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Treating non-motor symptoms of Parkinson's disease with transplantation of stem cells

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Summary

Parkinson's disease (PD) treatment-based research has focused on developing therapies for the management of motor symptoms. Non-motor symptoms do not respond to treatments targeting motor deficits, thus necessitating an urgent need to develop new modalities that cater to both motor and non-motor deficits. Stem cell transplantation is potentially therapeutic for PD, but the disease non-motor symptoms have been primarily neglected in such cell therapy regimens. Many types of stem cells are currently available for transplantation therapy, including adult tissue (e.g., bone marrow, placenta)-derived mesenchymal stem cells (MSCs). The fact that MSCs can replace and rescue degenerated dopaminergic, and non-dopaminergic cells suggest their potential for the treatment of motor, as well as non-motor symptoms of PD, which is we discuss here.

Keywords

Parkinson's disease; mesenchymal stem cells (MSCs); motor symptoms; non-motor symptoms; stem cell therapy

Shifting the focus of Parkinson's disease therapy to non-motor symptoms

Parkinson's disease (PD) is a debilitating condition characterized by severe motor and mental deficits caused largely by the degeneration of dopaminergic cells in the substantia nigra and the ventral tegmentum [1]. A pathological hallmark of PD is the presence of Lewy bodies, or intracytoplasmic inclusions [2, 3]. The result is impaired functioning of cortico-subcortical extrapyramidal circuits due to a dopamine (DA) deficiency in the nigrostriatal projections.

To date, motor deficits are the focus of therapeutic interventions aiming to improve disease prognosis in patients with PD. Motor symptoms range from bradykinesia, resting tremor, rigidity, and postural instability and affect the ability of patients to complete tasks of daily

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living [1]. In addition to the well-known motor symptoms observed in PD, further functional manifestations appear with disease progression as patients begin to experience cognitive decline [4, 5]. Non-motor deficits can be equally debilitating to patients and include neuropsychiatric symptoms, such as cognitive deficits, depression, anxiety, and psychosis [6]. In addition, patients may have autonomic symptoms ranging from gastrointestinal, cardiovascular, urinary and sexual dysfunction, sleep deficiencies including impairments in initiation and maintenance, rapid eye movement behavior disorder and excessive daytime sleepiness, and sensory impairments resulting in pain, hyposmia and visual dysfunction [7]. While motor symptoms are alleviated with levodopa, most of the non-motor symptoms do not respond to the treatment [8, 9]. At the present time there is a pressing need to develop a treatment aimed at alleviating these non-motor symptoms of PD.

Multiple neural circuits in PD pathophysiology

Multiple circuits are involved in PD pathology including ‘motor’, ‘association’, and ‘limbic’. In addition, DA deficiency is accompanied to some extent by reductions in central noradrenergic, serotonergic and cholinergic systems [6]. The pathophysiological involvement at multiple CNS levels is largely due to the anatomical projections of the basal ganglia, which connect specific striatal areas (putamen, caudate, and nucleus accumbens) involved in the orchestration of normal behavior, to the prefrontal cortex and limbic areas through pallidum and thalamic projections [6]. Disturbances in these parallel circuits are a far shift away from the ideal state of the neuronal environment and dictate the spectrum of symptoms patients with PD experience, ranging from motor deficits, mood disturbances, and cognitive deficits, sometimes leading to dementia [6]. Moreover, the associative and limbic circuits control adequate non-motor behavior based on a combination of internal and external stimuli. Complex behavior and cognitive functions are controlled by the associative circuit, which connects the ventromedial striatum with the prefrontal, parietal and temporal association areas. Motivational and emotional traits of behavior are linked by the limbic circuit to the ventral striatum by the limbic-related cortical areas, which includes the hippocampal formation and the amygdala [10].

Non-motor symptoms of PD regulated by multiple neurotransmitters

Oversight of cognition and mood is regulated by a variety of neurotransmitters controlled by dopaminergic, noradrenergic, serotonergic and cholinergic systems. Dopaminergic neurons are highly complex structures, releasing dopamine and synapsing with target neurons, such as glutamate, acetylcholine, and serotonin, to activate downstream signaling cascades that will further modulate transmission, volume, and neuron excitability [11]. The interactions between striatal dopamine, glutamate, and acetylcholine neurons promote desired motor actions while suppressing uncoordinated motor actions [11]. Deficiency of extracellular dopamine is thus only one of many consequences of striatal denervation in PD [11]. In the diseased PD brain DA deficiency induces an altered mental state due to the connections formed between the DA and non-DA transmitter systems [12]. Loss of dopaminergic neurons in the ventral tegmental area leads to motor as well as associative and limbic circuit deficits, the latter two manifesting as cognitive disabilities, disturbances of mood, and eventually leading to psychosis due to the brain’s inability to process external information

properly [13]. Moreover, as discussed in further detail in the next section, the evolution of these non-motor symptoms of PD may arise from dysfunctional neurotransmission of non-dopaminergic systems that cannot be attenuated by pharmacological dopamine replacement therapies [11]. Although dopamine replacement therapies can be successful in restoring extracellular dopamine concentrations, they are unable to reverse functional and anatomical changes in the non-dopaminergic systems associated with the denervated striatum of PD [11]. Non-motor deficits in PD vary between patients, likely explained by the disruption of cortico-striatal loops and functional disturbances in non-dopaminergic ascending tracts [6].

Frontal lobe processes are disturbed in patients with PD resulting in cognitive changes, including visuospatial memory and executive functioning [13]. Memory tests show deficits in non-demented PD patients, where PD patients remember fewer words during free recall on supraspan lists compared to age-matched controls. However, PD subjects compared to controls when cued to the semantic properties of the material [14]. Internal cueing is also defective in PD subjects, as observed in ordering/sequencing tests that require an intact working memory and an internal strategy to solve an ordering problem. PD subjects when given a random list of numbers that must be rearranged and repeated in a specified order, exhibit ordering/sequencing deficits compared to matched controls despite their intact short-term memory span [15].

Current therapies for PD patients

Available pharmacological therapy for PD includes DA replacement, which is effective in early stages of the disease, but can have deleterious side effects with long-term use. Levodopa or L-DOPA (3,4-dihydroxy-L-phenylalanine) remains the gold standard for drug treatment in PD. The therapeutic basis of levodopa for PD is to alleviate motor symptoms and does not work on non-motor symptoms of the disease. High doses of levodopa and related dopamine precursor drugs may produce better symptomatic control but are also documented to produce more severe complications at the chronic stage of PD [16]. Levodopa therapy is associated with the development of motor complications, especially at higher doses [16]. Current practice, therefore, is to use lower doses of levodopa to reduce motor complications, albeit at the cost of less effective symptomatic control [16]. Combination treatment has allowed the use of low dose levodopa to be effective. For example, the addition of the decarboxylase inhibitor, carbidopa to levodopa treatment regimen (known as Sinemet¹), improves the outcome significantly [17]. Cerebrolysin is another drug that has been approved for the treatment of Alzheimer's disease in the U.S. and has been extensively studied in Russia for the treatment of PD [18]. Cerebrolysin is a type of peptidergic drug that has been shown to be neuroprotective in animal models of stroke, Alzheimer's, and various other neurological models, and has neurotrophic properties, due to an upregulation of GLUT1 and MAP2 gene expression [18, 19, 20]. Several studies suggest that the drug stabilizes excitability of the brain and can reduce hyperkinetic syndromes associated with dopaminergic drugs used for PD. It may also be useful for preventing progressive deterioration in PD although no clinical trial has addressed this issue yet. Although these drug treatments for PD exist, they are limited in numerous ways. In particular, as the disease progresses higher doses are needed, often accompanied by disagreeable side effects, until the drugs are no longer effective. Side effects of levodopa

called levodopa-induced dyskinesias (LIDs) were more common than placebo, particularly for dyskinesias, nausea, infection, hypertonia, and headache [21]. Additionally, current drug therapy for PD remains palliative, and no drug either stops disease progression or reverses degeneration [22].

Catering novel therapies for motor and non-motor symptoms of PD

The ideal approach for the treatment of PD would be a restorative therapy, which is able to replace the disease-denervated dopaminergic network in an effort to, at the very least, retard the disease progression. One such method would be a cell-based therapy, more specifically neural transplantation of stem cells due to their self-renewal capacity and ability to differentiate into dopaminergic cells [22]. While restoring the DA neuronal circuitry and replacement of dead/dying dopaminergic cells may seem a logical tactic, such a method appears to cater only to motor symptoms of PD. Disautonomias, or diseases of the autonomic nervous system, present in PD are controlled by components of the autonomic nervous system, including the sympathetic noradrenergic system, the parasympathetic nervous system, the sympathetic cholinergic system, the sympathetic adrenomedullary system, and the enteric nervous system [23]. Therefore a cell-based therapy targeting the non-dopaminergic system underlying non-motor symptoms of PD remains to be explored, which will be discussed in subsequent sections.

Early clinical trials of neural transplantation for the treatment of PD

Modern neural transplantation began as early as the 1970's. PD was the first neurodegenerative disorder to be treated using stem cell grafts because the loss of nigrostriatal dopaminergic neurons was limited in number and area and symptoms were secondary to cell loss [24]. Successful trials of DA-rich fetal ventral mesencephalon grafts appeared in the 1980's, with improvements of Parkinsonian symptoms seen in rodents and non-human primates, which pushed clinical trials of neural transplantation in the latter part of the decade [25].

By the late 1990's Lindvall and colleagues in Sweden had pioneered the transplantation of fetal neural tissue. Trials of unilateral intrastratial grafts had showed improvements across fluorodopa positron-emission tomography (FD-PET), in motor symptoms including rigidity, hypokinesia, dyskinesia, and time in the 'off' state, and graft survival of fetal dopaminergic neurons correlating with clinical advancements as demonstrated by histological evidence [26, 27, 28, 29]. Already these early grafts showed neuritic outgrowth extending towards the host tissue and forming synaptic connections with the host tissue [27, 28]. The grafts demonstrated normal striatal innervation and were metabolically and dopaminergically active, with an intact blood-brain barrier. The early trials of neural transplantation were not without complications. While many of the patients who received transplants showed improvements in motor behavior, several of them experienced graft-induced dyskinesias (GIDs), otherwise known as involuntary movements as a result of transplantation [30, 31, 32, 33, 34, 35]. Of note, GIDs may be an immune response to the graft following early discontinuation of immunosuppressive therapy, although stronger evidence suggests they are caused by the content of the transplanted human fetal ventral mesencephalic tissue, in

particular a high ratio of serotonergic to dopaminergic neurons [32, 33, 34, 35, 36, 37]. Patients who had received grafts were discovered to have high serotonergic innervation in the striatum and showed a higher degree of GIDs [34, 38]. However, treatment with serotonin 1A receptor agonist was able to improve symptoms of GIDs [33, 34, 35, 36, 37, 38]. The promise of early trials of neural transplantation created the drive to produce novel sources of stem cells that were safer and more efficacious as early studies were done using human fetal tissue, an ethically controversial sources of stem cells.

Envisioned cell therapy for PD: Targeting motor and non-motor PD symptoms

Currently, there are a number of different sources of stem cells available, although their accessibility and efficacy varies. Somatic cell reprogramming allows generation of human pluripotent stem cells from PD patients and may permit correction of the mutations associated with PD pathology [39]. This methodology then allows specific cells, such as dopaminergic cells, to be produced. Although promising, there are several challenges that must be addressed before iPSCs can be used in future clinical settings. Inherent with reprogramming of iPSCs, karyotypic abnormalities, somatic point mutations, and aberrant epigenetic dysregulations may arise because of the nature of the technique, which involves in-depth rearrangement of cellular functions making the iPSCs prone to genotypic and phenotypic errors [39]. These mutations, however, are not only regarded to occur in reprogramming, but also during clonal expansion [39]. Moreover, identifying these and any alterations that may be involved with PD development in expanded cell lines is costly. Another important limitation of iPSCs is the heterogeneity of the generated cell populations. Hence, to circumvent this inefficiency, iPSCs would need to have protocols tailored to generate specific cell lineage, but such quality control regimens entail in vitro time-consuming procedures [39]. Accordingly, using iPSCs as a potential regenerative therapy is feasible, however, the limitations as noted above (as with other stem cells) would need to be resolved to ensure their safety and efficacy for PD application. A hypothesized procedure to overcome the safety risks associated with iPSCs is the elimination of non-neural oncogenic cells through sorting of surface proteins prior to transplantation followed by confirming the absence of these cells through in vivo testing in animal models [40].

Embryonic stem cells (ESC) are one type of stem cell that is pluripotent and proliferates indefinitely in culture; however, there is an ethical controversy similar to the use of fetal tissues surrounding ESC thus making them widely inaccessible. In addition, they are highly tumorigenic, meaning they often form tumors in vivo following transplantation [41]. On the other hand tissue-specific stem cells (TSC) are free of the ethical implications associated with ESC and thus far have been observed to lead to improvements in both human patients and rat models, including PD, stroke, Alzheimer's disease, and Huntington's disease [42, 43, 44, 45]. One important source of TSC is the human placenta, rich in MSCs, which hold great regenerative potential [41]. They are a multipotent subset of stromal cells able to self-regenerate and capable of differentiation into a multitude of mesodermal and embryonic lineages, such as adipocytes, osteocytes, chondrocytes, hepatocytes, muscle cells, epithelial cells, neurons, and others [46]. There are other tissues from which MSC can be derived such

as bone marrow (BM-MSC), cord blood (CB-MSC), and amniotic fluid (AF-MSC); the main differences of these tissue-specific MSC being the expansion capacity and life span of the cells. BM-MSC has the shortest life expectancy and begins a process of deterioration shortly after being cultured [47]. AF-MSC has shown to pose a much higher capacity for expansion at 4–8 times as great [47]. The placental MSC also have a higher expansion as well as greater engraftment ability because of VL4-mediating binding [47]. Despite the major criteria of MSC as being plastic-adherent cells, phenotypic markers of MSC slightly differ from cells derived from these different tissues. MSC are envisioned to be transplanted as autologous or allogeneic grafts, respectively as completely HLA type-matched or unmatched donors [48, 49]. These grafted MSCs may retain their stromal cell phenotype (i.e., MSC) and afford therapeutic benefits via the by-stander mechanism that involves secretion of neurotrophic, neurogenic, angiogenic, vasculogenic, and synaptogenic factors. Alternatively, grafted MSC have been thought to commit into a precursor lineage reminiscent of differentiating neurons, but this phenomenon has been vigorously challenged in that only a handful MSC can be detected to differentiate into neurons after transplantation and likely MSC fused with host neuronal cells [43, 50]. The therapeutic potential of MSC goes beyond their regenerative capacity as they have anti-inflammatory properties, trophic effects, and may be capable of immunomodulation [51]. In regards to PD, MSC thus far have been studied for their potential to alleviate motor symptoms associated with the disease. While in the past decade it has been found that a variety of intrinsic non-motor signs and symptoms accompany motor deficits in PD, some of these symptoms (constipation, orthostatic dizziness, hyposmia, rapid eye movement behavior disorder and depression) arise a considerable number of years before motor Parkinsonism. As such, many of these symptoms preceding PD negatively impact patients' ability to conduct tasks of daily living [7]. Therefore, we advance the notion that stem cells, such as MSCs, capable of multiple lineage differentiation, secretion of growth factors and therapeutic molecules for rescuing not only the dopaminergic system but other neurotransmitter systems as well, should be considered as a complement therapy to address the abnormal non-motor in addition to motor symptoms present in PD.

Multi-pronged therapeutic targets of MSCs in PD

MSCs have great potential, especially in neurodegenerative diseases such as PD. Beneficial effects such as anti-inflammatory responses, neurotrophic support and the capability of immunomodulation, provide potential treatment mechanisms for PD. MSCs' robust capacity to modulate immune responses may alter the progression of different inflammatory diseases [52]. Inflammatory factors may provide cues for MSCs to migrate to tissue sites with damage. Before MSCs repair tissue function, various growth factors are released in response to the inflammation status, which will promote the regeneration and repair of the damaged tissue [52]. Similarly, the growth factors that the MSCs release can provide neurotrophic support which may retard and even prevent progressive neurodegeneration, and may even promote growth of new neurons in the PD brain [53]. The capability of immunomodulation in MSCs is also a potent therapeutic action [54, 55]. When levels of inflammation are low MSCs have the capability to promote immune response, which is highly beneficial for neurodegenerative diseases [52]. An adaptive immune response, like that in PD patients, no

longer protects the brain from infection or injury causing an accumulation of neurotoxins and eventual neurodegeneration [56]. Altogether, MSCs' capability to promote immune response, create anti-inflammatory responses and provide neurotrophic support is beneficial for the change in progression of neurodegenerative diseases, especially PD.

Advancing MSC transplantation for PD

Most studies designed to optimize donor cell grafts for PD have focused in their ability to differentiate into dopaminergic cells along the line of restoring/replacing DA cell loss and alleviate motor symptoms. The need for stem cells to differentiate into other neurotransmitter phenotypes or to secrete growth factors to rescue non-dopaminergic system remains largely neglected. For instance, a number of different receptors that maintain behavior and non-motor function, including GABA, cannabinoid, purinergic and opioid, have been identified as able to modify striatal DA levels, with specific focus currently being placed on glutamatergic and cholinergic systems [57]. A multi-pronged cell death therapeutic approach in PD that encompasses other neurotransmitters may allow improved disease outcomes whereby both motor and non-motor symptoms of PD are alleviated.

In vitro studies have demonstrated differentiating both human and rodent MSC into neuron-like cells [58, 59]. In parallel, in vivo studies of MSC have been shown to improve disease outcome in a rat model of PD attributable to growth factor and cytokine secretion exerting immunomodulatory, anti-inflammatory, and neurotrophic effects [60]. A study conducted by Yasuhara and colleagues using a graft source of human HB1.F3 neural stem cells (NSC) transplanted in a rat model showed improvements in Parkinsonian symptoms despite minimal detection of fully matured dopaminergic neurons from the transplanted stem cells, thus attributed to the secretion of neurotrophic factors by the cells [61, 62, 63, 64]. The survival of neurons in vitro is enhanced by supplementing the cell culture medium with neurotrophic factors, which possess proteins that can modulate neuronal development, such as neuronal maintenance, survival, axonal growth, axonal guidance and synaptic plasticity [63]. Because of these capabilities, neurotrophic factors are regarded with much potential in preventing neurodegeneration and promoting neuroregeneration, especially for PD. Glial cell line-derived neurotrophic factor (GDNF) and neurturin are the two main neurotrophic factors most commonly used in animal models of PD, with both reaching clinical trials but failed to show efficacy for PD patients [65]. Despite these negative clinical readouts, both molecules may have adjunctive applications for stem cell therapy in that they may enhance graft survival and serves as migratory guidance factors in directing axonal growth along the nigrostriatal dopaminergic pathway [65]. Harnessing these neurotrophic factors as pro-survival and guidance molecules will allow a favorable microenvironment for stem cells grafts to integrate better and reconstruct the synaptic network with host dopaminergic and non-dopaminergic. An in-depth understanding of the mechanism of action underlying the potential benefits of these neurotrophic factors to stem cell therapy will help in their clinical applications for PD.

In limited clinical trials, MSC have been shown to afford efficacy in patients with PD. In a recent clinical trial, PD patients were treated with a unilateral autologous bone marrow-derived MSC transplanted into the sublateral ventricular zone, where they functioned as DA

precursor cells, resulting in modest improvements in facial expression, gait, and freezing episodes with no adverse effects, such as tumor formation [66]. This trial confirmed the safety of MSC treatment, and although the mechanism underlying the clinical improvement remains not fully understood, it is likely that stem cells need not be purely differentiated into dopaminergic neurons for treating the non-motor symptoms. MSC may alleviate non-motor PD symptoms through a variety of mechanisms, including via new neuritic outgrowth and formation of synapses as well as through modulation of a favorable environment for the preservation of host tissue under disease conditions. MSC's ability to differentiate to a variety of neuronal phenotypes, such as noradrenergic, serotonergic, and cholinergic cell types may be effective for abrogating the non-motor symptoms of PD. The cell types, numbers, locations, and regulation of the implanted cells are largely determined by donor elements and the local host environment [67]. Evidence exists to show that some of the therapeutic actions observed following transplantation of NSC are directed by a variety of cells owing to the ability of NSC to differentiate into a diverse set of cell types, including undifferentiated progenitor cells and glia [68, 69, 70]. A nonhuman primate PD model revealed that transplantation of human NSCs led to behavioral improvements ascribed to multiple homeostatic actions, in particular restoration in endogenous TH+ cell size and distribution in the TH nigrostriatal system and a reversal of abnormal alpha-synuclein aggregation [67]. Interestingly, a recent study of a novel rat model of progressive cortical synucleinopathy has shown that alpha-synuclein over-expression leads to a progressive reduction of striatal cholinergic neurons [71]. These reductions in cortical and striatal cholinergic transmission in PD patients result in symptoms such as psychosis and memory impairment [72].

On the other hand, there is a strong link between the improvement of TH+ cell expression and amelioration of PD motor symptoms [68, 73, 74]. Of note, tyrosine hydroxylase is the rate-limiting step in the synthesis of catecholamines required for the production of dopamine, which in turn regulates motor functions [74]. Altogether, these findings implicate that multiple neural systems are involved in PD pathology and treatments beyond the dopaminergic system are warranted to address the non-motor symptoms of PD.

Delivery routes for MSC transplantation

A key aspect of optimizing successful outcome of MSC transplantation is the delivery route. The ideal delivery route should provide the most regenerative benefit with the fewest side effects [75]. Widely used MSC cell delivery routes include intravenous, intra-arterial, or direct intra-tissue injection [75]. The intravenous route is the least invasive and allows for the distribution of cells throughout the entire body, which is advantageous if treating diseases with a diffuse presentation [76]. However, because cell homing is ultimately distributed to multiple organs such as the lungs, spleen, liver, bone marrow, thymus, kidney, skin, and to tumors, this delivery method would risk the ability of MSCs to home to one target organ, if at all [75]. It would also risk the survival of the cells once at the target organ due to the mechanical stress the cells have undergone before reaching the target tissue [75]. Because intravenous injection mostly results in cell trapping in the lung vasculature due to a pulmonary first-pass effect, pursuing the alternative peripheral route of intra-arterial delivery has allowed the cells to bypass the lungs at least once [76]. This would then facilitate a more

efficient homing to the target tissue and eventually aid in improving tissue homing [76]. The entrapment of MSCs in the lung may cause an embolus while entrapment in the spleen and liver may elicit suppression of destructive immune responses [75]. Direct delivery of MSCs in the brain permits a precise transplant localization, however, it is an invasive technique. In the case of alleviating PD motor symptoms, the areas of interest for MSC transplantation would be intraputamenal or intracaudate delivery [77]. However, striatal as well as extra-basal ganglia brain structures may need to be targeted for MSC transplantation to be effective in treating PD non-motor symptoms. Targeting these discrete areas would enable brain-region specific delivery of cells to the PD-lesions and replace dopaminergic and non-dopaminergic cell dysfunction [77]. Because much of the non-motor symptom complex involves many neurochemical substrates, the concept of stem cell therapy to replenish neurochemical pathways needs further exploration to determine which cell delivery route would be the most efficacious [78].

New targets for cell transplantation in PD

Recent studies link serotonergic dysfunction in primarily extrastriatal regions to non-motor symptoms, including depression [29], fatigue, alteration of body weight, and visual hallucinations [33, 79]. PET imaging with tracers targeting markers of the serotonergic system (C-DASB, a marker of serotonin transporter availability, and ^{18}F -setoperone, a marker of serotonin 2A receptors availability) revealed serotonergic involvement in the manifestation of non-motor symptoms in patients with PD [80]. Similarly, imaging the monoaminergic systems (using ^{11}C -DASB and ^{18}F -dopa as in vivo markers of DA terminal function) and correlative analyses of clinical evaluations of motor and non-motor symptoms following fetal cell transplantation in three PD patients indicated that 13–16 years post-transplantation of fetal dopaminergic cells patients continued to display non-motor symptoms, including daytime sleepiness, constipation, reduced concentration, weight loss, anxiety and depression, and visual hallucinations, despite a re-innervated dopaminergic network at the site of the basal ganglia and several limbic and cortical forebrain regions [81]. Furthermore, while the noradrenergic innervation of the locus coeruleus (LC) was intact, there was a reduced innervation of the serotonergic network at the raphe nuclei and cortical, subcortical, and deep nuclei regions in those same patients, indicating ongoing degeneration of serotonergic raphe nuclei and their projections even at several years after cell transplantation [80, 81]. The contribution of non-dopaminergic systems to PD pathology is exemplified by transplanted patients exhibiting non-motor symptoms despite restoration of the dopaminergic innervation and with noradrenergic LC remaining intact. This observation indicates that PD pathology involves widespread neurodegeneration beyond the nigrostriatal dopaminergic pathway causing malfunction of large parts of the cerebrum, likely a general monoaminergic transmitter loss not only limited to dopamine. Indeed, when monoaminergic systems were monitored/ scanned in transplanted PD patients, results indicated improvement of DA neurons, but degeneration of serotonergic neurons remained in extrastriatal locations [81]. This highly specific rescue of dopaminergic system by DA grafts limits the therapeutic benefits to motor symptoms, thereby necessitating the need for treatment of non-dopaminergic systems in order to also ameliorate non-motor symptoms. To this end, our overarching hypothesis advances MSC grafts as an effective disease-modifying strategy in

halting both dopaminergic and non-dopaminergic degeneration allowing attenuation of both motor and non-motor symptoms of PD.

Expert Commentary and Five-Year view

Moving forward with cell therapy for PD, the use of fetal and embryonic derived stem cells will need to be complemented by adult tissue-derived stem cell sources, which appear to circumvent many ethical and logistical issues associated with the former donor cells. We are presented with MSCs, known for their great regenerative capacity and ability to differentiate into a comprehensive array of cell lineages, requiring translational investigations on optimizing their safety and efficacy, but also on elucidating their mechanisms of action in order to appreciate their full potential for PD applications. To this end, the last two decades have documented that many PD patients and models benefit from cell transplantation to alleviate motor symptoms, but continue to suffer from non-motor symptoms of the disease [66, 82, 83, 84, 85]. That neurodegeneration occurs in key non-dopaminergic brain regions, not necessarily the pathological hallmarks of PD, but nonetheless primarily involved in non-motor PD symptoms, signifies new cell therapy targets for a more complete relief of disease symptoms. Because traditionally neurodegeneration in PD has been considered to critically involve the nigrostriatal dopaminergic depletion, this prompted the field of stem cell therapy to target repair of the nigrostriatal dopaminergic pathway [86]. However, the disease has now been recognized to exhibit extensive non-nigrostriatal pathology and as many non-motor as motor features, which currently are not targeted by cell therapy [83]. Accumulation of alpha-synuclein in Lewy bodies and Lewy neuritis is one of the neuropathological hallmarks of PD, which impairs hippocampal neurogenesis leading to the development of depression, a major non-motor symptom of PD [87]. Unfortunately, stem cell transplants for PD have largely ignored targeting the hippocampus for treating PD symptoms, especially the non-motor features. Interestingly, treatment with selective serotonin reuptake inhibitor (SSRI) has shown promise in attenuating impaired hippocampal neurogenesis in alpha-synuclein transgenic mouse model of PD, advancing the possibility that targeting the hippocampus via cell therapy may afford anti-depressive effects, and may also ameliorate other PD non-motor symptoms [87]. The ensuing phase of cell therapy for PD requires the development of transplantation regimens, such as the use of stem cells (i.e., MSC) that can abrogate both dopaminergic and non-dopaminergic degeneration with the aim to alleviate motor and non-motor symptoms in an effort to retard or halt the disease progression and possibly reverse the disease process, with the overall intent to improve quality of life for patients with PD.

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Key Issues

- The ideal approach for the treatment of PD would be a restorative therapy, which is able to replace the disease-denervated dopaminergic network in an effort to, at the very least, retard the disease progression
- While restoring the DA neuronal circuitry and replacement of dead/dying dopaminergic cells may seem a logical tactic, such a method appears to cater only to motor symptoms of PD. Therefore a cell-based therapy targeting the non-dopaminergic system underlying non-motor symptoms of PD remains to be explored
- Somatic cell reprogramming allows generation of human pluripotent stem cells from PD patients and may permit correction of the mutations associated with PD pathology
- Embryonic stem cells (ESC) are one type of stem cell that is pluripotent and proliferates indefinitely in culture; however, there is an ethical controversy similar to the use of fetal tissues surrounding ESC thus making them widely inaccessible.
- Grafted MSCs may retain their stromal cell phenotype (i.e., MSC) and afford therapeutic benefits via the by-stander mechanism that involves secretion of neurotrophic, neurogenic, angiogenic, vasculogenic, and synaptogenic factors.
- MSC may alleviate non-motor PD symptoms through a variety of mechanisms, including via new neuritic outgrowth and formation of synapses as well as through modulation of a favorable environment for the preservation of host tissue under disease conditions.
- MSC's ability to differentiate to a variety of neuronal phenotypes, such as noradrenergic, serotonergic, and cholinergic cell types may be effective for abrogating the non-motor symptoms of PD.
- We advance the notion that stem cells, such as MSCs, capable of multiple lineage differentiation, secretion of growth factors and therapeutic molecules for rescuing not only the dopaminergic system but other neurotransmitter systems as well, should be considered as a complement therapy to address the abnormal non-motor in addition to motor symptoms present in PD.

Table 1

Stem cell sources used in animal models and humans to assess their potential for the treatment of PD. Sourced from [PubMed.gov](https://pubmed.ncbi.nlm.nih.gov/)

Stem Cell Source	Animal	Human	PubMed ID
Fetal ventral mesencephalon	Yes	Yes	PMID: 8682173 ⁷⁹ PMID: 9711741 ⁸⁰
Neural stem cells	Yes	Yes	PMID: 22457112 ⁸¹
Mesenchymal stem cells	Yes	Yes	PMID: 25302802 ⁸² PMID: 25136260 ⁸³
iPSCs	Yes	No	PMID: 24672756 ⁸⁴

Table 2Current clinical trials of stem cell therapy for PD. Sourced from Clinicaltrials.gov

Study	Started/completed	Number of Participants	Stem Cell Type	Purpose	Clinicaltrials.gov ID
Autologous MSC Transplant for PD	Nov 2011/ Suspended	5	BM-MSC	Safety/ Efficacy	NCT00976430
MSC Transplantation with PD	Oct 2011/Jun 2014	20	BM-MSC	Safety/ Efficacy	NCT01446614
Study to Assess the Safety and Effects of Autologous Adipose-Derived Stromal in Patients with PD	May 2011/Jun 2015	10	Adipose-Derived Stromal Cells	Safety/ Efficacy	NCT01453803
Molecular Analysis of Human Neural STEM Cells	Jun 2011/Jun 2014	20	Neural Stem Cells	Methods for Isolation/ Propagation	NCT01329926
Clinical Trial to Evaluate BM-MSC Therapy for Progressive Supranuclear Palsy, a Rare Form of Parkinsonism	Dec 2012/Dec 2014	25	BM-MSC	Safety/ Efficacy	NCT01824121