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Review Article

Epigenetic Variations Underlying the Pathogenesis of Parkinson's Disease

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Abstract

Parkinson's disease is a progressive neurodegenerative disorder which leads to a significant loss in the quality of life. It is due to the death of dopaminergic neurons in the substantia nigra of the mid brain. However, the exact cause for this cell death remains elusive. In the last few years epigenetic mechanisms are gaining increasing importance due to their role in various cellular processes. The cardinal role played by epigenetic mechanisms in the function of the Central Nervous System (CNS) and in the regulation of neurological disorders is one of the most fascinating developments of modern-day neuroscience. Aberrant epigenetic mechanisms are involved in the development of many diseases including neuropsychiatric and neurodegenerative disorders. This manuscript will review the role of epigenetic mechanisms in the pathogenesis of Parkinson's Disease (PD).

Keywords: Parkinson's disease; Epigenetics; DNA methylation; Histone modifications; Non- Coding RNAs

Introduction

Parkinson's Disease (PD) is an enervating neurodegenerative disorder characterized by severe motor symptoms like tremor, muscle rigidity, dearth of voluntary movements and postural instability. Parkinsonism was first described by James Parkinson in his publication "An essay on the shaking palsy" in 1817 [1]. Since then, understanding the molecular mechanisms underlying the cause of Parkinson's Disease (PD) has enticed the attention of many researchers. However, the exact molecular mechanism that underlies the pathogenesis of PD is still not known. PD has always been described as a multi factorial disorder involving cross talks between genetic abnormalities, environmental toxins, mitochondrial dysfunction and other cellular processes [2]. Due to this, the treatment options are very limited. This calls for a deeper understanding of the molecular mechanisms underlying PD pathogenesis.

In the past few years, epigenetic mechanisms have been recognized as potential mediators of environmental factors participating in the pathogenesis of PD [3]. The term Epigenetics, refers to the modifications in gene expression which are heritable without changes in the DNA sequence. Epigenetic processes regulate numerous neurobiological and cognitive functions starting from early brain development and neurogenesisto memory formation, learning and synaptic plasticity [4,5]. Altered epigenetic mechanisms have been to underlie the pathogenesis of various neurological disorders, including Rett syndrome, autism, schizophrenia and Alzheimer, Huntington and Parkinson diseases [6].

In spite of having a familial aspect, PD does not show a clear Mendelian pattern of inheritance making it difficult to connect the genetic variations to the disease state. On this premise, an epigenetic context would be really helpful in shedding light on the impact of age and the environment on genetic predilection to the disease. An in depth understanding of the epigenetic mechanisms underlying PD can be a prominent step forward in the quest of understanding the disease better. Some of the standard epigenetic modifications include DNA methylation, Histone modifications and those involving non-coding RNAs. Recent evidences have demonstrated that all these play a role in PD pathogenesis [7-10]. This review focuses on some of these atypical modifications contributing majorly to the pathogenesis of PD.

DNA Methylation in PD

DNA methylation is one of the best studied epigenetic mechanisms. It refers to the process of shifting a methyl group from S-Adenosyl Methionine (SAM) to the fifth carbon of cytosine residues, resulting in the 5-methylcytosine (5-mC) formation. This is achieved with the help of DNA Methyl Transferases (DNMTs). The three most common DNMTs present in Mammals are DNMT1, DNMT3a and DNMT3b [11]. The process of DNA methylation has a great impact on the interaction between the DNA and their histones, changing the structure of the chromosome and gene expression [12].

Recently Masliah and co-workers [9] investigated genome-wide DNA methylation changes in brain and blood samples from PD patients in comparison to control subjects. This report clearly demonstrated the occurrence of differential methylation for several genes previously associated with PD pathology. Furthermore, this research also demonstrated comparable methylation alterations in a subset of genes in the PD brain and blood. Another report on peripheral blood leukocytes has shown that DNA, methylation level in CpG-2 sites in SNCA promoter was significantly decreased in PD patients compared to controls [13], there by proposing for a possible role for peripheral blood leukocytes as worthy indications for brain methylation alterations associated with PD, which might act as a new basis for biomarker discovery. Expression of alpha-synuclein (SNCA), one of the most important risk genes for PD, is regulated by DNA methylation [14] and a recent report has shown

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that hypo-methylation of SNCA introns 1 has been observed in post mortem samples of clinical PD cases [15]. This report was also confirmed *in vitro* in HEK-293 cells by Matsumoto et al., 2010 [16] where hypo-methylation of CpG lead to SNCA over expression and PD pathogenesis. Research by Desplats and co-workers [17] has presented evidence of decline in the levels of nuclear Dnmt1 in human post mortem brain samples from clinical PD cases as well as in the brains of α-synuclein transgenic mice models. Furthermore, they have also reported that sequestration of Dnmt1 in the cytoplasm leads to global DNA hypo-methylation in human and mouse brains, containing CpG islands upstream of SNCA, SEPW1, and PRKAR2A genes. Neuro-inflammation has been shown to play a major role in the pathogenesis of PD. Work by Pieper et al., 2008 [18] has demonstrated that hypo-methylation of the TNF-alpha promoter in SNpc cells might be the reason for increased susceptibility of dopaminergic neurons to TNF-alpha mediated inflammatory reactions. Another report by Kaut et al., 2012 [8] has reported a reduction in the methylation of the cytochrome P450 2E1 gene and a corresponding increase in the expression of CYP2E1 messenger RNA in clinical PD cases, suggestive that epigenetic modifications of this cytochrome contribute to PD vulnerability. These results accentuate a novel mechanism for epigenetic dysregulation mediated by DNA methylation in PD.

Histone post-translational modifications in PD

The histone tails are dynamically modified in a highly regulated manner. These usually occur during chromatin assembly, during establishment of specific transcriptional patterns, mitosis and development. Histone Acetyl Transferases (HATs) are co-activators that are required for transcriptional activation from a chromatin template and Histone Deacetylases (HDACS) act as co repressors.

Conformational modifications in histone proteins wrapped by the DNA in the nucleosomes may either change or facilitate the availability of the transcriptional machinery to the promoter region of some genes, leading to either gene silencing or activation.

Histone modifications include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and to an extent poly-ADP ribosylation. Alterations in histone modifications has been implicated in many neuropsychiatric and neurodegenerative disorders which includes Alzheimer's disease. Recently, it has been demonstrated that changes in histone PTMs play a central role in neurodegenerative diseases primarily characterized by motor deficits and cognitive dysfunctions, such as Huntington's and Parkinson's diseases [10].

One of the most frequently studied histone modifications includes histone acetylation. Acetylation of histone tail leads to chromatin relaxation and transcriptional activation whereas, deacetylation by HDACs leads to condensation of the chromatin and transcriptional repression. Although, histone modifications has been well studied in many neurological disorders, its role in PD still remains elusive, as there are very few studies on them. Hyper acetylation of H3 or H4 represents key epigenetic changes in dopaminergic neurons. Dysregulation of acetylation of H3 or H4 is implicated in the mechanism underlying pesticide-induced neuron loss in PD [19]. Alpha synuclein the major neuronal protein implicated in PD pathogenesis has been shown to inhibit histone acetylation thereby promoting neurotoxicity in both cell culture and drosophila model of PD [20]. This study has also shown that administration of HDAC inhibitors can reverse the effects of alpha synuclein induced neurotoxicity in PD models [20]. Kidd & Schneider, 2010 [21] also reported that HDAC inhibitors can protect dopaminergic neurons from MPP+ induced toxicity. Another study has demonstrated that αsynuclein reduced p300 levels and its HAT (histone acetyltransferase) activity within nigral dopaminergic neurons in αsyn-transgenic mice, thereby contributing to diminished PKCδ transactivation [22]. A recent report by the same group has indicated that histone hyper acetylation up-regulates protein kinase Cδ in dopaminergic neurons to induce cell death [23]. In addition, Valproic Acid (VPA) has been implicated in the inhibition of histone deacetylase activity and in an increase of histone H3 acetylation in brain tissues of rats and resulted neuroprotective in a rat model of PD [24]. Report by Su et al., 2011 [25] has demonstrated that HDAC6 participated in the degradation of MPP+-induced misfolded α-syn aggregates by regulating the aggresome-autophagy pathway. These results indicate that histone acetylation may be a potential clinical biomarker useful in the diagnosis of the disease.

Non-coding RNAs in PD pathogenesis

MicroRNAs (miRNAs) were first discovered in Caenorhabditis elegans in Lee et al. [26]. They constitute a copious family of small (~19-25 nucleotides long), non-coding RNAs derived from ~70 nucleotide hairpin pre-miRNA's. MiRNAs suppress mRNA expression via translation inhibition. They bind to the 3′-Untranslated Region (3′UTR) of target RNAs, leading to their degradation or de-adenylation of mRNA, thereby negatively impacting the protein output [27,28]. Deregulated expression of specific miRNAs has been implicated in cancers, heart disorders and neurodegenerative diseases [29-32]. MiRNAs are profusely expressed in the brain and are shown to be key regulators of neuronal development, and maturation and maintenance of the adult nervous system [33].

In recent years, the implications of miRNAs in the pathogenesis of PD are gaining increasing importance. Studies on embryonic stem cells differentiated into dopaminergic neurons and in adult mice, have demonstrated that miRNAs are essential for the dopaminergic neuronal survival and the loss of miRNAs can be involved in the development and progression of PD [34]. This study also identified miR-133b expression to be reduced in the midbrain of PD patients unlike control subjects. This miRNA is known to exist in a negative feedback loop with Pituitary Homeobox 3 Transcription Factor (Pitx3), regulating the midbrain dopaminergic neurons terminal differentiation and activity [34]. This was the first study demonstrating the importance of miRNAs in PD. Since then, several miRNAs have been proven to play roles in PD. Both miR-7 and miR-153, have been shown to regulate the expression pattern of alpha synuclein which is the major gene involved in the pathogenesis of PD [35,36]. Analysis of the SNc in PD patients revealed a decline in expression of Heat Shock Cognate Protein 70 (hsc70) and membrane receptor Lysosomal-Associated Membrane Protein 2A (LAMP-2A) which are important proteins in the chaperone-mediated autophagy that helps to clear out α-synuclein in the cells. This was associated with a corresponding increase in hsa-miR-21*; hsa-miR-224; and hsa-miR-373* targeting lamp-2a and hsa-miR-26b; hsa-miR-106a*; and hsa-miR-301b targeting hsc70. Increase in these miRNAs leads to the dysregulation of the proteins involved in clearing alpha synuclein

consequently, leading to the aggregation of this protein which is involved in PD pathogenesis [37]. Research by Cho and co-workers [38] has demonstrated that that down regulation of miR-205 may contribute to the impending pathogenic elevation of LRRK2 protein in the brains of patients with sporadic PD, whereas over expression of miR-205 might offer an appropriate therapeutic strategy to subdue the abnormal up regulation of LRRK2 protein in PD. Another study has demonstrated that discrepancy in the miRNA-433 binding site of Fibroblast Growth Factor 20 (FGF20) increases the risk for PD by over expression of α-synuclein [39]. Previous research from our lab has also demonstrated that miR-124 acts to modulate the expression of calpain/cdk5 pathway proteins in the dopaminergic neurons of the MPTP induced mouse model of Parkinson's disease [40]. Another recent study by Xiong et al., 2014 [41] has demonstrated that up regulation of miR-494 predisposes to oxidative stress induced neuronal death by inhibiting expression of DJ-1. In conclusion, the results provide an insight into the changes induced by miRNA expressions in the SNc of MPTP-treated animals, which eventually regulate several important genes and pathways implicated in PD. These results might pave way for the advancement of a range of miRNA-based PD therapeutics.

Conclusion

Epigenetic changes appear to be an ideal target for therapeutic applications as they are by nature reversible, unlike mutations. The epigenetic variations that have been described in PD share some common features similar to normal aging. Hence, in addition to giving us awareness to pathogenesis of neurodegeneration, they might also throw light on how aging by itself is a risk factor which predisposes human beings to the development of neurodegenerative disorder.

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