Potential mechanisms of non-coding RNA regulation in Alzheimer's disease

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From the Contents

Abstract

Alzheimer's disease, a progressively degenerative neurological disorder, is the most common cause of dementia in the elderly. While its precise etiology remains unclear, researchers have identified diverse pathological characteristics and molecular pathways associated with its progression. Advances in scientific research have increasingly highlighted the crucial role of non-coding RNAs in the progression of Alzheimer's disease. These non-coding RNAs regulate several biological processes critical to the advancement of the disease, offering promising potential as therapeutic targets and diagnostic biomarkers. Therefore, this review aims to investigate the underlying mechanisms of Alzheimer's disease onset, with a particular focus on microRNAs, long non-coding RNAs, and circular RNAs associated with the disease. The review elucidates the potential pathogenic processes of Alzheimer's disease and provides a detailed description of the synthesis mechanisms of the three aforementioned non-coding RNAs. It comprehensively summarizes the various non-coding RNAs that have been identified to play key regulatory roles in Alzheimer's disease, as well as how these non-coding RNAs influence the disease's progression by regulating gene expression and protein functions. For example, miR-9 targets the *UBE4B* gene, promoting autophagy-mediated degradation of Tau protein, thereby reducing Tau accumulation and delaying Alzheimer's disease progression. Conversely, the long non-coding RNA BACE1-AS stabilizes BACE1 mRNA, promoting the generation of amyloid-β and accelerating Alzheimer's disease development. Additionally, circular RNAs play significant roles in regulating neuroinflammatory responses. By integrating insights from these regulatory mechanisms, there is potential to discover new therapeutic targets and potential biomarkers for early detection and management of Alzheimer's disease. This review aims to enhance the understanding of the relationship between Alzheimer's disease and non-coding RNAs, potentially paving the way for early detection and novel treatment strategies.

Key Words: Alzheimer's disease; biomarkers; circular RNA; long non-coding RNA; microRNA; ncRNA regulation; neurodegeneration; non-coding RNA; pathogenesis; therapeutic targets

Introduction

Alzheimer's disease (AD) is classified as a neurodegenerative disorder characterized by specific pathological features. The accumulation of amyloid-β (Aβ) fragments outside neuronal cells results in plaque formation, commonly known as Aβ plaques (Abyadeh et al., 2024; Sola-Sevilla and Puerta, 2024; Sun et al., 2024). Furthermore, AD is associated with the abnormal aggregation of p-tau protein within neuronal cells, resulting in the formation of neurofibrillary tangles (NFTs) (Li et al., 2024). This condition is further distinguished by the dysfunction and reduction in the number of synapses, as previously documented (Long and Holtzman, 2019; Trejo-Lopez et al., 2022). However, despite several decades of research, the fundamental mechanisms underlying AD remain incompletely understood. The disease affects millions worldwide, placing a significant burden on the affected individuals and society. Gaining a deeper understanding of AD pathogenesis and identifying promising biomarkers and therapeutic targets is crucial for advancing treatment and care.

With more research on the pathogenesis of AD, researchers have begun to focus on the key role that non-coding RNA (ncRNA) may play. NcRNA was initially regarded as "junk RNA." However, insights from the Human Genome Project and ENCODE initiative reveal that a significant portion of the human genome is transcribed into various ncRNAs (Watson, 1990; Djebali et al., 2012). These discoveries have led to the recognition that numerous ncRNAs play pivotal roles in regulating gene expression and cellular processes, influencing both normal physiology and disease development. NcRNAs vary in size, shape, and localization and are classified into various types, such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) (Asim et al., 2021). Dysregulation of these ncRNAs has been observed in AD, where they are implicated in key AD-related mechanisms, including amyloid-β (Aβ) synthesis and clearance, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction.

Although dysregulation of ncRNAs in AD has been recognized, how different types of ncRNAs regulate specific AD-related processes is still poorly understood. This research gap limits our ability to fully uncover the pathogenesis of AD. Therefore, further study of the relationship between ncRNA and AD is of great significance in deepening our understanding of the basic mechanism of AD. Understanding the regulatory mechanisms of ncRNAs may not only shed light on the pathogenesis of AD, but may also provide innovative biomarkers or therapeutic targets for the development of new diagnostic approaches and therapeutic strategies. These findings are expected to significantly advance the future development of the diagnosis and treatment of AD, improving patient outcomes and quality of life. Therefore, this review aims to explore the relationship between AD and various types of ncRNAs, with a focus on uncovering their functions and regulatory mechanisms in AD. Summarizing these mechanisms could provide valuable insights to support future research efforts in this field.

Search Strategy

A comprehensive review of the available literature was conducted using the PubMed database, focusing on English-language publications from 2008 to 2024. Specific search terms were used for this review, including "Alzheimer's disease,"

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"ncRNA," "miRNA," "lncRNA," and "circRNA," alongside combined phrases such as "ncRNA and Alzheimer's disease," "miRNA and AD," "lncRNA and AD," and "circRNA and AD." Studies were selected by screening titles and abstracts, ensuring the inclusion of research on human and murine models that examined ncRNAs in AD, with an emphasis on identifying potential biomarkers or therapeutic targets.

Pathogenesis of Alzheimer's Disease

AD is a progressive neurodegenerative disorder primarily characterized by memory loss and cognitive decline (DeTure and Dickson, 2019). First identified in 1906 (Alzheimer, 1906; Hippius and Neundörfer, 2003), the precise etiology of the disease remains uncertain even after more than a century of research. Currently, the most widely recognized contributors to AD pathogenesis are Aβ accumulation and the abnormal phosphorylation of tau proteins (Ferrari and Sorbi, 2021). The pathogenesis of AD is characterized by significant complexity. This review outlines a potential framework for understanding the pathogenic mechanisms involved to the best of our knowledge (**Figure 1**). AD is typically classified into two forms: early-onset and late-onset AD (Long and Holtzman, 2019). Early-onset AD, often known as familial or hereditary AD, accounts for 5%–10% of all Alzheimer's cases and is characterized by the onset of symptoms before the age of 65 years (Ayodele et al., 2021). This form of early-onset AD is predominantly driven by inherited mutations, with the most significant mutations occurring in the amyloid precursor protein (*APP*) gene (Goate et al., 1991), presenilin 1 (PSEN1) (Sun et al., 2017a), and presenilin 2 (PSEN2) (Cai et al., 2015). These mutations modify the structure of the protein, disrupt the assembly of gamma-secretase, alter the processing of APP, increase the $A\beta_{42}$/$A\beta_{40}$ ratio, and cause excessive production of Aβ, ultimately contributing to the development of AD (Van Cauwenberghe et al., 2016). In contrast, late-onset AD, which typically manifests in individuals > age 65 years, lacks a definitive causative factor. The prevailing consensus indicates that the emergence of AD is influenced by a combination of various factors, including advanced age, sex, environmental influences, and individual lifestyle choices—such as stress management, alcohol consumption, tobacco usage, and physical activity (Eid et al., 2019).

Under normal conditions, APP is primarily cleaved by alpha-secretase, resulting in the production of a water-soluble APP fragment known as soluble APPα. This fragment is further processed by other enzymes, preventing the synthesis of Aβ. However, in patients with AD, APP undergoes an atypical cleavage pathway involving beta-secretase and gamma-secretase, ultimately leading to Aβ generation. Initially, beta-secretase cleaves APP, resulting in a soluble fragment, soluble APPβ, and a C-terminal fragment called C99, which contains the Aβ sequence (Hardy and Higgins, 1992). Subsequently, the gamma-secretase enzyme processes the C99 fragment, producing Aβ peptides with diverse lengths, primarily $A\beta_{40}$ and $A\beta_{42}$ (Hardy and Allsop, 1991). $A\beta_{42}$ is particularly prone to aggregation (Lendel et al., 2014), leading to the accumulation of Aβ oligomers and plaque formation, which are key features of AD neuropathology. The aggregation of these plaques initiates changes in kinase and phosphatase activities (Tiwari et al., 2019), resulting in the abnormal phosphorylation and aggregation of tau proteins, forming NFTs. These NFTs, along with Aβ plaques, impair neuronal function and their synaptic connections, disrupting synaptic structure and signal transmission (Bloom, 2014). Furthermore, Aβ oligomers, plaques, and NFTs activate surrounding microglia and astrocytes, initiating an inflammatory response (Sobue et al., 2023). This inflammatory response, through the release of various inflammatory mediators, including pro-inflammatory and anti-inflammatory factors, induces excessive neuroinflammation that is toxic to surrounding neurons, leading to further neuronal and synaptic connections (Martínez-Cué and Rueda, 2020). Over time, the accumulation of these toxic substances contributes to progressive neuronal degeneration and cell death, ultimately resulting in cognitive decline and the onset of dementia.

Non-coding RNA

MicroRNA

MiRNAs are a class of small RNA molecules typically ranging from 21 to 25 nucleotides in length (Saliminejad et al., 2019; Bellver-Sanchis et al., 2024). **Figure 2** illustrates their biological significance and regulatory mechanisms. MiRNA transcription originates from DNA, producing primary miRNA (pri-miRNA) transcripts (Jodder, 2021). These pri-miRNAs are characterized by a 5′ cap at one end, a poly(A) tail at the other, and a distinct hairpin-loop structure (Shang et al., 2023). Within the cell nucleus, a longer primary miRNA transcript is precisely cleaved by the microprocessor complex, comprising the Drosha enzyme and DGCR8 protein. This cleavage removes unnecessary intronic sequences and other noncoding regions, resulting in a pre-miRNA of approximately 70 nucleotides in length (Chen et al., 2019). Subsequently, the Exportin-5 protein facilitates the transport of pre-miRNA from the nucleus to the cytoplasm. Once in that region, the pre-miRNA is further processed by the Dicer enzyme, which cleaves it into a short double-stranded microRNA (ds-miRNA) (Ha and Kim, 2014). Subsequently, one strand of the mature miRNA is loaded onto the Argonaute protein, forming the core of the activated RNA-induced silencing complex (miRISC) along with other associated proteins. This complex interacts with the 3′ untranslated region (3′-UTR) of the target mRNA, leading to the degradation of the mRNA or the suppression of its translation. Consequently, this mechanism regulates gene expression at the post-transcriptional level (Fabian and Sonenberg, 2012).

The regulatory mechanism of miRNA primarily occurs through its binding to target mRNA. miRNA affects mRNA in two principal ways: degradation and translational inhibition. When miRNA exhibits complete complementarity with the 3′-UTR of the target mRNA, it typically directs the miRISC complex to degrade the mRNA (Chen et al., 2019). The miRNA-mRNA complex may serve as a direct target of degradation or can indirectly induce mRNA degradation by promoting decapping or shortening the poly(A) tail of the mRNA (Guo et al., 2010). In cases where miRNA exhibits partial or incomplete complementarity with the target mRNA, translation is typically inhibited rather than directly degrading the mRNA (Chen et al., 2019). This suppression occurs by preventing the formation of the translation initiation complex or disrupting the elongation of the translation process (Bartel, 2009).

Long non-coding RNA

LncRNAs are a category of RNA molecules characterized by sequences exceeding 200 nucleotides in length (Zeng et al., 2024). Similar to messenger RNA (mRNA), lncRNAs are synthesized by RNA polymerase II within the cell nucleus (**Figure 3**). However, contrary to mRNA, lncRNAs are generally not translated into proteins. Instead, they participate in various biological processes within the cell through various mechanisms (Bridges et al., 2021). LncRNAs can regulate transcription processes (Nojima and Proudfoot, 2022), facilitate post-transcriptional regulation (Herman et al., 2022), and interact with specific proteins (Ferrè et al., 2016).

In transcriptional regulation, lncRNAs can directly modulate the expression of adjacent gene loci. They may bind to transcription sites or recruit regulatory factors, such as transcription factors and RNA polymerase II (Pol II), to target the expression of cis or trans genes (Sun et al., 2020). Additionally, lncRNA can function as "decoys," sequestering transcription regulatory factors and preventing them from binding to their target genes (Kopp and Mendell, 2018). In post-transcriptional regulation, lncRNAs modulate post-transcriptional RNA, including splicing, RNA modification, and stability. They interact with mRNAs or other ncRNAs, affecting their degradation, translation, or localization. For example, lncRNAs can act as "sponges" for miRNAs, binding to miRNAs to regulate their activity and stability (Zhang et al., 2019). Regarding protein regulation, lncRNAs interact with proteins, modulating their function, cellular localization, and structural integrity. They can act as "scaffolds," facilitating the assembly and functional coordination of protein complexes (Rinn and Chang, 2012).

Circular RNA

Covalently closed circRNAs, unlike their linear counterparts, are generated via an unconventional splicing process known as "reverse splicing" (Tang et al., 2021; **Figure 4**). This mechanism involves the concatenation of the 5′ and 3′ termini of the pre-mRNA, resulting in a circular RNA structure. The connection between these termini is stabilized via a 3′–5′ phosphodiester bond, forming a stable, covalent bond (Li et al., 2018b). CircRNAs are widely present in various cell types and are characterized by their stability and conservation. The circular conformation of circRNAs renders them resistant to RNAase-mediated degradation, resulting in an extended half-life (Chen, 2016). They function as "miRNA sponges" by sequestering miRNAs, thereby inhibiting their activity and regulating the expression of target genes (Hansen et al., 2013). Additionally, certain circRNAs can form connections with RNA-binding proteins, influencing gene transcription and modulating post-transcriptional processes (Zang et al., 2020).

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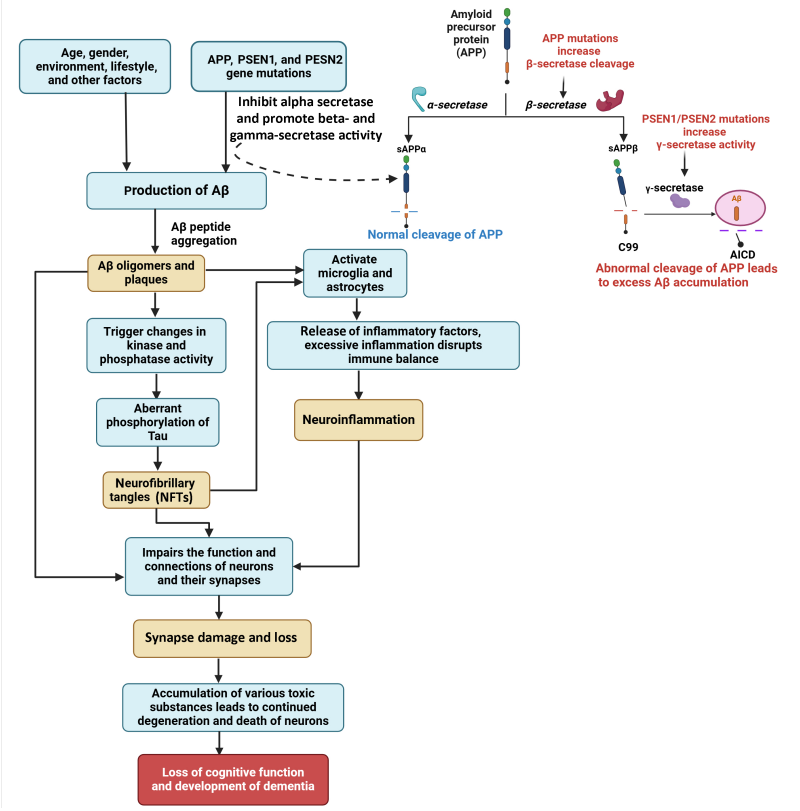

Figure 1 | **Possible mechanism of AD.**
This figure illustrates the potential development process of AD, with early-onset AD largely driven by genetic mutations, while late-onset AD is influenced by factors such as age, genetics, and lifestyle. The tan boxes highlight key pathological markers of AD: beta-amyloid deposits, NFTs, neuronal inflammation, and the breakdown and loss of synaptic connections. Created with BioRender.com. AD: Alzheimer's disease; AICD: APP intracellular domain; APP: amyloid precursor protein; Aβ: amyloid-β; C99: 99 aa C-terminal fragment; NFT: neurofibrillary tangle; PSEN1: presenilin 1; PSEN2: presenilin 2; sAPPα: soluble amyloid precursor protein alpha; sAPPβ: soluble amyloid precursor protein beta.

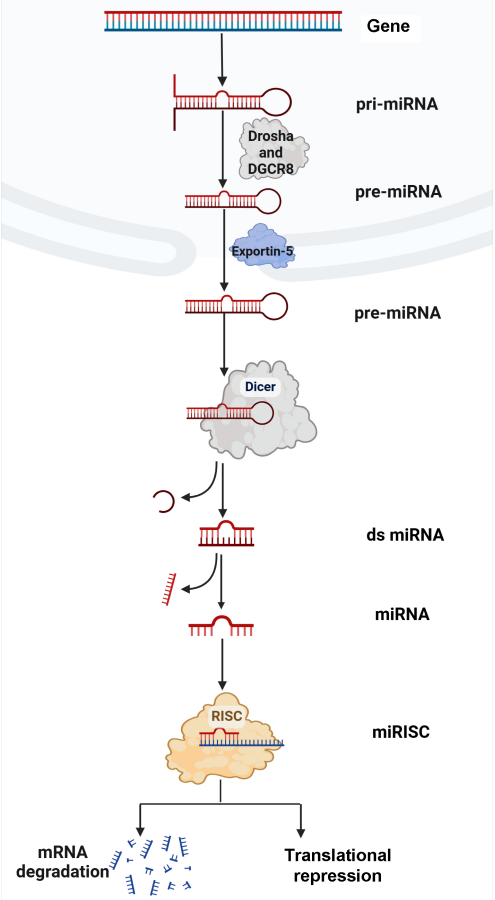

Figure 2 | **Generation and regulatory mechanisms of miRNA.**
MiRNA is transcribed by RNA Pol II, initially forming pri-miRNA, which is cleavaged to produce pre-miRNA, then ds miRNA, and finally, mature miRNA. The mature microRNA combines when paired with proteins to form the miRISC. This complex binds to the 3′-UTR of the target mRNA, regulating gene expression by degrading the mRNA or blocking its translation. Created with BioRender.com. DGCR8: DiGeorge syndrome critical region 8; ds miRNA: double-stranded microRNA; miRISC: miRNA-induced silencing complex; miRNA: microRNA; pre-miRNA: precursor microRNA; pri-miRNA: primary microRNA; RISC: RNA-induced silencing complex.

Regulatory Mechanisms of Non-coding RNAs in Alzheimer's Disease

Since the initial identification of AD and the discovery of circRNA, ncRNAs have been increasingly implicated in the development and progression of AD. **Figure 5** illustrates the major milestones in ncRNA and AD research from 1906 to date. Over recent decades, with advancements in the understanding of ncRNA regulation in AD, these molecules are now recognized as active contributors to the pathogenesis of the disease rather than passive entities.

MicroRNAs in Alzheimer's disease

MicroRNA regulates amyloid-β aggregation and clearance

Abnormalities in Aβ aggregation and clearance are central to the progression of the disease. **Figure 6** illustrates the role of miRNAs in regulating the production, metabolism, and elimination of Aβ.

In recent years, numerous miRNAs have emerged as crucial regulators in AD, influencing genes such as APP, a precursor to Aβ. Among the early identified miRNAs, miR-106a and miR-520c have garnered significant attention for their ability to reduce APP levels (Patel et al., 2008). This highlights their roles as post-transcriptional modulators. Additionally, miRNAs such as miR-101 (Vilardo et al., 2010), miR-20a, miR-17-5p, and miR-106b (Hébert et al., 2009), miR-16 (Zhang et al., 2015), miR-135a and miR-200b (Liu et al., 2014), miR-153 (Long et al., 2012), miR-298 (Chopra et al., 2021), and miR-342-5p (Dong et al., 2022) regulate APP by targeting its 3′-UTR. The upregulation of these miRNAs can lead to a reduction of APP. In contrast to the typical behavior of most miRNAs, miR-346 targets the 5′-UTR of APP, enhancing its translation and contributing to iron homeostasis (Long et al., 2019), subsequently increasing Aβ levels. Increased iron concentrations stimulate iron-responsive protein 1 (IRP1) to bind with excess iron, thereby releasing its grip on APP mRNA and facilitating uninterrupted translation. Conversely, reduced iron concentration dissociates IRP1 from its iron ligand, allowing it to reattach to the iron response element (IRE) in the 5′-UTR of the APP, inhibiting translation (Long et al., 2019).

MiRNAs are crucial in regulating the activity of the three pivotal secretases involved in the generation of Aβ: alpha-secretase, beta-secretase, and gamma-secretase. Under normal physiological conditions, alpha-secretase triggers the non-amyloidogenic pathway by cleaving the APP at the alpha site, thereby preventing Aβ synthesis (Lichtenthaler and Haass, 2004). Among these, ADAM10 is a prominent alpha-secretase enzyme, functioning as a transmembrane metalloproteinase and participating in the α-cleavage process of APP (Manzine et al., 2019). This enzyme truncates the external domain of APP, resulting in the formation of a soluble APP fragment known as soluble APPα (Yuan et al., 2017). miR-30a-5p represses the production of non-amyloidogenic proteins by inhibiting ADAM10 and SIRT1, thereby contributing to the increased synthesis of $A\beta_{1-42}$ (Sun et al., 2022). Additionally, miR-144 reduces ADAM10 levels by targeting its 3′-UTR, consequently obstructing the transcriptional and translational processes of ADAM10 (Sun et al., 2017b).

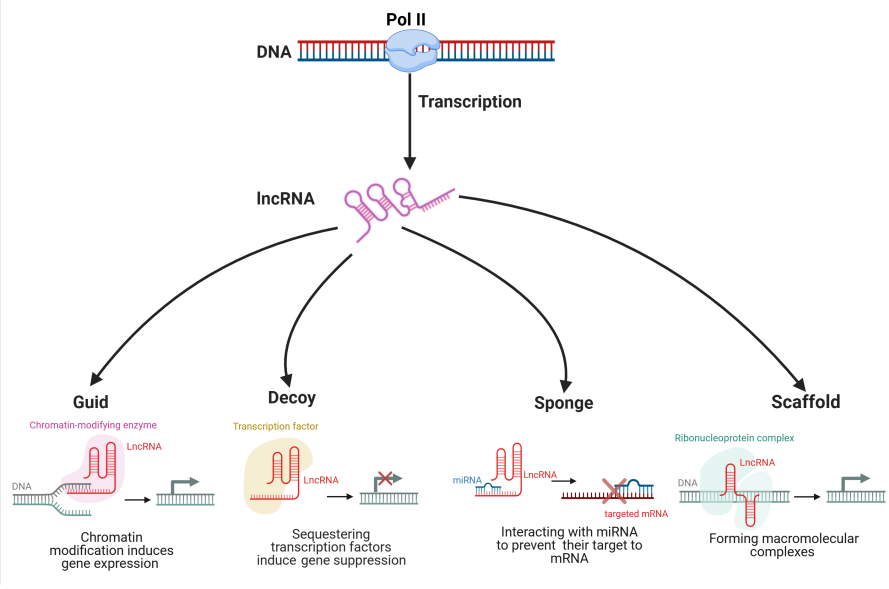

Figure 3 | **Generation and regulatory mechanisms of lncRNA.**
LncRNA is synthesized by RNA Pol II in the cell nucleus and regulates processes by functioning as a "guide," "decoy," "sponge," and "scaffold." Created with BioRender.com. lncRNA: Long non-coding RNA; Pol II: RNA polymerase II.

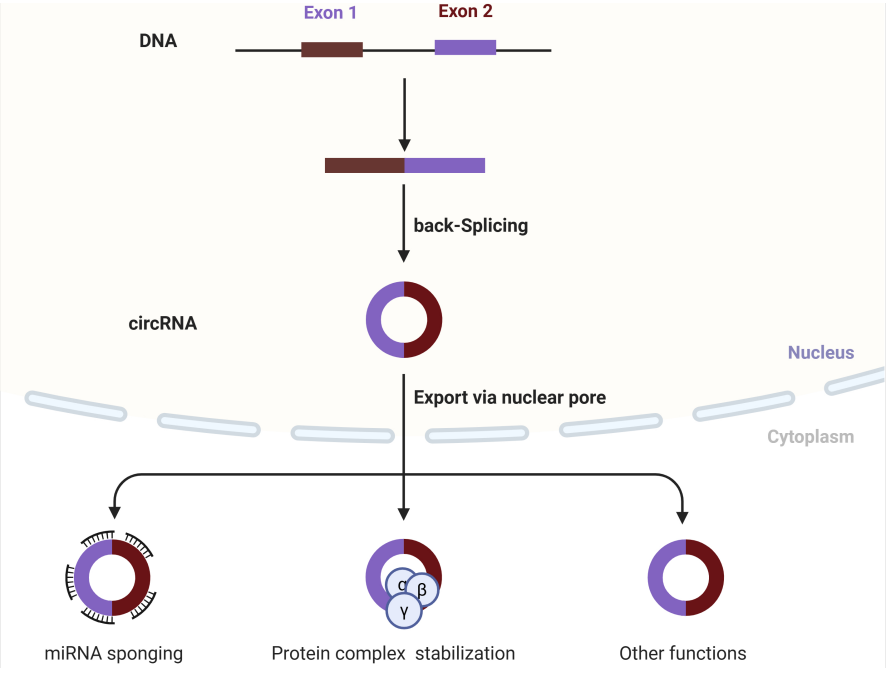

Figure 4 | **Biosynthesis and regulation mechanisms of circRNA.**
CircRNA is formed through a mechanism called back-splicing, which creates a circular structure. It mainly regulates biological processes by sponging miRNA and interacting with proteins. Created with BioRender.com. circRNA: Circular RNA; miRNA: microRNA.

Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) functions as the principal beta-secretase, cleaving the N-terminal region of β-APP to generate the C99 fragment, which contains Aβ. This fragment subsequently serves as a substrate for gamma-secretase cleavage (Takasugi et al., 2023). MiR-29a and miR-29b-1 regulate BACE1 expression *in vitro* by exploring changes in miRNA expression profiles in patients with sporadic AD (Hébert et al., 2008). The increased expression of these miRNAs leads to the downregulation of BACE1, resulting in a reduced accumulation of Aβ (Hébert et al., 2008)). MiR-107 (Wang et al., 2008), miR-186 (Kim et al., 2016), and miR-298 (Chopra et al., 2021), which complementarily bind to the 3′-UTR of BACE1, thereby regulating its expression and affecting Aβ levels. Additionally, aβ-induced neurotoxicity is mitigated by targeting BACE1 through miR-34a-5p and miR-125b-5p (Li et al., 2020a). MiRNA-340 demonstrates an inverse relationship with BACE1, exhibiting its ability to directly interact with this enzyme. Increasing miR-340 levels leads to reduced BACE1 expression (Tan et al., 2020).

The gamma-secretase enzyme is critical in the processing of APP. Its composition includes, at a minimum, PSEN1, PSEN2, Aph1, Pen2, and nicastrin (NCT) (Hur, 2022). Research on the absence of miR-34a demonstrates that the observed improvements in cognitive abilities are predominantly due to the suppression of gamma-secretase activity. This inhibition does not affect the activity of beta-secretase or alpha-secretase (Jian et al., 2017). Furthermore, research has confirmed a direct interaction between miR-3940-5p and PSEN1, inhibiting PSEN1, a critical catalytic component of the gamma-secretase complex (Qi et al., 2024).

The elimination of detrimental Aβ in AD occurs through the ubiquitin-proteasome system (UPS) and autophagy. The UPS is instrumental in regulating protein degradation. Both autophagy and the UPS are the primary protein degradation pathways in eukaryotic cells, contributing to the degradation of various proteins, including Aβ (Limanaqi et al., 2020). A previous study suggests that miRNAs can regulate specific proteins involved in the UPS. In the neocortex and hippocampus of patients with AD, levels of miR-7 have been associated with reduced UBE2A expression, a protein essential for Aβ degradation (Zhao et al., 2016).

Autophagy is crucial to the elimination of Aβ (Tang et al., 2024). The lysosomal pathway is essential for recycling cellular components by degrading excess or damaged organelles and misfolded proteins. This process facilitates cellular homeostasis by transforming misfolded proteins into their basic elements, thereby maintaining cellular integrity (Zhang et al., 2021). During AD progression, changes in miRNA regulation of autophagy-associated proteins may be pivotal in the onset and advancement of the disease. miR-331-3P and miR-9-5P target the autophagy receptors Sequestosome1 and Optineurin, respectively (Chen et al., 2021). In SH-SY5Y cellular models, the upregulation of these miRNAs disrupts autophagic homeostasis, leading to the accumulation of amyloid-like deposits. Moreover, in advanced stages of AD in mice, inhibition of miR-331-3P and miR-9-5P has been shown to enhance Aβ clearance and cognitive functions (Chen et al., 2021). Additionally, studies reveal that miR-140 directly interacts with PINK1. Inhibition of miR-140 reduces mitochondrial dysfunction, significantly lowering the risk of AD by enhancing PINK1-mediated mitochondrial activity (Liang et al., 2021). Additionally, miR-299-5p inhibits autophagy by targeting ATG5, and reduced levels of this miRNA have been observed in the cerebrospinal fluid of patients with AD. The introduction of miR-299-5p further diminishes autophagic response and suppresses Atg5 activity (Zhang et al., 2016). In AD, a significant decrease in miRNA-101a levels has been observed. Increasing miR-101a expression may indirectly promote autophagy by modulating MAPK activity (Li et al., 2019). Moreover, miRNA-101a demonstrates a significant potential as a diagnostic biomarker for predicting the onset of AD, as indicated by a receiver operating characteristic curve value of 0.8725, highlighting its significance in AD diagnosis (Li et al., 2019). Further research indicates that miR-23b directly targets the 3′-UTR of ATG12 mRNA, and its increased expression can decrease neuronal cell death, injury, and cognitive decline by triggering ATG12 (Sun et al., 2018). This pathway may hold significant potential for the prophylaxis and therapeutic intervention of AD.

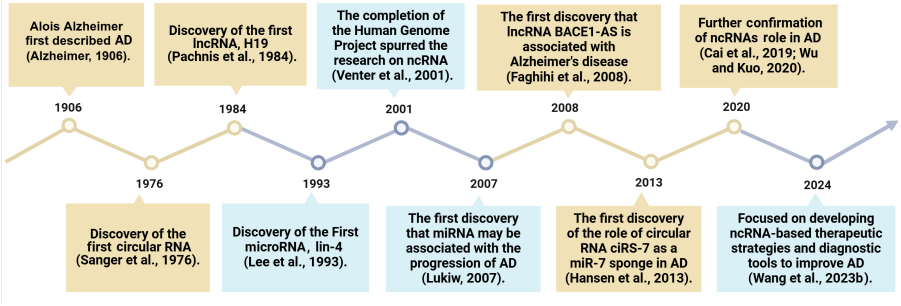

Figure 5 | Timeline of key milestones in ncRNA research related to AD.
This timeline highlights key milestones in ncRNAs research related to AD from 1906 to 2024. It starts with the first description of AD (Alzheimer, 1906) and the discovery of the first circRNA (Sanger et al., 1976), followed by identifying the first lncRNA (Pachnis et al., 1984) and miRNA (Lee et al., 1993). The completion of the Human Genome Project in 2001 significantly accelerated ncRNA research (Venter et al., 2001). By 2007, the first evidence linking miRNA to AD progression was found (Lukiw, 2007). Other breakthroughs include the association of lncRNA BACE1-AS with AD (Faghihi et al., 2008) and the discovery of circRNA ciRS-7 as a miRNA sponge in AD (Hansen et al., 2013). By 2024, the focus will shift to developing ncRNA-based therapies and diagnostic tools to improve AD management (Wang et al., 2023b; Karthik et al., 2024). Created with BioRender.com. AD: Alzheimer's disease; BACE1-AS: beta-site amyloid precursor protein cleaving enzyme 1 antisense RNA; ciRS-7: circular RNA sponge for miR-7; miRNA: microRNA; ncRNA: non-coding RNA.

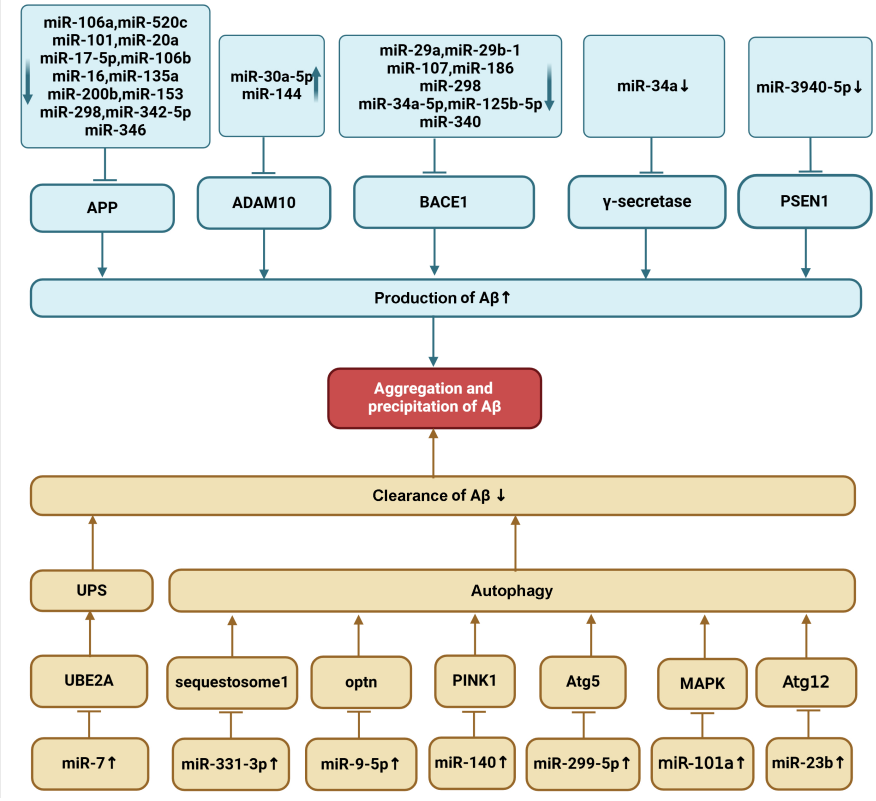

Figure 6 | MiRNA regulates Aβ aggregation.
The figure illustrates how miRNAs regulate the production and clearance of Aβ. It influences Aβ production by regulating APP, ADAM10, BACE1, and PSEN1 and affects Aβ clearance through the regulation of the UPS and autophagy. Created with BioRender.com. AD: Alzheimer's disease; ADAM10: A disintegrin and metalloproteinase 10; APP: amyloid-β precursor protein; Atg12: autophagy related 12; Atg5: autophagy related 5; Aβ: amyloid-β; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; MAPK: mitogen-activated protein kinase; optn: optineurin; miRNA: microRNA; PINK1: PTEN-induced kinase 1; PSEN1: presenilin 1; UBE2A: ubiquitin-conjugating enzyme E2 A; UPS: ubiquitin-proteasome system.

MicroRNAs regulate tau hyperphosphorylation and p-tau clearance

Tau plays a crucial role in AD as a microtubule-associated protein that stabilizes the cytoskeletal structure and supports the integrity of neuronal microtubules, ensuring their stability during normal physiological processes. However, under specific pathological conditions, tau protein may undergo changes predominantly via phosphorylation processes, which adversely affect neuronal health and contribute to the formation of NFTs (Avila et al., 2004; **Figure 7**).

MiRNAs directly influence tau protein expression by modulating the MAPT gene expression. The essential role of miRNAs in this modulation has been well-established, with miR-132 and miR-219 identified as significant regulators in this process (Santa-Maria et al., 2015; Smith et al., 2015). These miRNAs contain sequences complementary to the 3′-UTR of the *MAPT* gene, allowing them to bind to and inhibit the translation of tau mRNA, thereby diminishing its production (Santa-Maria et al., 2015; Smith et al., 2015). Studies reveal that miR-92a-3p, miR-320a, and miR-320b directly interact with MAPT mRNA, resulting in a decreased synthesis of tau protein in human neuroblastoma cell lines (Piscopo et al., 2023). Comparative analysis with healthy individuals reveals that miR-92a-3p concentrations are significantly reduced in patients with AD, while miR-320a exhibits increased expression, particularly among male patients when data is analyzed based on sex. These findings suggest that miR-92a-3p and miR-320a serve as pivotal biomarkers for distinguishing patients with AD from the healthy population (Piscopo et al., 2023).

Kinases and phosphatases, responsible for tau phosphorylation, are regulated by miRNAs. Glycogen synthase kinase 3β (GSK-3β) plays a crucial role in brain function, and its dysregulation can lead to neuronal damage and cognitive decline associated with AD. As a central component in the signaling network of the brain, GSK-3β acts as a pivotal molecular link between Aβ and tau neurofibrillary aggregates (Chauhan et al., 2022). Additionally, GSK-3β is one of the principal kinases involved in the phosphorylation of tau protein. It can phosphorylate tau at multiple sites, including Serine-262 (Song et al., 2022b), Serine-396, and Serine-404 (Godemann et al., 1999). MiR-23b-3p is downregulated during the progression of AD. This miRNA protects against Aβ-induced tau hyperphosphorylation by directly targeting GSK-3β, thereby regulating the GSK-3β/p-tau pathway to safeguard neuronal cells from programmed cell death (Jiang et al., 2022). The introduction of a miR-23b-3p analog suppresses GSK-3β production, increases the levels of GSK-3β phosphorylated at Serine-9 and reduces GSK-3β enzymatic activity. In cells treated with the miR-23b-3p analog, a significant decline in tau phosphorylation at Serine-396 and Serine-404 residues occurs, alongside a reduction in the generation of $A\beta_{1-42}$ (Jiang et al., 2022). Furthermore, a study indicates that miR-539-5p is significantly reduced in both patients with AD and murine models, correlating with decreased GSK-3β expression. This miRNA binds directly to GSK-3β, leading to reduced GSK-3β expression and a subsequent decrease in Aβ accumulation (Jiang et al., 2020). Regarding AD, miRNA-128 plays a critical role by downregulating GSK3β, ultimately inhibiting tau phosphorylation and reducing Aβ deposits (Li et al., 2023).

Furthermore, cyclin-dependent kinase 5 (CDK5) is a critical regulator within the nervous system, exerting significant regulatory effects. CDK5 phosphorylates tau protein at multiple sites, leading to an increase in the pathological accumulation and toxicity of tau, ultimately contributing to the formation of NFTs (Saito et al., 2019). Certain miRNAs can modulate the activity and expression of CDK5, thereby influencing the pathological mechanisms associated with tau proteins. MiR-504-3p serves as a prime example; studies indicate that melatonin can inhibit the hyperphosphorylation of tau in cellular and animal models. The neuroprotective effect of melatonin

on tau pathology is mediated through the upregulation of miR-504-3p levels, which targets the CDK5R2/CDK5 pathway to regulate protein expression (Chen et al., 2022b). Furthermore, miR-103/107 suppresses the expression of CDK5 (Peng et al., 2017). Similarly, miR-124 inhibits CDK5 expression (Angelopoulou et al., 2019). Additionally, miR-26a reduces CDK5 expression through its interaction with the 3′-UTR of the CDK5 gene (Farina et al., 2017).

The MARK family of kinases encompasses MARK1, MARK2, MARK3, and MARK4 (Chudobová and Zempel, 2023). The expression levels of MARK3 and MARK4 proteins in the nervous system significantly increased in patients with AD, correlating with the abnormal phosphorylation of tau (Lund et al., 2014). miR-515-5p has been identified as a negative regulator of MARK4 gene expression (Pardo et al., 2016). Similarly, miR-582-3p acts as a suppressor of MARK3 gene expression (Wang et al., 2023a). While no direct association with AD has been established, the regulatory effects of these miRNAs on MARK3 and MARK4 suggest a potential role in the abnormal phosphorylation of tau.

MiRNAs are crucial in eliminating tau and its phosphorylated form, p-tau. The BCL2-associated athanogene 2 (BAG2) protein is essential for the breakdown of these insoluble aggregates. BAG2 performs this function by binding to Hsp70 at the microtubules, capturing tau, and transporting it to the proteasome for degradation, independent of ubiquitination (Xu et al., 2008; Yang et al., 2023). In this mechanism, miR-128a serves as a pivotal regulator, precisely modulating the BAG2/Hsp70 complex within neuronal cells by specifically targeting the 3′-UTR of BAG2 mRNA (Carrettiero et al., 2009). Furthermore, the degradation of p-tau is significantly regulated by the autophagic pathway. A study conducted on Drosophila involved screening a collection of microRNAs, which led to the identification of the miR-9 cluster as a suppressor of excessive human tau expression (Subramanian et al., 2021). The gene CG11070, targeted by miR-9a, along with its mammalian counterpart UBE4B—a member of the E3/E4 ubiquitin ligase family—was found to alleviate symptoms in a Drosophila model exhibiting tau overexpression (Subramanian et al., 2021). Additionally, overexpression of CG11070 or UBE4B is associated with a reduction in tau phosphorylation. Experiments employing inhibitors targeting autophagy and the proteasome suggest that the autophagy-lysosomal pathway serves as the primary mechanism for tau protein degradation under these conditions. These findings indicate that UBE4B, a gene regulated by miR-9, in conjunction with STUB1, facilitates the autophagic degradation of tau (Subramanian et al., 2021).

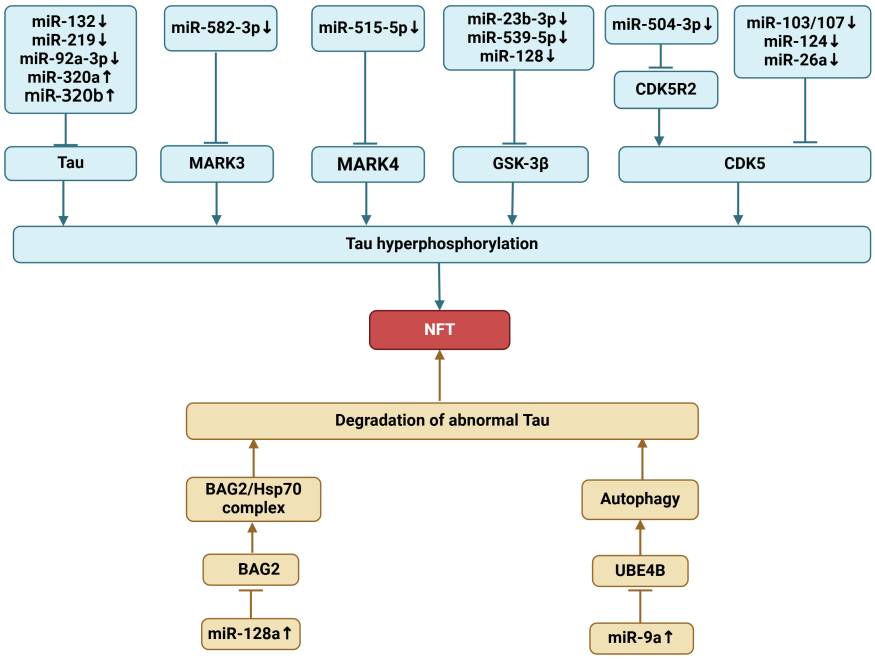

Figure 7 | MiRNAs regulate hyperphosphorylated tau to form NFT.
The figure illustrates how miRNAs regulate tau hyperphosphorylation and abnormal tau degradation. Abnormal tau production is influenced by targeting GSK-3β, CDK5, and the MARK family, while its clearance is affected by regulating BAG2 and UBE4B. Created with BioRender.com. BAG2: bcl2-associated athanogene 2; CDK5: cyclin-dependent kinase 5; CDK5R2: cyclin-dependent kinase 5, regulatory subunit 2; GSK-3β: glycogen synthase kinase 3 beta; HSP70: heat shock protein 70; MARK3: microtubule affinity-regulating kinase 3; MARK4: microtubule affinity-regulating kinase 4; miRNA: microRNA; NFTs: neurofibrillary tangles; UBE4B: ubiquitin-conjugation factor E4 B.

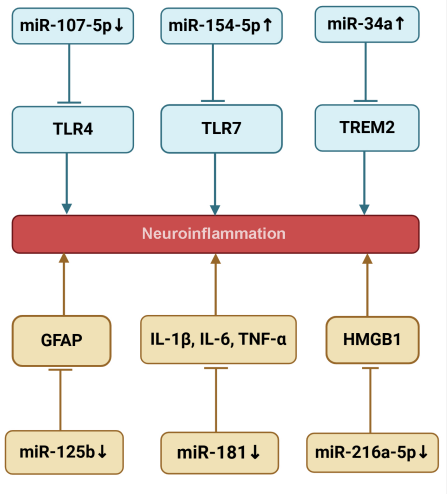

Figure 8 | MiRNAs regulate neuroinflammation.
The figure illustrates how miRNAs influence neuroinflammation by regulating TLR4, TLR7, TREM2, GFAP, IL-1β, IL-6, TNF-α, IL-10, and HMGB1. Created with BioRender.com. GFAP: Glial fibrillary acidic protein; HMGB1: high-mobility group box 1; IL-10: interleukin-10; IL-1β: interleukin-1β; IL-6: interleukin-6; miRNA: microRNA; TLR4: toll-like receptor 4; TLR7: toll-like receptor 7; TNF-α: tumor necrosis factor-α; TREM2: triggering receptor expressed on myeloid cells 2.

MicroRNAs regulate neuroinflammatory response

Various studies highlight the role of miRNAs in regulating neuroinflammatory processes through diverse mechanisms (**Figure 8**).

This regulation occurs by the modulation of microglial and astrocyte activation. Microglial activation is closely associated with a group of proteins, with Toll-like receptors playing a significant role (van Noort and Bsibsi, 2009). MiR-107-5p alleviates neuronal damage in AD rodent models by inhibiting the TLR4/NF-κB signaling cascade (Hu et al., 2024). MiR-107-5p achieves this by directly binding to TLR4, thereby suppressing its expression. Overexpression of miR-107-5p can inhibit microglial activation, reduce hippocampal neuron damage, and enhance cognitive functions related to learning and memory (Hu et al., 2024). In contrast, miR-154-5p directly activates TLR7, triggering cytokine secretion by microglia and leading to neuronal damage (McGurran et al., 2024).

The downregulation of miRNA-34a, which NF-κB regulates, is suggested to reduce TREM2 expression (Zhao et al., 2013). TREM2 functions as a transmembrane receptor that binds to multiple ligands, enhancing the phagocytic activity of microglia to clear pathological substances in the brain, including Aβ deposits (Kawanishi et al., 2018). Additionally, miRNA-34a binds to the 3′-UTR of TREM2, and its inhibition of TREM2 may contribute to compromised phagocytic function, deficiencies in innate immune responses, and progressive inflammatory damage (Zhao et al., 2013).

In AD-affected brains, a significant inverse relationship exists between the decreased expression of GFAP, an indicator of astrocyte activity, and increased levels of miRNA-125b (Pogue et al., 2010). Increased miRNA-125b expression facilitates astrocyte proliferation

and disrupts the normal cell cycle (Pogue et al., 2010). Furthermore, miRNAs play a crucial role in regulating the release of inflammatory cytokines and chemokines during neuroinflammatory responses. Among these, IL-1β, IL-6, and TNF-α are pivotal pro-inflammatory cytokines, while IL-10 functions as an essential anti-inflammatory cytokine. These cytokines are critical for regulating inflammation and immune system function (Pellicanò et al., 2010). Hutchison et al. highlights the role of miR-181 in regulating astrocytic inflammatory responses within the neural system. Inhibition of miR-181 increases the synthesis of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. In contrast, the upregulation of miR-181 significantly increased levels of the anti-inflammatory cytokine IL-10 (Hutchison et al., 2013).

High-mobility group box 1 (HMGB1) plays a significant role in the development of various diseases, including AD. This protein is typically released by activated microglial cells and it stimulates the production of inflammatory cytokines through the activation of specific inflammatory signaling pathways, which subsequently initiates a cascade of neuronal damage and dysfunction (Mo et al., 2023). Furthermore, miRNA miR-216a-5p is pivotal in regulating the HMGB1/NF-κB pathway, identifying HMGB1 as a target gene of miR-216a-5p (Liu et al., 2022). In the hippocampus of rodents of AD, the concentration of miR-216a-5p is reduced, while the levels of HMGB1 protein are increased. Increasing miR-216a-5p levels in mice with AD can improve cognitive functions related to learning and memory, along with reducing neuroinflammatory responses (Liu et al., 2022).

MicroRNAs regulate synaptic dysfunction

Synapses are essential structures that facilitate signal transmission between neurons. The human brain contains a multitude of synapses, which can be classified into two primary types: electrical and chemical synapses (Pereda, 2014). Electrical synapses facilitate rapid signal conduction, while chemical synapses are more numerous and predominant. Chemical synapses transmit information through the release of neurotransmitters. When a signal reaches the presynaptic membrane, calcium channels are activated, allowing calcium ions to flow into the neuron. This influx of calcium ions initiates the fusion of synaptic vesicles with the neuronal presynaptic membrane, resulting in the release of neurotransmitters into the synaptic gap (Fon and Edwards, 2001; Schneggenburger and Neher, 2005).

These neurotransmitters diffuse across the synaptic cleft and bind to receptors on the postsynaptic neuron, eliciting excitatory or inhibitory responses, which depend on the specific receptors that are activated (Petzoldt and Sigrist, 2014). The integrity of synaptic function is crucial for learning and memory processes (Li et al., 2018b). Synaptic dysfunction can result in decreased synaptic plasticity, which is essential for the capacity of the nervous system to adapt, learn, form memories, and store information (Horn, 1991). Synaptic plasticity includes two primary forms: long-term potentiation (LTP) and long-term depression (LTD) (Malenka and Bear, 2004). Abnormalities in synaptic plasticity are significant contributors to mnemonic impairments observed in patients with AD. Reduced synaptic plasticity adversely affects learning and memory capabilities, leading to disruptions in higher cognitive functions, including attention and executive functioning (Boggio et al., 2011).

Changes in synaptic plasticity involve numerous proteins, many of which are regulated by miRNAs (**Figure 9**). In presynaptic neurons, these processes primarily include neurotransmitter synthesis, storage, release, and vesicle recycling (Powell, 2006). Proteins such as the SNARE complex (which includes synaptosomal-associated protein 25 (SNAP25),vesicle-associated membrane protein 2 (VAMP), Syntaxin, and synaptophysin (Syp) are essential for synaptic vesicle release and the subsequent neurotransmitter exocytosis (Wang and Dudko, 2021; Anschuetz et al., 2024). Furthermore, miR-153 directly targets the 3′-UTR of SNAP25 and VAMP2, leading to the post-transcriptional downregulation of these proteins, which are crucial for vesicle release (Yan et al., 2020a). MiR-153 disrupts synaptic vesicle release by inhibiting key proteins involved in vesicle release, leading to a disruption in presynaptic plasticity (Yan et al., 2020a). Additionally, miR-210-5p targets SNAP25, thereby affecting neurotransmitter release (Ren et al., 2018). MiR-34c targets VAMP2 mRNA, modulating its expression (Hu et al., 2015). In patients with AD, VAMP2 is downregulated. However, reducing miR-34c can alleviate Aβ-induced synaptic transmission failure, prevent VAMP2 loss, and improve mnemonic deficits (Hu et al., 2015). MiRNA-455-3p identification by Kumar demonstrates its protective role against abnormal APP processing and Aβ toxicity (Kumar et al., 2019). They found that miR-455-3p can prevent the reduction of Syp caused by mutant APP, thereby mitigating synaptic abnormalities (Kumar et al., 2019).

Proteins associated with postsynaptic neurons play key roles in neurotransmitter uptake, signal propagation, and the maintenance and modulation of synaptic architecture (Ferreira and Paganoni, 2002). Glutamate receptors, including NMDA and AMPA types, are central to these functions. Gunasekaran and Omkumar (2022) found that administering miR-146a or miR-200b into the hippocampus causes cognitive impairments. These miRNAs target the 3′ UTRs of the Grin2A and Grin2B subunits of NMDA receptors, and their overexpression suppresses GluN2A and GluN2B in hippocampal neurons. Rodriguez-Ortiz et al. (2020) identified a novel pathway in which learning in the hippocampus downregulates miR-181a, increasing the protein levels of its target molecule, GluA2. Suppressing miR-181a can restore GluA2 and GluA1 levels in the hippocampus, reversing synaptic plasticity disruptions and mnemonic loss in the AD mouse model (Rodriguez-Ortiz et al., 2020). Furthermore, as early as 2013, Liu et al. proposed that miR-181a represses the synthesis of CREB1, a transcription factor critical for learning and memorial functions. Furthermore, post-synaptic density 95 (PSD-95) plays a key role in the postsynaptic membrane (Savioz et al., 2014). Pang and Shi (2021) introduced the miR-567, NEUROD2, and PSD-95, suggesting that miR-567 suppression increases NEUROD2 and PSD-95 levels. This improvement helps mitigate mild cognitive deficits associated with AD in murine models. Inhibiting miR-142-5p can regulate PSD-95 levels, aiding in the restoration of synaptic function (Song and Kim, 2017).

Long non-coding RNAs in Alzheimer's disease

In AD, lncRNAs are also significant. They regulate multiple key pathways that influence disease progression (**Figure 10**).

Long non-coding RNAs regulate amyloid-β production and clearance

LncRNAs also play a role in the formation of Aβ. Among these, SORL1-AS (also known as 51A) is a lncRNA associated with the SORL1 (Sortilin-related receptor 1) gene, serving as its antisense transcript (Ciarlo et al., 2013). This gene is strongly related to an increased risk of developing AD (Mishra et al., 2023). The 51A variant promotes the expression of alternative splicing protein variants of SORL1, which impairs the normal splicing variant A of SORL1. This impairment alters the processing of APP, leading to internal damage and ultimately increasing amyloid protein secretion (Ciarlo et al., 2013). Additionally, NDM29 is an ncRNA transcribed by Pol III that can induce APP synthesis, thereby increasing Aβ secretion (Massone et al., 2012). Certain lncRNAs can directly regulate BACE1. For instance, BC200 specifically targets BACE1 mRNA(Li et al., 2018a). Li et al. (2018a) demonstrate that BC200 not only increases BACE1 expression but also enhances the production of $A\beta_{1-42}$. Additionally, certain molecules regulate gene expression via competing endogenous RNAs (ceRNAs). In a groundbreaking 2019 study, Zeng et al. discovered that BACE1-AS contains multiple binding sites for miRNAs shared by BACE1. By forming RNA duplexes, BACE1-AS stabilizes BACE1 mRNA, and its overexpression prevents miRNA from binding to BACE1 mRNA, thereby protecting it from degradation (Zeng et al., 2019). A further investigation shows that increasing BACE1-AS levels leads to the suppression of miR-485-5p, which subsequently reduces the inhibition of BACE1 mRNA, as reported by Faghihi et al. (2010). The lncRNA BDNF-AS functions as a competing endogenous RNA in the progression of AD. BDNF-AS enhances BACE1 expression by sequestering miR-5-9p, thereby facilitating amyloid plaque formation (Ding et al., 2022). Additionally, the lncRNA NEAT1 significantly contributes to AD by modulating the miR-124/BACE1 pathway (Zhao et al., 2019). Moreover, suppressing the lncRNA XIST reduces BACE1 levels through miR-124 (Yue et al., 2020). PSEN1 plays a key role in regulating β-amyloid synthesis (Tandon and Fraser, 2002). A report in 2022 suggests that the interaction between lncRNA CYP3A43-2 and miR-29b-2-5p is related to Aβ production (Wuli et al., 2022). Targeting PSEN1 through the lnc-CYP3A43-2/miR-29b-2-5p axis may reduce Aβ plaque formation and enhance cognitive function. Furthermore, decreased levels of miRNA-29b-2-5p have been observed in the frontal cortex of the brains affected by AD (Wuli et al., 2022).

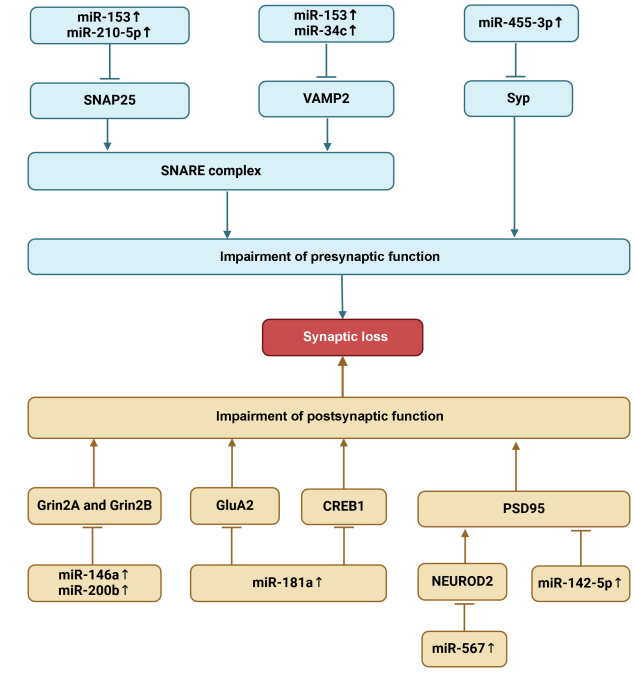

Figure 9 | MiRNAs regulate synaptic dysfunction.
The figure illustrates how miRNAs affect presynaptic and postsynaptic function. It regulates presynaptic function by targeting SNAP25, VAMP2, and Syp and influences postsynaptic function by targeting Grin2A, Grin2B, GluA2, CREB1, and PSD-95. Created with BioRender.com. CREB1: cAMP responsive element binding protein 1; GluA2: glutamate ionotropic receptor AMPA type subunit 2; Grin2A: glutamate ionotropic receptor NMDA type subunit 2A; Grin2B: glutamate ionotropic receptor NMDA type subunit 2B; miRNA: microRNA; NEUROD2: neuronal differentiation 2; PSD-95: postsynaptic density protein 95; SNAP25: synaptosomal-associated protein 25; SNARE: soluble N-ethylmaleimide-sensitive factor attachment protein receptor; Syp: synaptophysin; VAMP2: vesicle-associated membrane protein 2.

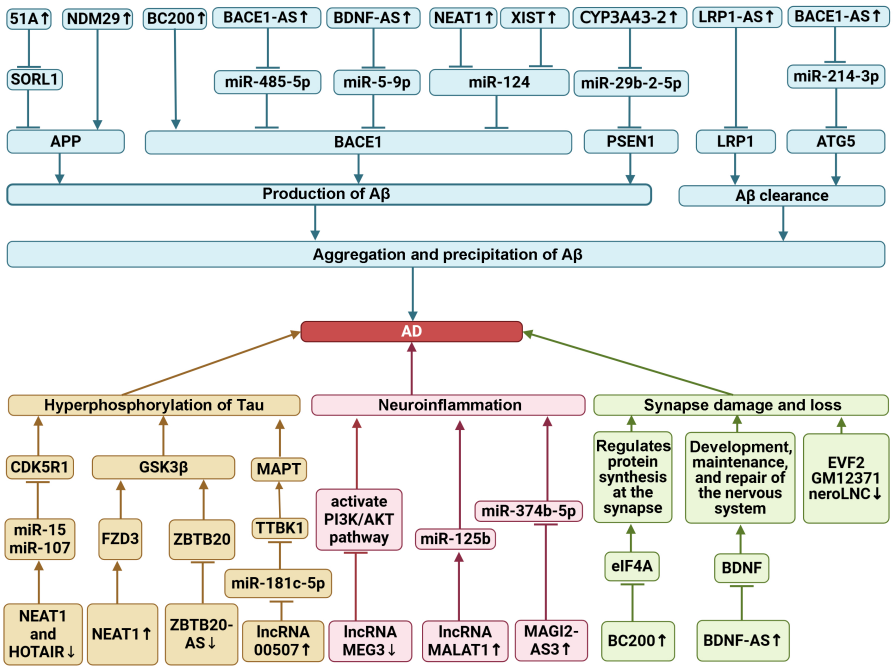

Figure 10 | LncRNAs regulate AD.
The figure illustrates the regulation of lncRNAs in four key areas. The blue boxes focus on how lncRNAs affect Aβ production and clearance by targeting APP, BACE1, PSEN1, LRP1, and ATG5. The tan-colored boxes show how lncRNAs influence AD by influencing abnormal tau and targeting CDK5R1, GSK-3β, and MAPT. The pink boxes highlight the role of lncRNAs in modulating neuroinflammation. The green boxes outline the effects of synaptic damage. Created with BioRender.com. 51A: SORL1 antisense RNA; AD: Alzheimer's disease; Aβ: amyloid-β; BC200: brain cytoplasmic RNA 200; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; BDNF: brain-derived neurotrophic factor; eIF4A: eukaryotic initiation factor 4A; EVF2: DLX6 antisense RNA 1; GSK-3β: glycogen synthase kinase 3β; HOTAIR: HOX antisense intergenic RNA; lncRNA: long non-coding RNA; LRP1: low-density lipoprotein receptor-related protein 1; MAGI2-AS3: MAGI2 antisense RNA 3; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; MAPT: microtubule-associated protein tau; MEG3: maternally expressed gene 3; NDM29: neuroblastoma differentiation marker 29; NEAT1: nuclear-enriched abundant transcript 1; PSEN1: presenilin 1; TTBK1: tau tubulin kinase 1; XIST: X-inactive specific transcript; ZBTB20: zinc finger and BTB domain-containing protein 20.

Low-density lipoprotein receptor-related protein 1 (LRP1) is crucial for the transport and clearance of Aβ (Faissner, 2023). As a carrier protein, LRP1 can form a complex with Aβ, promote the cross-membrane transfer of Aβ, transfer Aβ to the extracellular space or connect to other extracellular spaces, and promote Aβ clearance (Shinohara et al., 2017). The lncRNA LRP1-AS regulates the expression of the LRP1 receptor. Elevated levels of LRP1-AS are associated with reduced stability and inhibited translation of LRP1 mRNA, which is essential for Aβ clearance (Yamanaka et al., 2015). LRP1-AS binds directly to Hmgb2, blocking the Srebp1a-dependent transcription of LRP1, thus impairing the LRP1-mediated removal of Aβ. This interference increases the internalization of APP, leading to higher Aβ production and reduced clearance (Yamanaka et al., 2015). Autophagy is also a key pathway in the progression of AD, playing a significant role in Aβ disposal. The lncRNA BACE1-AS indirectly regulates ATG5 levels by interacting with miR-214-3p, which promotes autophagy-related neuronal damage (Zhou et al., 2021). Suppressing miR-214-3p can reverse the effects of shBACE1-AS and shATG5 in $A\beta_{1-42}$-induced cellular injury.

Long non-coding RNAs regulate tau phosphorylation

LncRNAs can also regulate tau phosphorylation. For example, CDK5R1 encodes p35, a key activator of CDK5. Moncini et al. (2017) uncovered that the miR-15/107 cluster could inhibit CDK5R1 expression, and a reduction in this cluster may lead to increased CDK5 activity owing to higher levels of CDK5R1/p35. Additionally, Spreafico et al. (2018) found that the lncRNAs NEAT1 and HOTAIR suppress CDK5R1 mRNA expression while promoting the miR-15/107 miRNA family. These molecules may have a coordinated regulatory relationship. NEAT1, a significant ncRNA molecule in AD, also affects microtubule integrity by modulating the FZD3/GSK3β/P-tau signaling pathway. Studies on SH-SY5Y cell lines and APP/PS1 murine models show that NEAT1 regulates tau protein phosphorylation through this pathway. This finding clarifies how NEAT1 contributes to tau hyperphosphorylation in AD (Zhao et al., 2020). Another report highlights that lncRNA 00507 interacts with miRNA-181c-5p to regulate the TTBK1/MAPT axis. Dysregulation of lncRNA 00507 is related to abnormal tau phosphorylation in AD (Yan et al., 2020b). The overexpression of the lncRNA ZBTB20-AS1 suppresses ZBTB20 while increasing GSK-3β levels, promoting tau phosphorylation (Wang et al., 2023d). ZBTB20 is a downstream target of lncRNA ZBTB20-AS1. In SH-SY5Y-AD cell lines, elevated levels of lncRNA ZBTB20-AS1 are accompanied by reduced ZBTB20 expression (Wang et al., 2023d).

Long non-coding RNAs regulate neuroinflammatory response

LncRNAs play a key role in regulating neuroinflammation. For example, elevated levels of lncRNA MEG3 enhance cognitive function, reduce neuronal damage, and inhibit the activation of hippocampal astrocytes in patients with AD by blocking the PI3K/Akt signaling pathway (Yi et al., 2019). In contrast, the increased expression

of lncRNA-MALAT1 in AD promotes miR-125b, leading to greater neuronal apoptosis, impaired dendritic growth, and heightened inflammation (Ma et al., 2019). The MAGI2-AS3/miR-374b-5p pathway plays a crucial role in regulating Aβ-induced neurotoxicity in SH-SY5Y cells and neuroinflammation in BV2 cells (Zhang and Wang, 2021). In the AD model, reducing MAGI2-AS3 expression enhances neuronal survival and reduces inflammation. Increasing miR-374b-5p levels yields comparable protective effects (Zhang and Wang, 2021).

Long non-coding RNAs regulate synaptic dysfunction

Furthermore, as AD progresses, synaptic degradation affects multiple cortical networks. The earliest signs of this decline emerge in the entorhinal cortex and hippocampus (Brouillette, 2014). Prolonged disruptions in synaptic plasticity reduce synapse numbers in the early stages of the disease, followed by neuronal loss in later stages (Skaper et al., 2017). LncRNAs play a key role in regulating neuronal and synaptic plasticity, essential for normal development and function, and it is strongly related to AD.

LncRNAs are crucial for regulating synaptic plasticity. BC1/BC200 RNAs play a vital role in controlling neuronal translation, and their loss may lead to abnormal neuronal activity and behavioral issues (Muslimov et al., 1998). BC1 and BC200 RNAs specifically target eIF4A, a key factor in initiating translation (Lin et al., 2008). By regulating synaptic protein synthesis, these RNAs are essential for maintaining long-term synaptic plasticity (Lin et al., 2008). In advanced AD, BC200 levels are abnormally high, significantly exceeding the levels observed in normal aging (Mus et al., 2007). Brain-derived neurotrophic factor (BDNF) is essential for synaptic plasticity. BDNF plays a key role in supporting, maintaining, and repairing the nervous system. It promotes the proliferation, survival, and differentiation of neurons and is heavily involved in forming synaptic connections and facilitating learning (Lu et al., 2014; Numakawa and Kajihara, 2023). BDNF production is suppressed by its antisense RNA, BDNF-As, which negatively regulates BDNF expression (Modarresi et al., 2012). BDNF-As levels in the bloodstream of individuals with AD are significantly elevated (Ding et al., 2022).

Many lncRNAs play a critical role in regulating neuronal maturation and synaptic functions. For instance, EVF2 is essential for the development of GABA-energic neurons (Bond et al., 2009). In hippocampal neurons, the lncRNA GM12371 is primarily located in the nucleus, influencing synaptic transmission, synapse density and structure, and dendritic spine complexity (Raveendra et al., 2018). Moreover, the lncRNA neuroLNC is associated with neurotransmitter activity and synaptic vesicle exocytosis (Keihani et al., 2019). This lncRNA is conserved across species, including rodents and humans, and is specifically expressed in neurons. Regulated by synaptic activity, neuroLNC influences key aspects of neuronal development, such as intracellular calcium influx, neurogenesis, and neuronal migration. These processes may be related to AD.

Circular RNAs in Alzheimer's disease

Figure 11 illustrates how circular RNAs significantly contribute to AD by regulating multiple key pathways. The circHDAC9/miR-138/sirtuin-1 pathway promotes the production of Aβ and induces neurotoxicity, causing synaptic dysfunction and abnormal APP processing (Lu et al., 2019). CircCwc27 binds to Pur-α, preventing Pur-α from attaching to the promoter of the AD gene cluster, including APP, thereby affecting its expression (Song et al., 2022). Additionally, circ_0004381 regulates the expression of the senescence marker PSEN-1 by absorbing miR-647 (Li et al., 2022a). Knocking out circ_0004381 reduces hippocampal neuron damage and promotes M2 microglia polarization via the miR-647/PSEN1 axis, improving cognitive function in an AD murine model (Li et al., 2022a). Furthermore, for Aβ clearance, ciRS-7 targets miR-7, reducing UBE2A levels, which consequently increases Aβ production and prevents the degradation of APP and BACE1 (Zhao et al., 2016). Moreover, hsa_circ_0131235 targets IGF2R, which promotes Aβ peptide clearance and regulates lysosomal enzyme function. Increasing circ_0131235 may help prevent Aβ aggregation and its associated damage (Bigarré et al., 2021). Additionally, for tau phosphorylation, circ-PCCA may inhibit miR-138-5p from activating GSK-3β, thereby promoting tau phosphorylation (Li et al., 2020b).

TREM2 plays a crucial role in neuroinflammatory responses as a key receptor protein on the surface of myeloid lineage cells, such as microglia (Qin et al., 2021). A study by Liu et al. (2022) found that the circular RNA circ-Epc1 interacts directly with miR-770-3p and TREM2. Increased circ-Epc1 expression lowers miR-770-3p levels, consequently boosting TREM2 expression. Research on live models shows that exosomes enriched with circ-Epc1, sourced from adipose-derived stem cells, partially reversed cognitive deficits caused by AD (Liu et al., 2022). This is achieved by improving cognitive function, reducing neuronal injury, and shifting hippocampal microglia from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Consequently, inflammatory cytokines decreased, and hippocampal neuronal apoptosis declined (Liu et al., 2022). Urdánoz-Casado identified a new circular RNA, circTREM2_1, derived from TREM2 (Urdánoz-Casado et al., 2022). circNF1-419 regulates autophagy in astrocytes through the PI3K-I/Akt-AMPK-mTOR and PI3K-I/Akt-mTOR signaling pathways (Diling et al., 2019). In mice, increased circNF1-419 expression enhanced autophagy by interacting with the proteins Dynamin-1 and AP2B1. This interaction modulated inflammatory factors (TNF-α and NF-κB) and reduced AD marker proteins, helping to delay senile dementia (Diling et al., 2019). Yang et al. (2019) identified the circular RNA circ_0000950 in AD, which sponge miR-103, increasing neurotoxic and pro-inflammatory genes such as PTGS2. This mechanism promotes neuronal death, triggers neuroinflammation, and inhibits neurite growth. The circular RNA AXL has emerged as a potential therapeutic target for AD by regulating BACE1 through miR-328 (Li et al., 2022c). CircRNA AXL binds to miR-328, and increasing miR-328 levels reduces the incidence of apoptosis, promotes neurite growth, and lowers inflammatory markers in AD cellular models (Li et al., 2022c). circLPAR1 is significantly upregulated in individuals with AD. The regulatory circuit involving circLPAR1, miR-212-3p, and ZNF217 contributes to neuronal damage caused by Aβ in AD (Wu et al., 2021). Moreover, inhibiting circLPAR1 counteracts neuronal apoptosis, inflammation, and oxidative stress induced by Aβ25-35 (Wu et al., 2021).

A newly discovered circRNA-based regulatory network enhances synaptic function, improving learning abilities and mnemonic impairments (Zhang et al., 2022). This network is regulated by Nrf2, which controls circ-Vps41. Circ-Vps41 positively correlates with Nrf2, synaptic plasticity, learning, and memory. Nrf2 increases circ-Vps41 levels, which subsequently elevates CaMKIV expression (Zhang et al., 2022). Overexpression of circ-Vps41 also boosts Syp levels, enhancing synaptic plasticity and reducing cognitive deficits (Li et al., 2022b). Circ-Vps41 increases Syp expression by directly interacting with miR-24-3p. Additionally, research shows that circHOMER1 supports synaptic function (Urdánoz-Casado et al., 2021). CircHOMER1, a circular RNA abundant in the brain, is derived from exons 2–5 of the HOMER1B mRNA variant (Hafez et al., 2022). The protein produced by the HOMER1 gene is crucial for the function of postsynaptic density (PSD), particularly in regulating synaptic plasticity (Zimmerman et al., 2020). Multiple factors control circHOMER1 production. In neurons, CREB is a key activator, boosting circHOMER1 synthesis and regulating the transcription of essential proteins involved in its formation (Urdánoz-Casado et al., 2021). Moreover, NMDAR inhibition reduces circHOMER1 levels, while mGluR5 receptor activation increases its concentration (Mellios et al., 2024). CircRIMS2 expression is significantly elevated in 4-month-old APP/PS1 rodents (Wang et al., 2023c). This increase in circRIMS2 causes synaptic and mnemonic dysfunction. The study identified miR-3968 and UBE2K as downstream targets of circRIMS2. Elevated UBE2K levels contribute to synaptic dysfunction in AD by ubiquitinating K1082 on GluN2B (Wang et al., 2023c).

Figure 12 provides a comprehensive schematic diagram detailing the roles and mechanisms of ncRNAs (such as miRNA, lncRNA, and circRNA) in AD, highlighting their involvement in key pathological processes. This visual summary highlights the complex regulatory roles of ncRNAs in AD, setting the stage for the discussion of their potential as diagnostic biomarkers and therapeutic targets.

Non-coding RNA in the Diagnosis and Treatment of Alzheimer's disease

Diagnostic and therapeutic role of non-coding RNA in Alzheimer's disease

NcRNAs hold significant potential for therapeutic and diagnostic applications in AD. AD, a neurodegenerative disorder, has a complex etiology influenced by genetics, environmental factors, and aging (Lozupone and Panza, 2024; Oasa et al., 2024). NcRNAs, including miRNAs, lncRNAs, and circular RNAs, are noncoding molecules that play a crucial role in regulating numerous cellular processes (Knight et al., 2024).

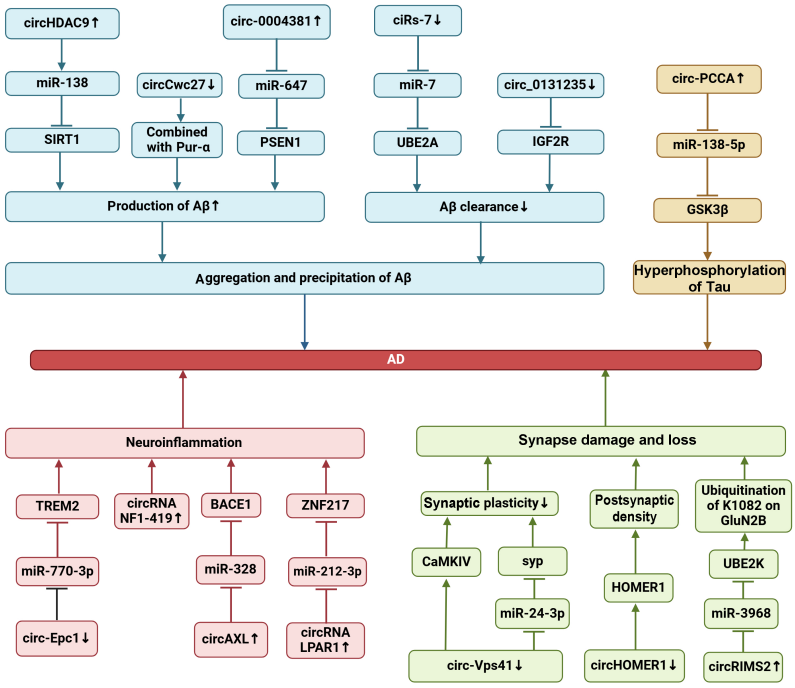

Figure 11 | CircRNA regulates AD.
The figure primarily illustrates the regulation of circRNAs across four various areas. The blue boxes focus on how circRNA influences the production and clearance of Aβ by targeting SIRT1, PSEN1, UBE2A, and IGF2R. The tan boxes detail how lncRNAs affect abnormal tau and influence AD by targeting GSK-3β. The pink boxes outline the effects of lncRNAs on neuroinflammation. The green boxes highlight the influence of synaptic damage. Created with BioRender.com. AD: Alzheimer's disease; Aβ: amyloid-β; CaMKIV: calmodulin-dependent protein kinase 4; circRNA: circular RNA; GluN2B: glutamate ionotropic receptor NMDA type subunit 2B; GSK-3β: glycogen synthase kinase 3β; HOMER1: homer scaffolding protein 1; IGF2R: insulin-like growth factor 2 receptor; lncRNA: long non-coding RNA; Pur-α: purine-rich element-binding protein alpha; SIRT1: sirtuin 1; TREM2: triggering receptor expressed on myeloid cells 2; UBE2K: ubiquitin-conjugating enzyme E2 K; ZNF217: zinc finger protein 217.

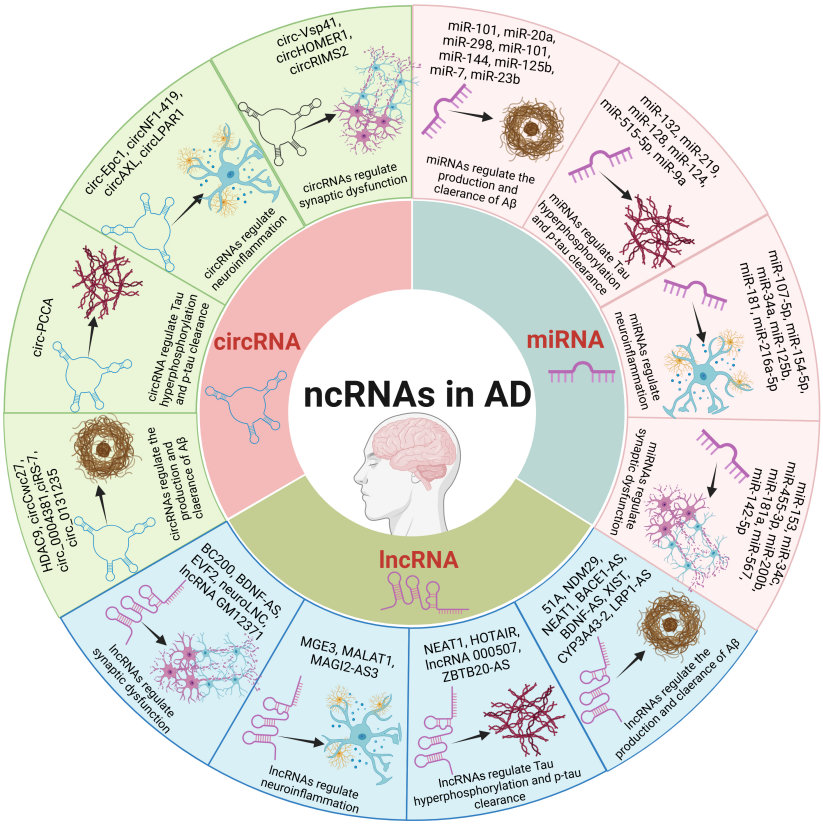

Figure 12 | Schematic overview of ncRNA roles in AD.
This schematic overview illustrates the role and mechanisms of ncRNAs (circRNA, miRNA, lncRNA) in AD, highlighting their involvement in key pathological processes, including Aβ production, tau phosphorylation, neuroinflammation, and synaptic dysfunction. Created with BioRender.com. AD: Alzheimer's disease; Aβ: amyloid-β; circRNA: circular RNA; lncRNA: long non-coding RNA; miRNA: microRNA; ncRNA: non-coding RNA; p-tau: phosphorylated tau.

In medical practice, ncRNAs have gained significant attention as biomarkers owing to their unique expression patterns across various diseases, such as cancer, cardiovascular conditions, and neurological disorders (Cipolla et al., 2018; Kristensen et al., 2019). Measuring ncRNA levels in blood serum or tissue samples allows for their use as non-invasive markers for early disease detection and progression monitoring. A meta-analysis performed by Wang et al. (2020) involving 12 miRNA datasets and three mRNA datasets from the blood of patients with AD revealed five miRNAs as key components of the miRNA-mRNA interaction network. Leidinger et al. (2013) identified a panel of 12 miRNAs that accurately differentiated patients with AD from healthy individuals, with a discrimination accuracy of 93% and a precision of 95%, producing statistically significant results. Additionally, several ncRNAs involved in regulatory processes have been highlighted, including miR-29a/b (Hébert et al., 2008), miR-9 (Subramanian et al., 2021), miR-132 (Smith et al., 2015), BACE1-AS (Zhou et al., 2021), NEAT1 (Zhao et al., 2019, 2020), MALAT1 (Ma et al., 2019), and ciRS-7 (Zhao et al., 2016), all of which show significant expression changes between AD and normal individuals. They also have the potential to serve as biomarkers. Furthermore, many ncRNAs remain unidentified, and it is hoped that further research will develop and validate these molecules as more robust biomarkers for AD.

NcRNAs also present potential as therapeutic targets in drug development. Their abnormal expression is closely related to the onset and progression of various diseases, making the regulation of ncRNA expression or function a promising therapeutic strategy. Approaches such as identifying small molecules that interact with specific ncRNA or designing nucleic acid-based drugs targeting ncRNA offer new avenues for treating diseases related to these molecules. Techniques such as miRNA mimics, inhibitors, and RNA interference for lncRNA or circRNA have been employed to modulate ncRNA levels for therapeutic purposes. Current methods for targeting lncRNA include small interfering RNA (Alshaer et al., 2021), antisense oligonucleotides (ASOs) (Kim, 2023), and CRISPR technology (Manghwar et al., 2019). Small interfering RNA binds complementarily to target lncRNA, silencing or inhibiting their expression and has been successfully applied in various disease models. ASOs, short chemically synthesized single-stranded oligonucleotides, bind to target RNA to trigger its degradation or inhibit transcription, reducing lncRNA expression. CRISPR technology allows precise genome editing and it can be used to modify the genomic sequence of lncRNA for targeted regulation. These methods enable selective modulation of dysregulated ncRNAs in AD, paving the way for more effective targeted therapies.

Furthermore, the expression patterns of ncRNA vary between individuals and environments, highlighting their potential in personalized medicine. Analyzing the ncRNA profile of a patient may enable the development of personalized diagnostic and treatment plans in the future, leading to more effective management of AD.

Challenges in the clinical application of non-coding RNA

NcRNA shows great potential for treating neurodegenerative diseases such as AD; however, its clinical application still encounters numerous challenges.

The primary challenge is delivery, as ncRNA is easily degraded in the body and requires an effective delivery system to reach target cells or tissues while remaining stable (Winkle et al., 2021). Current strategies being explored include chemical modification (Wang et al., 2022) and nanoparticle-mediated delivery (Wang, 2024); however, further research and optimization are necessary. While some ncRNA therapies have shown progress in other diseases, such as cancer (Chen et al., 2022a) and cardiovascular disease (Nappi, 2024), their clinical application in AD continues to face obstacles and demands additional research and validation.

Ensuring treatment specificity is also a crucial issue (Diener et al., 2022). The multi-target mode of action of ncRNAs necessitates extensive preclinical evaluation. One ncRNA can bind to multiple targets, while one mRNA can be regulated by several ncRNAs (Kasinski and Slack, 2011; Gebert and MacRae, 2019). Furthermore, some ncRNAs can target mRNA that play various roles within the same pathway, as seen with miR-34a (Rokavec et al., 2014). Therefore, accurately identifying and validating miRNA target is essential. Ensuring that ncRNAs act only on disease-relevant cells to prevent unintended effects on healthy tissues is essential.

Concerns regarding treatment safety, such as potential adverse reactions, toxicity, and immune responses, limit the clinical application of ncRNA-based therapies (Winkle et al., 2021). NcRNAs or their carriers can exhibit immunogenicity, resulting in immune responses that may reduce the therapeutic efficacy of ncRNA or cause side effects (Nappi, 2024; Seyhan, 2024). Furthermore, as our understanding of ncRNA biology and synthetic oligonucleotide technology deepens, the necessity for systematic preclinical efficacy and safety evaluations of ncRNA-based therapies for AD in relevant disease models becomes increasingly clear. While ncRNA-based strategies may offer certain advantages over traditional AD treatments, it is essential to address the limitations that currently exist within these therapies.

Despite these challenges, advancements in research and technology are anticipated to gradually overcome these obstacles, facilitating successful ncRNA therapies for treating AD. By addressing these issues, ncRNA research in AD shows significant promise, with collaborative efforts expected to accelerate the development of more effective treatments, bringing us closer to combating this neurodegenerative disease.

Limitations

This review had some limitations that warrant acknowledgment. While it extensively examines how ncRNAs regulate AD, it primarily focuses on specific types, such as miRNA, lncRNA, and circRNA. Other emerging classes of ncRNAs, which may also play significant roles in AD pathogenesis, are not adequately addressed. Additionally, the review omits potential causes of AD, including oxidative stress and the detrimental effects of metal ions such as iron and copper, both of which are associated with disease progression. This omission may limit the understanding of the multifaceted nature of AD and the interactions between ncRNAs and these additional pathological factors.

Conclusion and Future Perspectives

This review explores the potential pathogenesis of AD and the production and major regulatory mechanisms of three types of ncRNAs: miRNA, lncRNA, and circRNA. It details how these three ncRNAs regulate key pathological events in AD, such as Aβ production, tau phosphorylation, neuroinflammatory responses, and synaptic dysfunction. **Table 1** summarizes comprehensive studies on the regulation of ncRNAs in AD pathogenesis. Furthermore, this investigation examines the potential use of these ncRNAs as diagnostic indicators and therapeutic targets in medical practice, cataloging various ncRNAs implicated in diverse biological processes. This research opens new avenues for understanding the relationship between AD and ncRNAs. This study examines the potential pathogenesis of AD and the production and key regulatory mechanisms of three types of ncRNAs. It also highlights ongoing challenges in the clinical diagnosis and treatment of ncRNAs, such as issues with delivery mechanisms, accurate targeting, and ensuring treatment efficacy. Numerous studies have demonstrated the critical regulatory role of ncRNAs in AD, particularly in modulating key pathways related to the disorder's pathophysiology. Nonetheless, our understanding of the biological mechanisms and regulatory functions of ncRNAs in the context of AD is still limited, with many aspects needing further investigation. Our review indicates a lack of research on the regulation of tau phosphorylation by circRNAs, which presents a promising area for future study.

Research on the regulation of ncRNA in AD is substantial today; however, several key issues persist. First, few studies were found to synthesize the different types of ncRNAs and the networks they form. The interactions among ncRNAs are highly complex, with current studies primarily focusing on the influence of individual ncRNAs on specific pathologies. These studies rarely consider the network formed by various categories of ncRNAs and their collective effects on target molecules. More comprehensive research is needed to clarify the precise functions of these complex regulatory networks and feedback loops in AD. Second, the roles of ncRNAs at different stages of AD remain unclear, particularly regarding their expression changes and relationship with disease pathology from early to late clinical stages. Investigating the temporal dynamics and stage-specific roles of ncRNAs in AD progression is crucial. Furthermore, although the mechanisms of many ncRNAs in regulating AD have been preliminarily identified, much of this knowledge remains speculative and requires validation through *in vivo* and *in vitro* experiments. Several ncRNAs show promise as biomarkers for AD; however, their clinical relevance must be validated through large-scale, longitudinal studies. Additionally, standardized protocols for detecting and quantifying ncRNAs need to be established. Finally, while ncRNA-based therapies hold potential, they face challenges related to delivery efficiency, specificity, and safety. Developing effective delivery systems and ensuring precise, controlled regulation within the brain remain critical hurdles.

In summary, the relationship between AD and ncRNAs is a promising area of research. ncRNAs offer fresh insights into the pathogenesis of AD and the discovery of new biomarkers and therapeutic targets. Ongoing research is expected to fully illuminate the role of ncRNA regulatory networks in AD, leading to more effective strategies for its prevention and treatment.

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Table 1 | **Studies on the regulation of ncRNAs in Alzheimer's disease pathogenesis**

		Name	Target	Reference
miRNAs	MiRNAs regulate Aβ production	miR-106a, miR-520c	APP	Patel et al., 2008
		miR-101		Hébert et al., 2009
		miR-20a, miR-17-5p and miR-106b		Vilardo et al., 2010
		miR-16		Zhang et al., 2015
		miR-135a,miR-200b		Liu et al., 2014
		miR-153		Long et al., 2012
		miR-298		Chopra et al., 2021
		miR-342-5p		Dong et al., 2022
		miR-346		Long et al., 2019
		miR-30a-5p	ADAM10	Sun et al., 2022
		miR-144		Sun et al., 2017b
		miR-29a, miR-29b-1	BACE1	Hébert et al., 2008
		miR-107		Wang et al., 2008
		miR-186		Kim et al., 2016
		miR-298		Chopra et al., 2021
		miR-34a-5p, miR-125b-5p		Li et al., 2020a
		miR-340		Tan et al., 2020
		miR-34a	Gamma-secretase	Jian et al., 2017
		miR-3940-5p	PSEN1	Qi et al., 2024
	MiRNAs regulate Aβ clearance	miR-7	UBE2A	Zhao et al., 2016
		miR-331-3p, miR-9-5p	Sequestosome1, Optineurin	Chen et al., 2021
		miR-140	PINK1	Liang et al., 2021
		miR-299-5p	Atg5	Zhang et al., 2016
		miR-101a	MAPK	Li et al., 2019
		miR-23b	Atg12	Sun et al., 2018
	MiRNAs regulate abnormal tau phosphorylation	miR-132	tau	Smith et al., 2015
		miR-219		Santa-Maria et al., 2015
		miR-92a-3p, miR-320a ,miR-320b		Piscopo et al., 2023
		miR-23b-3p	GSK-3β	Jiang et al., 2022
		miR-539-5p		Jiang et al., 2020
		miR-128		Li et al., 2023
		miR-504-3p	CDK5	Chen et al., 2022b
		miR-103/107		Peng et al., 2017
		miR-124		Angelopoulou et al., 2019
		miR-26a		Farina et al., 2017
		miR-515-5p	MARK4	Pardo et al., 2016
		miR-582-3p	MARK3	Wang et al., 2023a
	MiRNAs regulate abnormal tau degradation	miR-128a	BAG2	Carrettiero et al., 2009
		miR-9	UBE4B	Subramanian et al., 2021
	MiRNAs regulate neuroinflammation	miR-107-5p	TLR4	Hu et al., 2024
		miR-154-5p	TLR7	McGurran et al., 2024
		miRNA-34a	TREM2	Zhao et al., 2013
		miR-125b	GFAP	Pogue et al., 2010
		miR-181	IL-1β, IL-6, TNF-α	Hutchison et al., 2013
		miR-216a-5p	HMGB1	Liu et al., 2022
	MiRNAs regulate synaptic function	miR-153	SNAP25	Yan et al., 2020a
		miR-210-5p		Ren et al., 2018
		miR-153	VAMP2	Yan et al., 2020a
		miR-34c		Hu et al., 2015
		miRNA-455-3p	Syp	Kumar et al., 2019
		miR-146a	Grin2A and Grin2B	Gunasekaran and Omkumar, 2022
		miR-200b		
		miR-181a	GluA2	Rodriguez-Ortiz et al., 2020
		miR-181a	CREB1	Liu et al., 2013
		miR-567	NEUROD2/PSD95	Pang and Shi, 2021
		miR-142-5p	PSD-95	Song and Kim, 2017
lncRNAs	LncRNAs regulate Aβ production	SORL1-AS51A	SORL1/APP	Ciarlo et al., 2013
		NDM29	APP	Massone et al., 2012
		BC200	BACE1	Li et al., 2018a
		BACE1-AS	miR-485-5p/BACE1	Faghihi et al., 2010
		BDNF-AS	miR-5-9p/BACE1	Ding et al., 2022
		NEAT1	miR-124/BACE1	Zhao et al., 2019
		XIST	miR-124/BACE1	Yue et al., 2020
		lncRNA CYP3A43-2	miR-29b-2-5p/PSEN1	Wuli et al., 2022
	LncRNAs regulate Aβ clearance	LRP1-AS	LRP1	Yamanaka et al., 2015
		BACE1-AS	miR-214-3p/ATG5	Zhou et al., 2021

Table 1 | **Continued**

		Name	Target	Reference
	LncRNAs regulate tau phosphorylation	NEAT1 and HOTAIR	miR-15/107/CDK5R1	Spreafico et al., 2018
		NEAT1	FZD3/ GSK3β/P-tau	Zhao et al., 2020
		lncRNA 00507	miRNA-181c-5p/TTBK1/MAPT	Yan et al., 2020b
		lncRNA ZBTB20-AS1	ZBTB20	Wang et al., 2023d
	LncRNAs regulate neuroinflammation	lncRNA MEG3	PI3K/Akt	Yi et al., 2019
		MAlAT1	miR-125b	Ma et al., 2019
		MAGI2-AS3	miR-374b-5p	Zhang and Wang, 2021
	LncRNAs regulate synaptic function	BC1/BC200	eIF4A	Lin et al., 2008
		BDNF-AS	BDNF	Modarresi et al., 2012
		EVF2		Bond et al., 2009
		GM12371		Raveendra et al., 2018
		neuroLNC		Keihani et al., 2019
circRNAs	CircRNAs regulate Aβ	circHDAC9	miR-138/sirtuin-1	Lu et al., 2019
		circCwc27		Song et al., 2022
		circ_0004381	miR-647/PSEN1	Li et al., 2022a
		ciRS-7	miR-7/UBE2A	Zhao et al., 2016
		circ_0131235	IGF2R	Bigarré et al., 2021
	CircRNAs regulate tau phosphorylation	circ-PCCA	miR-138-5p/GSK- 3β	Li et al., 2020b
	CircRNAs regulate neuroinflammation	circ-Epc1	miR-770-3p/TREM2	Liu et al., 2022
		circNF1-419		Diling et al., 2019
		circAXL	miRNA-328/BACE1	Li et al., 2022c
		CircLPAR1	miR-212-3p/ZNF217	Wu et al., 2021
	CircRNAs regulate synaptic function	circ-Vps41	miR-26a-5p/CaMKIV	Zhang et al., 2022
		circ-Vps41	miR-24-3p/Syp	Li et al., 2022b
		circHOMER1	HOMER1	Urdánoz-Casado et al., 2021
		circRIMS2	miR-3968/UBE2K	Wang et al., 2023c

ADAM10: A disintegrin and metalloproteinase 10; APP: amyloid precursor protein; Atg: autophagy related; Atg5: autophagy related 5; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; BAG2: bcl2-associated athanogene 2; BC200: brain cytoplasmic RNA 200; BDNF: brain-derived neurotrophic factor; CaMKIV: calmodulin-dependent protein kinase 4; CDK: cyclin-dependent kinase; CDK5R: cyclin-dependent kinase 5, regulatory subunit; circRNA: circular RNA; eIF4A: eukaryotic initiation factor 4A; EVF2: DLX6 antisense RNA 1; GFAP: Glial fibrillary acidic protein; GluA2: glutamate ionotropic receptor AMPA type subunit 2; Grin2A: glutamate ionotropic receptor NMDA type subunit 2A; Grin2B: glutamate ionotropic receptor NMDA type subunit 2B; GSK-3β: glycogen synthase kinase 3β; HMGB1: high-mobility group box 1; HOMER1: homer scaffolding protein 1; IGF2R: insulin-like growth factor 2 receptor; IL: interleukin; LRP1: low-density lipoprotein receptor-related protein 1; MAGI2-AS3: MAGI2 antisense RNA 3; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; MARK: microtubule affinity-regulating kinase; miR: microRNA; NDM29: neuroblastoma differentiation marker 29; NEAT1: nuclear-enriched abundant transcript 1; PSD-95: postsynaptic density protein 95; PSEN1: presenilin 1; Syp: synaptophysin; TLR: toll-like receptor; TNF-α: tumor necrosis factor-α; TREM2: triggering receptor expressed on myeloid cells 2; UBE2A: ubiquitin-conjugating enzyme E2 A; UBE4B: ubiquitin-conjugation factor E4 B; VAMP2: vesicle-associated membrane protein 2; XIST: X-inactive specific transcript; ZNF217: zinc finger protein 217.

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