The Epigenetics Changes in Parkinson's Disease: a Novel Therapeutic Target

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Neurodegeneration diseases such as Parkinson's disease (PD) dampen cognitive function severely in aged population. The neuropathological mechanisms underlying PD included progressive loss of midbrain dopamine neurons, due to the activation of oxidative stress pathways, for instance. The post-mortem characteristics of the brains from PD patients were described by the formation of Lewy bodies, through the pathological accumulation of the protein alpha-synuclein. In recent years, different loci and genes were identified to be associated with familial (with family history) PD, such as PARK1-15 and associated genes. In addition, there are genes such as LRRK2, SNCA, MAPT, and GBA that are associated with sporadic (without family history) PD [1].

Epigenetic modulation represents a newly identified mechanism to regulate gene expression or cellular phenotype without

the alteration of genome DNA sequences. The common epigenetic modulation approaches include DNA methylation, chromatin remodeling, and the gene expression regulation via small noncoding RNAs. In recent years, the epigenetic changes have been well recognized and documented in brain development, plastic changes, as well as different brain diseases, including the PD.

With an animal model (overexpression of α -synuclein in fly) of PD, the histone deacetylase (HDAC) inhibitor was firstly found to inhibit synuclein toxicity to the dopamine neuron [2], followed by a series of studies that established the importance of histone acetylation in pathogenesis of PD [3]. In a recent paper appearing on CNS Neuroscience & Therapeutics, Zhu et al. [4], the authors found that the application of HDAC inhibitor is able to block the mitochondrial fragmentation, which is an early event during

Table 1 Epigenetic changes related to Parkinson's disease

The associated gene, DNA methylation, Histone acetylation, Regulating miRNAs			
SNCA (α -synuclein)	Reduced [Jowaed et al. 2010]	Inhibited [Outeiro et al. 2007]	Decreased [Junn et al. 2009; Doxakis 2010]
Parkin	No change [Cai et al. 2011; De Mena L et al. 2013]	—	—
UCHL-1	No change [Barrachina and Ferrer 2009]	—	—
MAPT	No change [Barrachina and Ferrer 2009]	—	—
TNFA (TNF- α)	Unclear [Pieper et al. 2008]	—	—
PARK16–1q32, GPNMB, and STX1B,	Altered [IPDGC, 2011]	—	—
—	—	—	Altered expression of miRNAs in lymphocytes of PD patients [Margis et al., 2011]
—	—	—	miR-133b decreased [Kim et al. 2007]
—	—	—	miR34b decreased [Minones-Moyano et al. 2011]

MPP+ induced neuronal apoptosis. HDAC inhibitors therefore could provide potential therapeutic agents for neuroprotection in different neurodegeneration diseases.

Dysregulation of DNA methylation in PD was well documented as well. For instance, post-mortem brain analyses revealed decreased methylation of α -synuclein (SNCA) in dopaminergic brain regions [5,6], which might be responsible for the increased protein expression and therefore the PD progression. In addition, the methylation of several other genes such as PARK16/1q32, GPNMB, and STX1B was found to be dysregulated in PD brains [7].

Last but not least, different miRNAs were reported to be down-regulated or losing the binding site in PD animal models, as well as the brains from PD patients [8,9]. These studies established the roles of epigenetic regulation in pathogenesis and development of PD (Table 1).

Present investigations on epigenetic changes of PD patients largely rely on post-mortem brain analyses, therefore lacking evidences of progressive changes, and it is hard to differentiate if the changes are resulted from the previous therapeutic treatments. One recent study on epigenetics examined the genome-wide DNA methylation status from both brain and peripheral blood samples of PD patients, and the authors found concordant methylations in both brain and blood samples [10], suggesting for a new route of PD prognosis and drug discovery for epigenetics. In this study, the authors obtained fresh post-mortem brain and blood samples from PD patients and aged-matched healthy subjects. They found that the two sources of samples exhibited high similarity in DNA methylation status. Their results confirmed the utility of blood samples in surrogate of brain samples, especially for human subjects. The similarity or concordant changes persist in PD patients, suggesting that blood samples from PD patients could act as important substrate of both genetic and epigenetic studies. Finally, the authors

identified lists of genes with either increased or decreased DNA methylation in PD patients from brain and blood samples, showing highly correlated variations in both samples. Notably, with blood samples, it is possible to separate PD patients from healthy subjects simply based on epigenetic analyses, suggesting for a novel approach in PD prognosis and diagnosis. It will also be possible to track the efficiency of therapeutic treatments along the clinical management of patients as well.

The epigenetic changes in the blood DNA could act as important drug target in screening new therapeutic molecules, in both animal models and human subjects, in addition to the neurological assessment. The sensitivity and specificity are yet to be improved with increased number of subjects recruited. Conceivably, the epigenetic changes occur in prior to protein accumulation as well as the neurological impairment, therefore might act as early biomarkers in evaluating PD progression.

In summary, epigenetic changes represent important characteristics in PD diagnosis and treatment. The HDAC inhibitors provide intriguing possibilities in clinical management of PD, while blood-cells based detection of epigenetic changes would offer new possibilities in biomarker discovery.

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Conflict of Interests

The authors declare no conflict of interest.

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