Possible roles of epigenetics in stem cell therapy for Parkinson’s disease

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Parkinson’s disease (PD) is a neurodegenerative disease with loss of dopaminergic neurons. PD has genetic and epigenetic influences that determine specific changes in the brain. Epigenetic changes result in defective methylation of genes leading to differential gene-expression causing PD. This review provides an overview of stem cell transplantations as potential therapies for PD, with a focus on the epigenetic changes, prior or following transplantation. To date, no reports have addressed epigenetic alterations following stem cell transplantation into the PD brain. Given the potential for affecting the efficacy of stem cell therapy, increased attention needs to be given to the epigenetic processes that occur during stem cell culture and transplantation to maximize the therapeutic potential of stem cells to PD.

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Parkinson’s disease (PD) is a neurodegenerative disorder that results from the degeneration of the dopaminergic (DAergic) neurons in the substantia nigra pars compacta [1]. DAergic neurons are found in the mid-brain and produce the neurotransmitter, dopamine (DA). DAergic neurons act to maintain voluntary movement and specific behaviors such as mood, addiction and stress [2]. Loss of DAergic neurons leads to reduced production of DA resulting in the characteristic PD symptoms. Given that brain abnormalities increase with age in PD patients and knowing that the symptoms of PD usually manifest at the age of 60 years or older, age is the major risk factor for developing PD [1]. The disease involves both motor and nonmotor symptoms that affect the quality of life. The nonmotor symptoms of PD include dementia, insomnia, day-time sleepiness, hallucinations, excessive sweating, weight loss and impulse control disorders [3,4].

PD dementia and Lewy body dementia (LBD) have similar presentations and prognosis. Patients with LBD show motor deficits, hallucinations and cognitive impairment similar to PD patients. However, the progression of these symptoms is different in PD and LBD. Patients with PD will first exhibit abnormal motor symptoms followed by cognitive decline. Patients are diagnosed with PD if they develop dementia more than 12 months after the onset of motor symptoms. In contrast, patients with LBD present with cognitive decline followed by motor symptoms [5].

Some of the motor symptoms of PD include gait problems, bradykinesia, akinesia and rigidity [6]. PD is associated with both genetic and environmental factors. Familial PD is associated with mutations in the PARK gene family, which includes the SNCA. In addition, LRRK2 and PINK1 genes are associated with both familial and sporadic PD. Additionally, constant and frequent exposure to tobacco and pesticides are two of the environmental factors that may lead to sporadic PD [7]; interestingly, both have been shown to result in epigenetic changes [8].

One of the potential therapies for treating the symptoms of PD is to increase the amount of DA in the brain. However, DA does not cross the blood–brain barrier and treatment has relied on precursors of DA such as levodopa (L-dopa). Although L-dopa can provide symptomatic relief, individuals using L-dopa often experience significant side effects [9]. Another approach for treating PD is boosting the level of GDNF in PD patients. Although GDNF improves the survival of DAergic neurons, clinical trials attempting to increase GDNF levels in the brains of PD patients have not been successful to date [10–12]. Therefore, researchers have been looking for alternative strategies to provide long-term treatment for PD, including transplantation of different types of stem cells, such as mesenchymal stem cells (MSCs), neural stem cells (NSCs), induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) into the PD patient’s brain.

Epigenetic changes following stem cell transplantation may be affected by a variety of factors. Genetic and epigenetic changes that occur when NSCs are cultured and passaged prior to transplantations can affect the therapeutic efficacy of these cells following transplantation. Loss of expression of certain genes during in vitro cell passaging poses significant concerns about whether the transplanted NSC line will be able to differentiate into DAergic neurons in vivo. Treating NSCs with antioxidants and vitamins, specifically Vitamin C, has resulted in a significant increase in the NURR1 and FOXA2 gene expressions compared to untreated NSCs. Expression was maintained both before and after differentiation and transplantation. The NSCs generated were able to alleviate PD behavioral symptoms in a rat model by modulating epigenetic changes [13].

As indicated above, a genetic predisposition to PD involves alterations in certain genes, such as PARK (1–15) including, LRRK2 (PARK8), and SNCA (PARK1/4). In addition to the genetic alterations found in the PD brain, there are also specific epigenetic alterations that regulate the expression of certain genes in the brain of PD patients. The following sections will review the current knowledge of the epigenetics associated with PD and stem-cell-based therapy. Given that the objective of stem cell therapy for PD is to differentiate/trans-differentiate stem cells into a neuronal-like lineage, specifically DAergic neurons, the main population of cells that degenerate in PD [14], these epigenetic events have particular import for application of this therapeutic strategy.

Epigenetics & PD
Epigenetics plays an important role in the molecular basis of cellular function, relying on chemical modifications that alter the activity of DNA without changing its sequence. Epigenetic changes result from a variety of factors that can be intrinsic or extrinsic to the organism. Examples include hormones, metabolism, diet, temperature, light, drugs, air pollution, stress, etc. Epigenetic changes alter development, aging, adaptation, and can affect the course of neurodegenerative diseases, such as PD [15].
The specific mechanisms underlying the onset and progression of PD have yet to be elucidated. However, a number of genetic and cellular mechanisms have been implicated, as well as epigenetic modifications [8]. The epigenetic modifications include DNA methylation, histone modifications, altered expression of miRNAs and long noncoding RNAs (lncRNAs) that regulate expression of genes that also affect stem cells and their development. Thus, a thorough understanding of the epigenetic mechanisms mediating stem cell function and differentiation could enhance the efficacy of stem-cell-based treatments for PD [16] as detailed in the examples below.

DNA methylation
Methylation of DNA is one of the most extensively studied epigenetic mechanisms underlying many diseases. The addition of a methyl group to DNA generally results in inhibition of transcription. Although this can occur at many genomic sites, the most prevalent site of methylation is in CpG islands associated with promoter regions. In PD patients, these regions become dysregulated, resulting from either excess or reduced DNA methylation [17], which in turn results in under or overexpression of specific genes.

One of the first mutations linked to the development of familial PD is a missense mutation, p.Ala53Thr, in SNCA gene. Point mutations, gene duplication, copy number variants and overexpression of SNCA have all been associated with the formation of Lewy bodies, a neuropathological feature of PD [18]. In addition to mutations in SNCA, altered DNA methylation in introns has also been linked to the development of PD due to the dysregulation of SNCA gene expression in the substantia nigra and cortex [19]. Jowaed and colleagues studied epigenetic regulation of the SNCA gene. They found that DNA methylation in intron 1 of the SNCA gene decreased expression of SNCA. As expected, inhibiting methylation resulted in increased SNCA gene expression. These findings are supported by the observations of fewer methylated CpG sites in the DNA samples of PD patients compared with healthy individuals. Additionally, it is likely that the methylation state of intron 1 in SNCA gene may be affected by environmental factors that generate epigenetic changes providing an explanation for idiopathic PD [20].

Other genes, such as PARK16, NMB (GPNMB) and STX1B, GBA are also associated with the development of PD and exhibit an abnormal methylation status [21,22]. Recently, haploinsufficiency of GBA was shown to accelerate alpha synuclein pathology [23].

Histone modifications
Histone modification, another type of epigenetic change, alters the assembly of chromatin structures modifying gene expression. The modified histone proteins undergo conformational changes that can result in gene silencing or gene activation. These modifications include acetylation, phosphorylation, methylation, ubiquitylation or SUMOylation [24].

The most common modifications to histones are methylation and acetylation. Histone methylation occurs on either the arginine or lysine residues in the N-terminal of H4 histone altering transcriptional activity. Histone methyl-transferase catalyzes this reaction. Histone acetylation occurs at the ε-amino of lysine residues in the N-terminal tails of the histones H2A, H2B, H3 and H4, causing a transcriptional change. This transfer is catalyzed by histone acetyl-transferases and reversed by histone deacetylase enzymes [25].

Nicholas and colleagues demonstrated histone modifications in an acute murine model of levodopa-induced dyskinesia following dopamine depletion and levodopa treatment [26]. The specific histone change was a reduction in H3 acetylation and trimethylation and deacetylation of histone H4.

lncRNAs
Another major epigenetic mechanism used to regulate gene expression is provided through RNA-based mechanism. lncRNAs nonprotein coding transcripts can attach to genes and alter their expression [27]. Furthermore, studies have found that lncRNAs play an important role in regulating synaptic plasticity, cognitive function and memory [28].

SNCA is regulated by lncRNA resulting in increased expression of α-synuclein α-SYN. α-SYN contributes to DAergic neuronal differentiation and survival, as well as regulation of TH activity in the brain, TH catalyzes the production of L-dopa from tyrosine, a DAergic precursor that is critical for preventing the events leading to PD [29]. The expression of PINK1, another gene associated with PD, may be regulated by a lncRNA. Many of the lncRNAs that are dysregulated in PD modulate expression of PD-related genes [30]. Marki and colleague showed that polymorphisms in lncRNA genes such as PINK1, UCHL1-AS, BCYRN1, SOX2-OT, ANRIL and HARB were highly associated with PD patients in Hungarian populations [31]. Upregulation of SOX2-OT and 1810014B01Rik lncRNA genes are associated with PD [28].
Another RNA-based mechanism for regulating gene expression involves microRNAs (miRNA; containing around 22 nucleotides), which are noncoding RNAs that suppress protein production through degradation of mRNA or by inhibition of mRNA translation. These miRNAs control expression of their target gene post-transcriptionally and are used to control a wide variety of physiological and pathological functions. Several miRNAs regulate expression of α-SYN. Doxakis found that overexpression of miRNA7 and miRNA153 reduced α-SYN levels [32]. Leggio and colleagues showed that miRNAs participate in a negative feedback loop with PITX3 gene, which regulates differentiation and activity of DAergic neurons [27]. Moreover, miRNAs have been shown to mediate oxidative stress, one of the main causes of PD. The miR-124 agomir increases the density of TH+ neurons and decreases the upregulation of mRNA and protein levels that resulted in a decrease in apoptosis. Moreover, a number of large-scale studies of brain tissue samples have detected alterations in downstream targets of dysregulated miRNAs that are associated with PD. Single miRNAs have been shown to mediate the expression of hundreds of genes. Targeting these altered miRNAs has been shown to improve functioning in PD models [33].

Following the elucidation of the epigenetic mechanisms associated with the development of PD, expression of some important proteins and factors have been found to be altered by such epigenetic changes, including:

- NURR1 is a member of nuclear receptor subfamily 4 that is essential for the proper formation and maintenance of DAergic neurons from their precursors, the mesodiencephalic dopaminergic neurons. NURR1 is also crucial for the migration and survival of dopaminergic neurons. Additionally, NURR1 may also be involved in regulating the expression of some of the enzymes and transporters, such as TH and DAT), which play roles in the production and storage of DA [34].
- PITX3 is expressed by a subpopulation of DAergic neurons presented specifically in the substantia nigra and is required for DA neuronal differentiation, with its expression being associated with the age of onset of PD [35]. Synergistic expression of NURR1 and pituitary homeobox 3 is necessary for ESCs to differentiate into dopaminergic neurons in the midbrain, which are the neurons responsible for the production of TH and DAT in the brain [15].
- TH is an enzyme that is present in mature DAergic neurons and catalyzes the production of L-DOPA, the metabolic precursor of DA [36].
- Shh, a secreted glycoprotein, helps with the development of DAergic neurons in the neuroepithelial floor plate from the midbrain and hindbrain border. Shh also appears to increase TH gene expression in cells with dopaminergic phenotypes. Additionally, Shh increases resistance of mesencephalic DAergic neurons to MPTP and 6-OHDA insult to the brain [37].
- FGF8 and FGF2 are involved in the migration, differentiation and survival of DAergic neurons to establish the midbrain and hindbrain border [38,39].
- BDNF and GDNF promote the growth and survival of DAergic neurons. BDNF confers neurotrophic and neuroprotective effects as well as increasing dopamine reuptake and TH activity. Additionally, BDNF is thought to have autocrine, paracrine and retrograde effects on DAergic neurons. Similarly, GDNF enhances the survival of DAergic neurons and increases high affinity dopamine uptake, but is more effective than BDNF [40].
- Retinoic acid, a by-product of vitamin A, determines the maturation level of DAergic neurons from its precursor [41].
- ASCL1 is a transcription factor that activates transcription of genes leading to differentiation of DAergic neurons. Additionally, ASCL1 is also involved in the initiation of oligodendrogenesis and myelination in the postnatal cortex [42].
- LMX1a and LMX1b are also involved in the growth and maintenance of dopamine-producing neurons during embryogenesis. Downregulation of these genes results in impaired mitochondrial function and formation of α-SYN aggregates, thereby leading to the loss of DAergic neurons [43].

Epigenetic variations are now considered a major focus for understanding the changes that occur in the brain of PD patients. Thus, defining the epigenetic changes that occur after transplantation of stem cells in PD therapy also merits study.

**Stem cell transplantation in the PD brain**

Different types of stem cells have been utilized for treatment of PD. *In vitro* work with mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) has led to transplantation studies...
in both animal models of PD and in humans [44–48]. Transplantation studies provide further insight into whether and how the stem cells arrive at affected brain locations, whether and how each of the different types of stem cells successfully differentiate into a DAergic neuronal lineage and whether the differentiated DAergic cells can integrate into the brain circuit and reduce the behavioral symptoms of PD. To date, the epigenetic status of the transplanted stem cells are rarely assessed.

Dezawa and colleagues described induction of neuronal cells from bone marrow (BM)-derived stromal cells using trophic factors and gene transfer. These cells were then transplanted into animal models of neurodegenerative diseases such as PD. The study showed that the cells were able to successfully integrate into the neuronal circuit and provide therapeutic effects as evidenced by improved function [49].

Another study by Funk and Alexanian described a method for generating mature neural-like cells from BM-derived MSCs (BM-MSCs) by exposing them to epigenetic modifiers. This changed their innate characteristics and produced cells in a primitive pluripotent-like stage. Next, these pluripotent-like cells were exposed to an NSC environment, which resulted in their differentiation into mature neural-like cells. The re-programmed cells were then analyzed, and these cells were found to release neurotrophic factors, such as NGF and BDNF, which have shown potential for treatment based on their promoting the survival and growth of neurons in brain under neurodegenerative conditions, including PD [50].

**ESCs in PD**

ESCs have been studied extensively as a potential therapy for PD. An early study by Bjorklund and colleagues reported on the effects of ESC transplantation following lesions of the medial forebrain in female Sprague Dawley (SD) rats. The ESCs were derived from mouse blastocysts and injected into the right striatum of the PD rat. Following the ESCs injection, PET and MRI scans showed that ESCs readily develop along a DAergic neuronal lineage within the brain, exhibiting changes in the structure of the striatum following transplantation. In addition, behavioral improvement was also noted, indicating that these neurons successfully restored function in these models [51].

In order to assess the importance of gene alterations, Brederlau and colleagues conducted a study investigating the effect of predifferentiation time of human ESCs grafted into a female SD rats of PD. The ESC from human origin (hESC) cells were predifferentiated for 16, 20 and 23 days. SD rats were lesioned in the right nigra-striatal pathway and then received human embryonic stem cells (hESC) injections in anterior, lateral and ventral locations of the striatum. Grafted predifferentiated cells did not express DA phenotypes and no motor improvement was observed. In contrast, the cells that were allowed to predifferentiate for 16 days prior to grafting exhibited tumor growth in vivo, but those that predifferentiated for approximately 20 days or more did not exhibit this adverse effect [52]. This confirms the importance of the differentiation state of transplanted neurons and the need for characterizing epigenetic markers that indicate a propensity for cancer development or the ability to differentiate into DA producing cells.

Clinical trials for human transplantation of embryonic DAergic neurons have provided mixed results. In an early double-blind study, 40 randomly assigned PD patients with severe symptoms were either surgically injected with embryonic DAergic neurons bilaterally into the putamen or underwent a sham surgery that entailed drilling into the skull without disruption of the dura. The results of this trial indicated that the transplanted cells provided more relief for younger individuals with PD as opposed to older individuals [53].

However, hESC transplantation has provoked considerable controversy surrounding the ethical use of fetal tissue as well as other issues, such as transplant-induced dyskinesia, that has dampened the enthusiasm for pursuing this line of research [54]. Nonetheless, hESC transplantation has significant therapeutic potential for treating neurodegenerative diseases, like PD, and outcomes from this type of therapy could be improved if further insights into epigenetic alterations were understood well enough to optimize their effectiveness.

**iPSCs in PD**

iPSCs for treatment of PD are an alternative to hESC transplantation, where the patient’s own cells are differentiated into DAergic neurons. Ethical concerns have been raised about the potential for undesired genomic alteration via iPSC transplantations that may result in cancer. However, more recent research indicates that the reprogramming process for iPSCs is not excessively mutagenic, suggesting that iPSCs can be used safely for stem-cell-based therapy [55]. These cells are usually derived from either skin or blood and are re-programmed to a state similar to
that of ESCs. These iPSCs can be differentiated into a variety of lineages, including motor neurons, gametes and blood cells [56-58].

Transplantation of iPSCs have been performed in cynomolgus monkey (CM) models of PD that were generated by treating CMs with MPTP. The efficacy of the iPSCs treatment was evaluated following transplantation of the cells into the putamen. The iPSCs were derived from MF25-04 nonhuman primate models and trans-differentiated into a DAergic neuronal lineage prior to transplantation. The graft resulted in reduced PD symptoms following transplantation into CM models. Histological analysis showed that there was increased microglial density, without a concomitant increase in the immune response within the putamen [59].

Further primates show significant epigenetic effects on transplanted cells that subsequently differentiate into neuronal-like cells. Kikuchi and colleagues analyzed genetic factors affected by iPSCs following their transplantations into CM models. Lines from PD patients and healthy individuals have been established. These cell lines have been analyzed for FOXA2, TUJ1, NURR1, and multiple tumorigenic markers in in vitro. Following analysis, the cells were transplanted into the putamen of MPTP PD monkeys. The study showed that irrespective of the source of iPSCs (PD patient vs healthy individuals), the iPSCs were able to differentiate into DAergic neurons in vivo and the PD monkeys recovered from motor deficits compared with controls. Post-transplantation, histological analysis revealed that the characteristics and the morphology of the TH+ cells were similar to that of the graft recipient's cells, further showing that these cells were able to produce DAT in the mid-brain as well as GIRK2, which is produced by the DAergic neurons in the nigrostriatal pathway. Following this, the PD monkeys were randomly divided into two groups based on whether they had excellent or poor TH+ cell re-innervation. The study also found that the PD monkeys that had excellent innervation showed upregulation of 11 specific genes. Interestingly, the most prominent of these genes is Dlk1, which was previously shown to have a role in mid-brain facilitating migration of DAergic neurons, thereby improving the innervation of TH+ cells. This study demonstrates the efficacy of iPSC transplantations and the significance of the epigenetic changes that occur in them leading to upregulation of genes specific to DAergic neuron migration, location and dopamine release [60].

Reprogrammed iPSCs from fibroblast also effectively integrate into the embryonic mouse brain. Wernig and colleagues transplanted fibroblast-derived iPSCs into the brains of embryonic mice in utero and reported that they differentiated into a variety of neuronal and glial lineages. They then transplanted iPSCs into rats that were given the neurotoxin, 6-OHDA, which kills DAergic neurons, causes of symptoms of PD. When iPSCs that were differentiated toward a DAergic neuronal lineage were grafted into the striatum of these 6-OHDA-treated rats, the researchers observed the presence of more TH+ cells in their brain. However, they also noted the formation of tumors occurred frequently in the rats given iPSC transplantations, underscoring serious safety concerns that need to be addressed before grafting of iPSCs can be considered for clinical use [61]. Clearly, the epigenetic alterations of the iPSCs need to be studied thoroughly before any hope of them being used for clinical purposes can be seriously entertained. As a first step, Roessler and colleagues analyzed the epigenetic signatures of iPSC-derived DAergic neurons and confirmed that these markers are important for assessing the long-term functionality of the transplanted cells [35].

MSCs in PD

MSCs are adult multipotent stem cells that are used extensively in stem cell therapy studies for a variety of neurodegenerative diseases, including PD. MSCs can differentiate into a variety of lineages, including neuronal, adipocytes, chondrocytes and osteoblasts, as well as ectodermal neurocyte [62]. Transplantation of MSCs into the brains of rodents that are manipulated to model PD has often yielded improvements in motor function and increased TH and DA levels, demonstrating the promise of this approach. For example, MSC transplantation into the MPTP-treated mice showed reduced motor dysfunction, as well as trans-differentiation of BM-MSCs into a DAergic neuronal lineage. In addition, TH+ cells in the substantia nigra were increased, relative to what was observed in control mice [45].

PD research is predominantly conducted in rat models. However, some studies have investigated stem-cell-based therapy in murine PD models. BM-MSCs were extracted from male C57BL/6 mouse that were subsequently, treated with MPTP, and followed by implantation of the MSCs into the right striatum. As with the rat model, the mice showed improved rotational behaviors when subjected to motor coordination tasks following MSC transplantation [63].

Work in our lab indicates that the efficacy of transplanting BM-MSCs is dependent on the type of dopaminergic induction method and the number of passages the MSCs undergo prior to transplantation [39,64]. Shall and
colleagues analyzed changes in mRNA expression in BM-MSCs isolated from male SD rats at four or 40 passages following either direct or indirect induction of dopaminergic differentiation. The MSCs differentiated into a DAergic lineage (expressing TH, DAT and MAP2 genes) following either direct or indirect induction, although direct dopaminergic induction of early passed cells (P4) was more efficient than indirect dopaminergic induction of late passed cells [64].

Similarly, Welchko and colleagues genetically modified BM-MSCs using a virus carrying three different genes: ASCL1, LMX1A and NURR1, some of the factors important for inducing differentiation of DAergic neurons. A detailed description of each of these genes is given above. The results from this study showed that the BM-MSCs were successfully transduced with the virus and that the cells expressed TH and DAT [39]. Transplantation of these cells into 6-OHDA-treated rats reduced the motor deficits found in this PD model.

The studies from our lab indicate that BM-MSCs can be steered into a DAergic lineage by modifying them either by incubating the stem cells in specific media or by introducing genes that drive differentiation. Though the outcome of these studies was the production of DAergic neurons, the epigenetic makeup of the cells may be different following each type of DAergic induction. Future studies are required to define the epigenetic changes occurring under each of the conditions used.

Overall, these studies show promising therapeutic results for stem-cell-based transplantation in the treatment of PD. However, the genetic and epigenetic changes that occur in the PD brain can readily lead to increased or decreased expression of genes that contribute to the disease symptoms and conditions. As discussed above, epigenetic changes are associated with the development of PD, but how epigenetics impact transplantation for PD is a major focus of future research.

Conclusion

Epigenetic mechanisms regulate genes resulting in the increase/decrease of protein levels. The epigenetic state of the different types of stem cells and/or DAergic neuronal lineage of cells obtained by the transdifferentiation/differentiation of stem cells prior to transplantation into the PD brain may be different, affecting the outcome of the treatment. This may, in part, help to explain why the stem cell therapies for PD exhibit varying levels of efficacy. Results could be affected by unknown epigenetic factors that impact the progression of PD or the viability of the transplanted cells. As studies involving iPSCs, hESCs and MSCs indicate the emerging impact of genomic properties on treatment efficacy, more attention must be paid to stem cell epigenetics.

Importantly, more studies involving the epigenetic changes before and after of in vivo transplantation in PD are needed, especially to evaluate specific stem cell epigenetic markers. The critical data needed are the similarities and differences between the epigenetic signatures of the host DAergic neurons and the DAergic neurons that are transplanted following transdifferentiation of various types of stem cells. This important variable needs to be characterized in order to determine which approach to stem cell therapy will produce the cells that are most likely to eliminate the symptoms of PD.

Future perspective

Future transplantation studies should incorporate in their analysis information about the sources of the transplanted cells for PD. The potential epigenetic characteristics of these cell populations might play a critical role in rendering their therapeutic effects. It would also be beneficial for research in the future to record the different epigenetic changes that stem cells undergo during differentiation and transdifferentiating prior to transplantation. This might lead in choosing a specific stem cell type having epigenetic changes that may provide the most effective stem cell based therapy for PD.

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Executive summary

- Parkinson’s disease (PD) is a neurodegenerative disorder that results from the degeneration of the dopaminergic neurons in the substantia nigra pars compacta.
- The objective of stem cell therapy for PD is to differentiate/trans-differentiate stem cells into a neuronal-like lineage, specifically dopaminergic neurons, the main population of cells that degenerate in PD, the different epigenetic events have particular import for application of this therapeutic strategy.

Epigenetics & PD

- Epigenetic changes alter development, aging, adaptation, and can affect the course of neurodegenerative diseases, such as PD.
- There are many genes that exhibit mutations leading to PD with abnormal methylation status.
- There are various long noncoding RNAs and miRNA that are important for gene regulations are altered in PD.
- Some of the important proteins and factors that are altered in PD include Nurr1, pituitary homeobox 3, tyrosine hydroxylase, sonic hedgehog, FGF2, LIM homeobox transcription factor, brain-derived neurotrophic factor and GDNF.

Stem cell transplantation in PD brain

- Stem cell transplantation of differentiated/transdifferentiated stem cells into dopamine neurons and cell re-programming (induced pluripotent stem cells) are some of the strategies used as a potential therapy for PD.
- Transplantation of dopaminergic neurons obtained from various stem cell sources may exhibit different epigenetic signature that could be same/different than the host dopaminergic neurons leading to a differential therapy for PD.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

9. Allows us to learn all the basic concepts of epigenetic details that are associated with Parkinson's disease (PD).
15. Allows us to learn all the concepts associated with stem cell transplants for PD.
17. Gives details about epigenetic changes that happen during dopamine (DA) neuronal development.
Possible roles of epigenetics in stem cell therapy for Parkinson’s disease


● Gives details about stem cell re-programming and the genetic and epigenetic changes that happen following re-programming into DA neurons.


- Explains how the passage number of stem cells and the protocol method used can affect the differentiation of mesenchymal stem cells into dopaminergic neuronal like cells.