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CLINICAL IMPORTANCE OF THE RELATIONSHIP BETWEEN EPIGENETIC MECHANISM AND PARKINSON'S DISEASE

Summary

Today, epigenetics is more commonly used for heritable changes in gene expression. While no change is observed in the DNA sequence, chromatin changes such as DNA methylation, histone modification, and nucleosome positioning cause epigenetic events (10). Epigenetic processes; DNA includes chemical modifications of histones and various coding and non-coding RNAs. In recent years, the role of epigenetics in neuroscience has been extensively explored, thanks to technological advances. Therefore, the term "neuroepigenetics" appeared in PubMed in 2009 and is widely used today.

Key words: *Parkinson's disease, α-synuclein, mutation, neurons, dopaminergic, DNA*

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Epigenetik mexanizm və Parkinson xəstəliyi arasındakı əlaqələrin kliniki əhəmiyyəti

Xülasə

Bu gün epigenetika gen ifadəsindən irsi dəyişikliklər üçün daha çox istifadə olunur. DNT ardıcıllığında heç bir dəyişiklik müşahidə edilməsə də, DNT metilasiyası, histon modifikasiyası və nukleosomların yerləşdirilməsi kimi xromatin dəyişiklikləri epigenetik hadisələrə səbəb olur (10). Epigenetik proseslər; DNT histonların kimyəvi modifikasiyalarını və müxtəlif kodlaşdıran və kodlaşdırmayan RNT-ləri özündə əks etdirir. Son illərdə texnoloji tərəqqi sayəsində epigenetikanın nevrologiyada rolu geniş şəkildə tədqiq edilmişdir. Buna görə də "neyroepigenetika" termini 2009-cu ildə PubMed-də yaranıb və bu gün geniş istifadə olunur.

Açar sözlər: *Parkinson xəstəliyi, α-sinuklein, mutasiya, neyronlar, dopaminerjik, DNT*

Parkinson's disease (PD) is a common neurodegenerative disease that progresses with age, includes various motor and non-motor symptoms, and symptoms increase over time. Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease and affects 1-2% of the population over 65 years of age (1). PD is characterized by motor symptoms such as bradykinesia, tremor, rigidity, postural instability, and non-motor symptoms such as olfactory dysfunction, depression, constipation. These symptoms were first described by James Parkinson in 1817 (2).Pathologically, it is expressed as the death of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies in neurons in the affected brain regions. Lewy bodies contain a large amount of α-synuclein, with lesser amounts of ubiquitin and other proteins (3). The gradual decrease in fluid movements in Parkinson's patients is due to decreased dopamine synthesis in the substantia nigra pars compacta and especially the problem of its transmission to the dorsal striatum (4).

The cause of Parkinson's disease is unknown,but several factors appear to play a role, including:

- Genes. Researchers have identified specific genetic mutations that can cause Parkinson's disease. But these are uncommon except in rare cases with many family members affected by Parkinson's disease.

However, certain gene variations appear to increase the risk of Parkinson's disease but with a relatively small risk of Parkinson's disease for each of these genetic markers.

- Environmental triggers. Exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is relatively small.

Researchers have also noted that many changes occur in the brains of people with Parkinson's disease, although it's not clear why these changes occur. These changes include:

- The presence of Lewy bodies. Clumps of specific substances within brain cells are microscopic markers of Parkinson's disease. These are called Lewy bodies, and researchers believe these Lewy bodies hold an important clue to the cause of Parkinson's disease.
- Alpha-synuclein found within Lewy bodies. Although many substances are found within Lewy bodies, scientists believe an important one is the natural and widespread protein called alpha-synuclein (a-synuclein). It's found in all Lewy bodies in a clumped form that cells can't break down. This is currently an important focus among Parkinson's disease researchers.

The most cases (>90%) of PD are not genetic and are considered sporadic or idiopathic. Familial PD cases are seen in approximately 5-10% of cases. However, the underlying causes of sporadic Parkinson's disease still remain a mystery (1, 5). In this context, we come across mechanisms underlying individual differences,not a single cause. Low prevalence of familial Parkinson's disease;shows that environmental factors,pathogens,and mutations in both nuclear and mitochondrial DNA throughout life play an important role in the emergence of Parkinson's disease (6).

Insecticide exposure and traumatic brain injury are considered risk factors, while tobacco use and physical activity are considered protective factors (Table 1 and Table 2) (7). normal aging; It occurs due to disruption in pathways that result in increased oxidative stress, accumulation of iron and neuromelanin in the brain, impaired autophagy, accumulation of α-synuclein in the cell, activation of microglia and neuroenamel, and is characterized by neuronal reduction. In addition, genetic, environmental, and epigenetic factors translate the normal aging process into Parkinson's disease with increased dopamine neurodegeneration (8).

Table 1. Protective Factors and Biological Effects (7).

Protective Factor	**Biological Effects**
Tobacco use	Nicotine binds to the nicotinic acetylcholine receptor, reducing neural damage.
physical activity	Increases serum urate level, neurotrophic factors
urate	Shows antioxidant effect
Ibuprofen	It has an anti-inflammatory effect by activating PPARγ.
calcium channel blockers	Inhibits calcium channel-induced stress in the mitchondria of dopaminergic neurons
Caffeine	Blocks the adenosine A2A receptor

Table 2. Risk Factors and Biological Effects (7).

Risk Factor	**Biological Effects**
pesticide	Oxidative stress, mitochondrial toxin
Dairy products	Urea-lowering effects of dairy products
traumatic brain injury	Breakdown of the blood-brain barrier, brain inflammation, impaired mitochondria function, accumulation of α-synuclein
anxiety or depression	Loss of serotonergic neurons in the dorsal raphe nucleus in early PD (considered as a prodromal symptom)
beta-blockers	Increasing norepnephrine neuron loss and norepnephrine deficiency

Especially DNA methylation; regulates gene expression at promoter or intragenic loci. It also regulates by modifying noncoding (regulatory) DNA sequences. Epigenetic changes, including DNA methylation changes in CpG regions, play a role in neurodegenerative diseases such as Parkinson's disease (8, 9).

Studies on the role of DNA methylation in Parkinson's disease are increasing day by day. Parkinson's disease has been shown to be directly related to DNA methylation levels in blood and saliva (12).

Histone Modifications in Parkinson's Disease.

Histone modifications have been shown to play an important role in the development, differentiation, and maintenance of dopaminergic neurons (2). However, little is known about the effects of histone modifications on the pathogenesis of PH.

Treatment methods.

Treatments for Parkinson's disease are usually symptomatic and have limited effects on disease progression. Epigenetic mechanisms are of great importance in explaining the pathophysiology of the disease. Therefore, new treatment methods include the use of some drugs (epidrug, epidrug) targeting DNA methylation, histone modifications and chromatin reorganization. These drugs include DNA methyltransferase activators and inhibitors, histone deacetylase inhibitors, sirtuin activators, and histone methylation modulators (13).

Hypermethylation of some genes triggers neurodegeneration Hypermethylation of some genes triggers neurodegeneration. Therefore, approaches including DNA methylation inhibitors can be used in the treatment of PH. Therefore, approaches including DNA methylation inhibitors can be used in the treatment of PH. DNMT inhibitors such as 5-aza-20-deoxycytidine (Decitabine) and 5-aza-cytidine (Azacitidine) and small molecules such as hydralazine and procainamide, which are nucleoside analogues, are considered as potential treatments in neurodegeneration, although they have not yet been submitted to clinical trials. On the other hand, these epidrugs; it has been approved by the FDA for use in the treatment of diseases such as various types of cancer, thalassemia, cardiac arrhythmia, and hypertension (14, 15).

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