Molecular Insight Into the Therapeutic Potential of Long Non-coding RNA-Associated Competing Endogenous RNA Axes in Alzheimer’s Disease: A Systematic Scoping Review

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Alzheimer’s disease (AD) is a heterogeneous degenerative brain disorder with a rising prevalence worldwide. The two hallmarks that characterize the AD pathophysiology are amyloid plaques, generated via aggregated amyloid β, and neurofibrillary tangle, generated via accumulated phosphorylated tau. At the post-transcriptional and transcriptional levels, the regulatory functions of non-coding RNAs, in particular long non-coding RNAs (lncRNAs), have been ascertained in gene expressions. It is noteworthy that a number of lncRNAs feature a prevalent role in their potential of regulating gene expression through modulation of microRNAs via a process called the mechanism of competing endogenous RNA (ceRNA). Given the multifactorial nature of ceRNA interaction networks, they might be advantageous in complex disorders (e.g., AD) investigations at the therapeutic targets level. We carried out scoping review in this research to analyze validated loops of ceRNA in AD and focus on ceRNA axes associated with lncRNA. This scoping review was performed according to a six-stage methodology structure and PRISMA guideline. A systematic search of seven databases was conducted to find eligible articles prior to July 2021. Two reviewers independently performed publications screening and data extraction, and quantitative and qualitative analyses were conducted. Fourteen articles were identified that fulfill the inclusion criteria. Studies with different designs reported nine lncRNAs that were experimentally validated to act as ceRNA in AD in human-related studies, including BACE1-AS, SNHG1, RPPH1, NEAT1, LINC00094, SOX21-AS1, LINC00507, MAGI2-AS3, and LINC01311. The BACE1-AS/BACE1 was the most frequent ceRNA
INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder (NDD) and is a form of dementia that triggers difficulties with memory, thinking, and behavior (Kang et al., 2020). Based on the Alzheimer’s Association, AD makes up about approximately 60–80% of dementia cases. Currently, worldwide, 50 million people are living with AD and other dementias. AD incidence doubles every 5 years after age 65 (Fan et al., 2020). Symptoms generally develop slowly and aggravate with time. From a hereditary point of view, AD is a heterogeneous polygenic condition. The condition has been categorized into two groups according to age-onset: early-onset AD (EOAD) and late-onset AD (LOAD). LOAD also called sporadic AD (SAD), is the most common type of dementia. AD is a multifactorial condition as a result of interactions between the susceptible genes and environmental factors (Rezazadeh et al., 2019). Genes play an important role in AD. The heritability of LOAD is 58–79%, while it is more than 90% in EOAD. The genetic association has helped us to understand the etiology of AD. Over 50 loci are currently associated with AD. These findings highly suggest that AD is a complex disease (Sims et al., 2020).

Alzheimer’s Disease Pathogenesis

The pathophysiology of AD is defined by the accumulation of β-amyloid peptide (Aβ) in the brain, as well as hyperphosphorylated and cleaved structures of the microtubule-associated protein tau. It is known that metabolic dysfunction of Aβ precursor protein (APP) and abnormal tau protein phosphorylation (Kang et al., 2020) or maybe their interaction with each other (Busche and Hyman, 2020) results in senile plaques and neurofibrillary tangles (NFTs) formation. According to biochemical, behavioral, and genetic research, the pathologic development of the neurotoxic Aβ peptide resulting from serial APP proteolysis is a critical step in AD development. Moreover, APP is metabolized rapidly and in a highly complicated manner by groups of sequential secretases, including β-site APP-cleaving enzyme 1 (BACE1), γ-secretase, and the ADAM family as α-secretases. Regarding tau proteolysis, this process is crucial in neurodegeneration and the tau aggregation process. Tau is a microtubule-associated protein that is predominantly produced in neurons and is encoded by the Microtubule-Associated Protein Tau (MAPT) gene. Intracellular tau is sometimes hyperphosphorylated, resulting in hazardous oligomers and aggregates visible as NFTs (Kang et al., 2020). Aside from the tau and amyloid theory about AD, several additional ideas have been proposed, namely inflammatory reactions, oxidative stress, mitochondrial failure, and cholinergic hypothesis (Li et al., 2021). Although there are numerous hypotheses about AD pathogenesis, the actual triggers and ideal therapy strategies are still elusive.

Keywords: Alzheimer’s disease, antisense oligonucleotides, competing endogenous RNA, long non-coding RNA, miRNA sponge

Antisense Therapeutics

For therapeutic development, RNA is a novel target with numerous advantages, including: (Kang et al., 2020) it is applicable to a majority of RNAs in the cells, such as non-coding RNAs (ncRNAs), (Fan et al., 2020) genetic discoveries can directly be translated to drug discovery, and drug discovery would be more rapid and efficient. Whereas other promising progress has been made in the discovery of small-molecule medicines that affect RNA activity, antisense oligonucleotides (ASOs) provide a far straightforward technique (Bennett et al., 2019). ASOs are synthetic oligonucleotides or oligonucleotide analogs with lengths ranging from 12 to 30 nucleotides (nt) and are engineered for binding to RNA through Watson-Crick base pairing. ASOs can be constructed to bind to both protein-coding RNAs (mRNAs) and ncRNAs, including microRNAs (miRNAs) or long non-coding RNAs (lncRNAs). After ASOs bind with the RNAs of interest, antisense medicine can alter the activity of the RNAs in different ways (Bennett and Swayze, 2010; Crooke et al., 2018).

Long Non-coding RNAs

ncRNAs are classified into two types based on their lengths: short ncRNAs (less than 200 nt) and long ncRNAs (more than 200 nt). IncRNAs range in size from 200 nt to more than 100 kb and often lack a clear open reading frame. LncRNAs, resembling protein-coding genes, are widely transcribed by RNA polymerase II and are frequently post-transcriptionally changed by 5′ capping, 3′ polyadenylation, and RNA splicing processes. However, IncRNAs differ from protein-coding genes in that they possess shorter lengths and exhibit poorer sequence conservation among species (Quinn and Chang, 2016). Many biological functions rely on IncRNAs, including RNA transcription, translation, chromatin and DNA modifications, mRNA stability, and pre-RNA splicing (Li et al., 2021).

Long Non-coding RNAs and mRNA Stability

The rate of mRNA synthesis and degradation determines its steady-state level; hence, the degradation of mRNA is an important factor in controlling gene expression. Previous research has shown that instability of mRNAs that encode
synaptic transmission proteins leads to synaptic function loss in AD pathogenesis (Alkallas et al., 2017). Furthermore, in AD patients, the mRNA degradation rate of AD risk genes is abnormal (Beyer et al., 2009). It has been shown that lncRNAs have a role in AD pathogenesis via regulating mRNA stability (Li et al., 2021).

**Competing Endogenous RNA Hypothesis**

A new mechanism of interaction between RNAs, called ceRNA, is proposed by Pier Paolo Pandolfo’s group in 2011. This hypothesis suggests that cross-talk between RNAs, both coding RNAs and ncRNAs (such as lncRNAs, circRNAs: circular RNAs, and pseudogenes) through miRNA complementary sequences called miRNA response elements (MREs) builds a large-scale regulatory network throughout the transcriptome. Based on the ceRNA hypothesis, if two RNA transcripts regulate each other via a ceRNA mediated mechanism, the expression levels of these two RNA transcripts would be negatively correlated with the levels of target miRNAs, and the expression levels of these two RNA transcripts would be positively associated with each other (Salmena et al., 2011). Figure 1 demonstrates the most simplified ceRNA model. Studies of ceRNA interactions are according to the prediction of target RNA transcripts using multiple software programs (Shuwen et al., 2018) such as StarBase (Li et al., 2014), TargetScan (Agarwal et al., 2015), PicTar (Krek et al., 2005), and StarScan (Liu et al., 2015). These predictions are based on identifying the same MRE within multiple RNA sequences. As the precision of prediction programs is unclear (Amirkhah et al., 2015) due to insufficient raw data for algorithms to reference, the prediction results must still be validated (Shuwen et al., 2018).

Over the last few years, several studies have verified the ceRNA theory. It is well known that the disruption of the equilibrium of ceRNA cross-talk can play a role in various diseases (Sen et al., 2014). So far, the ceRNA mechanisms have been further studied in the field of cancer (Yang et al., 2016). During the last 4 years, the study in the field of NDDs has begun systematically, and significant improvements have been produced. Among NDDs, the ceRNA interactions in AD have been studied to a greater extent (Cai and Wan, 2018). Since 2017, there have been increasing studies to identify the genome-wide ceRNA networks in AD using bioinformatics prediction (Wang et al., 2017; Zhang et al., 2017; Sekar et al., 2018; Wang Z. et al., 2018; Yu et al., 2018; Ma N. et al., 2019; Zhang Y. et al., 2019; Zhou et al., 2019; Ma et al., 2020; Xu and Jia, 2020). Since interaction networks of ceRNAs are multifactorial, they might be advantageous in investigations of complicated diseases, like AD, in terms of therapeutic targets only by targeting one of them, the levels of several disease-related RNAs change at once (Moreno-García et al., 2020).

**Aim of Study**

In this study, we performed a scoping review to analyze validated ceRNA loops in AD. Our focus was on lncRNA-associated ceRNA axes that underlie AD pathophysiology and could potentially be therapeutic targets.

**METHODS**

The strategy for this review was according to the scoping review structure recommended by Arksey and O’Malley (2005) and later improved by Levac et al. (2010). This consists of five distinct steps: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting results. An optional sixth step in the scoping review, consultation, was not used in our study. This review was also well guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist (Tricco et al., 2018).

**Identifying the Research Question**

This study focused on mapping the current literature on lncRNA-associated ceRNA loops in AD. To address this aim, we sought to answer the following question: Precisely what is known from existing literature about lncRNA-associated ceRNA regulatory axes in AD?

**Identifying Relevant Studies**

An initial limited search of PubMed and Embase was performed, and then the keywords in the title and abstract were assessed, as well as the index terms that were utilized in the articles. A second search was performed across PubMed, Embase, Scopus, Web of Science, and Cochrane databases according to specific search tips of each database without any restriction, using keywords, MeSH, or Emtree terms recognized from the primary search. The search strategies for PubMed and Embase are shown in Appendix I. Additionally, searches were also carried out in two gray (i.e., difficult to locate or unpublished) literature databases: Google Scholar and ProQuest. The last search was performed on July 10, 2021. We also examined the reference lists of the relevant literature and review articles for additional sources.

**Selecting Studies**

The included studies fulfilled the following criteria: (1) explicitly discussing the lncRNA-associated ceRNA axes in AD, (2) written in English, and (3) be original research. The exclusion criteria were (1) studies of non-AD or unspecified dementia, (2) studies that did not use human specimens or cell lines, and (3) studies that did not use molecular techniques to validate the components of the ceRNA loop. The title and abstract of articles were first independently screened by three reviewers (HS, NA) for eligibility according to the above criteria. The full texts of the remaining articles were evaluated, and articles going to fulfill the eligibility criteria were included in the final data analysis. Any disagreements were solved through discussion or with a third reviewer (MR) if required.

**Charting the Data**

Three reviewers (HS and NA) independently extracted data into a predesigned charting form in Microsoft Excel. It provided details about the first author, year of publication, origin, type of study, cell line(s), human samples, methods, ceRNAs, shared miRNA(s), and key findings.
Collating, Summarizing, and Reporting the Results

We performed quantitative and qualitative analyses. For the quantitative part, we provided a descriptive numerical summary of the characteristics of the included articles. For the qualitative analysis, we provided a narrative review of the existing information addressing our earlier mentioned research question, focusing on the importance of results in the broader framework as suggested by Levac et al. (2010).

RESULTS

Search Results

The different steps of finding eligible studies are shown in the flow chart in Figure 2. A total of 395 articles were identified from different sources, of which 208 were duplicates. One hundred and fifty-three articles were excluded for irrelevance. The full texts of the remaining 34 articles were evaluated, and 20 more articles were also excluded because they did not validate the components of the ceRNA loop using molecular techniques (Wang et al., 2017; Yu et al., 2018; Zhou et al., 2019; Ma et al., 2020; Xu and Jia, 2020; Huaying et al., 2021; Lu et al., 2021; Ou et al., 2021; Tang et al., 2021; Zhang et al., 2021) and did not use human specimens or cell lines (Jiang et al., 2016; Cai et al., 2017; Wang J. et al., 2018; Wang X. et al., 2018; Ma P. et al., 2019; Zhao et al., 2019; Li L. et al., 2020; Li X. et al., 2020; Yue et al., 2020; Zhou et al., 2020). Lastly, a total of 14 eligible articles remained (Faghihi et al., 2010; Ke et al., 2019; Wang et al., 2019; Zeng et al., 2019; Zhu et al., 2019; Gao et al., 2020; Ge et al., 2020; Gu et al., 2020, 2021; He W. et al., 2020; Yan et al., 2020; Yue et al., 2020; Fan et al., 2021; Zhang and Wang, 2021).

Study Characteristics

The characteristics of the included studies are summarized in Table 1. Almost all studies have been published since 2019. All but one study (Faghihi et al., 2010) was conducted in China. Eleven studies examined the ceRNA regulatory loop on human cell lines (Ke et al., 2019; Wang et al., 2019; Zeng et al., 2019; Zhu et al., 2019; Gao et al., 2020; Ge et al., 2020; Gu et al., 2020, 2021; Yan et al., 2020; Yue et al., 2020; Fan et al., 2021) and three on both human specimens and cell lines (Faghihi et al., 2010; He W. et al., 2020; Zhang and Wang, 2021). All studies with human specimens had a case-control design. One study used brain samples (Faghihi et al., 2010), one used plasma samples (He W. et al., 2020), and one used serum samples (Zhang and Wang, 2021).

Bioinformatics analysis was used to identify the potential ceRNA interactions. Also, different molecular techniques were utilized to validate the components of the ceRNA loop and investigate their involvement in AD pathogenesis. The reported loops are shown in Figure 3. The IncRNA BACE1-antisense (BACE1-AS) was reported in four studies (Faghihi et al., 2010; Zeng et al., 2019; Ge et al., 2020; He W. et al., 2020), two of which had BACE1-AS/miR-485-5p/BACE1 regulatory axis (Faghihi et al., 2010; Zeng et al., 2019), as well as BACE1 was a target mRNA in three studies (Faghihi et al., 2010; Zeng et al., 2019; Zhang and Wang, 2021). The IncRNA small nucleolar RNA host gene 1 (SNHG1) (Wang et al., 2019; Gao et al., 2020) and the
IncRNA ribonuclease P RNA component H1 (*RPPH1*) (Gu et al., 2020, 2021) were each reported in two articles. The remaining ceRNAs were reported once each in six studies (Ke et al., 2019; Zhu et al., 2019; Yan et al., 2020; Yue et al., 2020; Fan et al., 2021; Zhang and Wang, 2021). Among the identified miRNAs, miR-107 was reported in three regulatory axes in three different studies (Ke et al., 2019; Zeng et al., 2019; Yue et al., 2020). According to these results, we found that three independent ceRNA interaction loops (loop A, loop B, and loop C) are regulated by miR-107. Loop A includes nuclear enriched abundant transcript 1 (*NEAT1*) and targets of miR-107, loop B includes SOX21 antisense RNA1 (*SOX21-AS1*) and targets of miR-107, loop C includes *BACE1-AS* and *BACE1* (Figure 4).

**DISCUSSION**

The most contentious issue with ceRNA regulation is whether or not it is effective in physiological contexts. Most studies questioning ceRNA functions reach the conclusion that regulation of ceRNA is highly improbable to yield biologically major impacts at physiological RNA concentrations; however, these experiments cannot rule out the potential of potent miRNA sponges or the marked downregulation or upregulation of ceRNAs and miRNAs at particular developmental stages or subcellular sites (Denzler et al., 2014; Cai and Wan, 2018). There are many reports indicating that ceRNA machinery operates in numerous diseases and that ceRNA is expressed differently with various tissues, cells, and subcellular situations. The literature represents novel visions by which designing ceRNA-mechanism-based therapeutical utilization can be facilitated for the manipulation of special developmental phases and disease pathogenicity with the use of synthesized oligonucleotides specific to sequences (Khvorova and Wolfson, 2012). Over the last decade, significant effort has been put toward the clinical use of RNA-based therapies, mainly using antisense oligonucleotides as well as small interfering RNAs, with many obtaining Food and Drug Administration (FDA)
TABLE 1 | Characteristics of studies included in the scoping review.

| First author | Year of publication | Origin | Type of study | Cell line(s) | Human samples | Methods | ceRNAs | Shared miRNA(s) | Key findings | References |
|--------------|---------------------|--------|---------------|--------------|---------------|---------|--------|----------------|--------------|------------|
| Faghihi et al. | 2010 | United States | Case-control, cell culture | HEK293T | Brain | Bioinformatics analysis, RT-PCR, high-throughput sequencing, enzyme complementation assay, luciferase activity assay | BACE1-AS and BACE1 | miR-485-5p | BACE1-AS and to a lower level BACE1 were up-regulated, and the expression of miR-485-5p was decreased in AD patients | Faghihi et al., 2010 |
| Ke et al. | 2019 | China | Cell culture | SH-SYSY, SK-N-SH, HEK293T | – | Bioinformatics analysis, qRT-PCR, cell viability assay, immunofluorescence, cell apoptosis assay, western blot, luciferase activity assay, RIP assay | NEAT1 and targets of miR-107 | miR-107 | NEAT1 had been up-regulated in Aβ-treated cell lines. It was pointed out as a sponge of miR-107. Knockdown of NEAT1 attenuated Aβ induced inhibition of viability and promotion of apoptosis and p-tau levels. miR-107 was down-regulated, and it reversed Aβ-induced injury when overexpressed in Aβ-treated cells. | Ke et al., 2019 |
| Wang et al. | 2019 | China | Cell culture | SH-SYSY, HEK293T | – | Bioinformatics analysis, RNA interference, qRT-PCR, western blot, MTT assay, flow cytometry, MMP assay, caspase-3 activity assay, luciferase reporter assay | SNHG1 and KREMEN1 | miR-137 | Neuronal cell damage caused by Aβ increased the expression of SNHG1. SNHG1 acted as a sponge for miR-137, and the knockdown of SNHG1 applied its neuronal protective effects through inhibiting KREMEN1. | Wang et al., 2019 |
| Zeng et al. | 2019 | China | Cell culture | HEK293 T, SH-SYSY, U251 | – | Bioinformatics analysis, RIP assay, western blot, real-time PCR, RNA interference, dual-luciferase assay | BACE1-AS and BACE1 | miR-29b-3p/miR-107/miR-124-3p/miR-485-5p/miR-761 | The overexpression of BACE1-AS repressed the miRNAs that target BACE1 and increased Aβ levels. Knockdown of BACE1-AS increased the expressions of these miRNAs and reduced the expression of BACE1. | Zeng et al., 2019 |
| Zhu et al. | 2019 | China | Cell culture | hCMEC/D3, HEK293T | – | Bioinformatics analysis, real-time PCR, microarrays, TEER assays, western blot, immunofluorescence, reporter assay, RIP assay | LINC00094 and SH3GL2 | miR-224-5p | LINC00094 was dramatically increased in the Aβ-incubated BBB model. LINC00094 reduction inhibited the expression of SH3GL2 through up-regulation of miR-224-5p/miR-497-5p and finally resulted in alleviated permeability of BBB in the AD microenvironment. | Zhu et al., 2019 |
| Gao et al. | 2020 | China | Cell culture | SK-N-SH, CHP 212 | – | Bioinformatics analysis, CCK8 assay, qRT-PCR, flow cytometry, western blot, ELISA, RNA interference, dual-luciferase reporter assay, RIP assay | SNHG1 and ZNF217 | miR-361-3p | SNHG1 expression was positively regulated by Aβ and negatively regulated by resveratrol. It sponged miR-361-3p and promoted cell injury via SNHG1/miR-361-3p/ZNF217 axis. SNHG1 knockdown could reverse the promotion effect of Aβ on cell injury. | Gao et al., 2020 |
| He et al. | 2020 | China | Case-control, cell culture | SK-N-SH, SK-N-AS | Plasma | Bioinformatic analysis, RNA interference, qRT-PCR, cell proliferation assay, flow cytometry, western blot, luciferase activity assay | BACE1-AS and targets of miR-214-3p | miR-214-3p | Up-regulation of BACE1-AS and down-regulation of miR-214-3p was found in the cell models treated with Aβ and isoflurane, as well as plasma samples of AD patients. BACE1-AS sponged miR-214-3p and exacerbated isoflurane-induced neurotoxicity. Both BACE1-AS reduction and miR-214-3p up-regulation reversed the suppression of proliferation and the facilitation of apoptosis and autophagy of Aβ-treated induced by isoflurane. | He W. et al., 2020 |

(Continued)
TABLE 1 | (Continued)

| First author | Year of publication | Origin | Type of study | Cell line(s) | Human samples | Methods | ceRNAs | Shared miRNA(s) | Key findings | References |
|--------------|---------------------|--------|---------------|--------------|---------------|---------|---------|----------------|-------------|------------|
| Xu et al.    | 2020                | China  | Cell culture  | SH-SYSY, SK-N-SH | –             | Bioinformatics analysis, RNA interference, qRT-PCR, cell viability assay, flow cytometry, western blot, dual-luciferase reporter assay, RIP assay | SOX21-AS1 and targets of miR-107 | miR-107 | Up-regulation of SOX21-AS1 and down-regulation of miR-107 were seen in Aβ-treated cell models. SOX21-AS1 sponged miR-107, and its silencing reduced Aβ-induced neuronal damage. | Yue et al., 2020 |
| Yan et al.   | 2020                | China  | Cell culture  | SH-SYSY       | –             | Bioinformatics analysis, RNA interference, qRT-PCR, western blot, FISH, luciferase reporter assay | LINC00507 and MAPT/TTBK1 | miR-181c-5p | The Up-regulation of LINC00507 was seen in the AD model. LINC00507 sponged miR-330-5p and caused the up-regulation of MAPT/TTBK1. This axis regulates tau hyperphosphorylation via P25/P35/GSK3β signaling pathway. | Yan et al., 2020 |
| Gu et al.    | 2020                | China  | Cell culture  | SK-N-SH       | –             | MTT assay, flow cytometry, caspase-3 activity, qRT-PCR, western blot, dual-luciferase reporter assay | RPPH1 and WNT1 | miR-122 | Over-expressed RPPH1 activated Wnt/b-catenin signaling to ameliorate amyloid-β induced neuronal apoptosis through direct miR-122. | Gu et al., 2020 |
| Ge et al.    | 2020                | China  | Cell culture  | HPN, SK-N-SH, HEK297T | –             | Bioinformatics analysis, MTT assay, cytotoxicity assay, apoptosis assay, western blot, qRT-PCR, RNA interference, dual-luciferase reporter assay | BACE1-AS and targets of miR-132-3p | miR-132-3p | The combined therapy of Berberine treatment with BACE1-AS depletion protected neuronal cells against Aβ25–35 through the BACE1-AS/miR-132-3p axis. | Ge et al., 2020 |
| Gu et al.    | 2021                | China  | Cell culture  | SH-SYSY       | –             | MTT assay, qRT-PCR, fluo-4 NW calcium assay, apoptosis assay, western blot, dual-luciferase reporter assay | RPPH1 and PKM2 | miR-326 | RPPH1 directly targeted miR-326. Thereby its inhibitory impact on the expression of PKM2 was counteracted, helping to attenuate endoplasmic reticulum stress and apoptosis caused by Ab25-35. | Gu et al., 2021 |
| Zhang and Wang | 2021                | China  | Case-control, cell culture | SH-SYSY, BV2, HEK293 | Serum  | RNA interference, dual-luciferase reporter assay, qRT-PCR, MTT assay, ELISA | MAGI2-AS3 and BACE1 | miR-374b-5p | The MAGI2-AS3 expression was increased, and miR-374b-5p expression was declined in cell models exposed to Aβ25–35. The miR-374b-5p and MAGI2-AS3 serum levels in patients with AD showed a negative correlation; however, they were correlated with the severity of the disorder. MAGI2-AS3 reduction enhanced neuronal viability and attenuated neuroinflammation in AD. The neurotoxicity induced by Aβ is regulated by MAGI2-AS3/miR-374b-5p axis. | Zhang and Wang, 2021 |
| Fan et al.   | 2021                | China  | Cell culture  | SH-SYSY       | –             | Bioinformatics analysis, qRT-PCR, RNA interference, apoptosis assay, proliferation assay, autophagy assay, endogenous APP assay, dual-luciferase reporter assay | LINC01311 and targets of miR-146a-5p | miR-146a-5p | LINC01311 was downregulated, whereas miR-146a-5p was up-regulated in the AD cell model. LINC01311 up-regulation and hsa-miR-146a-5p downregulation led to the protection of the apoptosis induced by AB1-42, autophagy, decelerated proliferation, and accumulation of APP in cell models of AD. | Fan et al., 2021 |

Aβ, amyloid-beta; BBB, blood–brain barrier; AD, Alzheimer’s disease; CCK8, cell counting kit 8; ceRNA, competing endogenous RNA; circRNA, circular RNA; ELISA, enzyme-linked immunosorbent assay; FISH, fluorescence in situ hybridization; lncRNA, long non-coding RNA; miRNA, microRNA; MMD, mitochondrial membrane potential; qPCR, quantitative polymerase chain reaction; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; RIP, RNA immunoprecipitation; RT-PCR, reverse transcription-polymerase chain reaction.
FIGURE 3 | Validated lncRNA-associated ceRNA axes in Alzheimer’s disease. The loops were visualized using Cytoscape v3.8.0 software (Shannon et al., 2003) based on lncRNA–miRNA–mRNA interactions. Red represents the damaging role, and blue represents the protective role of competing endogenous RNA axes. LncRNAs, miRNAs, and mRNAs are represented by hexagon, round rectangle, and ellipse, respectively. LncRNA, long non-coding RNA; miRNA, microRNA.

approval (Winkle et al., 2021). However, trial findings have been mixed, with some research claiming strong benefits and others showing minimal effectiveness or toxicity. Alternate entities, including lncRNA-based therapies, are gaining interest (Winkle et al., 2021). The lncRNAs’ wide function offers many possibilities for clinical application, the methods of which must be adapted to the lncRNA’s mode of action (Arun et al., 2018). Investigating natural antisense transcripts (NATs): lncRNAs that are transcribed from opposite strands of adjacent genes and negatively regulate them in cis is an intriguing discovery. AntagoNATs are ASOs that target NATs and have demonstrated extremely promising preclinical findings for gene reactivation in the central nervous system (CNS) (Winkle et al., 2021). AntagoNATs effectively increased the expression of brain-derived neurotrophic factor (BDNF), a protein important in memory development (Modarresi et al., 2012), and the healthy allele of SCN1A, the haploinsufficiency of which triggers Dravet syndrome (Hsiao et al., 2016). Remarkably, BDNF-AS-targeting antagoNATs were effectively delivered across the blood–brain barrier in a murine model utilizing a minimally invasive nasal depot (MIND). MIND is a medication delivery system that directs drug administration to the olfactory submucosal region and has achieved about 40% effectiveness compared to riskier invasive delivery methods (Padmakumar et al., 2021). Such encouraging findings imply that lncRNA-based therapies will soon enter clinical testing. Moreover, the therapeutical impact of ASO-based lncRNA knockdown has shown promise in patients with Angelman syndrome, a single-gene illness represented by intellectual disability (Bird, 2014; Meng et al., 2015). Despite no development of ASOs that target lncRNA in the therapy of NDDs, ASOs that target mRNAs have received approval by the FDA for the therapy of Duchenne muscular dystrophy and spinal muscular atrophy (Wurster and Ludolph, 2018). Furthermore, ASOs have presented potential effectiveness in the therapy of Huntington’s disease (HD) by affecting the huntingtin gene (HTT) as the target, in the therapy of amyotrophic lateral sclerosis by influencing SOD1 and C9ORF72 as the targets, and in the therapy of AD by affecting MAPT (tau) as the target (Scoles et al., 2019). Hence, lncRNAs and lncRNA-associated ceRNA axes can also serve as a new therapeutic target for AD therapy. In this study, we performed a scoping review and identified nine lncRNAs that were experimentally validated to act as ceRNA in AD in human studies. These lncRNAs are discussed below.

BASE1-AS

As mentioned above, in AD patients, the extracellularly deposited plaque of the Aβ peptide is one of the representative pathologic signs. To produce Aβ, APP needs to be sequentially cleaved proteolytically with β-secretase and γ-secretase. BACE1 is a critical enzyme in AD pathophysiology responsible for Aβ plaque formation through the cleavage of APP in collaboration with γ-secretase. Thus, a misregulated BACE1 can have a major contribution to this pathologic event. Both miRNAs and lncRNAs have been involved in regulating BACE1 post-transcriptionally, with which lncRNA BACE1-AS has the utmost relevance (Zeng et al., 2019). The lncRNA BACE1-AS was the first validated component of a ceRNA loop described in AD pathogenesis. Both BACE1-AS and BACE1 mRNA transcripts...
originates from a similar locus in chromosome 11 in humans; the transcription of BACE1 mRNA and BACE1-AS is triggered from the sense and antisense strands, respectively. An RNA duplex is formed by pairing BACE1-AS to BACE1, leading to a structurally changed BACE1 and improved stabilities of mRNA. Consequently, BACE1-AS has a role in increasing both the mRNA and protein concentrations of BACE1 (Faghihi et al., 2008, 2010). This cRNA pair was identified to be critical in AD pathogenesis through BACE1 post-transcriptional regulation (Faghihi et al., 2010). It was also shown that BACE1-AS and a lower level BACE1 were up-regulated, and the expression of miR-485-5p was decreased in the brain of AD patients (Faghihi et al., 2010). The second study showed that BACE1-AS prevented BACE1 mRNA degradation by sponging miR-29b-3p/miR-107/miR-124-3p/miR-485-5p/miR-761 in the pathophysiology of AD. In addition to the mentioned cRNA pair, it was shown that BACE1-AS exacerbated isoflurane (anesthetic)-induced neurotoxicity by BACE1-AS/miR-214-3p axis in AD (He W. et al., 2020). This drug increases the risk of AD by increasing Aβ production and its oligomerization, as well as neuronal apoptosis (Xie et al., 2006, 2008; Xie and Xu, 2013). It is noteworthy that increased expression of BACE1-AS and down-regulation of miR-214-3p in the plasma samples of AD patients was also reported. In addition, BACE1-AS is a cRNA for miR-132-3p. This axis was involved in the berberine-mediated neuroprotective effect in AD (Ge et al., 2020). Berberine is an isooquinoline alkaloid found in many medicinally important plants (Kumar et al., 2015). Berberine has been reported to play a crucial role in AD treatment (Yuan et al., 2019).

**MAGI2 Antisense RNA 3 (MAGI2-AS3)**

Alongside BACE1-AS, MAGI2-AS3 (via miR-374b-5p) could reportedly regulate BACE1 mRNA levels, Aβ-induced neurotoxicity, and neuroinflammation in AD (Zhang and Wang, 2021). This underlines that the BACE1 is complexly regulated in AD by the mediation of multiple cRNA networks. It was also shown that serum MAGI2-AS3 and miR-374b-5p expression was significantly up-regulated and down-regulated in AD patients compared with healthy controls, respectively (Zhang and Wang, 2021). LncRNA MAGI2-AS3 is reportedly a sponger of miR-374b-5p in ovarian carcinoma and hepatocellular carcinoma (Gokulnath et al., 2019; Yin Z. et al., 2019). It has been found to be involved in regulating cell survivability in a variety of diseases (Cao et al., 2020; He J. et al., 2020). There are also reports on the association between MAGI2-AS3 and chronic inflammatory illnesses (Liao et al., 2020).

**SNHG1**

In AD pathology, SNHG1 involves in Aβ-induced neuronal injury via two different cRNA regulatory axes, SNHG1/miR-137/Kringle containing transmembrane protein 1 (KREMEN1) (Wang et al., 2019) and SNHG1/miR-361-3p/zinc finger gene 217 (ZNF217) (Gao et al., 2020). SNHG1 has been well-studied in different types of cancers due to its oncogenic role (Huang et al., 2018). It is shown that it can also promote neuronal autophagy and neuroinflammation in Parkinson’s disease (PD) (Cao et al., 2018; Chen et al., 2018b). KREMEN1 encodes a receptor for Dickkopf (DKK) proteins that functionally cooperates with DKK1/2 to inhibit wingless (WNT)/beta-catenin signaling (Mulvaney et al., 2016; Stelzer et al., 2016). It exerts its pro-apoptotic activity in a Wnt-independent pathway (Causseret et al., 2016). It has been shown that the silencing of KREMEN1 prevents Aβ-mediated synapse loss in AD (Ross et al., 2018). Besides, the oncogenic role of ZNF217 has been shown in many cancers (Quinlan et al., 2007). In AD studies, the down-regulation of ZNF217 could relieve Aβ-induced neurotoxicity (Wang J. et al., 2018). It has also been shown that the neuroprotective effect of resveratrol could occur through SNHG1/miR-361-3p/ZNF217 axis (Gao et al., 2020). Resveratrol is a polyphenolic compound that its high concentrations are found in red grapes, blueberries, and peanuts (Evans et al., 2017). Various studies have proved its antioxidant and anti-inflammatory effects on AD (Gomes et al., 2018; Corspas et al., 2019; Kong et al., 2019).

**NEAT1**

NEAT1 aggravated Aβ-induced neuronal injury via acting as a sponge for miR-107 (Ke et al., 2019). Knockdown of NEAT1 attenuated Aβ induced inhibition of viability and promotion of apoptosis and p-tau levels. MiR-107 was down-regulated, and it reversed Aβ-induced injury when overexpressed in Aβ-treated cells (Ke et al., 2019). NEAT1 is frequently overexpressed in human tumors and proposed as a novel target for human cancer therapy and diagnosis by sponging miRNAs (Dong et al., 2018). According to previous studies, it also has a crucial role in HD and PD (Chanda et al., 2018; Liu and Lu, 2018). In AD studies, its increased expression levels were shown in brain tissues of AD patients, compared to controls (Spreafico et al., 2018).

**SOX21-AS1**

SOX21-AS1, similar to NEAT1, exacerbated Aβ-induced neuronal injury via sequestering miR-107 (Yue et al., 2020). SOX21-AS1 is a recently discovered lncRNA that can suppress neuronal apoptosis of hippocampal cells and mitigate oxidative stress in AD, hence, being involved as an agent in AD pathogenicity (Zhang L. et al., 2019).

It is noteworthy that, as mentioned above, the present study identified that miR-107 was at the center of three different loops, as shown in Figure 4, which suggests it is a key miRNA for both biological researches and cRNA-based therapeutic purposes in AD studies. The miR-107 family is a group of evolutionarily conserved miRNAs that show high expression in the human cerebral cortex. Numerous studies have shown misregulation of this miRNA in AD brains (Wang et al., 2008; Gupta et al., 2017; Moncini et al., 2017). It has been shown that it may have a protective role in AD by preventing Aβ-induced blood-brain barrier (BBB) disruption, endothelial cell dysfunction (Liu et al., 2016), and Aβ-induced neuronal damage (Jiao et al., 2016; Shu et al., 2018; Chen et al., 2020). miR-107 shows a certain potential to be used as a biomarker in AD (Herrera-Espejo et al., 2019; Prendkci et al., 2019; Swarbrick et al., 2019). The cRNA interactions are mediated by miRNAs, and altered miRNAs expression result in dysregulation of its competitive interactors. On the other hand, it is hypothesized that cRNA
FIGURE 4 | miR-107 regulates different competing endogenous RNA (ceRNA) loops. Loop A (NEAT1 and targets of miR-107), loop B (SOX21-AS1 and targets of miR-107), and loop C (BACE1-AS and BACE1) were all regulated by miR-107. Red represents the damaging role of ceRNA axes. Lon non-coding RNAs, microRNAs, and mRNAs are represented by hexagon, round rectangle, and ellipse, respectively.

in the modules play a role in disease progression as a whole instead of acting individually (Chen et al., 2018a). Thus, these identified ceRNA modules comprising NEAT1, SOX21-AS1, BACE1-AS, miR-107, targets of miR-107, and BACE1 can be further assessed as potential ceRNA modules for ceRNA-based therapeutic purposes in AD.

Long Intergenic Non-protein Coding RNA 507 (LINC00507)

It was reported that LINC00507/miR-181c-5p/tau-tubulin kinase-1 (TTBK1)/MAPT axis regulated tau hyperphosphorylation via P25/P35/GSK3β signaling pathway (Yan et al., 2020). LncRNAs are a subclass of lncRNAs. LINC00507 has an age-dependent expression pattern and is specifically expressed in the primate cortex (Mills et al., 2016). MAPT encodes the tau protein, and TTBK1 is a CNS-specific protein kinase that involves in tau hyper-phosphorylation and deposition in AD (Ikezu and Ikezu, 2014). It also has been shown that P25/P35/GSK3β signaling pathway deteriorates tauopathy (Noble et al., 2003).

Long Intergenic Non-protein Coding RNA 94 (LINC00094)

As indicated in previous reports, LncRNA LINC00094 (called BRD3OS as well) is involved in regulating BBB penetrability in the AD microenvironment by sponging miR-224-5p and miR-497-5p, and SH3GL2 mRNA is targeted by both of them (Zhu et al., 2019). LINC00094 may reportedly act as a prognostic biomarker of lung cancer (Li et al., 2017). Additionally, microarray examination revealed the LINC00094 down-regulation in Memantine-incubated cells. As an N-methyl-D-aspartate (NMDA) receptor antagonist, memantine has received wide applications for AD treatment (Zhu et al., 2019). SH3GL2 encodes Endophilin-1, an endocytosis protein that has a marked increase in the AD brain and is responsible for Aβ-induced postsynaptic dysfunction (Yin Y. et al., 2019).

Long Intergenic Non-protein Coding RNA 1311 (LINC01311)

It was reported that the LINC01311/hsa-miR-146a-5p axis could operate as a functional regulator in AB1-42-stimulated apoptosis, proliferation slowdown, autophagy, and accumulated APP in human-lineage neurons (Fan et al., 2021). As a new lncRNA, LINC01311 was discovered throughout human genome-wide screening, which has an aberrant expression in human liver and prostate cancers (Zhu et al., 2016; Imada et al., 2020). However, the functional activity of LINC01311 has never been clarified in other human disorders.

RPPH1

Unlike the lncRNAs discussed above, RPPH1 apparently exerts a neuroprotective compensatory mode of action in AD pathology via two varying ceRNA axes: RPPH1/miR-122/WNT1
(Gu et al., 2020) and RPPH1/miR-326/pyruvate kinase M2 (PKM2) (Gu et al., 2021). Specifically, evidence indicates that it can mitigate Aβ25–35-stimulated neuronal damage, apoptosis, and endoplasmic reticulum stress (Gu et al., 2020, 2021). RPPH1 is the RNA component of RNase P, which plays a role in tRNA maturation in Archaea, Bacteria, and Eukarya (Evans et al., 2006). Wnt/β-catenin signaling has a confirmed essential function in developing AD. Huperzine A, which reversibly and selectively inhibits acetylcholinesterase and is utilized for AD treatment, has been reported to have a neuroprotecting impact by activating Wnt/β-catenin signaling in AD (Wang et al., 2011). As shown previously, the BBB failure in AD is caused by an impaired Wnt/β-catenin signaling (Liu et al., 2014). Besides, research indicates that activating the Wnt/β-catenin signaling is capable of protecting neuronal cells by regulating survival and c-myc, as well as apoptosis-linked proteins Bcl-2 and Bax (Jeong et al., 2014). As a glycolytic sensor, PKM2 has a crucial contribution to the dephosphorylation of phosphoenolpyruvate to pyruvate and catalysis of the final stage of glycolysis (Nakatsu et al., 2015). The emergence of recent documentation has highlighted that PKM2 is involved in AD. According to reports, oxidatively inactivated PKM2 had an association with the progress of AD from mild cognitive impairment (Butterfield et al., 2006). The poly(ADP-ribose)/polymerase 1 could also modulate PKM2, indicating that the PKM2-linked glycolytic pathway has a contribution to AD (Martire et al., 2016).

**Limitations of Scoping Review**

A scoping review is different from a systematic review. It systematically studies the literature, quantitatively synthesizes the accomplishments and sums up the gaps in a particular field's literature rather than evaluating it to offer a solution to a particular question. The approach is not substantially different from a systematic review, but an evaluation of methodological limitations or risk of bias of the evidence contained in a scoping review is not usually undertaken. A scoping review is often conducted before a systematic review to examine the literature and determine pertinent research topics to be addressed by a subsequent systematic review. Additionally, a scoping review does not seek to aggregate results via meta-analysis but rather maps the literature to determine themes, gaps, and patterns (Arksey and O’Malley, 2005; Levac et al., 2010). Because ceRNAs and AD is relatively new, a scoping review was conducted to evaluate the extent, scope, and type of research effort in this field to bring attention to topics where further study is required. Our results, however, should be interpreted with caution because we decided to perform a scoping review, which omits quality evaluations of the articles. The most significant limitation of this study is most likely the dearth of evidence available for review.

**CONCLUSION**

LncRNA-associated ceRNA regulation produces biologically significant effects in various diseases so it can elucidate the pathogenic procedures and offer options for new therapies. Thus, our efforts to understand different aspects of ceRNA regulatory mechanisms in AD pathogenesis provide new insights into the potential molecular targets, discover ceRNA-based biomarkers, and design ceRNA-based therapeutic applications.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

**AUTHOR CONTRIBUTIONS**

MT, MR, and HS wrote the draft and revised it. MA, YD, OR, AJ, and NA collected the data and designed the tables and figures. All authors read the draft and approved the submitted version.

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