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Bridging the Genetical Environmental Gap in Parkinson's Disease through Epigenetics

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Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder affecting 2% of the population over 60 years old, yet the exact molecular mechanism underlying its pathogenesis remains elusive. PD is a multifactorial disease with genetic and environmental factors intricately associated.

Recently, epigenetic mechanisms have been recognized as potential mediators of environmental factors participating in the pathogenesis of PD. Epigenetics refer to the heritable changes in gene expression that do not involve changes to the underlying DNA sequence. Altered epigenetic mechanisms have been attributed to PD, Alzheimer's and Huntington's disease. Several studies have shown that DNA methylation, histone modifications and non-coding RNAs mechanisms contribute to the pathogenesis of PD. Accumulation of toxic metals such as manganese and iron, due to abnormal environmental exposure or increased dietary intake, can impact varied components of the epigenetic machinery through free radical formation.

Current pharmacological agents only provide symptomatic relief, of which levodopa still remains the gold standard. However, drugs that halt or delay progression of PD are still lacking. In recent years, there has been considerable progress in the development of epigenetic drugs as a novel therapeutic modality in the management of PD. Cell replacement therapy is a promising avenue for the treatment of PD with scientific research making great progress in the development of Induced Pluripotent Stem Cells (iPSCs) to produce midbrain dopamine phenotypes. With direct access to the neurons that are affected in PD, the pace of discovery should speed up and the cure for PD should become an attainable goal.

Keywords: Epigenetics; Parkinson's disease; Cell replacement therapy

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Pathological Features

The histopathological trait of PD is the presence of fibrillar aggregates known as Lewy Bodies (LBs), with α-synuclein as the primary constituent. The presence of LBs may be seen as a representation of neuronal degeneration since neuronal loss is primarily found in the substantia nigra, locus coeruleus, nucleus basalis of Meynert, and the dorsal motor nucleus of the vagus, all of which are regarded as the predilection sites for LBs. Familial forms of PD are the consequence of mutations in the α-synuclein gene with α-synuclein protein being the major component of LBs in patients with sporadic PD [1].

It is also well known that there are numerous groups of dopaminergic neurons in the CNS, but not all deficits in dopamine accounts for PD. It is primarily the deficit of dopamine cells in the Substantia Nigra Pars Compacta (SNpc) that is thought to be responsible for all the motor complications of the disease. This selectivity goes further, in that not all of the dopamine neurons of the SNpc are involved with the disease. In fact, it is predominantly the ventral-lateral tier which is more severely affected compared to the dorsal tier. However, in the normal ageing process, it is the dorsal tier which is preferentially affected by a ratio of over 3:1 compared to the ventral tier [2]. The pattern of cell loss seen in PD is unique as it neither occurs in other neurodegenerative diseases, nor in the normal ageing process. The reason behind such circumstantial susceptibility of cells affected in PD remains unclear.

Etiological Factors

Over the past couple of years, human genetics has been in the forefront at providing multiple entry points in the understanding of the pathogenesis of PD. Whereas, mutations in α-synuclein and LRRK2 are predominantly regarded as dominant forms of inheritance, the recessive modes of inheritance in PD differ significantly to the sporadic disorder. The physiological function of α-synuclein is yet unknown but it is stipulated that loss of function may be associated with disease pathogenesis. Mutations in the parkin gene are distinct in that they result in an early onset clinical syndrome adopting a slow progression as opposed to the idiopathic disorder [3]. Recessive Parkinsonism is also seen in mutations in the DJ-1 protein which is implicated in the response to oxidative stress, however this provides minimal or no pathology whatsoever. Another autosomal recessive mutation is that seen with ATP13A2 (PARK9) gene which is associated with a juvenile-onset syndrome, adopting a levodopa-responsive type of Parkinsonism called Kufor-Rakeb Syndrome (KRS). This involves a triad of pyramidal degeneration, cognitive impairment, and supranuclear palsy. Animal and cell culture studies taken from KRS patients suggest that PARK9 is important for both effective lysosomal and mitochondrial functioning, as well as for the clearance of divalent metals, wherein defects in any of these three processes would be intricately associated with neurodegeneration. Furthermore, recessive Parkinsonism may also be seen in mutations in PINK1, yet its pathological basis is yet to be characterized. However, there remain a considerable number of late-onset Parkinsonism patients bearing comparison to idiopathic PD with mutations in DJ-1, PINK1, and parkin, which supports their correlation to the sporadic disorder [4-6]. Research continues in an effort to shed additional light on the genetics of PD and to identify genes that contribute to its susceptibility.

Environmental risk factors for PD includes the exposure to heavy metals, pesticides and rural living, whilst cigarette smoking and caffeine are amongst two of the protective factors stipulated [2]. Accumulating evidence suggests that the exposure to pesticidal is associated with an increased risk for developing PD. Researchers have shown that there is a greater risk of developing PD in pesticide-exposed individuals with a gene variation affecting dopamine transport [7]. Heavy metals such as manganese, iron, copper, mercury, and lead are involved in neurologic disease. There is increasing recognition that heavy metals normally present in the body may also play a role in disease pathogenesis through free radical formation [8]. A collective study focusing on the effect of coffee consumption on Parkinson's Disease (PD) concluded that consumption of coffee is more protective amongst individuals with a particular genotype compared to another genotype [9]. Furthermore, multiple studies have synergistically concluded that the incidence of PD in cigarette smokers is less than nonsmokers, with the number of years of smoking, being closely linked to lowering the risk of PD among smokers [10]. These discoveries have led to the suggestion that PD might arise due to the combined effects of ageing and environmental exposures that accelerate the process of nigral cell death.

There is a higher prevalence in PD associated with age-related attrition and death of dopaminergic neurons in the SNpc. Molecular and cellular changes of ageing cross-link with environmental and genetic factors in order to undermine which of the cells age successfully and which of them cease to neurodegeneration. It is unclear how this concept of selective vulnerability occurs, giving rise to different patterns of neurodegeneration in varying diseases [2]. Ageing bears correlation with oxidative stress, mitochondrial dysfunction, and greater free radical production leading to DNA mutations and genomic instability. This subsequently results in the shortening of telomeres which correlates to reduced survival [11]. Such age-related changes are relevant to the pathogenesis of PD, but the pattern and timing of such deficits is not the same in patients with PD, as there is no programming for neuronal death to arise at a specific time. Hence, despite being a risk factor for the disease, its mechanism in disease progression still remains elusive.

Such studies all show the incremental effect that the trident of ageing, genetics and environmental factors play to explain the pathogenesis of PD. Nonetheless, there still remains a missing part of the puzzle-that of which is the role of epigenetics which shall be the main focus of this review article.

Epigenetic Involvement in Parkinson's disease

DNA methylation: DNA methylation is an epigenetic mechanism that cells use to control gene expression through the shifting of a methyl group (CH_3) which occurs with the aid of DNA Methyl Transferases (DNMTs). A recent study conducted by Masliah et al., reported a decay on DNA methylation in the brains of PD patients, associated with the interaction of α-synuclein with DNMT1, which results in sequestration of DNMT1 in the cytoplasm [12]. In addition to α-synuclein, a number of additional genes have been studied to determine their significance in terms of DNA methylation in PD. A significant role in the pathogenesis of PD is thought to be due to neuroinflammation, with TNF-α being a critical inflammatory cytokine. Increased levels of TNF-α is associated with dopaminergic cell death in PD. A study conducted by Pieper and co-workers reported that hypomethylation of the TNF-α promoter in SNpc cells may explain the increased susceptibility of dopaminergic neurons to TNF-α mediated inflammatory reactions [13]. The list of implicated genes in DNA methylation is by no means solely restricted to α-synuclein and TNF-α, as a number of significant loci have been experimented by Plagnol et al. [14]. A large-scale sequencing analysis of postmortem brain samples identified DNA methylation alterations in PD risk variants in GPNMB/7p15, STX1B/16p11, and PARK16/1q32 loci. Such findings stipulate that additional PD related genes may be epigenetically modified in PD brains.

Currently, DNA methylation is being used as a successful biomarker in a number of cancers representing an extremely promising biomarker for neurodegenerative disorders [15]. As surfacing techniques nowadays allow for DNA methylation monitoring from easily accessible peripheral sites such as blood, an important question emerges, whether DNA methylation changes from Peripheral Blood Leukocytes (PBLs) would bear correlation with the brain methylome. Masliah and colleagues investigated genome-wide DNA methylation of brain and blood samples from

PD patients to that of control subjects, concluding that there is a substantial difference in methylation for many genes that were previously associated with PD pathology. Notably, this study showed harmonious alterations in DNA methylations in a subset of genes of brain and blood samples from PD patients, suggesting that PBLs might represent a good proxy for brain methylation alterations associated with PD [12]. This further reiterates the explanation of epigenetics as a molecular pathological mechanism in neurodegeneration and may also comprise an innovative entry point for biomarker discovery and development.

Histone Modifications

Histones play a key role in epigenetics, where conformational changes in either histone proteins or modifications in DNA wrapping may lead to gene silencing or activation. Histone acetylation with the aid of Histone Acetyl Transferases (HATs) is mainly associated with transcriptional activation machinery, whilst deacetylation catalysed by Histone Deacetylases (HDACs), correlates to transcriptional repression [16].

The most frequently studied histone modification is that of histone acetylation. Acetylation of histone tail leads to chromatin relaxation and transcriptional activation, whilst, deacetylation leads to condensation of the chromatin and transcriptional repression. Although, histone modifications have been well studied in many neurological disorders, little is still known concerning histone modifications in PD brains due to limited number of studies, with the majority of today's knowledge obtained from cell studies and animal models, including mitochondrial toxins, such as rotenone, 1-methyl-4-phenylpyridinium (MPP+), and paraquat, or those over-expressing human α-synuclein. Studies have shown that α-synuclein inhibits histone acetylation thereby leading to neurotoxicity in both cell culture, as well as drosophila model of PD [17].

A number of studies have established a link between acetylation and neuroprotectivity, where Valproic acid has been implicated in the inhibition of histone deacetylase activity, and in an increase of histone H3 acetylation in brain tissues of rats with a subsequent neuroprotective effect in a rat model of PD [18]. This correlation was further solidified by Kidd and Schneider who reported that histone deacetylase inhibitors can protect dopaminergic neurons from MPP+ induced toxicity [19]. These varying studies indicate the potential of histone acetylation to be used as a beneficial clinical biomarker in the diagnosis of PD.

Another example of histone modification involves that of methylation, in which PINK1 is stipulated to be a major player. As previously described, mutations in PINK1 gene correlate to early onset recessive PD. It is stipulated to have a role in mitochondrial homeostasis but the exact mechanism by which it exerts its function remains elusive. A recent study which attempted to unveil its epigenetic molecular pathway stipulates that PINK1 regulates histone H3 trimethylation and gene expression by interacting with the polycomb protein EED/WAIT1. This interaction favored the delocalization of the polycomb protein to the mitochondria, which in turn down regulated H3-K27 trimethylation and altered gene transcription of differentiating SH-SY5Y human neuroblastoma cells [20].

Recent studies have also stipulated a role for PGC-1α in PD, which is involved in mitochondrial biogenetics and respiration. The activity of PGC-1α is under epigenetic control primarily through acetylation, as well as through methylation, sumoylation and protein phosphorylation. Transgenic mice showing overexpression of PGC-1α in dopaminergic neurons were found to be resistant to MPTP-induced cell degeneration, as well as showing elevated levels of the mitochondrial antioxidants Trx2 and SOD2 in the substantia nigra. The drug resveratrol activated PGC-1α in dopaminergic cells via the deacetylase SIRT1, causing a reduction in PGC-1α acetylation, which in turn causes an increase in PGC-1α gene transcription with enhanced levels of the mitochondrial antioxidants. These results correlate with a neuroprotective effect from oxidative stress and cell death. An increase in PGC-1α has been associated with a reduction in dopaminergic neuron loss induced by α-synuclein mutations, whilst PGC-1α knockdown correlates with increased α-synuclein accumulation and an increased vulnerability to MPTP-induced dopaminergic degeneration in the substantia nigra. These findings offer a promising avenue for PGC-1α as a vital therapeutic target for neurodegenerative diseases; however, a greater understanding of the molecular pathways by which PGC-1α exert their neuroprotective effect is essential to develop optimal treatment for PD [21].

Non-Coding RNAs

MicroRNAs (miRNAs) are non-coding RNAs which suppress mRNA expression via translation inhibition, through binding to the 3'-Untranslated Region (3'UTR) of target RNAs.

In recent years, a number of studies using adult mice and embryonic stem cells differentiated into dopaminergic neurons, have emerged linking miRNAs to the pathogenesis of PD. MiRNAs are vital for the survival of dopaminergic neurons and their loss can be involved in the development and progression of PD. The first study which was conducted by Kim and co-workers investigated the role of miRNAs in mammalian midbrain dopaminergic neurons and identified the absence of miR-133b in midbrain tissue from patients with PD, as opposed to control subjects. Subsequent studies further reinforced this finding, with several miRNAs found to play a key role in the pathogenesis of PD [22]. Decreased expression of miR-7 and miR-153 contributed to increased α-synuclein expression [23]. Furthermore, PD patients showed a decline in expression of hsc70 (targeted by miR-26b, miR-106a, miR-301b) and LAMP-2A (targeted by miR-21, miR-224, miR-373) which are important proteins in the chaperone-mediated autophagy responsible for the elimination α-synuclein in the SNpc. An increase in these miRNAs is the cause for the deregulation of proteins involved in clearing α-synuclein, thus leading to its aggregation which is involved in the pathogenesis of PD [24]. A recent study by Xiong et al. has demonstrated that upregulation of miR-494 predisposes to oxidative stress-induced neuronal death by inhibiting expression of DJ-1 [25]. Moreover, Cho and co-workers demonstrated that that downregulation of miR-205 may elevate LRRK2 protein in the brains of patients with sporadic PD, whereas over expression of the same miRNA may present a relevant therapeutic strategy to subdue the abnormal upregulation of LRRK2 protein in PD [26]. These results provide

an insight into the changes induced by miRNA expressions in the SNpc of PD subjects, which eventually regulate several important genes and pathways implicated in PD, which may subsequently provide a potential for the advancement of a range of miRNA-based PD therapeutics.

The most recent discovery of non-coding RNAs has been that of the long non-coding RNAs (lncRNAs) in the SN of PD patients. Despite being minimally understood over the past few decades, the latest study conducted by Ni and colleagues sought to investigate the lncRNA expression profiles and their potential functions in patients with PD. LncRNA expression profiles in the SN of PD patients were screened, in which 87 lncRNAs were identified that were altered significantly in the SN during the occurrence of PD. Among these, the two lncRNAs that varied most dramatically were AK021630 and AL049437. AK021630 was down regulated while AL049437 was up regulated in the PD samples. According to the results obtained, the potential roles of these two lncRNAs were further investigated in the pathogenesis of PD by the knockdown of the expression of AL049437 or AK021630 in human neuroblastoma SH-SY5Y cell line. The results showed that the knockdown of AK021630 level reduced cell viability, mitochondrial mass, mitochondrial trans membrane potential, and tyrosine hydroxylase (TyrH) secretion. On the other hand, the opposite effect was seen with reduction in AL049437. These findings suggest that the lncRNA AK021630 likely prevented the occurrence of PD whilst AL049437 likely contributed to the risk of developing PD [27].

Novel Therapeutic Approaches through Epigenetic Remodelling in PD

Despite a wide array of pharmacological drugs introduced since the discovery of levodopa, all current pharmacological agents available for managing PD solely provide symptomatic relief, since drugs that stop or retard PD progression are still lacking. Over the past few years, there has been a substantial progression in the development of epigenetic drugs for the treatment of neurodegenerative diseases, particularly the HDACs and DNMTs inhibitors.

DNMT inhibitors have been under a prolonged period of both preclinical and clinical investigations, with cytidine nucleoside analogs being the most widely studied of the DNMT inhibitors. They incorporate themselves into DNA following activation by a triphosphate moiety, with enzyme degradation taking place following the formation of an irreversible complex with DNMT1. This is responsible for the prevention of daughter DNA methylation in CpG islands during DNA replication [28].

The role of histone acetylation has been closely studied in multiple Parkinsonism models for its strong neuroprotective effects. Consequently, HDAC inhibitors are the latest derived therapeutic targets in treating PD. An important study conducted on both fly and cell models demonstrated that α-synuclein neurotoxicity may be protected by the administration of HDAC inhibitors. Alpha- synuclein has demonstrated to be capable of binding directly to histones, diminishing the amount of acetylated histone H3 in cultured cells [17]. The HDAC inhibitor VPA has shown to protect against rotenone, α-synuclein, lipopolysaccharide, and MPTP-mediated toxicity through the enhancement of H3 histone acetylation, and reduction of inflammatory mediators in microglial cells. Independent of their actions on histones, HDAC inhibitors also contribute to modulating significant cytoprotective pathways, providing an additional beneficial effect to therapy. For instance, phenylbutyrate has been stipulated to protect DA neurons, potentially through increased DJ-1 expression and the activation of the tyrosine hydroxylase promoter in the SNpc [29].

Conjointly, these studies propose that HDAC inhibitors may be responsible for disease altering therapeutic benefits in various Parkinsonian model systems, and that they may also lead to the activation of additional pathways or genes that may render adjunctive neuroprotective effects. These pharmacological studies further reiterate the role of epigenetic regulation in the pathogenesis of PD.

Stem Cell Potential in PD

Stem cells are a promising source for cell replacement therapy due to their self-renewal and pluripotency ability which allows them to generate various cell types. Over the past few years, Induced Pluripotent Stem Cells (iPSCs) were developed as a promising cell source to generate disease-specific and personally-tailored cells [30]. Pluripotent stem cells have been used primarily as a cell model in order to understand the molecular mechanism of cellular differentiation, as well as a means for regenerative medicine. The latest discovery of iPS cells allowed the dissection of epigenetic regulation during differentiation and reprogramming [31].

Traditional *in vitro* and *in vivo* experimental models to study PD are suboptimal due to the lack of patient-specific nigral dopamine neurons for mechanistic studies and drug discovery [32]. Various human iPSCs from patients suffering different genetic forms of PD have been differentiated into dopamine neurons, rendering iPSCs a beneficial tool in studying the pathogenesis of PD [33].

The significance of epigenetic regulation in reprogramming and maintaining pluripotency is becoming more and more relevant. Current advancements in technology have got us to the stage where screening for genomic alterations at the entire genome level, has become a plausible possibility. It is of paramount importance to examine the epigenetic profile of iPSCs, since the epigenetic landscape is a representation of not only the past, but also the current developmental state, which may be a useful indicator to predict their potential in the future [31]. Novel reprogramming strategies which deter abnormal permanent genetic and epigenetic alterations are necessary to generate clinically-qualified iPSCs. Future investigations into cell reprogramming processes are needed to generate the disease-specific iPSCs for personalised regeneration medicine of PD patients by disclosing detailed reprogramming mechanisms [34].

Concluding Remarks

We are now recognizing that epigenetic mechanisms are at the forefront in manipulating complex biological processes, yet we remain at the very surface in understanding the role which is played by such epigenetic variations in the pathophysiology of complex multifactorial diseases, as is the case with PD. We have

now benefitted from a better understanding of the pathways involved in dopaminergic neurodegeneration at a molecular level, thanks to the increasing number of published papers aimed at understanding the epigenetics of PD. In addition, many researchers are now working to gain understanding of the potential of pharmacological epigenetic drugs to counteract age-related neurodegenerative diseases [26]. Research revealed that histone modifications, DNA methylation, and miRNA alterations often precede disease pathology, which might prove useful as early disease biomarkers. Additionally, they might be targeted with epigenetic drugs, such as, HDAC inhibitors, DNMT inhibitors, or drugs that target histone methyltransferases and histone demethylases, or SIRTs. The Human Epigenome Project has reached the stages of interpreting epigenetic profiles and their correlation to a number of varying pathologies. This epigenomic data should sequentially amalgamate both phenomic and genomic profiles in the context of both sporadic and familial PD, in order to generate a comprehensive understanding of the disease [35]. Future research should be aimed at understanding the cross-link between genetic components, environmental factors, and epigenetic biomarkers, in order to further identify individuals at risk of developing PD.

While pharmacological therapies have been shown to reduce symptoms of PD, they are by no means a form of cure. Cell replacement therapy is a promising avenue for the treatment of PD and other neurodegenerative disorders, with scientific research making great progress in the development of iPSCs for PD. With these new technologies, PD research is poised to enter a new phase, in which mechanistic studies, biomarker discoveries, and drug development will become more dependent on using iPSC-derived human midbrain DA neurons, both *in vitro* and in the brain of an animal model. These will open up unrivalled opportunities to change PD research significantly by redefining the disease in molecular and cellular terms, by predicting PD and tracking its progression, and by identifying new therapeutic strategies that can prevent or slow down the degeneration of nigral dopamine neurons [32]. Animal models using iPSCs have shown promise, but they are yet to be used in clinical trials for PD [33]. However, with rapid progress in iPSC-based technology, one can envision a bright future for PD research and it is therefore quite likely that within our lifetime we will witness the jump from dish to clinic.

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