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Review Article

Long Non-Coding RNAs in Alzheimer's Disease: Mechanistic Insights, Early Diagnostic Biomarkers, and Therapeutic Horizons

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Abstract

Alzheimer's Disease (AD) is the leading cause of dementia worldwide, yet its molecular complexity continues to hinder early diagnosis and the development of disease therapy approaches. Long non-coding RNAs (lncRNAs), a diverse class of heterogeneous transcripts exceeding 200 nucleotides with limited protein-coding potential, have emerged as key regulators of neuronal development, synaptic function, epigenetic regulation, and neuroimmune homeostasis. Growing evidence demonstrates that dysregulated lncRNA expression contributes to multiple pathological processes of AD, including amyloid-β production, tau hyperphosphorylation, neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic impairment, and neuronal loss. Notably, lncRNAs exert these effects through chromatin remodeling, transcriptional and post-transcriptional regulation, and Competing Endogenous RNA (ceRNA) networks that coordinate interactions with miRNAs and mRNAs. Their remarkable tissue specificity, dynamic expression patterns, and detectability in peripheral blood have also placed lncRNAs as promising non-invasive biomarkers for the early diagnosis of AD. In parallel, functional studies have identified several lncRNAs, including BACE1-AS, MALAT1, NEAT1, BDNF-AS, GAS5, BC200, and FMR1-AS1, as potential therapeutic targets capable of modulating key neurodegenerative pathways. In this Review, I summarize the current understanding of lncRNA biogenesis and classification, discuss the molecular mechanisms by which lncRNAs regulate AD pathogenesis, and critically evaluate their emerging diagnostic and therapeutic potential. Altogether, lncRNAs represent a promising new frontier for precision medicine in AD, offering opportunities to improve early detection while enabling the development of more targeted and effective therapeutic strategies.

Keywords: Aβ peptide; Alzheimer's disease; Biomarker; LncRNAs; Neuroinflammation; Tau protein

Introduction

Surprisingly, ~88% of the human genome is non-coding sequences, of which a huge part of them are repetitive junk DNA sequences (~59%) and introns [1]. However, the data received from the Encyclopedia of DNA Elements (ENCODE) project confirms that ~80% of the human genome is involved in some key biochemical pathways, proving the functionality of the non-coding part of mammalian genomes [2]. In general, non-coding RNAs (ncRNAs) are divided into two groups, including small and long ncRNAs (lncRNAs). Small ncRNAs (sncRNAs) have less than 200 nucleotides in lengths and include Micrornas (miRNAs), Small Interfering Rnas (siRNAs), Small Nucleolar Rnas (snoRNAs), and Piwi-Interacting RNAs (piRNAs) [3]. The first lncRNA was discovered in 1990 in the human genome as one of the maternally imprinted transcripts known as H19. This molecule is 2.3 kb in size and transcribed by RNA polymerase II and spliced and polyadenylated like the other mRNAs, except it lacks coding potential [4]. Afterwards, Xist was identified and presented the same features as H19, while it is ~19 kb in length. Since then, it has been accepted that ncRNAs with more than 200 nucleotides are categorized as lncRNAs [5]. Of note, the discovery of lncRNAs, even in the genomics era, was not fast because of their low cellular abundance, cell type- and time-specific presence, wide-range biochemical mechanisms, and technology limitations. This resulted in the identification of only a few lncRNAs until the 2000s [4]. Our knowledge of the genome and its transcriptomic complexity was remarkably expanded by advances in array and sequencing technologies, particularly following the launch of the ENCODE project in 2007, which enabled the systematic cataloging of non-coding elements in the human genome and propelled large-scale annotation of lncRNAs [6]. In this context, the ENCyclopedia of DNA Elements (GENCODE) database has catalogued more than 35,885 lncRNA genes by June 2026, while it is estimated to have been the existence of over 100,000 lncRNA genes in the human genome [7]. The lncRNAs can be found in all aspects of an organism's life, and it is estimated that the number of lncRNAs outstrips that of protein-coding genes in humans. It is revealed that lncRNAs present a variety of functions in both prokaryotic and eukaryotic organisms [3]. In mammals, they regulate cell differentiation and development, cell division, genome architecture, immune responses, and the cell cycle. It should be noted that lncRNAs are highly involved in regulating gene expression at transcriptional and post-transcriptional levels [8]. LncRNAs might play a crucial role in some physiological processes such as DNA damage response, cytokine expression, cholesterol biosynthesis and homeostasis, inflammation, neuropathic pain, and endotoxic shock [3,9]. These elements are also the main mediators in synapse function and learning, glucose metabolism, transport pathways, and signal transduction pathways [10,11]. Of note, these elements have been associated with ribozymes and cell membrane integrity [12]. It is reported that changes in lncRNA expression levels have contributed to some disorders such as cardiovascular and

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neurodegenerative diseases and cancer as well. Interestingly, many lncRNAs present cell type- and tissue-specific expression patterns, of which ~40% are expressed in brain cells, confirming their important roles in brain development, neuronal function, and the pathogenesis of neurological disorders [13]. Alzheimer's Disease (AD) is the most prevalent irreversible neurodegenerative disorder defined by impairment in cognition, behaviour, and normal functions, often beginning with the loss of memory of recent activities. In addition, many patients may suffer seizures, confusion, muscle weakness, poor coordination, sensory loss, and paralysis [14]. In fact, AD is a progressive, neurodegenerative, and chronic condition that begins with extracellular amyloid beta (Aβ) peptide accumulation, intracellular Neurofibrillary Tangles (NFTs) aggregation, subsequent Tau protein aggregation and abnormal hyperphosphorylation, and deregulation of glial cells, which culminate in loss of neuronal homeostasis and neuroinflammation [15]. It is believed that the pathology of AD first starts in the medial temporal lobe and then spreads to the other parts of the temporal cortex and finally extends to the frontal lobes, in the latest stages. These phenomena can result in disrupting mitochondrial functions, cell traffic pathways, synaptic signaling, and endoplasmic reticulum and Golgi apparatus integrity [16]. Over 5 million patients suffer from AD, while this statistic is estimated to double in Europe and triple in other communities by 2050 [17]. It should be highlighted that some parameters, including aging, depression, hypertension, genetic variations, oxidative stress, diabetes, and vitamin deficiencies, might increase the progression of AD [18]. Current AD diagnosis approaches mainly rely on the assessment of neuropsychological parameters such as the concentration of Aβ peptide and hyperphosphorylated protein levels, and Positron Emission Tomography (PET) imaging techniques, which are effective after the onset of cognitive symptoms. Currently available treatment strategies for patients with AD are the use of cholinesterase inhibitors and NMDA receptor antagonists, which mainly manage the symptoms without inhibiting disease progression [19]. Accordingly, the elucidation of molecular underpinnings to explore novel therapeutic targets for efficient prevention and intervention of AD is highly demanding. Several reports have identified the contribution of lncRNAs in AD-related dysfunctions such as Aβ production, synaptic impairments, and oxidative stress [20]. Moreover, lncRNAs are significantly involved in the regulation of neuroinflammation and tau protein, and modulation of the expression of APP glycoprotein in AD [21]. In this context, lncRNAs exhibit promising potential for biomarkers and drug discovery for patients with AD.

Herein, the biology and biogenesis of lncRNAs will be comprehensively overviewed to shed light on their potential to explore biomarkers for the early diagnosis of patients with AD. Since the expression of many lncRNAs is enriched in some specific cells and tissues in the brain, these elements might present efficient and accurate therapeutic potential with high specificity and minimal side effects.

Biogenesis of lncRNAs

Early studies demonstrated that lncRNAs share several fundamental characteristics with mRNAs. Similar to mRNAs, the majority of lncRNAs are transcribed by RNA polymerase II (Pol II) from genomic loci enriched with active chromatin states such as histone H3 lysine 4 trimethylation (H3K4me3) at promoters and undergo canonical RNA processing phenomena including 5′ capping with 7-methylguanosine (m^7G), splicing, and 3′ polyadenylation [22]. Unlike mRNAs, lncRNAs do not have conserved open reading frames (ORFs) and have strong tissue specificity, and lower abundance [23]. Moreover, the transcription of lncRNAs is generally less efficient compared to that in protein-coding genes, resulting in lower expression levels, more cell-type specificity, and more transcriptional processes [24]. It should be noted that several characteristics of lncRNAs, including cis-regulatory capacity, the ability to template nucleic acid polymerization or assembly, and specialized 3′-end processing, are generally absent from mRNAs. Nevertheless, lncRNA biogenesis is regulated through distinct mechanisms at multiple stages of transcription, processing, localization, and degradation [25]. Several reports confirmed that lncRNA genes exhibit a higher enrichment of H3K27ac and are significantly repressed (not existing in mRNAs) through distinct chromatin remodelling complexes including Swr1, Rsc, Isw2, and Ino80. Moreover, transcription initiation from divergent promoters is frequently associated with antisense lncRNA production and is influenced by chromatin modifications such as H3K56ac and phosphorylation of Pol II Tyr1 [22,26,27]. Moreover, divergent transcription is further enhanced by the SWI/SNF chromatin-remodeling complexes and suppressed by Chromatin Assembly Factor-1 (CAF-1), highlighting the importance of chromatin architecture in controlling lncRNA expression. The lncRNA transcriptional elongation step is highly influenced by DICER1 and MYC compared to that of mRNA, regulated solely by MYC [22]. A major distinction between mRNA and lncRNA biogenesis lies in the competition between co-transcriptional splicing and premature cleavage/polyadenylation [28]. In protein-coding transcripts, Small Nuclear Ribonucleoprotein (U1 snRNP) binding sites suppress proximal Polyadenylation Signals (PASs), allowing Pol II to continue elongation and produce full-length mRNAs. By contrast, many lncRNAs are enriched in proximal PASs and depleted of U1 recognition sites, promoting early transcription termination and generating shorter, less abundant transcripts. In fact, the distribution of U1 snRNP recognition sites and PASs differs across bidirectional promoters, with the U1-PAS axis promoting productive splicing of sense mRNAs while favoring transcript cleavage and polyadenylation in the divergent antisense direction [22,28]. Unlike mRNAs, which are predominantly exported to the cytoplasm for translation, many lncRNAs are retained within the nucleus through interactions with chromatin, nuclear bodies, or RNA-binding proteins, whereas others are transported to the cytoplasm to regulate mRNA stability, translation, or cellular signaling pathways [29]. Unlike mRNAs, which are degraded in the cytoplasm by decapping and 5′ to-3′ exonuclease digestion using Xrn1, many lncRNA transcripts undergo nuclear exosome or cytoplasmic RNA decay mechanisms [30,31]. In the nucleus, lncRNAs are subject to the TRAMP and the Nrd1-Nab3-Sen1 complexes, causing the addition of short poly(A) tails and early transcriptional termination [32]. In addition to Xrn1, some cytoplasmic lncRNAs are degraded through the NMD protein UPF1 [33]. It should be noted that several characteristics of lncRNAs, including cis-regulatory capacity, the ability to template nucleic acid polymerization or assembly, and specialized 3′-end processing, are generally absent from mRNAs [4,34]. Notably, during transcription, lncRNAs undergo extensive post-transcriptional regulation affecting their stability, intracellular localization, and biological function [35]. Compared with protein-coding genes, lncRNA loci frequently exhibit unique chromatin signatures, divergent promoter activity, lower transcriptional efficiency, and less efficient co-transcriptional processing, resulting in a diverse population of transcripts with varying exon–intron structures, transcription start sites, and polyadenylation

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patterns [12,36]. Similar to most mRNAs, the majority of human lncRNAs undergo canonical cleavage and polyadenylation to process their mature 3′ ends. However, a few lncRNAs, such as Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) and Nuclear-Enriched Abundant Transcript 1 (NEAT1), instead undergo RNase P-mediated 3′-end processing, in which the RNase P ribonucleoprotein complex cleaves the precursor transcripts to produce mature non-polyadenylated RNAs [37]. Furthermore, the tRNA-like structures in MALAT1 and NEAT1 are cleaved, resulting in the formation of mature lncRNA transcripts [38]. Following transcription and processing, export-competent lncRNAs are transported from the nucleus to the cytoplasm through the canonical mRNA export pathway mediated by the NXF1-NXT1 heterodimer, which is recruited by the TREX complex. These lncRNAs are actively involved in post-transcriptional regulation of gene expression [39]. In addition, lncRNAs frequently undergo specialized processing events, including alternative splicing, alternative polyadenylation, RNA editing, and epitranscriptomic modifications such as N^6-methyladenosine (m^6A), which contribute to their functional diversity [40]. Their turnover also differs from that of in mRNAs, as numerous lncRNAs are preferentially degraded by nuclear RNA surveillance pathways, including the RNA exosome, although cytoplasmic decay mechanisms such as nonsense-mediated decay also contribute to the elimination of specific lncRNA transcripts [41]. These multiple regulatory layers generate highly dynamic, cell type-, tissue-, developmental stage-, and disease-specific lncRNA expression profiles, enabling lncRNAs to function as versatile regulators of gene expression in both physiological and pathological processes [42]. Another prevalent alternative splicing pathway is reported for lncRNAs, which frequently produce multiple transcript isoforms from a single genomic locus. Accordingly, lncRNAs undergo various post-transcriptional modifications, including adenosine-to-inosine (A-to-I) RNA editing and N6-methyladenosine (m6A) methylation, which influence their stability, subcellular localization, and biological functions [43,44]. Unlike most mRNAs, many lncRNAs display characteristic nuclear or cytoplasmic localization patterns, which are largely determined by RNA sequence, structure, and interactions with RNA-binding proteins (Figure 1) [45,46].

Classification of lncRNAs

LncRNAs can be categorized based on the location relative to the coding gene, the strand of genes used for transcription, and the direction of transcription [47]. Based on the position of transcription, lncRNAs divide into seven groups, including "intergenic, intronic, exonic, and overlapping lncRNAs" [3]. Intergenic lncRNAs are transcribed from genomic regions located between two protein-coding genes and are mainly situated at least 1 kb away from the nearest coding gene without overlapping with coding sequences. This type of lncRNA regulates gene expression through diverse mechanisms and participates in numerous cellular processes, including cell proliferation, differentiation, apoptosis, and development [48,49]. Intronic lncRNAs are mainly transcribed from the intronic regions of protein-coding genes without overlapping with exons. They are often co-expressed with their host genes and contribute to the regulation of gene expression through diverse molecular mechanisms [3,50]. The exonic lncRNAs contain retained introns and are transcribed solely from exonic regions. This type of lncRNA overlaps partially or completely with the exonic regions of protein-coding genes [51]. Overlapping lncRNAs are transcribed from genomic regions that overlap one or more introns or exons of protein-coding genes. They influence gene expression through multiple mechanisms, such as transcriptional interference, chromatin remodeling, and the regulation of RNA processing and stability [52]. It should be noted that some lncRNAs are encoded from the strand of protein-coding genes (so-called sense lncRNAs) and might share exonic or intronic regions with their corresponding transcripts. Sense lncRNAs can regulate gene expression through RNA splicing modulation, RNA-RNA interactions, and transcriptional interference [47]. Antisense lncRNAs are transcribed from the opposite strand of protein-coding genes and often overlap exonic or intronic regions, resulting in natural antisense transcripts. These lncRNAs are the second most prevalent category in humans and the largest type across eukaryotes. This group of lncRNAs is highly involved in genomic regulation processes, chromatin remodeling, mRNA stability, splicing, and translation in eukaryotic organisms and humans as well [53]. Moreover, lncRNAs could be categorized as divergent, convergent, and enhancer lncRNAs based on the direction of transcription. In divergent lncRNAs, the shared or adjacent promoters and coding genes are in proximity and located in a head-to-head structure, while convergent lncRNAs show the opposite pathway [54]. In Enhancer lncRNAs (eRNAs), transcription begins from active enhancer regions, in which they are often short-lived, non-polyadenylated, and transcribed from enhancer loci in a bidirectional manner. These lncRNAs function as gene expression regulators and enhancer-promoter looping facilitators. In some cases, lncRNAs are transcribed from enhancer regions, giving rise to Enhancer RNAs (eRNAs) that facilitate transcriptional activation of target genes [55].

Functions of lncRNAs

LncRNAs are capable of participating in gene regulation through interaction with DNA, RNA, and proteins, which enables them to function as molecular guides, scaffolds, decoys, and signaling molecules [56]. In this context, lncRNAs contribute to various biological processes, including cell proliferation, differentiation, apoptosis, immune responses, metabolism, neuronal development, and maintenance of tissue homeostasis [35,57]. One of the main roles of lncRNAs is the regulation of chromatin architecture and epigenetic modifications [58]. Many nuclear lncRNAs might act as molecular guides by using chromatin-remodeling complexes and epigenetic regulators such as Polycomb Repressive Complex 2 (PRC2), SWI/SNF chromatin-remodeling complexes, and lysine-specific demethylase 1 (LSD1) to specific genomic loci, allowing to alter chromatin accessibility and concontrol of gene expression [59,60]. Moreover, lncRNAs can modulate histone modifications by interacting with histone acetyltransferases, histone deacetylases, histone methyltransferases, and histone demethylases [61]. In addition, several lncRNAs regulate DNA methylation by recruiting DNA methyltransferases (e.i., DNMT1, DNMT3A, and DNMT3B) or Ten-Eleven Translocation (TET) enzymes to target loci, leading to stable epigenetic changes that control cellular identity, differentiation, and gene expression. These elements can function as transcriptional activators by interacting with transcription factors, transcriptional co-activators, or the mediator complex to facilitate the recruitment of RNA polymerase II and promote transcription of target genes [62,63]. Conversely, other lncRNAs recruit transcriptional repressors or chromatin-silencing complexes to suppress gene expression [64]. In some instances, transcription of a lncRNA itself interferes with the transcription of neighboring or overlapping genes, a phenomenon known as transcriptional interference. Through these mechanisms, lncRNAs integrate extracellular signals with intracellular regulatory

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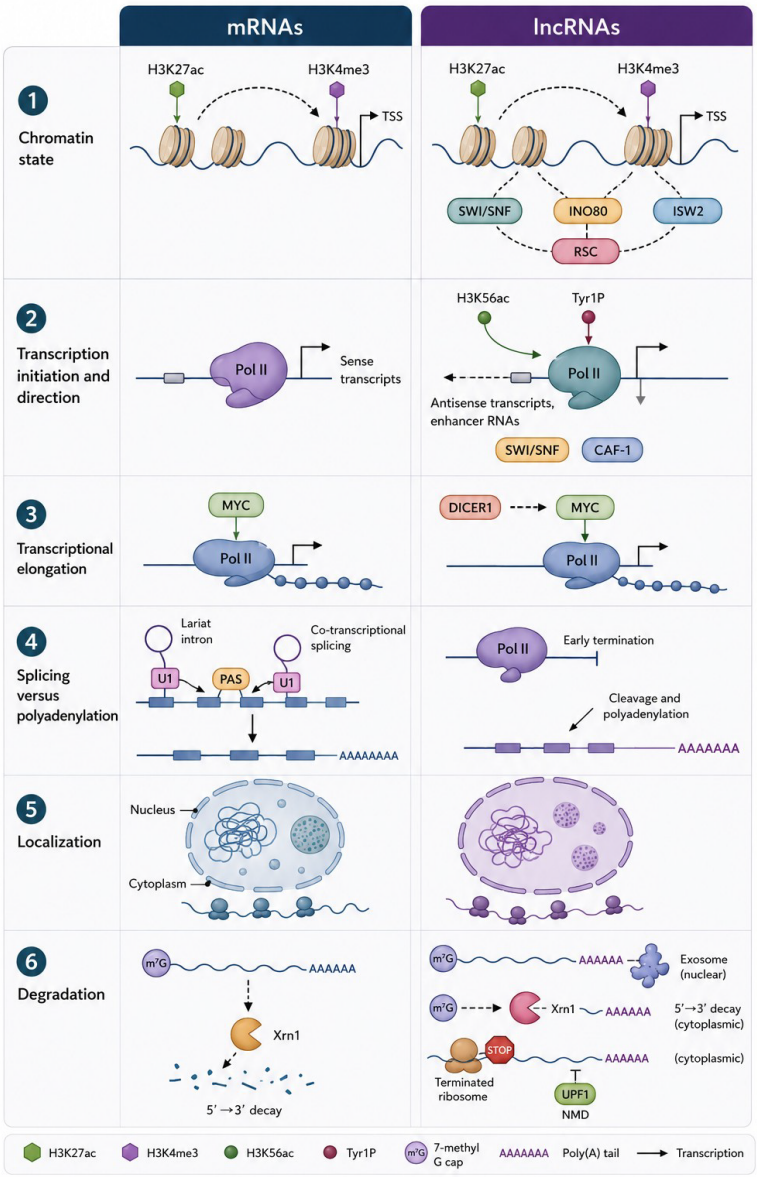


Figure 1: Distinctive features of the molecular mechanisms controlling the biogenesis of lncRNAs compared with mRNAs. These two classes of transcripts share several aspects of transcriptional regulation similarities but exhibit important differences in chromatin organization, transcriptional initiation and elongation, RNA processing, subcellular localization and degradation. In chromatin state (a): both mRNAs and lncRNAs can originate from regions marked by active chromatin modifications, including H3K27ac at enhancers and H3K4me3 near Transcription Start Sites (TSSs). The transcription of certain lncRNAs is additionally influenced by ATP-dependent chromatin-remodelling complexes, including SWI/SNF, ISWI, RSC and INO80. In the transcriptional initiation and direction step (b), Pol II initiates transcription of both mRNAs and lncRNAs, whereas lncRNA transcription frequently occurs in antisense or enhancer-associated orientations. Features of Pol II, including phosphorylation of its C-terminal domain by Tyr1, can differ between coding and non-coding transcription. In the transcriptional elongation step (c), the transcriptional elongation of both RNA classes involves Pol II and transcriptional regulators such as MYC; in lncRNA transcription, factors including DICER1 and MYC can influence transcriptional activity. In the splicing versus polyadenylation (d), many lncRNAs undergo co-transcriptional splicing, whereas alternative processing pathways can favour transcriptional termination and cleavage at polyadenylation sites. Notably, the snRNA-polyadenylation axis contributes to the balance between transcriptional elongation and premature termination. Subcellular localization (e). Whereas mature mRNAs are predominantly exported to the cytoplasm for translation, lncRNAs display diverse localization patterns and can accumulate in the nucleus, chromatin-associated compartments, subnuclear domains, or cytoplasm. In the degradation step, both mRNAs and lncRNAs are subject to regulated RNA turnover through nuclear and cytoplasmic degradation pathways. Unlike mRNAs, which are primarily degraded in the cytoplasm through decapping and Xrn1-mediated 5′-3′ exonucleolytic decay, lncRNAs can undergo distinct nuclear and cytoplasmic degradation pathways. Nuclear lncRNAs are targeted by the TRAMP and Nrd1-Nab3–Sen1 complexes, which promote short poly(A)-tail addition and premature transcription termination, whereas cytoplasmic lncRNAs can be degraded by Xrn1 or through NMD. This figure adopted from the following reference [22].

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networks, ensuring precise temporal and spatial control of gene expression during development, cellular adaptation, and stress responses [64]. Following transcription, lncRNAs continue to regulate gene expression at multiple post-transcriptional levels, in which the main mechanism is Competing Endogenous RNAs (ceRNAs). In this approach, the lncRNAs sequester miRNAs through complementary base pairing, thereby preventing miRNA-mediated repression of target mRNAs. This ceRNA network increases the stability and translational efficiency of numerous protein-coding transcripts [65]. In addition, lncRNAs directly interact with mRNAs and RNA-binding proteins to either stabilize transcripts or promote their degradation, regulating mRNA turnover [66]. Several lncRNAs also influence alternative splicing by interacting with spliceosomal components and splicing factors, leading to the generation of distinct protein isoforms with diverse biological functions [67]. Furthermore, cytoplasmic lncRNAs regulate protein synthesis by interacting with ribosomes, translation initiation factors, or translational repressors, enabling dynamic control of protein production in response to cellular demands [68]. Many lncRNAs act as molecular scaffolds that simultaneously bind multiple proteins, facilitating the assembly of functional protein complexes and coordinating intracellular signaling pathways. Others function as molecular decoys by sequestering transcription factors, RNA-binding proteins, or other regulatory molecules, preventing their interaction with physiological targets [69]. Certain lncRNAs also recruit enzymes, including kinases, phosphatases, ubiquitin ligases, and chromatin-modifying proteins, to specific genomic regions or protein substrates, conferring temporal and spatial specificity to enzymatic reactions. These protein-mediated interactions enable lncRNAs to fine-tune diverse cellular signaling pathways and coordinate complex regulatory networks [70]. In this sense, lncRNAs play fundamental roles in cell proliferation, cell-cycle progression, differentiation, apoptosis, senescence, immune regulation, inflammatory responses, mitochondrial function, energy metabolism, synaptic plasticity, neuronal communication, and maintenance of genomic stability through DNA damage response pathways [42,56]. Importantly, the biological functions of lncRNAs are strongly influenced by their subcellular localization. Nuclear lncRNAs predominantly regulate chromatin organization, transcription, RNA processing, and nuclear architecture, whereas cytoplasmic lncRNAs primarily control mRNA stability, translation, signal transduction, and miRNA activity [71]. This compartment-specific distribution enables lncRNAs to coordinate gene expression across multiple regulatory layers and rapidly adapt cellular programs to physiological and pathological stimuli (Figure 2) [12].

Pathogenesis and Progression of AD

AD occurs due to the deposition of Aβ and neurofibrillary tangles in the hippocampus [72]. It is reported that the accumulation of Aβ plaques begins initially in the basal, temporal, and orbitofrontal neocortex parts of the brain and subsequently develops in the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia, and even in the mesencephalon and cerebellar cortex [73]. This accumulation of Aβ plaque triggers the formation of tau protein in the coeruleus and transentorhinal and entorhinal regions of the brain, and in the advanced stages it extends to the hippocampus and neocortex [74]. In this context, there are two models, such as the amyloid and tau cascades, for explaining the pathogenesis of AD.

Amyloid cascade model

In the amyloid cascade model, Amyloid Precursor Protein (APP) is Abnormally cleaved by β-Secretases (BACE1) and γ-secretases to generate insoluble poisonous Aβ peptides, particularly Aβ40 and Aβ42 isoforms [75]. APP is a type I integral plasma membrane protein that is normally cleaved by secretases to generate some soluble peptides such as Secreted Amyloid Precursor Protein (sAPP) and C-Terminal Fragment 83 (CTF83) required for neuronal functions [76]. Insoluble Aβ peptide isoforms are then oligomerized to produce insoluble extracellular plaque cores, which diffuse into synaptic clefts and disrupt synaptic signaling and trigger a cascade of neurotoxic events [77]. Then, the oligomerized Aβ peptides are polymerized into insoluble amyloid fibrils and are deposited into plaques. This polymerization process causes the activation of some kinases such as GSKβ and CDK-5, hyperphosphorylation of tau protein, and further polymerization into insoluble NFTs [78]. Subsequently, the accumulation of amyloid plaques and neurofibrillary tangles is accompanied by the recruitment of microglia around the plaques, leading to microglial activation and the induction of a localized inflammatory response that contributes to neuronal dysfunction and neurotoxicity [79]. It should be noted that some specific proteins/receptors such as PrPC, EphB2, EphA4, NMDAR, and LiLRB2 interact with Aβ to contribute to synaptotoxicity. Accordingly, the amyloid cascade hypothesis proposes that Aβ accumulation initiates a series of pathological events, including neurofibrillary tangle formation, cell death, vascular dysfunction, and ultimately dementia [80]. Of note, impaired clearance through the glymphatic system, blood-brain barrier dysfunction, and reduced enzymatic degradation contribute to the excessive production of Aβ [81]. It should be highlighted that the dysregulation of Aβ metabolism, such as its breakdown and transportation, might contribute to the pathogenesis of AD (Figure 3) [82].

Tau protein hyperphosphorylation model

The presence of NFTs composed of abnormal accumulation of tau protein is considered another hallmark of AD pathogenesis. NFTs are intracellular aggregates of hyperphosphorylated tau protein that form paired helical and straight filaments within the cytoplasm of neurons, including their cell bodies and neuronal processes [83,84]. Moreover, the tau protein contains a microtubule-binding domain that assembles with tubulin to produce the mature form of microtubules. This protein is highly functional in the integrity and stability of microtubules, nutrient transport, and proper cellular activities in neurons [85]. Tau hyperphosphorylation promotes its dissociation from microtubules, leading to microtubule destabilization and the subsequent misfolding, oligomerization, and aggregation of tau into insoluble Paired Helical Filaments (PHFs) and Straight Filaments (SFs), which ultimately assemble into NFTs [86]. This results in the retraction of synaptic cells, the impairment of axonal transport, and aberrant neurites in patients with the early stage of AD. Furthermore, the lysine succinylation, tyrosine phosphorylation, and lysine acetylation of hyperphosphorylated tau weaken its interaction with microtubules, leading to microtubule destabilization, impaired axonal transport, and neuronal dysfunction [87]. Notably, the deposition of NFTs activates some inflammatory pathways within the brain in which microglia undergo hypertrophy and ramify in NFT-rich regions that exacerbate neuronal injury [72]. Alternatively, reports identified that tau protein aggregates can present prion-like properties by inducing the misfolding and aggregation of native tau in neighboring neurons, which enables their progressive propagation and spread across the brain (Figure 3) [77].

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In addition to the above-mentioned models, neuroinflammation, Oxidative Stress (OS), mitochondrial dysfunction, and genetic factors also contribute to the pathogenesis of AD [72]. Chronic inflammation or neuroinflammation is significantly implicated in AD progression, which is characterized by the activation of microglia and astrocyte cells and the release of some pro-inflammatory molecules, including chemokines, cytokines, Reactive Oxygen Species (ROS), and complement proteins [88]. Furthermore, this dysregulated inflammation and immune responses contribute to disrupting neuronal cells and exacerbate the progression of AD. Accumulating evidence indicates that several microglial receptors, including RAGE, LRP1, CD33, TLR4, CR1, CD36, and particularly Triggering Receptor Expressed On Myeloid Cells 2 (TREM2), recognize or regulate responses to Aβ and mediate microglial activation through intracellular signaling pathways, most notably the DAP12-SYK pathway, thereby promoting phagocytosis and Aβ clearance. Dysregulation of these responses might result in inadequate Aβ clearance and trigger neuroinflammation [72,89]. It is confirmed that the modulation of TREM2 may affect the expression of Aβ and plaque-related macrophages. Dysfunctional microglia also exhibit impaired phagocytic activity, reducing their capacity to eliminate toxic Aβ aggregates and thereby accelerating the progression of AD [90]. Dysregulated LRP1-mediated interactions with Aβ-ApoE complexes have been implicated in astrocyte dysfunction, leading to astrocyte activation and the subsequent release of pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, and IL-8, which contribute to neuroinflammation, excitotoxicity, and progressive neuronal injury [72]. Furthermore, oligomeric Aβ (oAβ) can activate astrocytes via multiple receptors, including AQP4, CD47, CaSR, α7-nAChR, and CD36, thereby amplifying neuroinflammatory signaling and exacerbating neuronal damage [91]. Notably, OS and mitochondrial dysfunction play inevitable roles in the pathogenesis and progression of AD. Excessive production of ROS damages nucleic acids, proteins, and lipids, while mitochondria are highly susceptible to oxidative damage, which impairs ATP production and calcium buffering and triggers apoptosis in neurons [92]. It is confirmed that some antioxidant-related enzymes such as glutathione peroxidase, catalase, and Superoxide Dismutase (SOD) are often disrupted in patients with AD, leading to highly increased oxidative stress [72]. It should be noted that Aβ peptide aggregates can accumulate within the mitochondrial membrane space and directly disrupt mitochondrial functions, leading to reduce the production ATP and the increase of ROS generation. These metabolic disturbances interact with Aβ and tau pathology to create a vicious cycle of cellular dysfunction [92]. In addition, the abnormal phosphorylation and accumulation of tau protein impair mitochondrial transport across neuronal axons, which leads to the generation of OS and energy deficits. In parallel, cerebrovascular abnormalities, including blood-brain barrier breakdown, cerebral hypoperfusion, and impaired glymphatic clearance, reduce nutrient delivery and hinder the removal of toxic proteins, thereby promoting neurodegeneration (Figure 3) [93].

Diagnostic and therapeutic potentials of lncRNAs in AD

It is increasingly reported that lncRNAs are involved in different pathological stages of AD through Aβ production, histone modification, tau hyperphosphorylation, neurogenesis, mitochondrial dysfunction, glucose dysregulation, neuroinflammation, insulin resistance, synaptic dysfunction, and oxidative stress (Figure 3) [94]. Moreover, lncRNAs control gene expression epigenetically in patients with AD through altering histone methylation and DNA modification. These elements contribute significantly to modulating gene expression levels in the central nervous system, in which their dysregulation might result in neuronal death in neurodegenerative disease [95]. Furthermore, lncRNAs can epigenetically interact with miRNAs and mRNAs to generate a ceRNA network to regulate gene expression, mRNA stability, and subsequently the development and progression of AD. It is reported that lncRNAs influence the biology of AD by modulating histone modification, mRNA degradation, and alternative transcript splicing (Figure 2) [94].

Involvement of lncRNAs in Aβ peptide production

It is found that the lncRNA named BDNF-AS is highly increased in the bloodstream of patients with AD, resulting in neurotoxic effects, impairment of cognitive abilities, and the progression of the disease. Further findings confirmed that the induction of BDNF-AS caused the enhancement of BACE1 expression via the inhibition of miR-9-5p, culminating in the formation of amyloid plaques [96]. The BACE1 Antisense Transcript (BACE1-AS), a highly conserved lncRNA approximately 2 kb in length, is significantly upregulated in patients with AD, where it enhances the stability and expression of BACE1 mRNA, thereby promoting Aβ1-42/Aβ1-40 production and accelerating the progression of AD. It should be noted that lncRNAs can act as sponges for miRNAs to sequester them and modulate their activity [97]. In this sense, lncRNAs function as ceRNA networks to sponge target miRNAs and thereby inhibit their functionality. Accordingly, BACE1-AS can link to miR-485-5p and BACE1 mRNA to generate a ceRNA network where it inhibits the expression of miR-485-5p, increasing the expression level of the BACE1 gene [98]. Silencing of BACE1-AS alleviates Aβ-induced neuronal injury

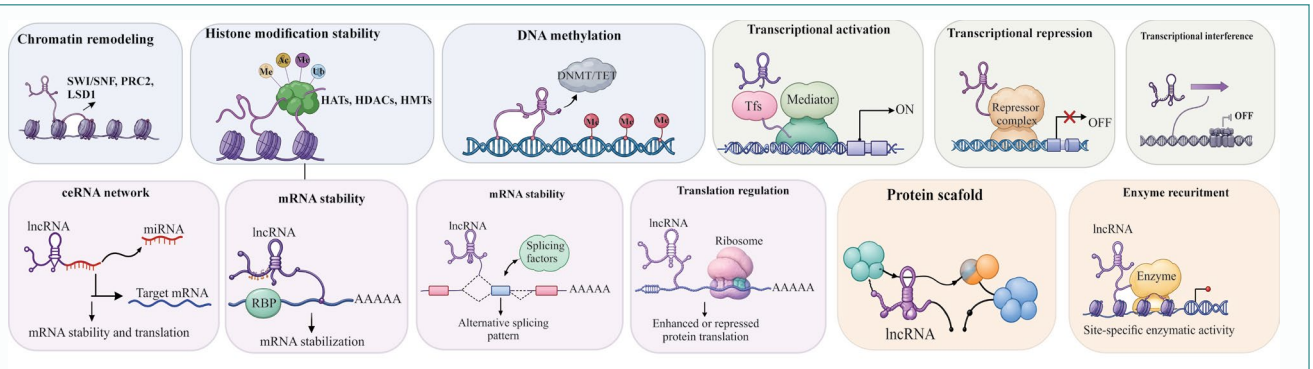


Figure 2: Main functions of lncRNAs in humans. The lncRNAs are extensively involved in pre-transcription, transcription, post-transcription, and translation pathways, regulating cellular and physiological pathways.

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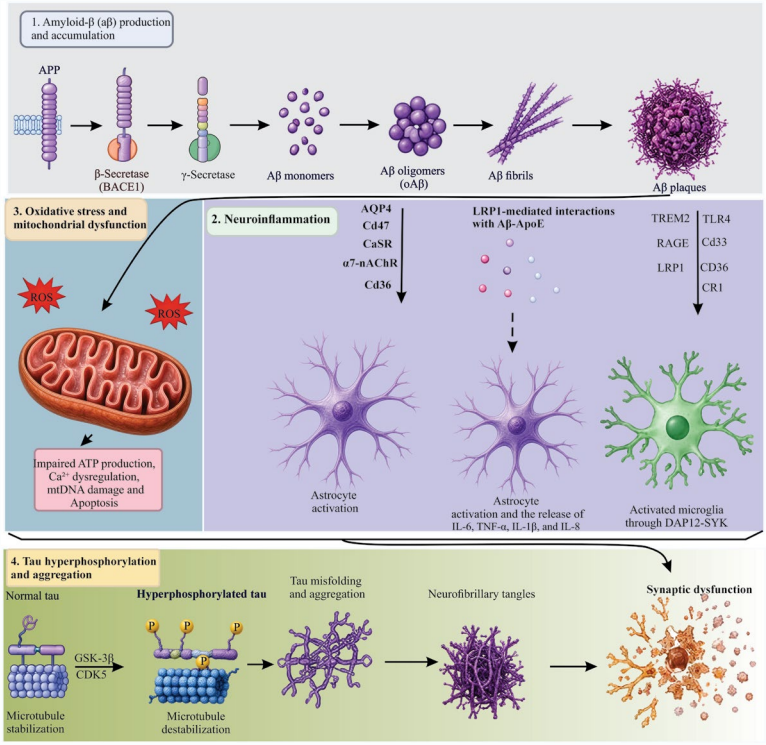


Figure 3: Principal molecular and cellular pathological mechanisms of AD. 1; Aβ production and accumulation: Amyloid Precursor Protein (APP) is sequentially cleaved by β-secretase (BACE1) and γ-secretase to produce Aβ peptides, which can assemble into soluble Aβ monomers, Oligomers (oAβ), fibrils, and ultimately extracellular Aβ plaque cores. 2; Neuroinflammation: Aβ-ApoE interactions with receptors and innate immune molecules, including LRP1, TREM2, TLR4, RAGE, CD33, CD36 and CR1, together with signaling through AOP4, Cd47, CaSR, α7-nAChR and Cd36, trigger astrocyte and microglial activation. Activated glial cells release pro-inflammatory mediators, including IL-6, TNF-α, IL-1β and IL-8, culminating in neuroinflammation. 3; Oxidative stress and mitochondrial dysfunction: Accumulation of ROS is associated with impaired mitochondrial function, reduced ATP production, Ca^{2+} dysregulation, mitochondrial DNA damage and apoptosis, resulting in neural dysfunction. 4; Tau hyperphosphorylation and aggregation: Dysregulated kinases such as GSK-3β and CDK5 promote tau hyperphosphorylation, resulting in microtubule destabilization, tau misfolding and aggregation, formation of neurofibrillary tangles and, ultimately, synaptic dysfunction.

by modulating autophagy through the miR-214-3p/ATG5 axis. Moreover, the knockdown of BACE1-AS may protect neuronal cells from damage induced by Aβ25-35 through the inhibition of miR-132-3p [97]. Similarly, BACE1-AS functions as a Competing Endogenous RNA (ceRNA) by sequestering miR-29, thereby stabilizing BACE1 mRNA and increasing BACE1 expression, which promotes amyloidogenic APP processing and Aβ production. In this sense, the lncRNA BACE1-AS could be regarded as a promising target for AD treatment [98]. Membrane-associated guanylate kinase inverted 2 (MAGI2-AS3) is a novel lncRNAs which shows regulatory functions in AD and also in various cancers such as lung cancer. It is reported that the expression of MAGI2-AS3 is markedly upregulated in serum samples of patients with AD. Accordingly, it seems this lncRNA functions as a molecular sponge for miR-374b-5p to modulate the expression of BACE1 required for the degradation of Aβ peptides. Further results revealed that the inhibition of MAGI2-AS3 may attenuate neurotoxicity and neuroinflammation induced by Aβ25-35 [99]. In this context, the expression levels of MAGI2-AS3 in the serum samples might be considered as a diagnostic biomarker for AD [100]. Brain Cytoplasmic 200 (BC200) is a lncRNA that specifically expresses in the cytoplasm of neurons. This lncRNA exhibits low expression levels in normal tissues, whereas its expression is significantly elevated in the hippocampus of patients with AD. Recent findings indicate that the lncRNA BC200 is aberrantly upregulated in AD, in which increased BC200 expression enhances BACE1 expression, resulting in elevated Aβ production and subsequent neuronal death [101]. Of note, BC200 contributes to the regulation of apoptosis and neuroinflammation through the PI3K/AKT signaling pathway in AD [100]. Moreover, some lncRNAs such as RP11-543N12.1 and XIST can exacerbate neuroinflammatory responses and apoptosis by affecting microglia during the pathogenesis of AD, resulting in Aβ deposition [102,103]. The lncRNA 17A, which is transcribed by RNA polymerase III, is aberrantly upregulated in the brain tissue of patients with AD, where it contributes to disease pathogenesis by modulating alternative splicing of the GABA B2 receptor and enhancing Aβ production. Further data showed that the expression of the lncRNA Brain Cytoplasmic RNA 1 (BC1) is enhanced in the brains of mouse models with AD. This lncRNA triggers the translation of APP mRNA through the interaction with Fragile X Mental Retardation Protein (FMRP), which leads to enhanced production and deposition of Aβ peptides [104]. The downregulation of BC1 could remarkably reduce the APP expression in the hippocampus of mice with AD, confirming the importance of the interaction between BC1 and FMRP in the pathogenesis of this disease [105]. Neuroblastoma Differentiation Marker 29 (NDM29) is another lncRNA transcribed by RNA polymerase III, and it is expressed more in patients with AD compared to normal human brains. The lncRNA NDM29 promotes the amyloidogenic processing of APP by increasing APP mRNA and

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protein expression and enhancing β- and γ-secretase activities. As a result, total Aβ production is elevated, accompanied by an increased Aβ42/Aβ40 ratio, a hallmark of enhanced amyloid pathology [106]. The BDNF Antisense Transcript (BDNF-AS) is a conserved lncRNA that triggers the production of Aβ via inhibition of miR-9-5p to stimulate the expression of BACE1. Furthermore, the formation of a positive loop between Aβ and BDNF-AS can inhibit the expression of BDNF, which is essential for neuronal development, synaptic plasticity, and the release of neurotransmitters. Accordingly, the suppression of the lncRNA BDNF-AS could be regarded as an efficient strategy for the treatment of AD [96]. MALAT1 in intergenic lncRNA whose upregulation is accompanied by the suppression of neuronal death and neuroinflammation in patients with AD. Further studies demonstrated that MALAT1 interacts with miR-125b to suppress Aβ-induced neuronal apoptosis and inflammation while promoting neurite outgrowth through a lower production of inflammatory cytokines [107]. It has recently been reported that the novel ceRNA network composed of MALAT1/miR-30b/CNR1 increase the viability of neurons and reduces neuronal injury via the Aβ-related pathway in both *in vivo* and *in vitro* experiments [108]. Notably, MALAT1 overexpression attenuates Aβ1-42-induced cytotoxicity by regulating the miR-200a/miR-26a/miR-26b–EPHA2 axis, leading to the activation of downstream neuroprotective effectors, including CREB, p38, and synaptophysin. It seems that the lncRNA MALAT1 plays a vital role in controlling AD through the ceRNA regulatory mechanism and could be considered as an important target for the treatment of the disease (Table 1) [109].

Regulation of hyperphosphorylation of tau protein by lncRNAs

A significant association between lncRNAs and the tau protein in patients with AD. The lncRNA NEAT1, for example, contributes significantly to the acceleration of the progression of AD, in which its downregulation enhanced the production of P-tau and Aβ levels, resulting in neuronal injury through the inhibition of miR-107 [110]. NEAT1 is a cytosolic-enriched lncRNA transcribed from the Multiple Endocrine Neoplasia Type 1 (MEN1) gene, where its expression was enhanced in the temporal cortex and hippocampus of patients with AD [100]. NEAT1 functions as a ceRNA network by sponging miR-124, thereby upregulating BACE1 mRNA and protein expression. In turn, Aβ accumulation further enhances NEAT1 and BACE1 expression while suppressing miR-124 levels, whereas NEAT1 silencing reverses these effects [111]. Emerging evidence indicates that NEAT1 exhibits stage-dependent expression during AD progression. Reduced NEAT1 expression in the early stages of the disease may compromise Aβ clearance, whereas increasing Aβ burden subsequently induces NEAT1 expression, further promoting BACE1-mediated Aβ production. This positive feedback loop is thought to accelerate amyloid pathology and neurodegeneration [100,111]. Furthermore, *in vivo* and *in vitro* experiments confirmed that the lncRNA linc00507 is highly expressed in both mice with AD and the Aβ42-SH-SY5Y cell line, affecting the phosphorylation of tau protein. This elevation hinders miR-181c-5p in the ceRNA network, resulting in the regulation of Microtubule-Associated Protein Tau (MAPT) and Tau-Tubulin Kinase-1 (TTBK1) expression. Mechanistically, LINC00507 acts as a ceRNA that sequesters miR-181c-5p, thereby increasing MAPT and TTBK1 expression and activating the p25/p35/GSK3β signaling pathway, ultimately promoting tau hyperphosphorylation [112]. The lncRNA MEG3 has a regulatory role in the pathogenesis of AD, where *in vitro* studies using SH-SY5Y cells under high-glucose conditions demonstrated that MEG3 contributes to tau hyperphosphorylation by regulating the PI3K/AKT1/GSK3β signaling pathway. These findings highlight the potential function of MEG3 in neuronal vulnerability in the brain and offer novel therapeutic approaches for the treatment/inhibition of AD (Table 1) [113].

Modulation of neuroinflammation and neuronal survival by lncRNAs

The lncRNAs SNHG14 and GAS5 act as a ceRNA network by sponging miR-223-3p and miR-137, respectively. Because both miRNAs negatively regulate NLRP3 inflammasome activity, their sequestration by these lncRNAs promotes NLRP3 activation, thereby enhancing neuroinflammatory responses and microglial apoptosis [114,115]. In many cases, one miRNA can be sponged by multiple lncRNAs, confirming the existence of redundant or synergistic regulatory mechanisms [116]. The lncRNA NEAT1 can target both miR-124 and miR-132 to modulate the expression of BACE1 and SOX2, respectively. Moreover, the lncRNA MALAT1 suppresses miR-125b in a ceRNA network to regulate downstream genes such as PTGS2 (COX-2), CDK5, and FOXQ1, contributing to neuronal survival and inflammation. It is also reported that the NEAT1/miR-146a and MALAT1/miR-146a axes are highly involved in the activation of microglia and the release of inflammatory cytokines [117]. Together, these findings demonstrate that lncRNA-miRNA regulatory axes are key modulators of innate immune signaling and represent promising therapeutic targets for limiting neuroinflammation and slowing disease progression in AD [100]. It has been demonstrated that silencing lncRNA BDNF-AS, a negative regulator of BDNF expression, enhances the viability of Aβ25-35-injured PC12 cells and reduces apoptosis and OS. The knockdown of BDNF-AS suppresses neuroinflammatory responses and inflammatory signaling pathways in AD models, suggesting that this lncRNA may represent a potential biomarker and therapeutic target for AD (Table 1) [96].

LncRNAs as promising biomarkers for early diagnosis and treatment of AD

Nowadays, several bioinformatics tools have been developed for the identification of biomarkers for early diagnosis of various diseases and AD as well. These tools, especially Weighted Gene Co-expression Network Analysis (WGCNA), use publicly available RNA-seq and microarray datasets to explore the informative elements associated with AD [118]. In this context, the lncRNA FMR1-AS1 was identified as a key target for the detection and treatment of patients with AD. The overexpression of FMR1-AS1 in the Aβ1-42-induced SH-SY5Y cell model remarkably enhanced cell viability, suppressed apoptosis, and reduced the hyperphosphorylation of tau protein [95]. Moreover, FMR1-AS1 alleviated OS by reducing ROS levels, increasing SOD activity, and decreasing Malondialdehyde (MDA) content. Conversely, knockdown of FMR1-AS1 exacerbated neuronal injury. Accordingly, FMR1-AS1 presents neuroprotective impacts by regulating apoptosis, OS production, and tau protein pathology [95]. Blood has emerged as an attractive source for disease-associated biomarkers because of the pivotal role of circulating immune cells in responding to physiological and pathological stimuli [119]. Notably, gene expression profiles in peripheral blood cells exhibit considerable similarity to those of brain tissue, supporting the use of whole blood or Peripheral Blood Mononuclear Cells (PBMCs) for the molecular diagnosis of neurological diseases. As increasing evidence links early alterations in peripheral blood biomarkers to the onset of AD, blood-based biomarkers offer considerable promise

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Table 1: The list of lncRNAs involved in diagnosis/treatment of AD.

LncRNA	Expression status	Function	Biomarker/therapeutic potential
H19	Up	Promotes neuroinflammation and neuronal injury	Therapeutic target
XIST	Dysregulated	Regulates neuronal apoptosis and inflammation	Biomarker
MALAT1	Dysregulated	Neuroprotection, neurite outgrowth, anti-inflammatory effects	Biomarker; therapeutic target
NEAT1	Up	Regulates neuroinflammation, Aβ metabolism, neuronal survival	Biomarker; therapeutic target
BACE1-AS	Up	Promotes Aβ production	Biomarker; therapeutic target
BDNF-AS	Up	Promotes neuronal apoptosis	Therapeutic target
MAGI2-AS3	Up	Promotes neuronal injury	Therapeutic target
BC200	Up	Synaptic dysfunction and increased BACE1 expression	Biomarker
17A	Up	Increases Aβ42/Aβ40 ratio	Therapeutic target
BC1	Up	Promotes APP translation and Aβ accumulation	Therapeutic target
NDM29	Up	Increases APP synthesis and secretase activity	Therapeutic target
LINC00507	Up	Promotes tau phosphorylation and neuronal injury	Therapeutic target
MEG3	Dysregulated	Regulates neuronal vulnerability and tau phosphorylation	Therapeutic target
SNHG14	Up	Promotes neuroinflammation	Therapeutic target
GAS5	Up	Promotes inflammation and apoptosis	Blood biomarker; therapeutic target
FMR1-AS1	Up	Reduces oxidative stress, suppresses apoptosis	Therapeutic target
RN7SK	Up	Regulates neuroinflammation	Blood biomarker
LINC00641	Down	Promotes Aβ42 accumulation	Plasma biomarker
RPL21P28	Down	Contributes to synaptic function	Blood biomarker
ATP2B1-AS1	Up	Contributes to neurodevelopment	Blood biomarker
TUG1	Up	Promotes neuronal apoptosis, enhances OS, regulates neuroinflammation	Blood biomarker; therapeutic target
FEZF1-AS1	Down	Not reported	Blood biomarker
LINC02067	Up	Not reported	Blood biomarker
NORAD	Up	Represses AD progression by sponging miR-26b-5p	Blood biomarker
THCAT158	Up	Not reported	Blood biomarker
LINC00987	Up	Not reported	Blood biomarker
ANKRD34C-AS1	Up	Not reported	Blood biomarker
LOC107987206	Down	Not reported	Blood biomarker
LOC105378179	Down	Not reported	Blood biomarker
AL445989.1-2	Up	Not reported	Biomarker
LINC01420	Up	Not reported	Biomarker
LOC401557	Down	Not reported	Biomarker
CSTB-1	Down	Not reported	Biomarker
CH507-513H4.4	Up	Not reported	Biomarker
CH507-513H4.6	Up	Not reported	Biomarker
CH507-513H4.3	Up	Not reported	Biomarker
RP11-543N12.1	Up	Regulates neuronal apoptosis and inflammation	Therapeutic target

for early diagnosis due to their accessibility, low cost, and minimally invasive collection [120]. In this context, the lncRNA RN7SK is proposed as a novel blood-related biomarker for the early diagnosis of AD by bioinformatics approaches. Further experimental data confirmed that this element is highly upregulated in patients with AD. It seems RN7SK and its co-expressed genes, including TNF and TNFAIP3, are the key elements involved in the development of AD. However, the accurate molecular mechanism of RN7SK remains to be elucidated, while it seems to function as a molecular linker between neuroinflammation and transcriptional dysregulation in patients with AD [121]. Similarly, the plasma level of LINC00641 can be regarded as a biomarker for the diagnosis of AD, in which its expression is lower in patients than in controls. Further findings showed that the overexpression of LINC00641 can restore the viability of H19-7 cell lines treated with Aβ42 and also reduce the levels of cleaved Aβ42, p-Tau217/Tau, Caspase-3, and p-Tau181/Tau. It seems this lncRNA sponges miR-501-3p to restore neuronal cell viability and reduce cell damage; however, this needs further validation in animal models [122]. Transcriptomic analysis of 349 RNA-seq datasets from patients with AD and healthy controls demonstrated significant downregulation of RPL21P28 and simultaneous upregulation of ATP2B1-AS1 in plasma samples, showing a remarkable potential as non-invasive blood-related biomarkers for early diagnosis of the disease [123]. A meta-analysis composed of 553 AD patients and 513 healthy controls showed that the lncRNAs including BACE-AS1, NEAT1, and GAS5 were upregulated and MALAT1 was downregulated in plasma samples of patients with AD, which presented a high precision capacity in the detection of patients with AD [124]. A study including 100 patients with AD and 100 healthy individuals aged 60-90 years found that plasma TUG1 expression was increased in patients with AD, whereas FEZF1-AS1 expression was significantly decreased. TUG1 predominantly functions as a pro-neurodegenerative lncRNA that promotes Aβ-induced neuronal apoptosis, OS, neuroinflammation, and neuronal dysfunction, mainly by acting as a ceRNA network [125]. Interestingly, several studies have evaluated the diagnostic utility of lncRNAs in differentiating AD from other neurodegenerative disorders, including vascular dementia, dementia with Lewy bodies, Parkinson's disease, and behavioral variant frontotemporal dementia. The study demonstrated that plasma lncRNAs, including LINC02067, NORAD, THCAT158, LINC00987, and ANKRD34C-AS1, were significantly upregulated in patients with AD, whereas LOC107987206 and LOC105378179 were remarkably downregulated. Moreover, these lncRNAs are AD-specific, and none of them were dysregulated in other types of dementia, confirming their great potential in detecting patients with AD [126]. The in-silico study showed that the levels of NEAT1 and

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BC200 were significantly higher in the plasma of patients with AD compared to the control group, which might be regarded as potential blood-based biomarkers for the evaluation of AD development and progression [127]. Elevated lncRNA HOTAIR expression in patients with AD has been associated with poorer cognitive performance, as demonstrated by its correlation with MMSE and ADAS-Cog scores, highlighting its potential as a diagnostic biomarker. Furthermore, exercise significantly decreases serum HOTAIR expression while improving cognitive function, suggesting that this lncRNA may serve as a molecular indicator of the beneficial effects of physical activity in AD [128]. Elevated peripheral lncRNA GAS5 expression is associated with cognitive decline and hippocampal atrophy in patients with AD. The robust diagnostic performance of GAS5, particularly when integrated with hippocampal volume measurements, underscores its potential as a non-invasive indicator for the early diagnosis of AD or for monitoring its progression [129]. Notably, several studies have been conducted to investigate the potential of lncRNAs in blood as biomarkers for diagnosis or targets for the treatment of AD. The analysis of microarray data revealed the upregulation of AL445989.1-2, LINC01420, and particularly TTC39C-AS1, as well as the downregulation of LOC401557 and CSTB-1 in patients with AD compared with controls in PBMC. Moreover, the data showed that the lncRNAs CH507-513H4.4, CH507-513H4.6, and CH507-513H4.3 are differentially expressed in PBMCs from patients with AD compared with controls, confirming the potential of blood lncRNAs for the diagnosis of the disease [130]. These lncRNAs may exert their functions by regulating pathways involved in MAPK signaling, cytokine receptor interactions, chemokine signaling, and natural killer cell-mediated cytotoxicity (Table 1) [131].

Conclusion

LncRNAs have emerged as fundamental regulators of gene expression and are now recognized as integral components of the molecular networks underlying AD. Accumulating evidence demonstrates that dysregulated lncRNAs participate in virtually every stage of AD pathogenesis, including amyloid-β production, tau hyperphosphorylation, neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic impairment, and neuronal death. These regulatory functions are mediated through diverse mechanisms, including chromatin remodeling, transcriptional and post-transcriptional regulation, RNA-binding protein interactions, and ceRNA networks, underscoring the remarkable complexity of lncRNA-mediated gene regulation in the diseased brain. Beyond their mechanistic roles, lncRNAs have attracted considerable interest as non- invasive biomarkers because many are detectable in peripheral blood and exhibit disease-specific expression patterns. The molecular functions of many AD-associated lncRNAs remain incompletely characterized, and differences in transcript annotation, tissue specificity, cellular heterogeneity, and analytical methodologies complicate comparisons among studies. Furthermore, efficient and cell-specific delivery of RNA therapeutics across the blood-brain barrier, together with comprehensive assessments of long-term safety and off-target effects, continues to represent a major obstacle to clinical implementation. Future studies integrating bulk and single-cell transcriptomics, spatial transcriptomics, epigenomics, proteomics, and artificial intelligence-assisted network analyses will substantially improve our understanding of lncRNA regulatory circuits during disease initiation and progression. Such integrative approaches are expected to facilitate the identification of robust biomarker panels and master regulatory lncRNAs with high translational value. Collectively, the growing body of evidence indicates that lncRNAs represent a promising new frontier in AD research, with the potential to transform early diagnosis, patient stratification, and the development of precision therapeutics.

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