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Review article

Epigenetic mechanisms in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, but its pathogenesis is not fully understood. The selective neuronal cell death in PD has been considered to result from a complex interaction between genetic and environmental factors, but the nature of the relationship between the two chief modifiers remains to be elucidated. There is a growing body of evidence supporting the role of epigenetics in the development and progression of many neurodegenerative diseases including PD. Epigenetic modification refers to changes in gene expression or function without changes in DNA sequence, which mainly includes DNA methylation, post-modifications of histone, and non-coding RNAs. In this review, we will focus on the abnormal epigenetic modifications involved in the pathogenesis of PD and their implications for the development of future diagnostic and therapeutic strategies.

Contents

1. Introduction

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, affecting approximately 1% of the population over 60 [1]. It is clinically characterized by bradykinesia, rest tremor, rigidity, gait and postural abnormalities, and a variety of other motor and non-motor symptoms [2]. Pathologic hallmarks of PD include depigmentation of substantia nigra (SN) and cytoplasmic Lewy bodies (LB), which stain for α-synuclein [3–5]. Emerging evidence has provided support for the hypothesis that PD is the result of complex interactions between genetic abnormalities, environmental toxins, mitochondrial dysfunction and other cellular processes [6]. Recently, epigenetic modifiers have been identified as a potential mediator of environmental factors participating in the pathogenesis of PD [7]. In this review, we will focus on the aberrant epigenetic modifications underlying PD.

2. Epigenetic modification

Epigenetics refer to alterations in gene expression or function without changes in DNA sequence [8]. This process can be influenced by lifestyle, environmental factors and modifying genes, resulting in

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phenotypic changes. Epigenetic modifications not only affect gene expression but also play a vital role in development, regeneration, and in human diseases [9]. In the central nervous system, many neurobiological and cognitive functions, from brain development and neurogenesis to learning and synaptic plasticity, are all regulated by epigenetic processes [10,11]. Primary epigenetic modifications include DNA methylation, post-transcriptional modifications of histone and non-coding RNA-mediated changes of gene expression [7,9].

2.1. DNA methylation

The most widely studied epigenetic modification is DNA methylation. In eukaryotic cells, DNA methylation refers to the process of transferring a methyl group from S-adenosyl methionine (SAM) to the fifth carbon of cytosine residue with the help of DNA methyltransferases (DNMT), resulting in the 5-methylcytosine (5-mC) formation [12,13]. Three common DNMTs, termed DNMT1, DNMT3a and DNMT3b, mediate the DNA methylation in mammals. While DNMT1 binds to hemimethylated DNA to maintain methylation pattern after DNA replication [14], DNMT3a and DNMT3b bind to unmethylated or hemimethylated DNA to mediate de novo DNA methylation [15]. Generally, DNA methylation could exert great impact on interaction between histone and DNA, changing chromosome structure and gene expression [16]. Moreover, DNA methylation could recruit methyl CpG-binding domain (MBD) proteins which then recruit epigenetic-related factors, resulting in chromosome conformational changes and gene silencing, whereas unmethylated promoters are mostly linked to gene activation [17].

2.1.1. Factors associated with DNA methylation in PD

The process of DNA methylation can be affected by many factors, including factors involved in one-carbon metabolism [18]. Folates and vitamins participate in the process of homocysteine turning into methionine and then to SAM, which is the universal methyl donor. After supplying a methyl, SAM becomes S-adenosylhomocysteine (SAH) and then homocysteine [19]. Dietary folate deficiency and elevated homocysteine have been found to be harmful to dopaminergic neurons in a mouse model of PD [20]. Moreover, serum folic acid and vitamin B12 have been reported to be decreased in some PD patients [21]. Thus, dysfunction of one-carbon metabolism may result in aberrant DNA methylation which can contribute to the pathogenesis of PD.

High level of homocysteine, resulting from either lack of one-carbon-related substances or long-term levodopa treatment, has long been considered as a potential risk factor for many neurodegenerative diseases, including PD [22,23]. Hyperhomocysteine induces oxidative stress via NMDA receptor-mediated neuronal nitric oxide synthase activation and formation of radicals, which leads to mitochondrial dysfunction and the release of Cytochrome c and of apoptosis inducing factor (AIF), ultimately causing cell apoptosis [24]. Administration of the antioxidant uric acid and inhibitor of poly (ADP-ribose) polymerase ameliorates homocysteine-induced neurotoxicity and dopaminergic neuronal death [25,26]. Increased level of homocysteine may also lead to increased mutation frequency via oxyradical-mediated DNA damage [27]. Homocysteine-induced DNA damage has been demonstrated in embryonic hippocampal neurons, leading to downstream caspase activation and neuronal apoptosis. Similar apoptotic process also exists in SN dopaminergic neurons of both patients with PD and animal models of PD, implicating homocysteine toxicity in the pathogenesis of PD [27] (Fig. 1).

Smoking has been shown to confer protective effect for both dopaminergic and non-dopaminergic neurons. A recent study focused on the role of smoking on methylation of a less studied gene related to PD, LINE-1. Cigarette smoke condensate can lead to reduced LINE-1 methylation [28]. Interestingly, the inverse relationship between smoking and PD risk was most marked in patients with the lowest LINE-1 methylation, which diminished significantly with hypermethylation of LINE-1. Furthermore, an inverse relation between coffee consumption and PD has been also observed, but no such relationship has been found with alcohol [29].

2.1.2. DNA methylation in PD-related genes

Expression of alpha-synuclein (*SNCA*), one of the most important risk genes for PD, is regulated by DNA methylation [30,31]. Hypomethylation of SNCA intron 1 has been shown in the brains of patients with PD [32]. This was also demonstrated in HEK-293 cells where hypo-methylation of CpG contributed to SNCA overexpression and PD development [33]. Furthermore, using DNA from peripheral blood leukocytes, methylation level in CpG-2 sites in SNCA promoter was found to be significantly decreased in PD patients compared to controls [34]. These findings suggest that the level of DNA methylation in peripheral blood leukocytes may be a potential noninvasive biomarker for PD. However, a recent study failed to show any difference in DNA methylation levels of CpG sites in intron 1 of SNCA between PD patients and controls [35]. This discrepancy might be explained by different CpG sites and different sequencing methods involved. Furthermore, the reduction of nuclear DNMT1 level not only in brains of SNCA transgenic mice models but also in postmortem brain tissue of patients with PD may explain the molecular mechanism underlying decreased methylation of SNCA. DNMT1, mainly located in the nucleus of neurons, is abundantly expressed in adult brain. While SNCA accumulates and aggregates in rat B103 neuronal cells via lentivirus transfection, it associates with DNMT1 and alters proper shuttling of DNMT1 into the nucleus, leading to subcellular mis-localization of DNMT1 and global hypomethylation of genes, which is consistent with the decreased level of DNMT1 demonstrated in the brains of patients with PD [36].

The well-known observation that PD occurs more frequently in men than women might be in part explained by the methylation pattern of sex-specific genes, such as microtubule-associated protein tau (*MAPT*). *MAPT*, which encodes the protein tau that helps stabilize the axonal cytoskeleton, is one of the major risk factors not only for Alzheimer's disease but also for PD. Aberrant methylation of MAPT gene might be implicated in the pathogenesis of PD through affecting its expression and axonal cytoskeleton stability. In one study, a higher level of MAPT methylation has been observed in leukocytes of women than men, in accordance with another study that convincing the opposite effects of methylation played by sex-specific genes [37]. Hypermethylation of MAPT gene leads to reduced expression of this gene, which might help explain why women have a lower risk of developing PD than men [38].

Several other genes have also been reported to be regulated by DNA methylation. Increased activity of CYP2E1 has been found to promote the formation of toxic metabolites, which eventually contributed to degeneration of dopaminergic neurons [39]. Reduction in Cyt P450 2E1 methylation level shown in patients with PD is consistent with the observation that CYP2E1 mRNA expression is increased in PD brains [40].

Tumor necrosis factor alpha (TNF-α), an important inflammatory factor, has been also implicated in the pathogenesis of PD. Pieper et al. [41] provided evidence for hypomethylation of TNF-α promoter in the SNpc compared to cortex both in PD patients and in neurologically healthy controls, indicating increased susceptibility of neurons located in SNpc to TNF-α-mediated inflammation.

2.2. Histone modifications

Histones are important components of eukaryotic cell chromosome with N-terminals protruding from the nucleosome, so they interact with other factors and can be easily modified [42]. Many types of post-transcriptional modifications of the residues at histone tails have been found, such as methylation, acetylation, phosphorylation, ubiquitination and sumoylation, among which acetylation at lysine residues is particularly important. Histone acetylation is catalyzed by histone acetyltransferases (HATs), producing a more loosened chromatin structure that allows transcriptional activation, whereas histone