Epigenetics and Alzheimer's Disease: A Literature Review

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Abstract. Over half of the dementia cases are from Alzheimer's disease, which represents about 55 million patients diagnosed with the condition and the number is rapidly increasing. Several hypotheses as to what the disease's mechanism is, how it develops, and how it could be prevented and treated have been by scientists around the world. As a result of the above-mentioned, epigenetic mechanisms have been widely mentioned as influential to the development of the disease. Epigenetic mechanisms are techniques that are able to modify the chromatin and gene expression without making any alterations to the DNA itself, as a consequence the gene expressions are altered. The main ones are DNA methylation, histone modifications, and microRNAs. Furthermore, genes are also associated with Alzheimer's disease, as well as, more lifestyle factors, such as diet, stress levels, and physical activity. In this brief literature review, all the points already stated will be explained, overviewing their significance. Finally, it will allow readers to have a succinct knowledge of how epigenetics is associated with Alzheimer's disease, along with a better understanding of what the disease is and the mechanisms and pathways researchers believe lead to the condition.

Keywords. Epigenetics, Alzheimer's disease, epigenetics mechanisms, genes , lifestyle.

1. Introduction

According to studies, every 3,2 seconds someone is diagnosed with Alzheimer's, and over 10 million each year worldwide. Whereas in 2019, 55 million people had the disease, in 2030, it is estimated that 78 million, and in 2050, 139 million. These estimations show the significance and necessity of studying this illness and finding ways to prevent, diagnose early on stage, treat it properly, and hopefully discover a cure. Having that in mind, this literature review was made to briefly explain the main subjects associating epigenetics with Alzheimer's disease.

2. Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition and the most common type of dementia, representing about 60% to 70% of cases. Alzheimer's most characteristic symptom is short-term memory loss, but as the disease progresses, the patient may also suffer from personality changes, mood swings, and language problems. In the last stages, body functions begin to diminish gradually. After diagnosis, the life expectancy is around three to nine years.

AD is also characterized by the accumulation of protein amyloid β and tau, associated with mitochondrial dysfunction, neuroinflammation, and flawed cell stress response, among others. [1, 2, 3, 4, 5, 6]

3. Epigenetics

First introduced by Conrad Waddington in the 1940s, the epigenetics field is being subject of several studies worldwide. Epigenetics are alterations in the DNA that do not modify its sequencing, but the way our genes express. The modifications may affect positively or negatively and are prone to happen at specific times throughout life, such as childhood. They are hereditary and transmitted from one generation to the other. [1,7, 8, 9]

4. Epigenetic factors

4.1 Diet and Nutrition

Studies have shown the importance of healthy nutrition in preventing and managing Alzheimer's disease. An anti-inflammatory diet was proven to decrease the risk and incidence of Alzheimer's disease. It is also important to mention the need for metal ions such as Copper and Zinc for the brain. Studies have shown that Alzheimer's patients tend to have a dysregulation of the levels of copper, and zinc

is known to participate in the pathogenesis of Alzheimer's disease by modifying the amyloid metabolism. [6, 10,11, 12,13]

4.2 Exercise

Epidemiologists have studied for a while now how exercise can help to prevent neurodegeneration. At first, studies showed that exercise may reduce up to 45% of Alzheimer's. Later on, it was introduced as a potential therapy for neurodegenerative diseases, like it has been used for many other illnesses, such as cardiovascular, neurological, and metabolic. Motivated by the positive outcome of previous studies, more advances were made. Molecules created by stimulation of exercise and could be the key were found. Some of those are superoxide dismutase, endothelial nitric oxide synthase, brain-derived neurotrophic factor, insulin-like growth factor-1, vascular endothelial growth factor, and nerve growth factor. More research is happening now to understand how each molecule may help to prevent Alzheimer's and as a non-drug therapy. [14,15]

4.3 Stress

A longitudinal cohort epidemiological study, together with endocrinologic evidence allowed scientists to associate early life stress with late-onset Alzheimer's disease (LOAD). This information allowed the association of catecholamine and corticosteroid systems in LOAD. [16]

5. Epigenetic mechanisms involved in Alzheimer's Disease

The epigenetic mechanisms are the techniques used to modify the chromatin and the gene expression [17].

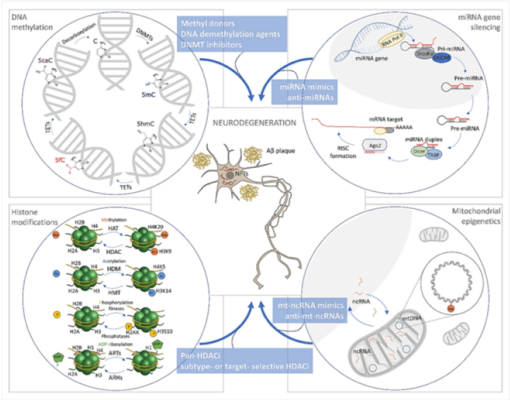

Fig. 1 – Epigenetic mechanisms associated with neurodegeneration [17].

The following mechanisms are the most important ones known to be involved in the epigenetic changes that cause Alzheimer's disease:

5.1 DNA Methylation

DNA methylation consists of implementing a methyl group on the cytosine ring. The mechanism is regulated by DNA methyltransferases (DNMTs), a family of enzymes, and is the most studied and known. Nowadays, next-generation sequencing (NGS) allows scientists to determine the exact location of the 5-methylcytosine (5mC) formed by the process. The methylation is responsible for the silencing of gene expression. This mechanism is essential for suppressing repetitive element transcriptions that may occur, which is crucial to normal development. Although DNA methylation is a necessary mechanism, it becomes an issue when genes that should be expressed are silenced.

Studies are trying to identify the genes silenced by DNA methylation, which may be causing the disease. The most cited one to date is the APOE, which will be discussed in the following sections. There are recent observations of hydroxymethylation associated with Alzheimer's, but further details on how the mechanism works are yet to be found. [1, 7, 18, 19, 20]

5.2 Histone Methylation

Histone methylation consists of adding to the N-terminal of arginine or lysine of methyl groups by histone methyltransferase. It changes the chromatin's structure, resulting in it being part of the transcription, replication, and repair of DNA. Scientists are searching for the consequence of the methylation in different positions of histones. The most studied by now is the lysine methylation on the fourth position of histone H3, which has been related to synaptic transmissions, shaft bursts, and nerve development, all directly linked to Alzheimer's development. Furthermore, trimethylation of histone H3K4 is associated with the expression of genes related to memory and the protein *ZIF268* that helps to maintain long-term potentiation in the recognition memory. Overall, the histone methylation participates in several cell processes, from mitosis up to respose to stress and aging. [1, 7]

5.3 Histone Acetylation

Histone acetylation is similar to histone methylation. The difference is that an acetyl group is added, instead of a methyl, by acetyltransferases. It promotes gene expression for learning and memory in the nervous system. [7]

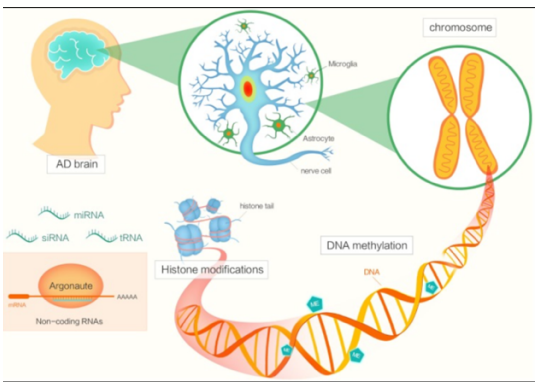

Fig. 2 – Detailed image of histone modifications and DNA methylation mechanisms [21].

5.4 MicroRNA

Regularly, RNA is translated for protein synthesis, but microRNAs are non-coding RNAs that do not translate into proteins but are essential for regulating cellular functions by binding NDA, RNA, and proteins to influence gene expression. The early studies correlating microRNAs to Alzheimer's disease were published in the 1990s, and scientists are still trying to understand the mechanism to its full extent. [1,22]

6. Genetic Factors

6.1 Genes

Tab. 1 – Principal genes associated to Alzheimer´s disease.

Gene Symbol	Function	Location
MEG3 [23]	Activates necroptosis in human neuron xenografts. It is a long non-coding RNA (IncRNA).	Chromosome 14q32.3
APOEε4 [5, 24]	Crucial in the amyloid β downstream effect on the aggregation of phosphorylated tau in the brain. The variant ε4 is the main genetics risk factor for Alzeimer's disease known by now, but the mechanism by what method it affects the pathophysiological progression is yet not known.	Chromosome 19q13.32
APP [25]	When mutations occur in this gene the amyloid β production increases.	Chromosome 21q21
PSEN1 [25]	Associated with severe forms of Alzheimer's disease. Patients with mutations in this gene could develop the disease earlier than expected.	Chromosome 14q24.2
PSEN2 [25]	Affects the clinical presentation and inheritance of the disease.	Chromosome 1q42.13

6.2 Gender

Although both men and women develop Alzheimer's disease, the way it affects each gender is different, and the number of patients is not equivalent. That is because men and women are predisposed to different neurological and neuropsychiatric disorders. For example, Parkinson's disease is more prevalent in men, whereas Alzheimer's disease is more prevalent in women. In most studies and clinical trials, there are more male patients than females, who tend to be under-recruited, making it harder to fully understand how and why the diseases have different clinical presentations and prevalences in each gender. [26]

7. Conclusions

As shown above, epigenetics is a significant area of study to understand the cause of Alzheimer's disease and how to figure out how to prevent, diagnose, treat, and hopefully one day cure it. Although there are a considerable amount of articles reporting research around the world studying Alzheimer's disease, there are still many available fields. That means, in the future years several other studies can be made, allowing scientists to understand the disease better each day. Overall, both genetics and lifestyle are associated with the development of the condition and should be considered.

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