Role of non-coding RNAs as biomarkers and the application of omics technologies in Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder that has a significant association with age. Despite its increasing incidence in the population, the etiology of the disease remains poorly understood, and there are currently no effective treatments readily available. The main genes that are associated with AD are the amyloid precursor protein, presenilin-1 and presenilin-2, as well as the apolipoprotein E gene. In addition to genetic factors, a wide range of environmental and lifestyle factors are equally characterized as risk factors for the development of AD, while non-coding RNAs (ncRNAs) and other epigenetic mechanisms play a key role in their detrimental effects. Multiple types of ncRNAs, such as microRNAs, circular RNAs, Piwi-interacting RNAs and long non-coding RNAs are being increasingly implicated in AD. Alterations in ncRNAs can be detected in cerebrospinal fluid, as well in as the brain, highlighting these as promising biomarkers for the detection and treatment of AD. Developments in high-throughput technologies have led to the so-called 'omics' era, which involves the collection of big data and information at both molecular and protein levels, while combining the development of novel computational and statistical tools capable of analyzing and filtering such data. The present review discusses the role of ncRNAs and their use as biomarkers for AD, and summarizes the findings from the application of omics technologies in AD.

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1. Introduction

Alzheimer's disease (AD) is a complex disorder characterized by the gradual loss of memory and the self-sufficiency of patients, the deterioration of thinking, and of the usage and understanding of written and spoken language, social isolation. It is also associated with behavioral changes, due to a confused state accompanied by apathy, depression and aggression (1-6). This disease occurs mainly in individuals >60 years of age; however, there is an increasing prevalence of the disorder in ~40% of the population <65 years of age (7). Considering this increasing prevalence of the disease, as well as the considerable socio-economic burden and the absence of any specialized treatment, it is important to make efforts to enhance the understanding of the pathophysiological mechanisms that lead to the development of AD (2,5,8).

AD occurs mainly sporadically without being due to a specific genetic background, with age being the main risk factor (1). The progressive atrophy of the cerebral regions of the hippocampus and cortex are representative macroscopic features of the disease and are clearly visible on a neuroimaging examination, while extracellular deposits of the amyloid- β peptide (A β 1-42) and intraneuronal tangles of hyperphosphorylated forms of microtubule-associated protein

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tau are some of the microscopic features of the disease. The activation of microglia associated with β -amyloid behavior, as well as the inflammatory response have been the focus of several studies on the contribution of β -amyloid cataracts to the development of AD (9-13).

Duing the early onset of AD, causal mutations in specific genes have been identified. The main genes are amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2). PSEN1 and PSEN2 are proteases involved in the conversion of APP into Aβ42, and are related neurotoxic products. The production of Aβ42 does not necessarily increase due to the abnormal variants of presenilin, but causes the production of other forms with a high tendency to cause agglomeration (14-16). On the other hand, the apolipoprotein E (ApoE) gene is the most well-known and important risk factor for the development of AD. This gene has three isoforms; however, 25% of AD cases carry the ɛ4 allele, while generally, the presence of two ApoE4 alleles increases the risk 10-fold compared to the presence of one allele (6,17). Although the mechanisms through which ApoE4 increases the risk of developing AD are not yet known, when this protein is poorly lipidated it binds to Aβ42 and is associated with its greater accumulation and oligomerization in the brain, as well as with reduced extracellular, microglial and the blood-brain barrier-mediated clearance of Aβ42. Thus, the destructive effect of A β 42 on the function of synapses is aggravated (18-20).

A number of recent studies have focused on the search and detection of genetic loci or genes that are risk factors for AD, through the study and analysis of the genome (21). Genetic loci or genes, such as NME8, FERMT2, PICALM, PTK2B, CD2AP, CD33, CELF1SLC24A4/RIN3, FERMT2, CASS4 and DGS2 appear to be associated with the development of late-onset AD due to the single nucleotide polymorphisms (SNPs) that they contain (22). Aside from genetic factors, an array of environmental and lifestyle factors are known as risk factors for the development of AD, ranging from exposure to toxins to a high-cholesterol diet, while non-coding RNAs (ncRNAs) and other epigenetic mechanisms play a key role in their harmful effects (19,23,24).

Currently, various ncRNAs have been detected and studied in accordance with their involvement in AD. The main categories of these molecules are microRNAs (miRNAs/miRs), circular RNAs (circRNAs), Piwi-interacting RNAs (piRNAs) and long non-coding RNAs (lncRNAs). The functions of these molecules, and their ability to interact with each other, as well with DNA and proteins result in the regulation of gene expression, since they either promote or inhibit the expression of genes. In addition, their expression is altered due to a pathological condition, rendering them effective biomarkers for the early diagnosis of diseases, including cancer and neurodegenerative diseases.

The emergence of 'omics' technologies has revolutionized the study of complex pathologies and diseases, including AD. The applications of omics platforms involve the recognition and the study of genes (genomics), messenger RNAs (mRNAs, transcriptomics), epigenomic factors (epigenomics), proteins (proteomics), metabolites (metabolomics) and lipids (lipidomics). In addition, the interest of the gut microbiota (the microbiome/microbiomics) is increasing due to its association with various diseases (25). The analysis and combination of data derived from different omics technologies is crucial for complex pathologies, such as AD in order to acquire a complete knowledge of the disease. Cerebrospinal fluid (CSF) and blood were the main samples used in omics studies on patients with AD, with the former being in close contact with neurons, containing several soluble biomarkers of the brain, and thus reflecting the changes that occur during the disease (26,27). More specifically, the increase in total tau protein (t-tau) and phosphorylated tau protein (p-tau), as well as the decrease in A β 42 in the CSF, reflect the formation of amyloid plaques and neurofibrillary tangles in the brain tissue, which are characteristics of AD. However, the etiology of AD depends on, and is due to multiple factors, including genetic alterations, proteins and ncRNAs (28).

Omics technologies are a promising tool for studying the multifaceted pathology of AD. With the advancement of technology, the era of omics enables the collection of diverse data, as well as the analysis and filtering of data, which is carried out through cutting-edge computational tools. The importance and value of omics and ncRNAs are highlighted through the process of the development of personalized diagnostic and therapeutic tools. For this purpose, various studies have focused on novel pathways and networks, demonstrating novel pathological mechanisms related to AD and linked to other diseases (29-31). The present review aimed to summarize the current evidence on the role and utilization of ncRNAs as biomarkers in AD, as well as to describe the application of omics technologies and large-scale data in the efficient prediction, diagnosis and treatment of AD.

2. Role of ncRNAs in AD

ncRNAs have several distinct classes. The most well-studied category is that of miRNAs, whose function is now well-understood. The role of miRNA epigenetic and genetic defects has been shown in a variety of diseases, including cardiovascular diseases (32), metabolic syndrome (33) and cancer (34) and pathologies of the nervous system, such as AD (35). However, in addition to miRNAs, there are several other classes of ncRNAs, such as small nucleolar RNAs (snoRNAs), circRNAs, piRNAs, Y RNAs and the large heterogeneous group of lncRNAs, key factors in the development of various human disorders, including AD, and with potential use as biomarkers (36) (Table I).

miRNAs. miRNAs are a class of small ncRNAs ~20-24 nucleotides in length, which bind to the 3'untranslated region (3'UTR) of target mRNAs, leading to post-transcriptional silencing either by transcription, degradation, or translational repression. To date, >2,000 miRNAs have been identified in the human genome that play a key role in critical biological processes (37), such as development, apoptosis, signal transduction and proliferation. With respect to the brain, they are expressed in neurons and are involved in processes of neuronal differentiation, synaptogenesis and plasticity (38). According to the literature, miRNAs have a significant impact on the development of several neurological diseases and disorders, such as AD, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease (39,40).

miRNAs	(Refs.)	circRNAs	(Refs.)	piRNAs	(Refs.)	lncRNAs	(Refs.)
miR-106a	(42)	ciRS-7	(71,81-83)	piR-38240	(92)	BACE1-AS	(100-103)
miR-520c	(42)	circHOMER1	(63,84)	piR-34393	(92)	NAT-Rad18	(104,105)
miR-20a	(43,44)	circCORO1C	(63,84)	piR-40666	(92)	51A	(105,106)
miR-19	(43,44)	circRNA KIAA1586	(63,85)	piR-51810	(92)	17A	(107)
miR-106b	(43,44)	circHDAC9	(63,86)	piR-hsa-1282	(92)	BCYRN1	(105,109)
miR-20a family	(43,44)	circRNA_0000950	(63,87)	piR-hsa-23538	(92)	AD-linc2	(111)
miR-101	(45)	circNF1-419	(63,88,89)	piR-hsa-23566	(92)	HAO2-AS	(111)
miR-147	(46,47)			piR-hsa-27400	(92)	EBF3-AS	(111)
miR-124	(48-50)			piR-hsa-27725	(92)	AD-linc1	(111)
miR-339-5p	(36)			piR-hsa-28116	(92)	MAGI2-AS3	(108)
miR-195	(61)			piR-hsa-28189	(92)		
miR-107	(62)			piR-hsa-28390	(92)		
miR-9	(64)			piR-hsa-29114	(92)		
miR-144/miR-451	(66)			piR-hsa-7193	(92)		
miR-181c	(71,72)			-			
miR-146a	(73-75)						
miR-298/328	(57)						
miR-135a	(58)						
miR-135b	(59)						
miR-455-3p	(76)						
miR-485-3p	(77)						

Table I. ncRNAs in AD.

In the table, columns 1, 3, 5 and 7 contain the miRNAs, circRNAs, piRNAs and lncRNAs that are involved in AD, respectively. In a similar manner, column 2 contains the studies that are referring to each miRNA, respectively, column 4 contains the studies that are referring to each circRNA respectively, column 6 contains the studies that are referring to each piRNA, respectively, and column 8 contains the studies that are referring to each nicRNAs; circRNAs; circRNAs; piRNAs, piNAs, Piwi-interacting RNAs; lncRNAs, long non-coding RNAs; AD, Alzheimer's disease.

As regards AD, miRNAs have been shown to be involved in A β pathology by regulating APP expression and other enzymes involved in A β processing, such as β -secretase (BACE1). The first study to record the regulatory role of miRNAs in APP mRNA involved the homologous APP gene in C. elegans, APL-1, which showed its developmental regulation by miRNA let-7 (41). Subsequent studies have demonstrated that APP is regulated by miRNA in humans, where the overexpression of miR-106a and miR-520c has been shown to lead to the translational suppression of APP mRNA, thereby significantly reducing APP levels (42). In addition, miR-20a, miR-19, miR-106b, the miR-20a family (43,44) and miR-101 (45) have been shown to directly regulate APP mRNA in human cells in vitro. In addition, the effect of SNPs on miRNA binding sites in the 3'-UTR of APP mRNA in AD pathology and the risk of AD are demonstrated, where more specifically, miR-147 and miR-20a were shown to be the affected SNPs variants associated with AD in the 3'-UTR of APP mRNA (46,47). Finally, miRNAs, such as miR-124, which regulates the expression of the polypyrimidine tract-binding protein 1 (PTB1) in neuronal cell lines, have also been implicated in the regulation of the alternative splicing of APP (48-50). In general, there is significant evidence of the increased levels of exon 7 and 8 isoforms of APP in brains of patients with AD, while abnormal APP splicing has been shown to be associated with an increased A β production (51,52).

The importance of BACE1 activity in AD lies in the fact that this factor cleaves APP as the first and rate-limiting step in the formation of A β (53). In this case, miRNAs belonging to the miR-29 family have been well-studied *in vitro* and *in vivo*. The three major mature miRNAs in this family are miR-29a, miR-29b and miR-29c, the latter of which has been shown to regulate BACE1 expression by targeting the 3'-UTR in both human and mouse cell lines (54-56). The aforementioned miR-29, as well as other miRNAs that directly target BACE1 *in vitro*, such as miR-298/328 (57), miR-135a, miR-135b (59), miR-9 (60), miR-298, miR-339-5p, miR-195 (61) and miR-107 (62), are deregulated in brains affected by AD, mainly exhibited a reduced expression (36,63).

miR-9 is another miRNA involved in A β regulation, targeting calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2), thereby attenuating A β -induced synaptic toxicity (64). In addition, this miRNA appears to be involved in insulin signaling, which may be associated with an increased risk of developing diabetes in patients with AD (65). The miR-144/miR-451, finally, has been shown to regulate α -secretase ADAM10, which protects the brain from the production of A β (66).

The search and discovery of specialized and effective biomarkers for the prediction and early detection of AD is of utmost importance for the better management of symptoms and timely intervention (67,68). For this purpose, miRNAs have been proposed as promising candidate biomarkers due to their high stability under storage and handling conditions (69). Through qPCR and RNA-seq studies, it has now become possible to identify circulating miRNAs in plasma and CSF that serve as biomarkers for AD and to construct miRNA catalogs that are differentially expressed between AD and control groups to identify new biomarkers (70). Two miRNAs that have been identified as suitable biomarkers for AD are miR-181c (71,72) and miR-146a (73-75). The former was found to be downregulated in the serum and CSF of patients with AD, while the latter was found to be upregulated in brains affected by AD, as well as in the CSF of patients with AD. miR-455-3p is another potential biomarker for AD, as its level is higher in the serum of patients with AD (76), as well as miR-485-3p, whose expression was found to be upregulated in patients with AD and cell models (77).

circRNAs. circRNAs are a class of non-coding RNAs that originate primarily from the exonic regions of the genes encoding proteins. Their length is variable, while they display significant stability. These ncRNAs act as regulators of miRNAs, to which they bind through specific binding sites. circRNAs are expressed in central nervous system (CNS) tissue and tend to accumulate during the normal aging process of the brain, exhibiting susceptibility to age-related neurodegenerative diseases, such as AD. This renders them potential therapeutic targets and biomarkers for the diagnosis and treatment of AD (78-80).

A well-studied circRNA that has been linked to AD is ciRS-7. This RNA binds to the well-preserved miRNA-7, which is abundant in the human brain. More specifically, ciRS-7 contains several binding sites specific for miRNA-7 and acts as a 'sponge', thus inhibiting the functions of miRNA-7 (81). In the hippocampus of patients with AD, there is a downregulation of ciRS-7 and, consequently, of its activity as a miRNA-7 sponge, causing the latter to exhibit increased endogenous levels in AD (71,82). The upregulation of miRNA-7 has the ability to target and downregulate ubiquitin protein ligase, UBE2A, which is involved in the autophagic clearance of amyloid peptides in the brain affected by AD (83).

In addition, additional studies have reported two other circRNAs that are dysregulated in cortical areas in AD, namely circHOMER1 and circCORO1C. These ncRNAs are significantly associated with the neuropathological status of AD, as they bind two miRNAs, miR-651 and miR-105, respectively, which target both APP and SNCA42 and are associated with the pathology of AD (63,84). circRNA KIAA1586 is another circRNA that functions as a miRNA sponge, which specifically binds several miRNAs, including miR-29b, miR-101 and miR-15a, that regulate different AD-associated genes (63,85). Moreover, circHDAC9 binds miR-138 and its expression is decreased in AD, resulting in the downregulation of ADAM10 by miR-138, thus promoting A β production (63,86).

In this context, circRNA_0000950 functions as a miR-103 sponge, leading to the upregulation of the prostaglandin-endoperoxide synthase 2 and interleukin (IL)-6 and IL-1 β , as well as tumor necrosis factor (TNF), and results in an increase in neuronal cell apoptosis (63,87). CircNF1-419 is related to early neuropathological changes and interacts with dynamin-1 and adaptor protein 2 B1. Its overexpression reduces the levels of AD marker proteins, such as tau, p-tau, A β 1-42 and ApoE, and inflammatory factors, including TNF and the nuclear factor kappa B subunit 1, resulting in delayed senile dementia and AD progression (63,88,89). It is therefore clear that circRNAs may play a critical role in AD, mainly as miRNA sponges (63), where the inhibition of 'sponging miRNA activity', which translates to the upregulation of specific miRNAs, is a possible reason for the downregulation of important genes associated with the brain in AD (83).

piRNAs. piRNAs are also a class of ncRNAs that are \sim 24-34 nucleotides in length and are associated with AD, as they are involved in CNS stress and physical damage response. These ncRNAs interact with a specific family of Argonaute-associated 'MILI/MIWI' RNA-binding proteins and can affect the cytoplasmic translation of mRNAs into proteins, as well as the transcription of genes by influencing histones and the methylation of DNA (17).

In general, piRNAs appear to be overexpressed in neurodegenerative diseases (90). In the study by Qiu et al (91), 9,453 piRNAs were detected in the brains of patients with AD, and 103 piRNAs were associated with the risk of developing AD, of which 81 were upregulated and 22 were downregulated. piRNAs are considered a potential biomarker for AD due to their association with SNPs of genome-wide significant risk, such as ApoE (91). In addition, in the study by Roy et al (92), 146 piRNAs were found to be upregulated in patients with AD, while they were associated with five critical AD-related pathway targets. More specifically, the enrichment of the CYCS, LIN7C, KPNA6 and RAB11A genes was observed, regulated by four piRNAs, piR-38240, piR-34393, piR-40666 and piR-51810 (92). Finally, the analysis of two different AD datasets led to the identification of 10 overlapping, differentially expressed piRNAs, with potential as biomarkers for AD. These piRNAs include piR-hsa-1282, piR-hsa-23538, piR-hsa-23566, piR-hsa-27400, piR-hsa-27725, piR-hsa-28116, piR-hsa-28189, piR-hsa-28390, piR-hsa-29114 and piR-hsa-7193 (92).

lncRNAs. lncRNAs are another class of ncRNAs that has attracted scientific interest in the battle against neurodegenerative diseases. They are >200 nucleotides in length and can be derived from different regions of the genome, such as promoters, enhancers, introns, UTRs, overlapping or non-coding isoforms of coding genes, antisense (AS) to other transcripts and pseudogenes (93,94). Through technological advances and new laboratory techniques, a vast amount of information has been collected on the role of lncRNAs in a variety of vital biological processes (95), including transcription (96), alternative splicing (97), translation, apoptosis (98) and the cell cycle (99).

RNA sequencing methods have enabled the study of lncRNAs and their role in various diseases, including AD. In general, the majority of examples of lncRNAs whose activity has been studied belong to the subcategory of AS lncRNAs. A well-studied lncRNA with an elucidated involvement in AD is lncRNA BACE1-AS (100), which is transcribed from the complementary strand of the BACE1 gene. This lncRNA is in direct involvement with elevated levels of A β 1-42 in AD, as it drives the feed-forward regulation of β -secretase (63,101,102),

and it can bind to miR-214-3p, promoting autophagy-mediated neuronal damage through the miR-214-3p/ATG5 signaling axis in AD (103). In addition to BACE1-AS lncRNA, NAT-Rad18 (104,105) and 51A (63,105,106) are two other lncRNAs involved in AD, as the former has been shown to be upregulated in rat neurons in response to the A β peptide, and the latter affects the formation of $A\beta$ and is upregulated in AD by overlapping it with SORL1. 17A is another AS IncRNA, which is complementary to an endogenous region of the GABA receptor gene. The expression of this lncRNA leads to the production of alternative splicing transcripts of this receptor which, in combination with its upregulation in AD, leads to increased A β secretion in neuroblastoma cells (107). According to the study by Zhang and Wang (108), the expression of MAGI2-AS3 lncRNA was increased in AD cell models. This lncRNA is a regulator of cell viability in diverse diseases. Its overexpression enhances the effects of A β 25-35 on neuronal viability and neuroinflammation, and its knockdown reduces neurotoxicity and neuroinflammation, highlighting the potential role of MAGI2-AS3 in AD progression and treatment. Moreover, this lncRNA functions as an miR-374b-5p sponge, a miRNA that targets BACE1 mRNA and interacts with AKT1, RECK, WNT16, VEGFA, TACC1 and SRSF7 mRNAs, and with compounds including cisplatin, gemcitabine, tamoxifen and 5-fluorouracil (108). Long intergenic ncRNAs (lincRNAs) are another subcategory of lncRNAs that are abundant in the human genome. The primate-specific BC200 RNA (BCYRN1) is a lincRNA that may be involved in AD. This RNA was detected in the dendritic domains of neurons and its downregulation was observed during aging (63,105,109).

The critical role of lncRNAs in AD was first evidenced through the study of Zhou and Xu (110), which used an algorithm to analyze microarray data from the brain and identified ~100 lncRNAs that were altered in AD. Notably, a number of these lncRNAs were specific to the brain and could be used as biomarkers for AD, since altered expression signatures of lncRNAs provided the ability to predict AD with the same accuracy as the altered protein-coding genes, while requiring fewer lncRNAs for optimal prediction in comparison to protein-coding genes (110). In addition, in a study by Magistri et al (111), significant alterations in the IncRNA expression profile were observed in brains affected by AD, with the majority of the altered lncRNAs found to be intergenic. According to the results of that study, the AS IncRNAs, AD-linc2, HAO2-AS and EBF3-AS were dependent on neuronal activity, while AD-linc1 was upregulated in response to A β (111). These efforts are only the beginning of a long road toward the complete elucidation of the involvement of lncRNAs in AD, with further studies required to explore their potential as novel biomarkers and pharmacological targets.

In summary, the main ncRNAs that are involved in AD are classified into four categories, miRNAs, piRNAs, circRNAs and lncRNAs. These non-coding molecules function via several mechanisms, such as inhibiting or promoting the expression of genes that are associated with AD, or they can be used as effective biomarkers as their expression is altered in AD-affected brains. These two types of classification of those ncRNAs, based on their category and based on their function, are illustrated in Fig. 1.

3. Application of omics technologies in AD

The wave of 'omics' has been taking the scientific world by storm, encompassing genomics, transcriptomics, epigenomics, proteomics, metabolomics and lipidomics as part of a rounded approach (112). When faced with complex diseases, such as AD, the efficient analysis and integration of data that omics technologies yield is critical for the development of diagnostics and therapeutics (28,113,114).

Genomics. Genetics studies, genome-wide association studies (GWAS) and next-generation sequencing (NGS) technologies have helped to gain knowledge about the genes which are associated with a risk of developing AD. Genetic studies have enabled the detection of rare mutations in the genes of APP, PSEN1 and PSEN2, which are associated with the dominantly inherited early-onset AD, as well as the identification of genetic components that affect the development of the sporadic cases of the disease. In addition, genomics analysis has shown that gene-gene interaction can be a significant risk factor for the development of AD (115,116).

GWAS can lead to the identification of genes with common variants involved in various diseases. By comparing the whole genome set of genetic variants in different individuals, GWAS shed light on SNP characteristics of different diseases, highlighting the possibility of associations between the detected variants. Several genomic loci of interest have been identified that may increase the risk of an individual for developing late-onset AD, including genes involved in β -amyloid processing and clearance, immune response and inflammation, such as CR1, CD33, MS4A, ABCA7 EPHA1 and MEF2C, in the metabolism of cholesterol, such as ApoE, SORL1, ABCA7 and CLU, and in the regulation of endocytosis, such as BIN1, CD2AP, PICALM, EPHA1, SORL1 (117,118).

In addition to GWAS, NGS technologies, including whole genome sequencing and whole exome sequencing, enable the detection of rare mutations that affect complex diseases. Significant are the findings of NGS studies, which have identified new risk genes with low-frequency variants, including TREM2, which encodes the ADAM10 activation receptor expressed in myeloid cells and leads to defective α -secretory activity, phospholipase D3, UNC5C and AKAP9 (119,120).

Epigenomics. Non-hereditary epigenetic changes have the potential to equally affect the risk of developing AD. Epigenetic modifications mainly involve DNA methylation and histone modification, thereby regulating gene expression. In the case of AD, the reduced methylation of DNA is described, while at the same time, a number of genes that have been characterized in AD exhibit a high level of methylation in their promoters and in the cytosines that precede guanines (CpG islands) (121). Two large-scale epigenome-wide association studies have identified four new genetic loci, including RHBDF2, RPL13, C10orf54-CDH23 and ANK1, with differential methylation, suggesting an association with the risk of developing AD (122,123). However, histone modification studies have yielded conflicting results regarding histone acetylation levels in AD (124-127). Thus, the heterogeneity of results from epigenomics studies indicates that the further evaluation of epigenomics alterations is necessary, reflecting



Figure 1. Illustration of the main ncRNAs of each category (miRNAs, circRNAs, piRNAs and lncRNAs) that are involved in AD and their mode of function and regulation in AD, including their upregulation or downregulation and the results of this alteration in their expression levels, as well their usage as biomarkers. ncRNAs, non-coding RNAs; miRNAs/miRs, microRNAs; circRNAs, circular RNAs; piRNAs, Piwi-interacting RNAs; lncRNAs, long non-coding RNAs; AD, Alzheimer's disease.

both changes in cell composition and cell-specific changes associated with AD pathology.

Transcriptomics. Transcriptome analysis provides the ability to evaluate the number of transcripts that result through alternative splicing, novel transcript identification and long and small ncRNAs. Several studies have highlighted the critical role of ncRNAs, mostly focusing on the role of miRNAs in AD (68,128-130). As aforementioned, miRNA profiles can be investigated in several biological fluids, including blood and CSF (131), as several AD-related miRNAs have been identified following an analysis of brain tissue in patients with AD (132). The analysis of circulating miRNAs is very promising for the study of the pathogenesis of AD; however, the heterogeneity of the research results requires the participation of a greater number of patients for the study of the transcriptome.

Proteomics. Proteomics studies provide the ability to discover and record potential biomarkers and validate potential candidate proteins in various diseases. Furthermore, mass spectrometry (MS) offers effective capabilities in the analysis and determination of proteins in combination with chromatographic or other separation techniques (133).

Through a standard proteomics platform, which includes two-dimensional gel electrophoresis in combination with MS, novel candidate biomarkers were identified in the biological fluids of patients with AD, primarily involved in the processing pathway of the A β peptide (134,135). Additionally, proteomics studies have identified eight protein biomarkers among 100 candidates, the levels of which tend to decrease in cases of AD (136).

A notable finding of extensive target proteomics studies is the presence of different isoforms of A β peptides, which arise through alternative pathways of APP degradation, identifying the isoforms A β 42, A β 40 and A β 38, as well as APP α and APP β in CSF and brain tissue samples from patients with AD (137-139). In addition, a significant increase in neurogranin levels in CSF was evidenced in patients with AD (140), in contrast to a significant decrease in ApoE levels in the serum of patients with AD (141).

Through a proteomics study, the interaction of brain transglutaminase interaction with APP, huntingtin and α -synuclein was observed, thus demonstrating the role of brain transglutaminase in the formation of protein aggregates in various neurodegenerative diseases (142). In addition, oxidatively modified proteins associated with tau and A β pathology have been identified in the brains of patients with AD through redox proteomics studies (143). Lastly, the study by Chiasserini *et al* (144) yielded information on 1,315 proteins, including neurodegenerative disease biomarkers such as APP, prion protein and DJ-1.

Metabolomics. Metabolomics studies examine and focus on metabolites, which are small molecules (<1,500 Da) that are involved in numerous biological functions and vary as a result of genetic, transcriptional and protein changes, as well as environmental influences. The main techniques used in metabolomics studies are MS and nuclear magnetic resonance spectroscopy (28).

Significant alterations in the abundance of metabolites in the biological fluids of patients with AD have been observed. According to a previous study, a change in eight metabolites was detected, including acylcarnitine, sphingomyelins and glycerophospholipids, which were significantly increased in the CSF of patients (145). Furthermore, the quantitative analysis of 17 metabolites led to the observation of a significant increase in glycine and S-adenosylhomocysteine levels, with a concomitant decrease in the levels of S-adenosylmethionine in the CSF of patients diagnosed with AD (146). Similarly, shifts of 13 key metabolites were recorded at different stages of AD by researchers at the Alzheimer Disease Metabolomics Consortium, exhibiting associations with the CSF AB42 and t-tau/A β 42 ratio, with cognitive function or brain atrophy (147). Finally, through two previous studies, 10 and 24 plasma lipids were detected to predict the conversion of healthy individuals to patients with AD (148,149).

Big data analysis. The development and analysis of a wealth of big data have been accompanied by advances in bioinformatics and computational programming (150,151). An example of a large-scale omics platform for AD is the Dominantly Inherited Alzheimer Network (DIAN) Central Archive (https://dian. wustl.edu/), which provides all the cognitive information, biomarkers and brain imaging information for AD, while allowing the data analysis of different domains and wide access to them (28).

The analysis and interpretation of big data are one of the most important issues of concern to the scientific community, with the main goal of analyzing the cross-platform association between data from different omics technologies. Furthermore, computational biology pipelines can aid the development of antibody-interacting drugs against neurodegenerative diseases, such as AD, a rapidly emerging field of increasing medicinal interest (152). Big data allow for rapid advances in personalized medicine; however, the heterogeneity and variability of omics data hinder the application of omics science (28).

Alterations in genomics, proteomics, epigenomics, transcriptomics, metabolomics and lipidomic levels may be associated with the development of neurodegenerative diseases, such as AD, worldwide. The development of computational tools for big data analysis based on phenotypic analytical prediction models remains a challenge for de novo drug design or effective drug repurposing (28). Deep learning methods can provide a potential solution to this challenge, allowing the exploitation of multi-omics data and helping to form an accurate representation of AD patients. This approach can allow researchers to develop effective personalized treatments and early diagnostic tools, as well as guide the design or repurposing of drugs in complex neurodegenerative pathologies (153). An integrative multi-omics approach, as previously described by Clark et al (154), yielded promising results, identifying novel molecular and pathway alterations which are related to the pathophysiological processes of AD. A notable strength of this approach is the identification of the main axes of inter-individual heterogeneity, critical for the development of tailored therapeutic interventions (154).

4. Conclusions and future perspectives

AD is a multifactorial disease, which in addition to the genetic and hereditary background, also occurs sporadically, due to epigenetic factors, which include ncRNAs. These molecules are implicated in a wide range of cellular processes and human diseases, including neurodegeneration. Several studies at various levels, including the molecular, cellular, physiological and epidemiological ones, have detected a rising number of ncRNAs involved in AD. As aforementioned, they participate in the three major pathogenic traits of AD that include the formation of A β plaques, the phosphorylation of tau, and the establishments of an inflammatory zone. In order to identify these ncRNAs, various studies have examined both cultured cell models and biological samples, such as brain, CSF and serum. In this context, their identification can be managed using sensitive methods of RNA analysis, including reverse transcription followed by conventional PCR or qPCR analyses for the survey of individual RNAs, or RNA-sequencing and analysis by microarray for the survey of larger panels of RNAs. These methods would be particularly useful if the diagnostic and prognostic ncRNAs were tested in tissues and fluids easily accessible, such as blood, urine and some epithelia (129).

In conjunction with these non-coding biomarkers, omics technologies are a promising tool for the study of AD pathology and patient variation, providing the ability to combine and correlate different types of data, the analysis of which could lead to personalized therapy and *de novo* development of more effective drugs. The integration of omics and clinical data and the development of novel experimental and computational strategies are essential in multifactorial diseases, such as AD. In these cases, high-throughput omics technologies can lead to the better understanding of the pathological changes in the brain, to the development of more accurate tools for the early diagnosis and prediction of the disease, to the development of new drugs, as well to the selection of the most beneficial and personalized therapies.

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Authors' contributions

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