Chapter 3

Mechanisms for Neuronal Cell Death in Parkinson's Disease: Pathological Cross Talks Between Epigenetics and Various Signalling Pathways

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Abstract

Parkinson's disease (PD) is an incapacitating neurodegenerative disorder affecting the population over the age of 65 years. Clinically, most patients present with the symptoms of bradykinesia, resting tremor, rigidity, and postural instability. A number of patients also suffer from autonomic, cognitive, and psychiatric disturbances. The symptoms of PD result from the selective loss of dopaminergic (DA) neurons in the substantia nigra (SNc) pars compacta. However, the exact molecular mechanism that causes this cell death still remains elusive. The cross talk between various molecular signals facilitates the cell to undergo developmental and differentiation programs with such tantalizing accuracy. In recent years, epigenetic mechanisms have advanced as a regulatory driver of processes such as signal transduction, cell cycle control, and stress response. These include DNA methylation, histone modifications, and small RNA-mediated mechanisms. Increasing evidence suggests that epigenetic mechanisms play a major role in the pathogenesis of PD. Researchers are now working to comprehend the therapeutic promises of epigenetic molecules to offset age-related neurodegenerative diseases. In this chapter, we focus on some examples of the cross talk between epigenetic processes and various signal transduction pathways that underlie the pathogenesis of PD.

Keywords: Parkinson's disease, epigenetics, DNA methylation, histone modifications, non-coding RNAs

1. Introduction

Parkinson's disease (PD) is a devastating disorder of the brain characterized by continuous deterioration of motor functions owing to the loss of dopaminergic neurons in the substantia nigra of the mid brain. It is the second most common neurodegenerative disorder after Alzheimer's disease. The first clear medical explanation about PD was written in 1817 by an English physician James Parkinson in his work titled *An Essay on the Shaking Palsy* [1]. The SNc of the midbrain contains the DA neurons which produce dopamine. Dopamine is a neurotransmitter responsible for coordinating movements. Although few in number, these DA neurons play a vital role in controlling multiple brain functions including voluntary movement and a broad array of behavioural processes [2]. In PD, there is a severe depletion in the levels of dopamine due to the degeneration of DA neurons. This results in the lack of control over body movements [2]. Nevertheless, the precise cause of this neuronal cell death still remains an enigma.

The signs and symptoms of PD may vary from person to person. The symptoms have a gradual onset and usually advance simultaneously with the progression of the disease. Early signs may be mild and may go unnoticed and later tend to worsen over time. If left untreated, it may lead to disability with associated immobility. The early classic symptoms of PD include motor symptoms such as postural instability, resting tremor, bradykinesia, and rigidity [3]. These symptoms are linked to the progressive loss of dopamine and are usually improved by treatment with levodopa or dopamine agonists [4]. Nevertheless, as the disease progresses, symptoms that fail to respond to levodopa develop [5]. These symptoms include flexed posture, freezing phenomenon, and loss of postural stability [6]. Although the motor symptoms lead the clinical picture of PD, some patients are also associated with a range of non-motor symptoms such as sleep, sensation, autonomic, mood disturbances as well as cognitive disturbances such as dementia [7].

The diagnosis of PD is extremely complicated, mainly during its early stages. This is due to the fact that as the disease advances, the symptoms might mimic other ailments. Moreover, at present, there is no specific lab test available to diagnose the disease. In most cases, physical examination of the patient forms the basis for the diagnosis of PD. Levodopa continues to be the most effective treatment for PD [8]. Another feasible option is deep brain stimulation, although some patients encounter the necessity for surgery. New treatments that offer better control over the symptoms stay on developmental demand.

2. Possible pathways involved in the pathogenesis of PD

Several enthralling theories have shown that different molecular pathways are involved in the propagation of PD pathogenesis. Accumulating evidence has confirmed that mitochondrial dysfunction, impairment of the ubiquitin proteasome system (UPS), and oxidative stress may perhaps represent the prime molecular pathways that generally mitigate the pathogenesis of

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both sporadic and familial forms of PD [9]. In addition to these, inflammation and loss of neurotrophic factors have also been shown to play a major role in the progress of PD [9].

3. Potential risk factors in PD

Age is one of the prominent risk factors in PD [10, 11]. Studies have shown that dopaminergic neuronal populations appear selectively susceptible to loss with ageing compared to many other brain regions and those related to other neurodegenerative disorders [12]. Furthermore, studies have also shown that the dopaminergic neurons are particularly vulnerable to the mitochondrial dysfunction with advancing age [13, 14].

4. Genetic factors in PD

Although PD was long considered to be sporadic in origin, monogenic Parkinsonism disorders are gaining growing importance in recent years. Genetic factors appear to be the main cause in about 5–10% of the PD patients [15]. However, in both cases, the degeneration of nigrostriatal DA neurons remains a general overlapping characteristic [16]. Studies have shown that around 13 genetic loci are involved in the rare forms of PD [17]. Out of the 13, around 6 PARK loci genes have been identified and have been reported to carry mutations that are related to relatives who are affected by PD. Out of the six genes, four have similarly been shown to be involved in sporadic PD [17].

There is considerable evidence that, in addition to well-defined genetic mechanisms, environmental factors play a crucial role in PD pathogenesis. Nevertheless, the exact mechanism by which the environment could affect the genetic factors and contribute to PD development remains obscure. In recent years, epigenetic mechanisms such as DNA methylation, chromatin remodelling, and alterations in gene expression via non-coding RNAs (ncRNAs) are surging in importance as potential factors in the pathogenesis of PD.

5. Epigenetics

Epigenetics refers to mechanisms which can alter the expression of genes without modifying the actual DNA sequence and are heritable [18]. Epigenetic modulation exists throughout life, beginning in prenatal stages, is dependent on the lifestyle, environmental exposure, and genetic makeup of an individual and may serve as a missing link between PD risk factors and development of the disease [18].

At the molecular level, epigenetic mechanisms influence protein expression through post-translational modifications of histones (e.g. acetylation, methylation, phosphorylation, and ubiquitination), the methylation of cytosine bases and positioning of nucleosome, and by activation/deactivation of microRNAs (miRNAs). These processes act as a switch for the fate of the cell through regulating gene and miRNA expression, as well as through parental

imprinting, X chromosome inactivation, suppressing transposons, and regulating developmental processes [19]. The epigenome offers the flexibility to address a fluctuating environment above the relatively rigid architecture of DNA sequence information and thus influences the formation of a phenotype without altering the genotype. The three distinct mechanisms of epigenetic regulation that are complex and interrelated are DNA methylation, histone modification, and RNA-based mechanisms.

5.1. Epigenetic mechanisms in PD

In spite of having a familial aspect, PD does not show a clear Mendelian pattern of inheritance, making it difficult to correlate the genetic variations with the disease state. In this case, an epigenetic framework would be most useful in understanding the age dependence (which is not clearly explained by the accumulation of genetic mutations) and the environmental impact on genetic predisposition to the disease. A better understanding of the complex interplay of genetic and epigenetic factors can help in improving the existing knowledge on disease mechanisms and therapeutic strategies. In diseases where age and environment play an important role, the identification of epigenetic variations contributing to the age- and environment-mediated control of disease mechanism will simplify the disease diagnosis [20]. Studying epigenetic mechanisms involved in PD can hence be a major milestone in the pursuit of understanding the disease better. In recent years, the impact of epigenetic mechanisms in PD has been increasingly studied [21]. DNA methylation, histone tail modifications, and microRNA-mediated pathways are considered to play a role in the pathogenesis of PD based on recent evidence ([22–26]).

6. DNA methylation

6.1. Principle of DNA methylation

DNA methylation is one such epigenetic modification that has been studied extensively for the past several decades since its discovery in cancer in 1983 [27]. DNA methylation involves the transfer of a methyl group to the 5′ position of a cytosine residue. This dinucleotide unit is always written as CpG (representing a cytosine followed by guanine and a phosphate group between them). Regions that are enriched with CpGs are called CpG islands. These CpG islands are usually located in the promoter region of genes. CpG islands are usually non-methylated, except in some rare cases where methylation of CPG islands is required. On the contrary, CpGs outside CpG islands are usually methylated [28, 29]. Methylation of CpG sequences can modify gene expression levels by inducing conformational changes in the chromatin. This impedes the availability of the gene promoter region for the transcriptional machinery [30]. Therefore, it is obvious that promoter hyper-methylation leads to gene silencing while hypo-methylation will augment gene expression. CpG methylation within promoter and intragenic sites has been extensively studied, and moreover, there has been surging interest regarding non-CpG methylation. This denotes the methylation that occurs at cytosine of non-CpG dinucleotides, such as CA, CT, or CC. DNA methylation works in

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congruence with histone modification (such as histone acetylation) to control memory formation and synaptic plasticity [31], and it also has a possible impact on genetic and neuronal function affecting behaviours [32]. Moreover, the association between DNA methylation, chromatin structure, and gene silencing has been extensively studied for many years, and gene silencing is thought to be an epigenetic intervention on neurodegenerative diseases like Alzheimer's disease (AD) [33]. Therefore, it seems justified to suggest that there is a very strong potential link between DNA methylation and neurodegenerative diseases.

6.1.1. DNA methylation in PD

Methylation can be instigated by a variety of factors, which can be the cause of many serious diseases including PD. Ageing has been shown to decrease global DNA methylation [34], while it increases methylation in specific promoters. This could be a contributing factor in PD as it is an age-related disorder.

Although there have not been many reports, there are indications of impaired methylation in PD patients [25]. DNA methylation has been widely studied in the SNCA gene. Methylation of intron 1 of the SNCA gene is associated with decreased transcription [35]. Decreased methylation of the SNCA gene and of the SNCA intron 1 has been observed in the SNc of clinical PD cases [36]. It is obvious from these results that the increased α-synuclein production (that is associated with PD) is caused by the increased SNCA gene expression, as a result of a decreased methylation state of the SNCA gene. Furthermore, it has been demonstrated that α-synuclein could sequester DNA methyltransferase 1 (which maintains DNA methylation) in the cytoplasm. DNA methyltransferase 1 is an important enzyme which is expressed copiously in the brain and maintains DNA methylation in the cytoplasm. Sequestering DNMT1 leads to global DNA hypo-methylation in PD patients with dementia and presence of neuronal Lewy body (DLB) [37]. A GWAS on methylation of candidate genes identified changes in methylation status of proximal DNA CpG sites of other genes such as PARK16/1q32, glycoprotein (transmembrane) nmb (GPNMB), and syntaxin 1b (STX1B), *ARK16*. This is indicative of the fact that other PD-related genes may possibly be susceptible to these methylation changes (International Parkinson's Disease Genomics and Welcome Trust Case Control, 2011). Nevertheless, the clear undeviating link between DNA methylation and PD still remains obscure. The epigenetic regulation of SNCA gene has also been reported in an A53T-linked familial case of PD. A recent methylation study on brain and blood samples from PD patients has revealed that there is differential methylation of CpG sites [25]. Of these, over 80% of the sites were hypo-methylated in both blood and brain. The same study has reported that genes such as major histocompatibility complex, class II (MHC II), dq alpha 1 (HLA-DQA1), glutamine-fructose-6-phosphate transaminase 2 (GFPT2), MAPT, and vault RNA2-1 (VTRNA2-1) are highly associated with PD being similarly methylated in brain and blood samples from clinical PD cases [25].

The number of methylated sites in DNA has been reported to increase with ageing [34] which is a major risk factor for PD. Results from the GWAS have already provided many novel and important perceptions for molecular mechanisms underlying the pathogenesis of complex diseases such as PD. Nevertheless, it is probable that understanding exact epigenetic modifi-

cations might be significantly assisted by knowledge of genetic susceptibility loci determined from GWAS.

7. Histone modifications

7.1. Principle behind histone modification and the different types of histone modifications

Histones are proteins that pack and order DNA into nucleosomes. Each nucleosome contains two subunits each of histones H2A, H2B, H3, and H4, known as the core histones (octomers). A 147-bp segment of DNA wrapped around the histone octamer and neighbouring nucleosomes are separated by, on average, 50 bp of free DNA. Histone H1 is termed the linker histone, and it does not form the integral part of the nucleosome. However, it binds to the linker DNA (that is, the DNA separating two histone complexes), sealing off the nucleosome at the location where DNA enters and leaves.

Histones play a crucial role in epigenetics. All histones are subject to several post-transcriptional modifications such as acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation, among others [38]. These post-translational modifications made to histone tails can influence gene expression by altering the structure of chromatin or using histone modifiers. Histone protein modifications can alter the availability of transcriptional machinery to specific promoters leading to gene activation or silencing [39]. Histone modifications have vital roles in transcriptional regulation, DNA repair, DNA replication, alternative splicing [40], and chromosome condensation [41]. With respect to its transcriptional state, the human genome can be roughly divided into actively transcribed euchromatin and transcriptionally inactive heterochromatin. Euchromatin is characterized by high levels of histone modifications such as acetylation and trimethylated H3K4, H3K36, and H3K79. On the contrary, heterochromatin is characterized by low levels of acetylation and high levels of H3K9, H3K27, and H4K20 methylation [42]. Recent studies have demonstrated that actively transcribed genes are characterized by high levels of H3K4me3, H3K27ac, H2BK5ac, and H4K20me1 in the promoter and H3K79me1 and H4K20me1 in the gene body [43].

7.1.1. Histone acetylation/deacetylation

Histone modifications such as acetylation and deacetylation play important roles in gene regulation. These are associated with transcriptional activation and repression respectively [41]. Histone acetylation is a reversible process. Acetylation is catalysed by histone acetyltransferases (HATs), which are categorized into three families (GNAT, MYST, and CBP/p300) [44]. HATs catalyse acetylation via the transfer of an acetyl group from acetyl-coenzyme A to the ε-amino group of lysine side chains on the N-terminal tails of H2A, H2B, H3, and H4 [44]. It has recently been shown that HATs can catalyse acetylation at lysine 56 (K56) within the core domain of H3 [41]. Histone deacetylation is performed by a class of enzymes known as histone deacetylases (HDACs). These HDACs remove the acetyl groups from the ε-amino

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group of lysines. HDACs are classified into four classes based upon sequence homology and cofactor dependencies.

7.1.2. Histone methylation/demethylation

Histone methylation involves the transfer of methyl groups from S-adenosyl-L-methionine to lysine or arginine residues of histone proteins by histone methyltransferases (HMTs). As described earlier, DNA methylation and histone modifications work in association with each other. HMTs control DNA methylation through transcriptional repression or activation which is chromatin dependent. Several different histone methyltransferases exist, and each of them is specific for the lysine or arginine residue they modify. For example, on histone H3, SET1, SET7/9, Ash1, ALL-1, MLL, ALR, Trx, and SMYD3 are the histone methyltransferases that catalyse methylation of histone H3 at lysine 4 (H3-K4) in mammalian cells [45]. ESET, SUV39-h1, SUV39-h2, SETDB1, Dim-5, and Eu-HMTase are histone methyltransferases that catalyse methylation of histone H3 at lysine 9 (H3-K9) in mammalian cells [45]. G9a and polycomb group enzymes such as EZH2 are histone methyltransferases that catalyse methylation of histone H3 at lysine 27 (H3-K27) in mammalian cells [46]. Arginine methylation of histones H3 and H4 promotes transcriptional activation and is mediated by a family of protein arginine methyltransferases (PRMTs) [47]. Based on the position to which the methyl groups are added, PRMTs are classified into type I (CARM1, PRMT1, PRMT2, PRMT3, PRMT6, and PRMT8) and type II (PRMT5 and PRMT7) [47].

7.2. Histone modifications in PD

The precise role of histone modifications in the pathogenesis of PD still remains indefinable, and most of the data are obtained from experimental cell cultures and animal models of PD.

α-synuclein, the major protein involved in PD pathogenesis, is known to interact with histones and inhibit histone deacetylation [48]. Several histone deacetylase inhibitors have been reported to protect against α-synuclein-mediated toxicity in PD models [48]. Inhibition of the histone deacetylase sirtuin-2 is known to decrease α-synuclein-mediated toxicity and protect against dopaminergic neuronal death [49]. When mouse nigral neurons were treated with the herbicide paraquat, alpha-synuclein translocated into the nucleus and was able to interact directly with histones [50]. Another study in Drosophila model of PD has demonstrated that alpha-synuclein interacts directly with histones by inhibiting histone acetylation. This neurotoxic effect of alpha-synuclein was counteracted by the administration of HDAC inhibitors [51]. Together with alpha-synuclein, HDAC6 and HDAC4 are the chief components of Lewy bodies in PD [52]. It is interesting to note that HDAC6 protects dopaminergic neurons from alpha-synuclein toxicity by promoting inclusion formation [53]. This has been confirmed by various other reports on neuronal cell lines expressing mutant alpha-synuclein wherein they have reported that the neurons are rescued from alpha-synuclein toxicity by HDAC6. In PD, histones seem to be more involved in aggregate formation, than in epigenetic dysregulation of gene expression. It has also been demonstrated that α-synuclein, interact with histone H1, which is localized in the cytoplasm of neurons and astrocytes from affected brain areas in PD. This has been shown to play a role in fibril formation [54]. Although not

directly linked to histone acetylation, alpha-synuclein overexpression can downregulate the expression of histone genes. Previous reports on *C. elegans* model have demonstrated that overexpressing human alpha-synuclein leads to downregulation of nine genes coding for histones H1, H2B, and H4 [55]. It is clear from these studies that most of histone PTM evidence in PD is derived from the effects of alpha-synuclein. Moreover, few other genes associated with PD pathogenesis have been linked to HDAC function. Mutations in parkin cause early onset of familial PD (AR-JP) [56]. Parkin has been shown to promote mitophagy by catalysing mitochondrial ubiquitination, which in turn employs ubiquitin-binding autophagic components, such as HDAC6 [56]. The treatment of a dopaminergic cell line with the HDAC inhibitor phenylbutyrate resulted in increased levels of DJ-1 which protected these cells from mutant alpha-synuclein toxicity. An increase in DJ-1 expression was also observed in mice treated with phenylbutyrate and protected MPP^+-challenged dopaminergic neurons [57]. In addition, PINK-1 is also affected by HDAC activity. Transgenic expression of sirtuin 2 in PINK-1 Drosophila mutants rescued mitochondrial defects and spared dopaminergic neurons [58]. This suggests that depending on the PD model, HDACs may have a neuroprotective role. Levodopa remains as the most effective and extensively used therapy in the treatment of PD although it is tied with some serious side effects. Prolonged treatment with levodopa leads to the development of abnormal involuntary movements, termed levodopa-induced dyskinesia (LDID). Interestingly, histone PTMs have been shown to play a role in LDID. Previous reports on primate model have demonstrated that LDID is associated with marked deacetylation of histone H4, hyperacetylation, and dephosphorylation of histone H3 in the striatum [59]. In mouse models of LDID, histone H3 exhibited decreased trimethylation [59]. Histone H3 phosphorylation changes have also been demonstrated in striatonigral medium spiny neurons, thereby linking ERK-dependent histone phosphorylation in striatal plasticity leading to dyskinesia [60]. Future studies are warranted in order to understand the underlying molecular mechanism and the direct link between histone modifications in PD. This will enhance our knowledge and light up new avenues for the identification of epigenetics-based therapeutics for the better treatment of PD.

8. Non-coding RNAs

8.1. What are microRNAs?

miRNAs are critical regulators of gene expression. Their discovery adds a new facet to our understanding of intricate gene regulatory networks. These are a family of small, ncRNAs that regulate gene expression in a sequence-specific manner. They were first identified in *Caenorhabditis elegans* as genes that were responsible for the regulation of developmental events. Since then, hundreds of microRNAs have been identified in almost all species [61]. MicroRNAs have diverse expression patterns and play a vital role in various developmental and physiological processes. These small ncRNAs are transcribed by RNA polymerase II (RNA Pol II) from two primary genomic loci: miRNA genes and intronic sequences. In the canonical biogenesis pathway, pri-miRNAs are transcribed from miRNA genes [62]. These are processed in the nucleus by the Drosha/DGCR8 microprocessor complex to produce pre-

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miRNAs. The processed pre-miRNAs are then exported to the cytoplasm by Exportin-5. In the cytoplasm, these pre-miRNAs are further cleaved by the RNase III enzyme Dicer to yield a mature miRNA duplex. The mature strand also termed the guide strand is 20–22 nucleotides in length and associates with Argonaute proteins, AGO 1–4, to form a functional RNA-induced silencing complex (RISC) [62]. The antisense strand, denoted by miRNA*, was previously thought to be degraded; recent evidence suggests that some of these may have biological activity. The mature miRNA functions by aligning the RISC to target mRNA by binding at complementary seed sequences in the 3'UTR. This association of target mRNA with the miRNA-containing RISC results in silencing the gene expression by translational repression and recruitment of protein complexes causing deadenylation and degradation of target mRNA [63].

9. Interaction between miRNAs and PD-related genes

Overproduction of a gene product is one of the cardinal mechanisms by which the gene contributes to PD pathogenesis (a best known example is α-synuclein). There is a strong association that miRNA-mediated gene suppression could hold prospective approaches to improve the disease phenotype.

On this ground, miR-7 was first discovered as a regulator of α-synuclein expression [64, 65]. Junn et al. [64] demonstrated that miR-7 level is 40 times higher in neurons than in other cells. Further miR-7 is higher in the substantia nigra and striatum of mice, compared to cerebral cortex and cerebellum. This provides support for endogenous miR-7 regulation of α-synuclein levels in neurons. To further this study and to understand the clear mechanistic underpinnings of miR-7 in PD, the same group investigated miR-7 levels in MPP+-treated SH-SY5Y cells, and MPTP-intoxicated mice [65]. From this study, it was demonstrated that overexpressing miR-7 reduces endogenous α-synuclein levels. Hence it seems justified to suggest that a reduction in miR-7 might be a major contributor to nigrostriatal degeneration. In addition to miR-7, Doxakis [65] described the role of miR-153. In the regulation of α-synuclein, overexpression of miR-153 in cultured cortical neurons has been shown to reduce endogenous α-synuclein levels to around 30–40%. These results advocate the potential role of miR-7 and miR-153 as promising therapeutic targets to promote neuroprotection in patients with known α-synuclein gene multiplications. Another major gene involved in the PD pathogenesis is LRRK2 gene. Although the function of the leucine-rich repeat kinase 2 (LRRK2 gene) still remains largely unknown, some recent evidence suggests that this gene could be involved in membrane trafficking [66]. Mutation in the LRRK2 gene has been implicated as a risk factor for both familial and sporadic PD [67]. Reports have demonstrated that LRRK2 gene inhibition blocks neurotoxicity *in vitro* and *in vivo* [68]. These reports provide further support for its role in PD [69]. Cho et al. [70] have demonstrated that normal LRRK2 gene levels are higher in the frontal cortex of sporadic PD and PD with dementia (PDD) patients compared to controls (NPC) . Interestingly, MiR-205 has been identified as a putative regulator of LRRK2 gene. In addition, further investigations revealed significantly lower levels of miR-205 in the frontal cortex and striatum of PD patients, compared to NPC. Inhibition of miR-205 is

associated with upregulation of the LRRK2 gene protein and vice versa. DA neurons in rodent brain displayed a high level of miR-205. Reports on transgenic mice overexpressing mutant LRRK2 gene, miR-205 treatment rescued impairment of neurite outgrowth. Like miR-7 and miR153, miR 205 is a potential target for therapeutic intervention, particularly for sporadic cases in which LRRK2 gene levels were found to be elevated, and miR-205 levels were found to be low [70]. DJ1 and parkin are other genes that are regulated by miR34b and miR34c, respectively. Miñones-Moyano et al. [71] first discovered a dysregulation of miR-34b and miR-34c in the post-mortem brains of clinical PD cases. Their study demonstrated that miR-34 reduction compromises neuronal viability by mitochondrial dysfunction and production of reactive oxygen species in an SH-SY5Y neuroblastoma culture model. They further characterized that the miR-34b/c reduction is correlated with decreased expression of DJ1 and Parkin, noting that these proteins were indeed downregulated in PD brain tissue as well [71]. This provides evidence that miR-34b/c downregulation may involve DJ1 and Parkin; however, the exact molecular mechanism by which this interaction occurs remains unclear. Previous work from our group has demonstrated that downregulation of MiR124 in the MPTP-induced mouse model of PD modulates the expression of Calpain/CDK5 pathway proteins [72]. This study proves that miRNAs can serve as a powerful tool to gain in-depth knowledge about the underlying mechanism that leads to the pathogenesis of the disease, and miRNA-based therapies can be used to validate drug targets for PD.

10. Examples of cross talks between epigenetics and signalling pathways underlying PD pathogenesis

MAPK pathway has been reported to cause neurodegeneration in PD. In addition, it has also been demonstrated that cocaine induces the MAPK pathway and through MSK1 phosphorylates histone H3 at Ser10 [73]. In addition, DNA methylation has been shown to affect the stimulation of aurora-B kinase which has been reported to phosphorylate H3S10 [74]. Casein kinase II (CKII) which is a serine/threonine kinase has been reported to phosphorylate histone H4 serine 1 in response to DNA damage [75]. CKII can also phosphorylate synphilin-1, reducing its interaction with α-synuclein and formation of inclusion bodies [76]. In addition, CKII phosphorylates Ser-129 of α-synuclein in human brain and inhibits Cdk5 [77]. It is well known that α-synuclein by the activation of nitric oxide synthase (NOS) and releasing NO considerably reduces PARP-1 [78]. Activation of PARP-1 in response to DNA damage inhibits aurora-B kinase, which is required for H3S10 phosphorylation [79]. Reports on miRNAs have shed light on the fact that miRNAs regulate various signalling pathways such as checkpoint transduction cascades or transcriptional repression that are associated with PD pathogenesis [80]. An interesting study in human H4 neuroglioma cells identified a large set of putative α-synuclein target (interacting) genes which are widely used as a model for studying the molecular basis of PD, providing the first insight into the interaction of endogenous α-synuclein. Their study identified several primary targets of α-synuclein, with the glycosphingolipid biosynthesis and the protein ubiquitination pathways being common to miRNome IPA analysis. In addition, they have also shown that miR-30b, miR-30c, and miR-26a which are

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among the most abundant miRNAs in primary human neuronal and glial cells and are reported to be involved in the regulation of α-synuclein [81] emerged as the main modulators of these two pathways. Taken together, these reports highlight a few examples on the role of epigenetic mechanism that may act as modulators of cellular mechanisms leading to PD.

11. Conclusion

Evidence has shed light on the role of epigenetics in PD and has increased our understanding of the genetics of PD since the first report. The studies described in this chapter provide evidence that targeting the epigenome, with small drugs such as HDAC inhibitors that are able to cross the blood-brain barrier, can be one of the potential candidates to delay the onset and progression of the symptoms in animal models of PD. Further studies aiming at understanding the complex interplay between genetic and epigenetic biomarkers, lifestyles, and environmental factors are warranted in order to completely counter the progression of PD in the near future.

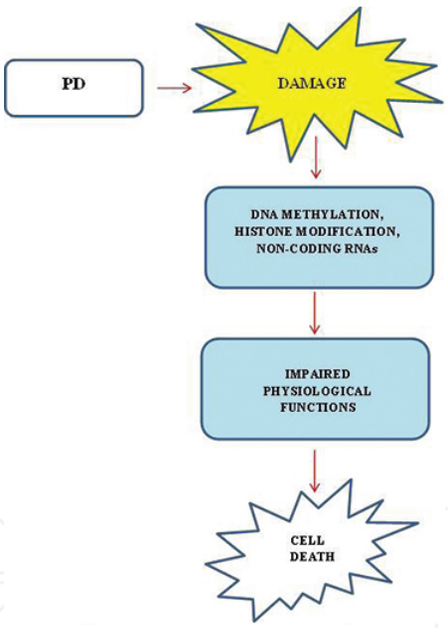

Figure 1. Epigenetics and cell death in PD.

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