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(REVIEW ARTICLE)

Epigenetics in the Development of Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD), a cause of dementia, has emerged as a significant public health concern that affects societies worldwide. Statistics of 2021 reveal that there are 55 million reported cases of this disease globally, this disease is characterized by the gradual deterioration of nerve cells in the brain, which inevitably leads to a decline in cognitive abilities.

The progression of AD is significantly influenced by genetic factors. Scientific research has helped identify over 40 genetic risk loci that are associated with the disease, giving an idea on the molecular mechanisms behind its development. However, environmental factors and epigenetic modifications, which are changes in gene expression not caused by alterations in the DNA sequence, also play important roles in the disease's development and progression. The current treatment strategies for AD primarily aim to manage the symptoms and slow the rate of cognitive decline, but these treatments are not curative and the disease continues to progress. This underlines the importance of early diagnosis, which can significantly improve the effectiveness of these treatments. Decoding the role of genetics and epigenetics in the development of AD is key to identifying potential therapeutic targets and developing effective treatments. The understanding of these factors will provide valuable insights into the pathophysiology of AD, contributing to advancements in medical research and healthcare strategies aimed at combating the disease.

Keywords: Alzheimer; Genetics; Epigenetics; Healthcare; Neurodegenerative

1. Introduction

According to a report released in 2021, Alzheimer's Disease (AD) ranks among the top deadly diseases globally, occupying the 7th position. In that same year, 55 million people worldwide were recorded with this diagnosis [1], and it is estimated that this number will triplicate by the year 2050 [2], with approximately 10 million new cases being added each year [3].

Dementia is a condition stemming from various diseases that gradually deteriorate nerve cells and harm the brain, typically causing a decline in cognitive abilities (such as thinking processes) beyond what would be expected due to normal aging. Although consciousness remains intact, this cognitive decline often coincides with, or is sometimes preceded by, changes in mood, emotional regulation, behavior, or motivation. Dementia imposes physical, psychological, social, and economic burdens not only on individuals affected by the condition but also on their caregivers, families, and society as a whole. Being a progressive disorder, symptoms manifest gradually over the years, leading to difficulties in language, visuospatial abilities, executive functioning, among other complications [4], resulting in increased dependence on others by the patient. Lack of awareness and understanding about dementia often leads to stigma and creates barriers to diagnosis and proper care. The most common way of dementia is AD and may contribute to 60–70% of cases [5].

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A precise and early diagnosis of AD is crucial for providing the best possible care to the patient and is essential in clinical trials focused on the fundamental neuropathological characteristics of the disease. Additionally, biomarkers are of particular importance for both selecting individuals in the preclinical stage of AD and those in the early symptomatic phase [6].

Today, the diagnosis of the disease is mainly based on the use of positron emission tomography with tracer molecules and the analysis of proteins in cerebrospinal fluid [7]. Timely diagnosis of AD involves shifting the focus from advanced stages of dementia to earlier stages of the disease, such as mild dementia or even mild cognitive impairment to AD [8].

AD is a major public health issue, and there are currently only two approved categories of medications for its treatment. These categories are cholinesterase inhibitor, which encompass naturally derived, synthetic, and hybrid analogs, and N- methyl D-aspartate (NDMA) receptor antagonists [9].

Pharmacological treatments for the disease aim to manage symptoms rather than cure the condition. They focus on slowing the progression of cognitive decline and addressing the behavioral and psychosocial symptoms associated with dementia [10].

Early diagnosis and treatment currently represent a challenge in the healthcare sector. This neurodegenerative disorder may require various approaches for medical intervention. Therefore, it is necessary to take these factors into account for a comprehensive understanding of the disease and to identify potential treatments.

2. Alzheimer's Disease

Alzheimer is a neurological disorder in which the death of brain cells causes memory loss and cognitive decline, leading to dementia. It is more common in the elderly, typically developing in individuals over the age of 65, with the incidence increasing with age [11].

It is possible to identify two types of AD: Early Onset and Late Onset. The initial stage of AD, known as the cellular phase, occurs concurrently with the accumulation of amyloid β, which triggers the propagation of tau pathology. The likelihood of developing AD is influenced by hereditary factors to a significant extent, accounting for approximately 60-80% of the risk. Over 40 genetic risk loci associated with AD have been identified, with the APOE alleles exhibiting the most pronounced association with the condition [12].

2.1. Genetics

For early-onset AD (whose symptoms begin before age 65), more than 400 mutations have been identified in three genes: amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2); which represent 5% of Alzheimer's disease cases with an autosomal recessive pattern. On the other hand, late-onset Alzheimer's disease (whose symptoms begin after the age of 65) is associated with polymorphisms of the apolipoprotein E (Apo E) gene, present in up to 65% of cases [13].

The APP gene is on chromosome 21q, which encodes a transmembrane protein from which B-amyloid (AB) is derived by the action of gamma-secretases, its mutation represents 10-15% of cases of autosomal dominant familial AD, since its function is altered and the production of AB increases [14].

The PSEN1 and PSEN2 genes are on chromosomes 14q and 1q respectively, which encode the proteins PSEN1 and PSEN2 that are part of the gamma-secretase complex where they regulate the proteolytic activity of gamma secretase on the APP gene, mutations in these genes have an indeterminate meaning with dominant autosomal inheritance pattern [15].

On chromosome 19 is the isoform of the gene Apo E, Apo E4; carriers who have an ApoE4 allele are at increased risk of developing AD [16].

Apo E4 competitively binds to AB receptors on the surface of astrocytes, preventing AB uptake, promotes AB aggregation in oligomers and fibrils, reducing its elimination from the interstitial fluid, these AB depositions in the form of amyloid plaques which cause cerebral amyloid angiopathy and cerebral vascular damage, important factors in the pathogenesis of AD [17].

2.2. Environmental factors in the development of Alzheimer

The exposome is defined as the set of environmental influences, including exposure to endogenous and/or exogenous processes, and how biology responds to these processes [18]. An exposome model shows the interconnection between different exposures of an individual to environmental factors and their genetic predisposition to develop a disease, including a neurodegenerative one [19]. It is stated that interactions between genetics and the environment can lead to human pathologies [20].

Among the neurodegenerative diseases that can develop, dementia can be found, which can manifest in different forms. An observational study on early-onset dementia revealed that AD is the primary cause of these impairments [21]. In another study made in northern Italy, connections were found between dementia and exposure to various chemicals, aluminum, smoking habits, among others. Similarly, protective factors against these diseases were identified, such as exercise [22].

On the other hand, late-onset AD is also affected by environmental stress, which includes factors such as metals, pollution, social or psychological stress, smoking, etc., ultimately altering the organism at systemic, intracellular, and intercellular levels, leading to pathological mechanisms, such as epigenetic modifications, that result in this disease [23].

2.3. Epigenetics

The term "Epigenetics" was first used by Conrad Waddington in 1942 through a model in which he showed the relationship between genetics and epigenesis, this referring to the gradual evolution of living organisms from simpler to more complex forms [24]. A cell can take different directions during its differentiation process, and these pathways are mainly influenced by genes, so their absence or presence will determine the path the cell will take. This process is illustrated in Waddington's "epigenetic landscape" model [25].

The term "Epigenetic" has a Greek origin, where "epi-" means "in addition to" or "above", and "genetic" is related to genes. In general, epigenetics is described as the developmental process that connects genotype with phenotype, but without generating any alterations in DNA sequences. Within these processes are histone modifications, DNA methylation, non-coding Ribonucleic Acids (RNAs), etc., which together play a role in vital processes of the human body [26]. Among these, histone modification is the most widely known process and is associated with a significant number of neurological diseases [27].

2.4. DNA methylation

DNA methylation is a mechanism involved in gene expression, the DNA is methylated by DNA methyltransferases (DNMTs), those are enzymes that play a role in the epigenetics of organisms [28].

Both in animal and human models, individuals with AD show a different methylation pattern compared to healthy individuals, these patterns are used as a diagnosis or biomarkers of the disease, research shows that the patterns of gene methylation in individuals with a diagnosis of AD are often hypermethylated or hypomethylated (more frequently) in comparison with healthy individuals [29].

In research about methylation biomarkers in patients with AD, alterations in the genes BDNF (brain-derived neurotrophic factor), APP (Amyloid Precursor Protein), APOE (Apolipoprotein E), TOMM40 (Translocase of Outer Mitochondrial Membrane 40), and PIN1 (Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1) were shown [30].

The main enzyme in charge of the maintenance of DNA methylation is DNMT1, it is responsible for regulating gene expression and maintaining genome stability. The dysregulation of this enzyme is often observed in neurodegenerative diseases, including Alzheimer Disease, in which the protein levels are increased in very important areas of the brain, like the frontal cortex, temporal cortex, and cerebellum, but decreased in the hippocampal and temporal brain region [31].

Usually, the DNA methylation happens at CpG sites in the genome, those are located in the first exon region, gene promoter region or intron region, around 90% of the CpG sites are methylated, the most abundant modified base is 5-methylcytosine, but other bases can be modified too [32].

The gene PM20D1 codifies a protein involved in in neuroprotection, in blood and cerebral samples of patients with mild cognitive impairment and moderate cognitive impairment, also known as the early stages of AD, it's been identified a

decrease of PM20D1 methylation, which can be used as a biomarker of the transition from mild to moderate cognitive impairment [33].

Studies indicate that a hypomethylation of PM20D1 in patients with AD show an increased expression of the gene, this overexpression is correlated to the B-amyloid accumulation, so it's very likely that this is a neuroprotective mechanism, in other hand, the hypermethylation of PM20D1 leads to a faster progression of AD [34].

Amyloid plaques are a pathological feature of Alzheimer, they are mostly made of amyloid peptides (Aβ), specially the Aβ 42 isoform, which is a poisonous hydrophobic peptide, causing aggregation and creation of the amyloid plaque core. Research has demonstrated that the accumulation Aβ in the brain is a primary factor associated with the pathology of AD, serving as a primary element in the disease's onset [35].

The accumulation of Aβ reduces the 5-hydroxymethylcytosine levels, resulting in DNA hypomethylation, affecting the pathological progress of AD [36].

Due to the changes in DNA methylation, it is closely related to AD, because these changes are related to neuronal differentiation in multiple brain regions, so far, DNA methylation has a major role in amyloid production, fibrogenesis, inflammation and oxidative pathways [37].

Studies have also shown that DNA methylation can interact with multicomb-inhibitory complex 2 (PCR2), which reduces silencing of neurodegenerative genes involved in PRC2 and affects neural development [38].

2.5. miRNAs in Alzheimer's Disease

Non-coding RNAs (ncRNAs) are classified into short and long species, with the former being those with fewer than 200 nucleotides and the latter with more. Among short ncRNAs are microRNAs (MiRNAs) [39]. Significant variation in the levels of numerous miRNAs has been observed in various areas of the brain in AD, both in increases and decreases variations in miARN levels can trigger or worsen Alzheimer disease by either increasing or decreasing its severity. To date, 61 different miRNAs widely studied and associated with the development of AD have been identified [40].

One such miRNA is miR-9, involved in the regulation of proliferation, migration, and differentiation of neuronal progenitor cells. Its role in AD pathogenesis is attributed to its negative effects on the regulation of BACE1, leading to increased production and aggregation of Aß [41]. Furthermore, recent research has focused on the expression of the profile of miR-9 in the brains of AD patients, as well as its potential use as a biomarker [42].

Another relevant miRNA is miR-29a, b, c has been found in blood samples, cerebrospinal fluid, and different brain regions of AD patients. It has been suggested that miR29 regulates the expression of BACE1.The decreased regulation of miR-29 in AD could be responsible for the observed increase in apoptosis rate in these individuals [43].

The relationship between miR- 146 and the development of Alzheimer disease has been widely studied. However, researcher results show both negative and positive regulation of this miRNA in the serum, plasma, CFS and CNS of patients with Alzheimer. NF-kB has been found to promote the transcription of miR-146, which suppresses the translation of complement factor H, thereby affecting the inflammatory response in the central nervous system [44].

Neuroinflammation has been pointed out as a possible source of neural damage in the development of Alzheimer inflammatory agents such as interleukin-1B increase the activity of miR-146a, and elevated regulator Alzheimer's. It is suggested that miR-146a could act as a molecular control mechanism, reducing other inflammatory pathways through negative feedback [45].

2.6. Histone modification

Histones are proteins that are in charge of giving the chromosomes their shape by merging with DNA; these structures are also part of the most important regulators of the genes [47]. The post-translational modification (PTM) in histones includes factors that can alter the chromatin structure and can intervene in different biological processes such as the damage and repair of the DNA. If there's any failure in the PTM, neurodegenerative disorders, like AD, can be triggered. PTMs involves methylation, phosphorylation, acetylation, ubiquitylation, among others [48].

The expression of genes and proteins that play a role in learning, neuronal growth, memory, and synaptic transmission are affected by histone methylation. A study has shown that the trimethylated histone H3K4 (H3K4me3), located in the prefrontal cortex, is associated with synaptic transmission, cognition and nervous system development, leading to

disorders such as AD when this epigenome is altered [49]. In another study that included H3K4me3 (also associated with gene transcription) and H3K27me3 (related to transcriptional repression), a comparison was made between healthy people and people who have AD, which resulted in lower H3K4me3 and higher H3K27me3 signals in this last group. Also, it has been proven that histone modification changes with age [50].

Histone acetylation plays an opposite role, as this PTM prevents cognitive degeneration and helps delay the progression of AD [51]. Some histone acetyltransferases (HATs) play a role in long-term memory mechanisms, like CBP, P300 or PCAF [52]. Their damaged expression can result in neuronal apoptosis and neurodegenerative diseases, which is why HATs play a neuroprotective role by preventing the development of AD [53]. A study published in 2022 focused on H3K9 acetylation, showed that this histone modification is found at higher levels in the cerebellum and at lower levels in the hippocampus of patients with AD [54].

On the other hand, histone phosphorylation, specifically histone H3 located in the neuronal cytoplasm, represents a factor that leads to neuronal dysfunction and degeneration associated with AD [55]. The ubiquitination of histones and its relationship with this disease is still under investigation [51].

A very valuable report based on human donors with AD, focused on PTMs in histones specifically in the frontal cortex of these individuals, showed for the first time a 25% decrease in H2B K108 methylation and a 35% decrease in H4 R55 methylation, a 91% increase in H2B K120 ubiquitination, and a loss of H4 acetylation [56].

3. Conclusion

Alzheimer's Disease emerges as a complex interplay of genetic, environmental, and epigenetic factors. Genetic predisposition, notably mutations in genes like APP, PSEN1, PSEN2 and APOE, alongside environmental stressors, contribute significantly to disease development. Epigenetic mechanisms, such as DNA methylation and miRNAs, add another layer of complexity to AD pathology.

Research emphasizes the importance of early diagnosis and the use of biomarkers in identifying individuals in preclinical or early symptomatic stages. Although current treatments aim to manage symptoms rather than cure the disease, understanding these intricate relationships is crucial for advancing diagnostic and more effective therapeutic approaches and strategies. Identifying specific biomarkers and therapeutic targets promises customized interventions for improved patient outcomes. Therefore, understanding the multifaceted nature of AD holds promise for more effective management strategies and better quality of life for those impacted by disease, ultimately intending to mitigate the impact of this debilitating disease on individuals and society.

Compliance with ethical standards

Disclosure of conflict of interest

No conflicts of interest to be disclosed.

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