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THE ROLE OF DAMAGES AND EPIGENETIC MODIFICATIONS OF DNA IN ALZHEIMER'S DISEASE

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Abstract:

Today, Alzheimer's disease is a progressive and common neurodegenerative disease. The active study of this pathology reveals more and more mechanisms of its development. Currently, there is a large amount of evidence that the processes of neurodegeneration are caused by damage tothe genetic apparatus of the cell, as well as its epigenetic modifications. This article discusses the main causes of changes in the structure of DNA in nerve cells and analyzes their participation in the pathogenesis of Alzheimer's disease.

Keywords: *Alzheimer's disease, neurodegeneration, DNA damage, mutations, oxidative stress, repair, epigenetics.*

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INTRODUCTION:

Alzheimer's disease is a common neurodegenerative disease, and one of the most common forms of dementia. According to the epidemiological data of 2017, more than 44 million people worldwide suffered from this disease, and by 2050, a threefold increase is expected in this number due to the rise in life expectancy and, as a result, the general aging of the population [1]. All this makes Alzheimer's disease an important issue in today's health care and society as a whole, creating a whole host of serious social and economic problems for humanity. In Alzheimer's disease, neurodegenerative processes are observed in various areas of the brain, such as the parietal, temporal lobes, frontal cortex, cingulate and para-hippocampal gyrus. These changes lead to the deterioration of cognitive functions, impaired memory, which makes a person isolated from society and prevents his socialization, and he/she becomes incapable and helpless [2]. Damaged areas of the brain are characterized by clusters of senile plaques - deposits of beta-amyloid protein (Aβ), as well as a hyper-phosphorylated form of tau protein, forming neurofibrillary tangles in neurons. Aβ is formed from the amyloid precursor protein (Amyloid precursor protein APP) by a mechanism of limited proteolysis. Mutations in the APP and Preseneline genes (PSEN1, PSEN2) in some way influencethe formation of Aβ. According to the amyloid hypothesis, abnormalities in the formation of Aβ from APP lead to the aggregation of amyloid particles and deposition of senile plaques in the brain, which leads to pathological processes and changes in it [3]. In general, with the help of a poly-genomic search for associations, today it is possible to identify more than 20 genes that have the appearance of Alzheimer's disease. The products of these gene translations involve synaptic transmission, endocytosis, an immune response, and fat metabolism [4]. Obviously, damage to these genes or mutations that occur in them can significantly affect the functions and vital activity of nerve cells, sometimes even causing their death. Indeed, DNA damage, especially if it occurs in the tissue of the developing spinal cord and brain, can subsequently lead to the formation of large populations of neurons prone to neurodegenerative processes. These damages may be done due to genetic predisposition (improperly functioning repair mechanisms), and the effects of various mutagens and neurotoxins as well as the aggressive effects of reactive oxygen species (ROS). It should be noted that DNA damage refers to not only genetic material localized in the nucleus but also the mitochondrial genome, defects in which can lead to serious disorders of various enzyme systems. Moreover, at present, scientists are greatly interested in the mechanisms of epigenetic regulation of gene expression, which, as we have already found out, influence the processes of learning, memory, thinking, and most importantly, neurodegeneration [5].

The DNA damage caused by reactive oxygen species (oxidative damage):

In Alzheimer's disease, cells experience oxidative stress, which is especially evident in areas of the brain affected by the disease. This state in cells occurs much earlier than symptoms appear, which indicates the role of this state in the further development and formation of pathology [6]. As you know, the damaging factor in oxidative stress is an excess of reactive oxygen species (ROS), which leads to the oxidation of cellular structures and macromolecules in it.Thus, the oxidation of nitrogenous bases of DNA molecules and mitochondria leads to the emergence of new bases, such as 8-hydroxyguanine, 8-hydroxyadenine, 5-hydroxyuracyl, and 5-hydroxycytosine, which are markers of oxidative damage to DNA [7]. Such a change in DNA molecules complicates transcription or even leads to an incorrect flow of this process. Using a wide range of analytical methods - immunological analysis, mass spectrometry, and chromatography - it is possible to quantify the content of these markers in the studied tissues [8]. A number of studies that analyzed the amount of

oxidized nitrogenous bases of DNA molecules showed that in Alzheimer's disease, in both clinical and preclinical stages, there is a noticeable increase in the number of oxidized bases compared to control groups [9-11]. The temporal lobe is most susceptible to damage [12]. It is important to note that in patients with elevated levels of ROS can be traced in peripheral tissues, for example, in urine, CSF and blood leukocytes. At the same time, a reduced amount of antioxidants is noted in plasma [13].

Another important consequence of the action of ROS on DNA isits occurrence in the latter of single and double-stranded breaks. The first suggestion that DNA breaks may contribute to neuro-degeneration was put forward in 1990 by Mullaart and colleagues [14]. The researchers found that in the neurons of the brain affected by Alzheimer's disease, the number of these breaks was 2 times greater than in healthy tissue. However, Su et al. found that DNA breaks in neurons contribute to the formation of neurofibrillary tangles in them responsible for the pathogenesis of the disease [15].

Indirect DNA damage during oxidative stress:
In addition to direct effects on DNA molecules, an excess of ROS can affect them through other cellular structures. The oxidation of polyunsaturated fatty acids of cell membrane phospholipids was found to produce Acrolein, Malondialdehyde and Hydroxynonenal, which form DNA adducts [16]. Liu and colleagues, examining DNA extracted from the hippocampus, found an elevated content of Acrolein and guanine adducts compared tothe control group [17]. Acrolein, as noted by Dang et al., inhibitsmitochondrial activity, and also promotes the phosphorylation of tau protein, which, as noted, is involved in the pathogenesis of Alzheimer's disease [18].

Mitochondrial DNA damage:
Mitochondrial DNA (mtDNA) encodes the components of the electron transport chain (ETC), as well as the structure of the molecules of mitochondrial rRNA and tRNA. Damage to mtDNA caused bythe action of mutagens or ROS on them can lead to disruptions in the enzyme systems of mitochondria. According to the idea of Swerdlow and Khan, the effectiveness of the ETC, which is determined by the mtDNA genes, directly determines the number of ROS formed in mitochondria [19].Thus, damage to mtDNA leads, firstly, to energy losses, and secondly, to the formation of a state of oxidative stress, and thirdly, to the accumulation of Aβ. These events, like a vicious circle, cause degenerative processes in the nerve cells. However, despite the presence of genetic defects in mitochondria in patients with Alzheimer's disease, today there is no reliable evidence of a direct connection of the disease with one of them.

Epigenetic regulation of genes:
In recent decades, increasing attention has been paid to epigenetics and the mechanisms by which it influences memory thought processes, and neurodegeneration. The most well-known and well-studied epigenetic mechanism of regulation of gene expression is the methylation of its regions. For example, Basha and colleagues found that hypermethylation of the promoter of the APP gene in mice at an early age leads to the subsequent accumulation of Aβ in the nervous tissue [20]. At present, models of Alzheimer's disease have been proposed, linking between each other epigenetic modification of DNA sites, their damage, and also repair. The mechanism itself is as follows: hyper-methylated regions of DNA become less accessible for repair enzymes, and they gradually accumulate damage, which in turn leads to the further development of pathology.

Another model of epigenetic involvement in the development of Alzheimer's disease is associated with the metabolism of folic acid (vitamin B9). Lack of folate, which is often observed in patients, leads to the development of hyper-homocysteinemia. At the same time, DNA methylation processes are significantly weakened in cells [21]. Reduced methylation affects not only the APP and PSN genes but also the repair factors, for example, OGG1. Thus, the cell becomes more vulnerable to various damaging influences. It is also important that folate deficiency contributes to hyper-phosphorylation of tau protein, forming neurofibrillary tangles that inhibit the metabolism in neurons [22].

Conclusion: Thus, Alzheimer's disease, as a consequenceof neurodegenerative processes, is the result of the interaction of a number of different factors, including genetic predisposition, the influence of the external environment, and the work of epigenetic mechanisms. Despite the fact that the etiology of this disease today is ambiguous, it is safe to say that many pathological processes are caused by changes in DNA molecules, which in the long term determine neurodegeneration itself.

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