xenograft

The limited availability of human embryonic tissue and ethical concerns led to consideration of alternative tissue sources including xenogenic donor tissue for DA replacement. Porcine embryonic tissue is physiologically similar to human DA neurons and can be easily collected due to large litter size. After survival of porcine xenografts and improvement in animal models,[26] in a phase I clinical study, 2 patients received embryonic porcine ventral mesencephalic tissue. Patients were treated with either cyclosporine or monoclonal antibodies directed against histocompatibility complex class I antibodies and exhibited 19% improvement in Unified Parkinson's Disease Rating Scales scores (UPDRS) though F-DOPA PET failed to show any change.[27] The basis of any beneficial effect on UPDRS scores in this study is not known. The mesencephalic fetal porcine cells present a challenge related to severe immunological reaction triggered by the xenograft.

### Retinal Pigment Epithelial Cells

Retinal pigment epithelial cells (hRPE) neuroectodermal cells lining the inner layer of retina, are rich in dopamine, protect retina and are capable of producing dopamine. These cells do not survive unsupported but do so when attached to scaffolding such as gelatin microcarriers.[28,29] hRPE cells attached to microcarriers (Spheramine) when implanted in striatum of 6-OHDA lesioned rats showed significant improvement in motor scores, with in-situ good survival as xenograft without inflammatory response in the absence of immunosuppression.[28] Spheramine transplantation in MPTP primates similarly showed motor improvement and increased uptake on F-DOPA PET imaging. Based on these results, a pilot study on 6 PD patients was performed who underwent intrastriatal implantation of hRPE cells attached to Spheramine.[30] The implantation was well tolerated post operatively and improvement of 48% in UPDRS motor sub-scores was seen up to 24 months without any evidence of dyskinesia. On the basis of these results, a phase II trial was initiated. The trial, however, had to be abandoned after 12 months follow up, as the results did not meet the primary end point of the study. Pathological examination done on a patient who received 325,000 hRPE

cells with Spheramine and died 6 months after surgery due to unrelated cause revealed poor survival of implanted cells (0.036%) with inflammatory and astrocytic reaction.[31]

**Fetal Mesencephalic Transplantation**

Initial studies of fetal neural tissue transplantation on primate brain were performed on parkinsonian monkeys.[32,33] A number of reports of successful transplantation in non human primates followed. The surgical target in most of these studies was caudate nucleus and no immunosuppression was used. The first human cases of fetal mesencephalic transplants were reported from Sweden[34] and Mexico.[35] Several open label reports followed with clinical benefit and graft survival.[36] Three open label trials reported 30-40% improvement in UPDRS score in "off" phase, 43-59% reduction in daily "off" period and 16-45% reduction in daily L-dopa dose.[37-39] These studies also showed increase in F-DOPA uptake by about 60% though it did not reach normal levels.

Two National Institute of Health (NIH) sponsored double blind randomized placebo controlled trials reported disappointing results.[40,41] In Denver/New York trial,[40] 40 patients were randomized to receive either human fetal mesencephalic tissue or sham surgery. Fourteen of the sham surgery patients later received mesencephalic transplantation. Ventral mesencephalic tissue was obtained from elective abortions of 7 to 8 weeks post conceptional age fetuses and cultured up to 4 weeks before transplantation. No immunosuppressive agent was used in this study. There was no benefit in primary outcome. However, the subgroup consisting of younger patients ($<$ 60 years) showed improvement in UPDRS scores and Schwab and England scores of activity of daily living but no effect was seen in patients above 60 years of age. There was late occurrence of dystonia/dyskinesia in 5 of 33 patients who received transplantation. These patients had severe fluctuations in motor symptoms before surgery. F-DOPA PET scans revealed 40% increased uptake from baseline which was significant but not significantly different as compared to patients in the sham surgery group. Pathological examination in two patients who died of unrelated causes showed growth of transplanted DA neurons in the putamen with survival of 2,000-22,000 cells at transplant site.

In the second double blind, placebo controlled trial led by Warren Olanow,[41] 34 patients were randomized into three groups: those receiving either one or four donor human fetal nigral transplantation in bilateral postcommissural putamen or bilateral placebo procedures. Eleven patients received one donor tissue, 12 patients received four donor tissue and 11 patients were in placebo group. Immunomodulation in the form of cyclosporine was given to the patients receiving transplantation for a period of 6 months. Solid mesencephalic grafts from donor fetuses aged 6 to 9 weeks post-conception were used without pre culture. There was no overall treatment effect for the primary end point which was change in UPDRS score in practically "off" state. Significant improvement was seen in patients with less severe disease manifested by not very high "off" motor UPDRS scores. Significant increase in F-DOPA uptake on PET studies was seen in both the treatment groups in comparison to placebo group which reached its peak at 12 months without additional improvement at 24 months. Thirteen out of 23 patients who received graft developed "off" period dyskinesias which were not seen in patients in placebo group. Five pathological studies were available from patients who died during the follow up due to unrelated causes. High number of dopamine neurons with robust cell survival in each graft deposit (70,000-120,000) was seen in four donor group, but it was about 30,000 cells on each side in one donor group.

The disappointing outcome of these two well conducted trials raised many questions concerning the characteristics of patients who derive greatest clinical benefit. These include number of donors, site of graft implantation, preparation of graft tissue, culture and storage of cells, use of immunosuppression, pre implantation UPDRS score and "off" medication dyskinesias.[42]

*Graft Induced Dyskinesias (GID)*

The occurrence of stereotyped choreiform movements unrelated to dopamine agonist therapy in patients who had received grafts is termed as Graft Induced Dyskinesia (GID). The frequency of GID varies between 5-56% in open label and placebo controlled trials.[40,41,43] Analysis of "off" medication dyskinesias suggests negative correlation with preoperative F-DOPA PET uptake suggesting that patients with more severe striatal DA denervation more frequently have GID. GID was found to be more frequent in those patients in whom the tissue was stored before transplantation.[38,43] Patients who develop GID, developed it within 5-6 months from transplantation and their clinical features included preferential involvement of legs, lower doses of L-dopa, better "on" motor UPDRS scores,[44] and non receipt of immunosuppressive agents. Focal areas of increased F-DOPA uptake in the grafted striatum suggesting an uneven, patchy innervations rather than diffuse generalized overproduction of dopamine is also suggested as one of the causes of "off" medication dyskinesias.[45] The ratio of serotonergic to DA neurons and pre-graft L-dopa treatment has also been associated with GID.[46]

*Neuropathological changes in transplanted dopamine cells*

Neuropathological studies done early on after implantation ($\sim$18 months) showed robust survival of tyrosine hydroxylase (TH) positive DA neurons with extreme innervations of host striatum, whereas studies done after several years (9-16 years) showed TH positive neurons in the periphery of graft with neuromelanin.[47] In the latter group, one half of the surviving neurons proved to be serotonergic. Some of the neurons also showed presence of Lewy body pathology in transplanted cells.[48,49] Lewy body and Lewy neurites in the long surviving grafted DA neurons were morphologically similar to those seen in SNc in PD. Two forms of $\alpha$-synuclein-positive aggregates were distinguished in the grafts, the first: a classical and compact Lewy body and the other a loose meshwork aggregate. Lewy bodies in the grafts stained positively for ubiquitin and thioflavin-S, and contained characteristic $\alpha$-synuclein immunoreactive electron dense fibrillar structures on electron microscopy.[50] These findings suggest the possibility that the implanted neurons had been adversely affected by the disease process causing impaired trophic support to the grafted cells, unfavorable microenvironment at the transplanted ectopic site, and transmission of mis-folded host $\alpha$-synuclein into grafted cells. These reports raise concern about long term efficacy and longevity of transplanted DA neurons and the etiology of PD.

The studies with adrenal, hRPE, carotid body and mesencephalic cells have clearly demonstrated that patients could clearly benefit from grafted DA neurons if cer-

tain criteria (related to patient selection, cell handling, storage and culture of cells, type of surgical technique, and role of immunosuppression) are appropriately fulfilled. These studies provided "proof of principle" that DA neuron can be replaced in PD. However, significant variability in the clinical outcome, variable response of different groups of patients and emergence of "off" medication dyskinesias raises a number of concerns regarding long term efficacy and safety of the therapy. For extensive reinnervation of the host striatum, number of surviving DA neurons should be approximately 100,000. The appearance of Lewy bodies in the donor cells 9-16 years after transplantation indicates that even young, healthy, genetically independent DA cells can be affected by PD pathological process. The issue of procuring adequate fetal tissue for transplantation is also associated with a number of logistic and ethical concerns. Therefore, the development of alternative source of DA neurons becomes absolutely necessary. Such alternatives include embryonic stem cells, fetal and adult neural stem cells, induced pluripotent cells and adult multipotent stem cells.

**Stem cells**

Stem cells are undifferentiated unspecialized cells with an ability to self-renew over long periods and can give rise to various highly specialized fully functional and mature cell types. Stem cells can be totipotent with ability to form every cell type within the body and placenta, pluripotent with ability to form every cell type except placenta and multipotent cells which have ability to form different cell types arising from the organ where they reside.

*Embryonic Stem Cells (ESCs)*

ESCs are attractive candidates for cell transplantation because of their ability to differentiate into all cells present in adult organisms, self renewal capacity and their ability to be engineered *in vitro*. ESCs can be differentiated in to neural stem or precursor cells and subsequently into DA neurons.[51-53] Differentiation into DA neurons is established for mouse, primate, and human ESCs.[54-56]

The two major principle pathways for neuronal differentiation of human embryonic stem cells (hESCs) are formation of embryoid bodies[56] and co-culturing of hESCs with a layer of feeder cells capable of inducing differentiation[57] Differentiation of ESCs into DA neurons requires several steps, processes and procedures requiring co-culturing with feeder cells, growth factors, genetic modifications, use of transcription factors and regulator proteins. Over the years these procedures have been improved to increase the yield of DA neurons.[51,52,56,58-61] The best protocol for inducing DA neurons from mouse embryonic stem cells (mESCs) yielding about 90% of TH positive cells has been achieved by combination of Nurr1 over expression, PA6 co-culture and soluble factors (SHH, FGF8, ascorbic acid).[58]

Implantation of undifferentiated ESCs in the striatum of 6-OHDA rat model of parkinsonism, results in formation of graft derived, functionally integrated, DA neurons within the dopamine-depleted striatum with sustained improvement in motor behavior in 56% of animals.[62] However, 24% rats did not show any evidence of graft survival and 20% had teratoma formation.[62] MPTP lesioned monkey model showed recovery in motor functions including motility and posture when grafted with DA neurons derived from primate ESCs with increased F-DOPA uptake in striatum.[63] Functional recovery and survival of DA neurons derived from hESCs using soluble factors has been reported to show improvement in motor scores in parkinsonian rats but with teratoma formation.[64] Transplantation of differentiated ESCs into DA neurons derived from mouse and monkey ESCs survive in brains without teratoma formation.[61,63,65] There are no published reports which could throw light on the presence of hESCs derived DA neurons that survive grafting, integrate in the host brain, release dopamine and improve motor function in animal models of parkinsonism. The strategies to get rid of pluripotent or partially differentiated ESCs in order to avoid teratoma formation include Fluorescence activated cell sorting[66,67] and eliminating the expression of tumor forming genes like 'Cripto'[68,69] Signaling molecules like 'Cripto' that regulate excessive proliferation and tumorigenesis may prove to be an important key in ESCs research.

These results encourage the use of ESCs in cell replacement therapy for PD. However, poor survival and/or phenotypic stability of the transplanted cells and risk of teratoma formation limit their use in PD patients. A number of problems still remain to be overcome. These include: 1. obtaining large number of DA neurons and DA committed cells in human culture conditions, 2. improving survival rate of transplanted cells and functional integration at the transplanted site, and 3. minimizing the risk of teratoma formation.

*Fetal Neural Stem Cells (NSCs)*

NSCs are multipotent stem cells that can give rise to cells belonging to all three major cell lineages of the nervous system i.e. neurons, oligodendrocytes and astrocytes.[70] NSCs have been identified in various areas of adult and fetal brain including forebrain, hippocampus and subventricular zone.[71,72] NSCs from midbrain can be differentiated to form functional and mature DA cells. Expansion of neural stem cells isolated from rodent embryos at embryonic day (E) 14 to E15 with appropriate growth factors can lead to formation of 'neursospheres' with reasonable *in vitro* DA differentiation. Different genetic, epigenetic and growth conditions can also modify DA differentiation of NSCs. These include Nurr1 over-expression, astrocyte conditioned medium, presence of factors like Interleukin 1 $\beta$ (IL1$\beta$ ) Interleukin 11 (IL11), glial-derived neurotrophic factor (GDNF) and exposure to 3% $O_2$[73-76] However, differentiation from NSC to DA neurons in human has been discouraging in comparison to rodents.[77,78]

Transplantation of human fetal NSCs into rat model of parkinsonism and their survival, migration, proliferation and differentiation in host brain has been documented.[79,80] Transplantation of expanded human fetal NSCs into 6-OHDA lesioned rats with survival of TH positive cells and improvement in rotational behavior has also been documented.[81] Human fetal NSCs can provide a high yield of DA cells out of a small cell source with the possibility to standardize cell source in clinical setting. However, survival in animal models must be demonstrated before these cells can be considered as a potential source of DA cells for human use.

*Adult neural stem cells*

Neuronal stem cells in adult brain are present in subventricular zone (SVZ) of the lateral ventricle and sub granular zone (SGZ) of the hippocampus.[82,83] Migration of neurons from anterior portion of SVZ along rostral migratory stream (RMS) up to the olfactory bulb and their differentiation into neurons has been documented in primates and rodents.[84-86] An analogue of RMS in human brain has also been suggested.[87] NSCs are able to proliferate in response to different growth factors

like basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF).[88] These cells are normally not programmed for midbrain DA function, however, gene modification can push them towards a definite phenotype. Nurr 1 over-expression of adult SVZ NSC with differentiation into mature DA neurons and *in vivo* survival in rat parkinsonism models has been demonstrated.[89] In one study, NSCs from cortical and subcortical tissue samples taken from a PD patient during a neurosurgical procedure were isolated and expanded and injected unilaterally into striatum. A long lasting improvement in both "on" and "off" UPDRS scores along with 33% increase in dopamine uptake in the implanted putamen was observed.[90] Highly proliferative precursors present in subependymal zone with dopamine receptors which receive dopamine afferents are promising source of DA neurons. In rat models of parkinsonism, there is decrease in proliferation of these precursors.[91] Similarly, loss of endogenous neurogenesis in SVZ has also been reported in PD patients.[92] Adult NSCs derived from SVZ are a promising candidate for neurogenesis due to their potential for DA differentiation, migration into damaged areas of brain and close proximity to striatum.

*Induced Pluripotent Stem Cells (iPSCs)*

Reprogramming of differentiated somatic cells by over-expression of certain transcription factors to iPSCs has been achieved in both animal and human models. Pluripotent stem cells from mouse fibroblasts and human dermal fibroblasts developed in all three germ layers in presence of Oct4, Sox2, Klf4, and c-myc but it was also associated with teratoma formation.[93,94] Differentiation of reprogrammed rat fibroblast into DA neurons and functional integration into the rat brain has been reported.[95] iPSCs provide an option of autologous cell transfer without any risk of graft rejection or immunosuppression. However, use of iPSCs is limited due to many other issues, like risk of oncogenesis by use of viral vectors for gene delivery, low reprogramming efficacy and use of transcription factors like c-Myc, Klf4 and Oct4 which have been reported to cause dysplasia.[46]

*Adult Multipotent stem cells*

Multipotent adult stem cells are of special interest as they offer an option of autologous transplantation. Multipotent stem cells which have shown promise in neural differentiation include umbilical stem cells; bone marrow derived mesenchymal stem cells and adult adipose stromal tissue (ADAS). Umbilical cord blood (UCB) is a valuable alternative source of hematopoietic stem cells (HSCs). It has unique advantages of easy procurement, absence of risk to donors, low risk of transmitting infections, immediate availability, greater tolerance of human leukocyte antigen (HLA) disparity, and lower incidence of inducing severe graft-versus-host disease (GVHD).[96] Differentiation of human umbilical cord blood cells into glial or neuronal phenotypes both *in vitro* and in vivo was demonstrated by injecting cells into neonatal rat brains.[97] A certain fraction of umbilical cord cells expressing Nestin, could be isolated and these could be oriented to neuronal phenotypes in presence of specific factors.[98] These reports demonstrate that UCB cells can differentiate into neurons. Differentiation of UCB cells into DA neurons and their viability 4 months after implantation in rat model of parkinsonism has been shown.[99]

*Bone Marrow Derived Mesenchymal Stem Cells (MSCs)*

MSCs represent $<$0.01% of all nucleated bone marrow cells. These are primordial cells of mesodermal origin that are capable of multipotency, differentiating under appropriate conditions into chodnrocytes, skeletal myocytes, and neurons.[100] Human MSCs are easy to isolate and can be expanded over a long period of time without ethical or technical problems.[101,102] MSCs are able to express properties of neuroectodermal cells *in vitro* using combinations of cytokines and growth factors like EGF and BDNF. Protocols for high yield generation of undifferentiated neural stem cells like cells from MSCs have been reported. These human MSCs derived neural stem cells grow to form neurosphere like structures and can be differentiated into neuronal phenotypes-astroglia, oligodendroglia and neurons.[103] The first transplantation study of adult bone marrow cells in rats was done by Mezey and co-workers.[104] They injected bone marrow cells intra peritoneally in rats and were able to demonstrate bone marrow derived cells in cerebral cortex, hypothalamus, hippocampus, amygdala, periaquedutal gray and striatum. The authors suggested that bone marrow derived cells could be a source of neural stem cells. First report of intrastriatal injection of bone marrow derived stem cells in MPTP lesioned mouse model was published in 2001[105] with improvement in rotation tests and survival of transplanted cells 4 weeks after transplantation. DA differentiation of MSCs has been done using differentiation factors like sonic hedge hog (SHH) and FGF and serum free conditions with efficacy of induction into DA neurons up to 67% based on TH expression.[106,107] A number of *in vitro* as well as in vivo studies suggest that MSCs or pro-neurally converted derivatives could display protective or regenerative effects on DA cells in parkinsonism models.[70] Human bone marrow derived MSCs expanded using xenofree conditions in cord blood serum differentiated into DA neurons in the presence of factors like FGF, nerve growth factor and noggin. These cells showed presence of neural markers like Nestin, $\beta$ tubulin, and DA markers TH and Nurr1. These cells were transplanted intrastriatally in 6-OHDA lesioned rats and survival of human origin DA neurons could be demonstrated histologically at 12 weeks. Transplanted animals also showed improvement in apomorphine-induced rotations.[108]

MSCs can be potential source of cell therapy for PD, however, final comments on their suitability can only be made after results of systematic transplantation studies are available. These cells provide an excellent opportunity due to ease of procurement, their potential of differentiation into DA neurons, absence risk of rejection and hence absence of any immunosuppression, and possible expansion in xenofree conditions.

*Adult Adipose Tissue Stem (ADAS) Cells*

Adult adipose tissue also contains stromal progenitor cells with neurogenic potential. Mc Coy and colleagues[109] reported neuronal differentiation *in vitro* of ADAS cells for transplantation and examined their neuroprotective benefit in rat model of parkinsonism. The effect of differentiated cells was measured against naive grafts of ADAS cells and both had DA neuroprotective effect in hemiparkinsonian rats which was attributed to production of trophic factors at the lesioned site.

**Conclusions**

The success of cell based therapy in animal model of PD and in human in a limited manner raises a lot of excitement regarding the possibility of using this method to

deliver new drugs, genes and vectors in addition to dopamine. The studies so far suggest that:

1. Controlled release of DA cells in large amounts for cell replacement therapy is technically possible.
2. Fetal and adult brains harbor neural stem cells which can be programmed and expanded for DA phenotype.
3. Re-differentiation of different cell types to neuronal phenotype is possible *in vitro*.
4. Adult multipotent stem cells can be a potential source of neuronal cells.

However, a number of challenges and problems facing cell based therapies must be addressed. The safety is of highest concern for any therapeutic modality. The risk of tumor and teratoma formation after the use of undifferentiated embryonic cells is one of the biggest concerns. Although, adult stem cells have a lower oncogenic potential, caution is still needed. The propagation of PD pathology in transplanted mesencephalic cells, similar to the consistent pathology of PD raises concern regarding use of cell based therapy in young PD patients and possibility of presence of some transmissible factor. Though, use of autologous cells avoids the risk of rejection and immunosuppression, the propagation of PD like pathology in autologous transplanted cells remains a matter of concern. The risk of graft induced dyskinesia seen with mesencephalic transplantation is another matter of concern.

Successful cell based therapy in PD has to meet certain goals including:

1. Long term survival in the host brain.
2. Adequate differentiation into DA neurons with establishment of required neuronal circuitry.
3. Release of dopamine in physiological and adequate manner.
4. Long term efficacy for motor and non motor symptoms
5. Low or no risk of side effects like dyskinesias
6. No risk of tumor formation

The greatest challenge facing effective stem cell-based approaches remains the generation of large, homogenous populations of cells which are of human origin, remain viable and retain their phenotype following transplantation.

The article complies with International Committee of Medical Journal Editor's uniform requirements for the manuscripts.

Competing interests – None, Source of Funding – None
Received Date : 5 March 2011
Revised Date : 9 April 2011
Accepted Date : 30 April 2011

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