

## Review article:

# INSIGHTS INTO THE MECHANISMS OF NON-CODING RNAS' IMPLICATION IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

Majid Khodayi-Shahrak<sup>1</sup>, Mohammad Khalaj-Kondori<sup>1\*</sup>,  
Mohammad Ali Hosseinpour Feizi<sup>1</sup>, Mahnaz Talebi<sup>2</sup>

<sup>1</sup> Department of Animal Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran

<sup>2</sup> Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

\* **Corresponding author:** Mohammad Khalaj-Kondori, Department of Animal Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran.  
E-mail: [khalaj@tabrizu.ac.ir](mailto:khalaj@tabrizu.ac.ir)

<https://dx.doi.org/10.17179/excli2022-5006>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>).

## ABSTRACT

Non-coding RNAs including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are implicated in the regulation of gene expression at transcriptional, posttranscriptional, and epigenetic levels. Several studies in cell lines, animal models, and humans, have revealed that non-coding RNAs play crucial roles in the pathogenesis of Alzheimer's disease (AD). Detailed knowledge on their mechanism of implication in the AD pathogenesis can help to develop novel therapeutic and disease management strategies. The two main pathological hallmarks of AD are amyloid plaques resulting from the  $\beta$ -amyloid accumulation, and neurofibrillary tangles (NFT) due to the phosphorylated tau accumulation. Several lncRNAs and miRNAs play crucial roles in both these hallmarks of the AD pathogenesis and other AD-related pathological procedures such as neuronal and synaptic plasticity, neuroinflammation, neuronal differentiation and neuronal apoptosis. In this review, we outlined the non-coding RNAs and further discussed how they are implicated in these AD-related pathological procedures.

**Keywords:** Alzheimer's disease, miRNAs, lncRNAs, marker

## INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disorder and the most common cause of dementia, accounting for approximately 60 % to 80 % of cases among the elderly worldwide (Doxtater et al., 2020; Zhang and Wang, 2021). AD is characterized by clinical features such as memory loss, cognitive impairment and behavioral function decline (Zhao et al., 2017). The hallmark pathologies of Alzheimer's disease are the existence

of extracellular plaques composed of amyloid-beta ( $A\beta$ ) peptide resulting from abnormal proteolytic cleavage of amyloid precursor protein (APP) and intracellular neurofibrillary tangles (NFT), which result from hyperphosphorylation of the microtubule-associated tau proteins (Hoogmartens et al., 2021; Mattson, 2004). The cause and molecular mechanism of AD pathogenesis is very complex (Fotuhi et al., 2020; Talebi et al., 2020), and a couple of coding and non-coding genes and their polymorphisms are involved in AD development and progress (Mardokh Rohani

et al., 2020; Zhao et al., 2019). Currently, the clinical diagnosis of AD is made by imaging and the measuring of A $\beta$  levels in cerebrospinal fluid (CSF) during later clinical stages of AD (Cheng et al., 2015; Mangialasche et al., 2010). Thus, reliable biomarkers for early diagnosis are required to halt the disease development and improve the effects of therapeutic strategies. Genome wide analyses has revealed that only 2 % of the mammalian genome is made up of protein-coding genes (Wei et al., 2018), and according to the ENCODE, most of what was already considered as nonfunctional or junk DNA is transcribed into non-coding RNAs (ncRNAs) (Ahmadi et al., 2020; Ecker et al., 2012). The ncRNAs can be classified either as housekeeping or regulatory subgroups. The former group plays crucial roles in functional homeostasis, whereas the latter are involved in regulation of genes. Regulatory ncRNAs can further be divided into ncRNAs with a length of fewer than 200 nucleotides (microRNAs, miRNAs, small interfering RNAs, and siRNAs), and the lncRNAs which contain more than 200 nucleotides and lacking the potential to be translated into proteins (Hombach and Kretz, 2016; Idda et al., 2018). Increasing evidence has suggested that ncRNAs are involved in the pathogenesis of AD (Wang et al., 2018b; Zhang et al., 2018). In this review, we discuss both lncRNAs and microRNAs that are associated with Alzheimer's disease and provide new insights into our understanding of the etiology and pathophysiology of the disease.

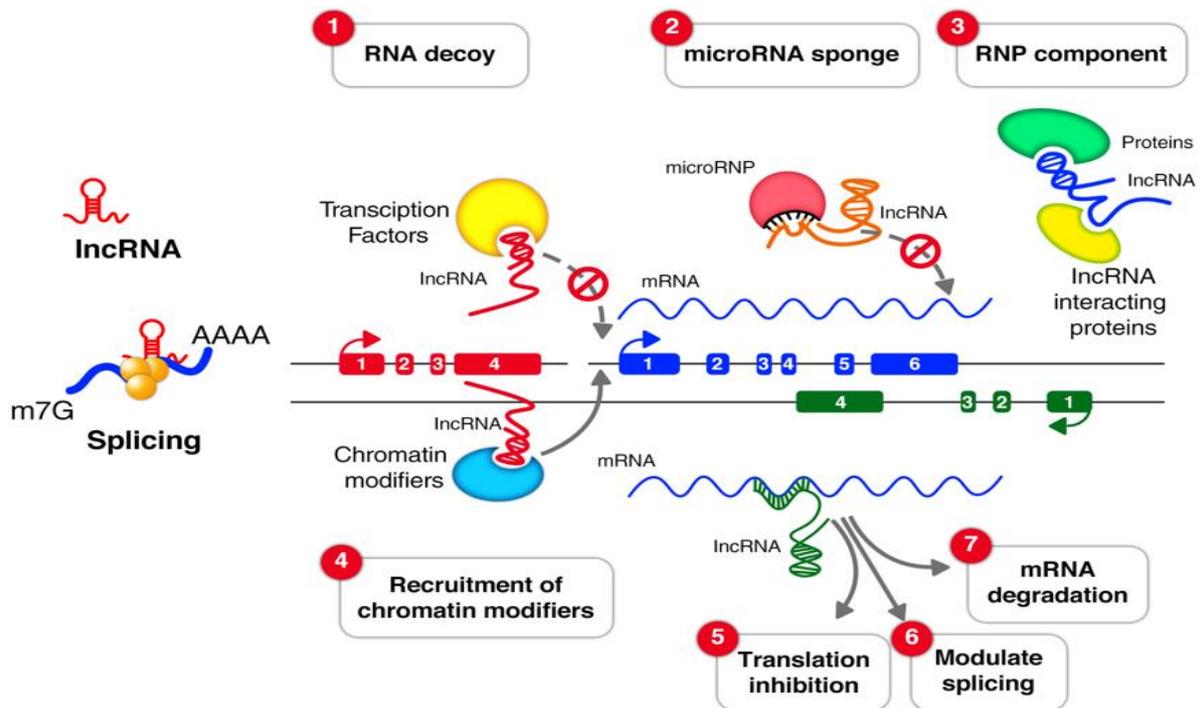
### CHARACTERISTICS OF LNCRNAS

Long non-coding RNAs (lncRNAs) comprise a class of endogenous regulatory RNA molecules that are over 200 nucleotides (nt) in length, without protein-coding capacity, and make up the largest proportions of the mammalian non-coding transcriptome (Ma et al., 2013; Sun and Kraus, 2015). Like protein-coding genes, lncRNAs are frequently transcribed by RNA polymerase II, contain 5' end cap, may be polyadenylated or non-polyadenylated, and are located within nucleus or

cytoplasm (Laurent et al., 2015; Wei et al., 2018). lncRNAs have a specific secondary structure that provides multiple sites for interaction with DNA, RNA and proteins (Wei et al., 2018). In contrast to mRNAs, lncRNAs are expressed at lower levels, contain fewer exons and have attenuation sequence conservation across species (Cabili et al., 2011; Yao et al., 2019). The number of lncRNAs have been estimated from 59,000 to 102,000 listed in the NONCODE database (Iyer et al., 2015; Jandura and Krause, 2017). lncRNAs are not considered to be the dark matter, rather, they can control gene expression during a variety of cellular processes (Luo and Chen, 2016), such as development (Roberts et al., 2014), differentiation, genome rearrangement, and metabolism (Khorkova et al., 2015; Zhu et al., 2013). They also participate in chromatin modification regulation of the cell cycle and genetic imprinting (Goff and Rinn, 2015; Kazemzadeh et al., 2015). Besides, lncRNAs can impact gene expression at transcriptional, epigenetic, and post-transcriptional levels (Bhat et al., 2016; Khajehdehi et al., 2021) by involving in the splicing of RNA, messenger RNA (mRNA) decay, and mRNA stability (Quinn and Chang, 2016). A schematic view of the lncRNA function is outlined in the Figure 1.

### LNCRNAS INVOLVED IN ALZHEIMER'S DISEASE

It was reported that up to 40 % of differentially expressed lncRNAs in the human genome are specific to the brain (Derrien et al., 2012), and the aberrant lncRNA expression is implicated in the pathogenesis of many diseases, including cancer, cardiovascular and neurodegenerative diseases such as AD (Kwok and Tay, 2017; Wan et al., 2017). Transcriptome profiling analyses have identified that the lncRNA expression patterns appear disrupted in the brains of human and rat AD models compared to those in normal subjects (Crist et al., 2021; Tang et al., 2019). Annesse and colleagues used RNA sequencing to assess changes in the lncRNA expression profiles of LOAD patients and observed that the



**Figure1:** The lncRNA mechanisms of action. **(1)** RNA decoys; lncRNAs can act as decoys for transcription factors and sequester them away from their targets. **(2)** microRNA sponge; lncRNAs can bind to microRNAs as sponges to prevent them from their regulatory function. **(3)** Ribonucleoprotein (RNP) component; lncRNAs can play scaffolding roles to aid in the formation of Ribonucleoprotein (RNP) complexes. **(4)** Recruitment of chromatin modifiers; lncRNAs can recruit different kind of protein components which change the patterns of chromatin organization. lncRNAs can modulate **(5)** translation inhibition **(6)**, splicing **(7)** and mRNA degradation.

expressions of 47 lncRNAs were significantly deregulated in the hippocampal region of LOAD patients (Annese et al., 2018). Being differentially expressed in AD patients or animal models, lncRNAs can be considered as biomarkers and therapeutic targets for AD. At the molecular level, lncRNAs impact AD pathogenesis via a variety of regulatory mechanisms, including transcriptional, posttranscriptional and post-translational regulation (Luo and Chen, 2016; Zhang, 2016). Several lncRNA are known to implicate in synaptic impairment, APP processing, A $\beta$  production and inflammation, the major causal factors in

AD (Mufson et al., 2015; Yang et al., 2017). The most studied lncRNAs involving in AD are outlined in Table 1. lncRNAs contribute to the AD development by affecting different AD-related pathological procedures, including A $\beta$  accumulation, neuron plasticity, neuroinflammation, neuronal differentiation and neuronal apoptosis. In this regard, we categorized the AD-related lncRNAs and outlined them in Figure 2. In the following sections, we discuss these lncRNAs and how they are involved in each of the AD-related pathological procedures.

**Table1:** The lncRNAs involved in Alzheimer's disease

LncRNA	Expres- sion	Source	Result	Target gene/ expression	References
<b>BACE1-AS</b>	up	brain tissue of SH-SY5Y AD mice	Increased A $\beta$ production	BACE1	Faghihi et al., 2010
<b>51A</b>	up	brains of AD cases	Increased A $\beta$ production	SORL1	Ciarlo et al., 2013
<b>LRP1-AS</b>	up	brains of AD cases	Its overexpression decreases A $\beta$ levels	LRP1	Yamanaka et al., 2015
<b>BC200</b>	up	AD cell model	Its silencing reduced apoptosis and increased cell viability by regulation of BACE1	BACE1	Li et al., 2018
<b>BDNF-AS</b>	up	PC12 cells	Its silencing decreased ROS intensity and inhibited apoptosis and promoted cell viability in PC12 cells	BDNF	Guo et al., 2018
<b>EBF3 -AS</b>	up	brain tissue of SH-SY5Y AD mice	Its knockdown inhibited apoptosis in SH-SY5Y cells by regulation of EBF3	EBF3	Gu et al., 2018
<b>Sox2OT</b>	up	Hippocampus of AD rats	Its silencing decreased oxidative stress and inhibited apoptosis by upregulation of FZD3/5	FZD3/5	Zhang et al., 2019
<b>GDNFOS</b>	up/down	CSF and serum of AD patients	Neurotrophin depletion	GDNF	Zhang, 2016
<b>17A</b>	up	cerebral tissue of AD patients	Increased A $\beta$ production	GPR51	Massone et al., 2011
<b>NDM29</b>	up	cerebral cortex of AD cases	Its overexpression induced APP synthesis and increased A $\beta$ <sub>x-42</sub> /A $\beta$ <sub>x-40</sub> ratio		Luo and Chen, 2016
<b>AD-linc1</b>	up	Hippocampus of AD patients	nuclear-related cellular processes		Magistri et al., 2015
<b>AD-linc2</b>	up	Hippocampus of AD patients	nuclear-related cellular processes		Magistri et al., 2015
<b>HAO2-AS</b>	up	Hippocampus of AD patients	nuclear-related cellular processes		Magistri et al., 2015

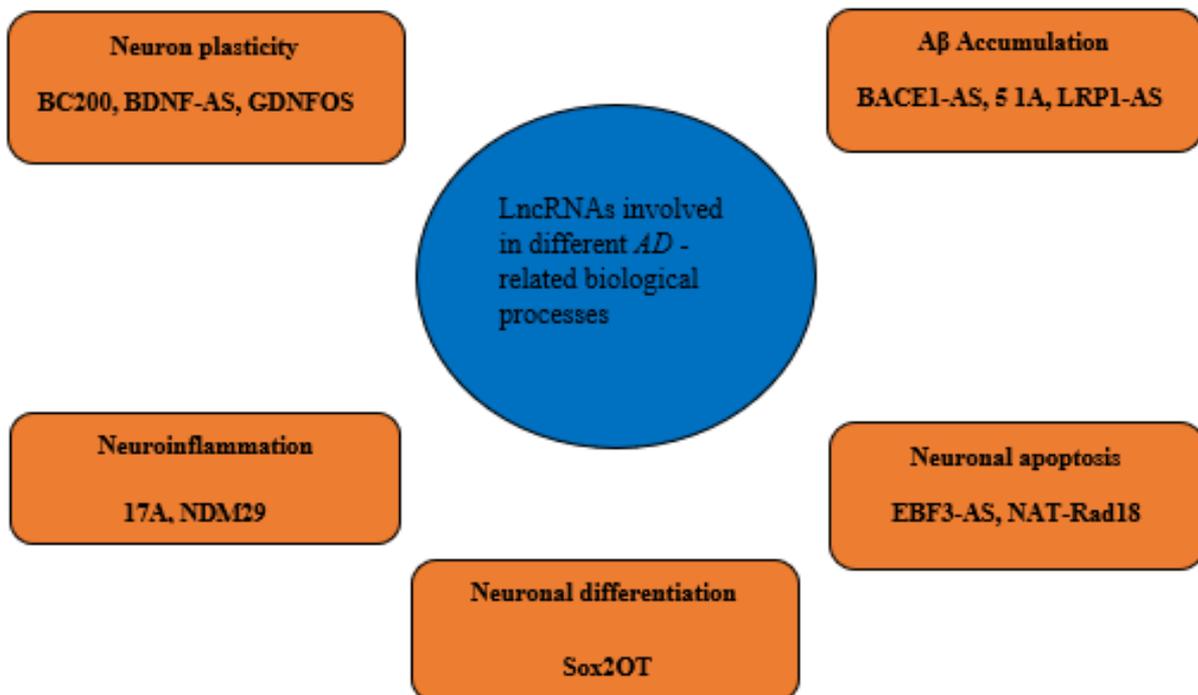
LncRNA	Expres- sion	Source	Result	Target gene/ expression	References
<b>n336934</b>	up	postmortem tis- sue of AD pa- tients	Its overexpres- sion linked to cholesterol ho- meostasis		Zhou and Xu, 2015
<b>NAT-Rad18</b>	up	brains tissue of AD rats injected A $\beta$ 1–40	Its overexpres- sion reduced the ability of neurons to re- sponse to DNA damage stress	Rad18	Parenti et al., 2007
<b>NEAT1</b>	up	brain tissues of SH-SY5Y AD mice	Its overexpres- sion interacts with NEDD4L and induces degradation of PINK1.	NEDD4L, PINK1	Huang et al., 2020
<b>MALAT1</b>	down	PC12 cells, brain tissue of HEK293T rat	Its overexpres- sion de- creased neu- ronal injury of the hippocam- pus region in rat brain	miR-30b, CNR1	Li et al., 2020a
<b>SNHG1</b>	up	SK-N-SH and CHP212 cells	Its knockdown reduced neu- ronal injury and apoptosis rate	miR-361-3p	Gao et al., 2020
<b>MEG3</b>	down	Hippocampus of AD rats	Its overexpres- sion leads to cognitive im- pairment and reduces neu- ronal damage		Yi et al., 2019
<b>lncRNA-ATB</b>	up	PC12 cell	Its knockdown decreased neurotoxicity in PC12 cells by targeting miR- 200 and regu- lation of ZNF217	miR-200, ZNF217	Wang et al., 2018
<b>TUG1</b>	up	Hippocampus of BALB/c AD mice	Its knockdown suppressed neuronal apop- tosis by target- ing miR-15a and regulation of ROCK1	miR-15a, ROCK1	Li et al., 2020b

## LNCRNAS MODULATE AB ACCUMULATION IN AD

### **BACE1-AS**

Beta-secretase 1 (BACE1) is an enzyme central to the pathology of AD that contributed to the formation of A $\beta$  peptides and extracellular plaque deposition (Chen et al., 2019). BACE1 antisense transcript (BACE1-AS) is a conserved lncRNA that is mapped on the chromosome 11, transcribed in an antisense orientation regarding to the BACE1 locus, and can positively regulate both the BACE1 mRNA and its protein expression (Faghihi et al., 2008). BACE1-AS is elevated in AD patients and in the APP transgenic mice (Faghihi et al., 2008; Singer et al., 2005). Binding of lncRNA BACE1-AS to the BACE1 mRNA increases the stability of BACE1 mRNA, and results in the high expression of BACE1 protein (Faghihi et al., 2008, 2010; Wei et al., 2018). Furthermore, cell stresses such as A $\beta$ 1-42 stimulation, high glucose, serum starvation, and H<sub>2</sub>O<sub>2</sub> increase the expression of lncRNA BACE1-AS, which

in turn makes BACE1 mRNA more stable, leading to enhanced APP processing and toxic A $\beta$  production by a post-transcriptional feed-forward mechanism (Faghihi et al., 2008). Production of more A $\beta$  can in turn affect the up-regulation of BACE1-AS, leading to the formation of more plaques in the brain of AD patients, and finally aggravating the disease development (Faghihi et al., 2008) (Figure 2). Liu et al. observed that silencing of the lncRNA BACE1-AS expression with short interfering RNA (siRNA) in SH-SY5Y cells attenuated the beta-secretase cleavage of APP and reduced the formation of the senile plaque in the cells (Liu et al., 2014). Besides, knock-down of lncRNA BACE1-AS by siRNA alleviated the disease symptoms in AD animal models, including memory and learning behaviors (Singer et al., 2005). BACE1-AS is upregulated in plasma of AD patients, suggesting that it may serve as a potential blood-based biomarker for AD development (Feng et al., 2018; Fotuhi et al., 2019).



**Figure 2:** LncRNAs involve in different pathological aspects of Alzheimer's disease. Each AD-related lncRNA is grouped according to the involved AD-leading pathological procedure.

### **51A**

The neuronal sortilin-related receptor 1 (SORL1) gene encodes SORLA protein, which is involved in the processing of amyloid- $\beta$  protein precursor (APP) and decrease A $\beta$  peptides production in neurons (Andersen et al., 2005). Studies have demonstrated that low levels of SORL1 in AD patients enhance the amyloidogenic process (Nicolas et al., 2018; Scherzer et al., 2004). SORL1, as a sorting receptor for APP and A $\beta$ , interacts with cytosolic adaptor to guide APP between the trans-Golgi network and early endosome, where it affects trafficking and proteolytic processing (Reitz, 2012). Decreased SORL1 expression might shift APP to the  $\beta$ -secretase cleavage pathway, increasing secreted APP production and subsequent A $\beta$  production (Reitz, 2012). The lncRNA 51A is located on the antisense orientation to the intron 1 of SORL1 gene (Yin et al., 2015), and in contrast to the SORL1, the expression of lncRNA 51A is upregulated in the brain of AD cases. Mechanistically, lncRNA 51A changes the splicing pattern of SORL1 to an alternatively spliced short form which is associated with the abnormal APP processing, and promotes increased A $\beta$  production (Ciarlo et al., 2013). Furthermore, Deng et al. found that lncRNA 51A is increased in the plasma of AD patients, indicating its possible involvement in the pathobiology of AD (Chen et al., 2019; Deng et al., 2017).

### **LRP1-AS**

Low density lipoprotein receptor-related protein 1 (LRP1), as a receptor is involved in a variety of cellular processes including cell signaling, lipoprotein metabolism, and APP trafficking and processing (von Einem et al., 2010). LRP1 is abundantly expressed in different cell types in the brain including neurons, vascular and glial cells (Auderset et al., 2016; Bruno et al., 2010). LRP1 plays a pivotal role in the beta-amyloid uptake and beta-amyloid clearance, accordingly the level of LRP1 expression is critical for the AD progression (Asadi et al., 2021; Van Gool et al., 2019). Studies showed that LRP1 levels are

increased in the AD brain (Matsui et al., 2007). On the other hand, LRP1-AS is the natural antisense transcript of LRP1 gene (Bruno et al., 2010). Yamanaka et al. observed that overexpression of LRP1-AS attenuated the LRP1 expression. It was clearly indicated that LRP1-AS negatively regulated the LRP1 gene expression at both the mRNA and protein levels (Yamanaka et al., 2015). It directly binds to the high mobility group box 2 (Hmgb2) and prevents the activity of Hmgb2 to enhance the LRP1 transcription (Matsui et al., 2007).

## **LNCRNAs IN SYNAPTIC AND NEURON PLASTICITY**

### **BC200**

One of the neuropathological features of AD is synaptic dysfunction that occurs in the first stages of the disorder (Kim and Song, 2018; Strobel et al., 2015). It has been demonstrated that the failure of synaptic plasticity is the foundation of memory deficits in AD patients (Shankar et al., 2008; Singh et al., 2016). Synaptic dysfunction occurs in the various cortical circuits of the brain, from the entorhinal cortex to the hippocampus (Amid et al., 2001). Implication of the lncRNA BC1/BC200 in the synaptic plasticity has been reported in previous studies (Labzin et al., 2018; Lin et al., 2008; Wang et al., 2002). BC200 lncRNA is a small untranslated RNA that selectively targets eIF4A activity in the somatodendritic domains of neurons, modulates protein synthesis in the postsynaptic dendritic microdomains and contributes to the maintenance of long-term synaptic plasticity (Li et al., 2018; Wang et al., 2002; Wu et al., 2013). In one postmortem study, Mus et al., reported that expression of the dendritic BC200 RNA was differentially regulated in the normal aging and AD. They found that during normal aging, BC200 RNA level was reduced in the synaptic regions of the hippocampus, while, compared with the age-matched normal brains, BC200 RNA was significantly upregulated in the AD, and its level was significantly increased with the severity of the disease (Mus et al., 2007). Recently, Li

et al. showed that the treatment of an AD cell model with A $\beta$ 1–42 increased BC200 and BACE1 expression, and knockdown of BC200 rescued this A $\beta$ 1-42-mediated dysfunction. They also showed that BC200 might be a potent positive regulator of BACE1, and could reduce apoptosis and increase viability of the AD cells (Li et al., 2018). Remarkably, BC200 plasma levels have recently been reported to be higher in AD patients, implying its potential as a blood-based biomarker for early diagnosis of AD (Khodayi et al., 2022).

### **BDNF-AS**

Brain-derived neurotrophic factor (BDNF), is widely synthesized in the central nervous system, has a physiological role in synaptic plasticity and survival of neurons (Gu et al., 2018; Zagrebelsky et al., 2018). In addition, BDNF can prevent neuronal function loss, facilitates the regeneration and differentiation of injured neurons (Huang et al., 2017; Li et al., 2017). Previous studies indicated that the reduced mRNA and protein levels of BDNF in the serum and human brain are closely associated with the pathogenesis of AD (Azizi Aghali et al., 2018; Buchman et al., 2016; Holsinger et al., 2000). Consistently, *in vitro* and *in vivo* experiments revealed that BDNF has potential protective effects against the neurotoxicity and learning deficits induced by A $\beta$  peptides (Jiao et al., 2016; Zhang et al., 2015b). BDNF gene delivery in A $\beta$  precursor protein (APP)-transgenic mice showed a compensatory event to slow down the cognitive decline (Nagahara et al., 2013, 2009). BDNF-AS is an antisense lncRNA of BDNF, located on the opposite strand of the BDNF on chromosome 11, and can negatively regulate the BDNF level both *in vivo* and *in vitro* (Modarresi et al., 2012). Guo et al. reported that silencing of BDNF-AS diminished the A $\beta$ 25-35-induced neurotoxicity of PC12 cells and suppressed the cell apoptosis and oxidative stress (Guo et al., 2018). It was reported that BDNF-AS level was significantly elevated in the peripheral blood of AD patients (Azizi Aghali et al.,

2018; Ding et al., 2022), and that elevated expression levels of BDNF-AS might be related to the cognitive decline of AD patients (Ding et al., 2022). More recently, Ding et al. reported that BDNF-AS could promote neurotoxicity in an *in vitro* model of AD by promoting the expression of BACE1, thereby resulting in the amyloid deposition.

### **GDNFOS**

Glial cell line-derived neurotrophic factor (GDNF) is an important biologically active trophic factor for development and survival of the midbrain dopaminergic neurons (Airavaara et al., 2011; Lin et al., 1993). However, its role is not specific for dopaminergic neurons. GDNF is also involved in neurite branching, synaptic plasticity and increase of neural stem cell migration and differentiation (Airaksinen and Saarma, 2002). A recent report indicated that GDNF levels are significantly increased in cerebrospinal fluid and decreased in serum in patients with early AD (Straten et al., 2009). A cis-natural antisense transcript, termed GDNF opposite strand (GDNFOS), is transcribed from the opposite strand of the GDNF gene (Straten et al., 2009). The GDNFOS or GDNF-AS gene has four exons that are spliced into different isoforms. GDNFOS1 and GDNFOS2 are long non-coding RNAs, with no obvious ORF. GDNFOS1 can pair to the 5'-UTR of the GDNF, but GDNFOS2 has no overlapping with the GDNF transcript. GDNFOS3 transcript is not lncRNA, contains an ORF and has potential for protein translation with no known homologs in GenBank. Dysregulation of human GDNF and GDNFOS may contribute to vulnerability to neurodegenerative diseases (Airavaara et al., 2011). However, more evidence is required to elucidate the relevance between GDNF-AS and GDNF mRNA as well as the relationship with AD pathogenesis.

## LNCRNAS IN NEUROINFLAMMATION

### *17A*

LncRNA 17A is a 159-nt lncRNA which is transcribed by RNA polymerase III and maps to an intronic region of the GABA receptor gene (Zhou et al., 2014). It has been shown that overexpression of 17A leads to the production of alternative splicing GABA receptor B (GABAB) and formation of a non-functional heterodimeric receptor (Gavazzo et al., 2013). GABA(B2) receptors significantly affect the GABA-B signaling pathway by inhibition of intracellular 3'-5'-cyclic adenosine monophosphate accumulation and the activation of specific potassium channels (Massone et al., 2011). The inflammatory stimulations in the brain of AD patients can activate the expression of 17A and increase the secretion of A $\beta$  and the A $\beta$ 42/A $\beta$ 40 ratio (Massone et al., 2011). Wang and collaborators showed that LncRNA 17A expression was involved in cellular functions and biological processes of neuroblastoma cells in an AD cell model, indicating that it could directly or indirectly be implicated in the progression of AD (Wang et al., 2019).

### *NDM 29*

Neuroblastoma differentiation marker 29 (NDM29), a RNA pol II-transcribed lncRNA, mapped to a genomic region of chromosome 11, and its synthesis is regulated by an extragenic type 3 promoter (Massone et al., 2012). NDM29 was actively transcribed in cells of the central nervous system (Gavazzo et al., 2011). Massone and collaborators reported that high levels of NDM29 transcripts induced APP synthesis, and subsequently the level of A $\beta$  and the ratio of A $\beta$ -42/A $\beta$ -40 were increased. They also found that the expression of NDM29 was induced by inflammatory stimuli and inhibited by anti-inflammatory drugs (Massone et al., 2012). Furthermore, this lncRNA was abnormally expressed in the cerebral cortex of AD patients, demonstrating that NDM29 is linked to AD pathology (Massone et al., 2012).

## LNCRNA IN NEURONAL DIFFERENTIATION

### *Sox2OT*

Sox2 is a component of the core transcriptional regulatory network that is essential for maintaining pluripotency of stem cells and neurogenesis (Sarlak et al., 2016). Sox2 overlapping transcript (Sox2OT) as an evolutionarily conserved transcript among vertebrates, has been linked to cognitive impairment in a mouse model of Alzheimer's disease (Amaral et al., 2009; Fantes et al., 2003). Knauss et al. recently found that Sox2OT is expressed in developing mouse cerebral cortex, where it promotes neuronal differentiation and neurogenesis by repressing Sox2 in neuronal progenitors (Knauss et al., 2018). Furthermore, whole genome microarray analysis indicated that Sox2OT is differentially expressed in early and late stages of the disease in an AD model mouse, suggesting that Sox2OT might be related to the AD pathobiology (Arisi et al., 2011).

## LNCRNAS IN APOPTOSIS OF NEURONS

### *EBF3-AS*

Recently, Magistri et al. used RNA sequencing in order to discover significant alterations in expression profile of the lncRNAs from AD brains and found that lncRNA EBF3-AS is abundantly expressed in the brain of late-onset AD cases compared to control individuals (Magistri et al., 2015). Furthermore, a recent study reported that the expression of early B cell factor 3 (EBF3) and lncRNA EBF3-AS were up-regulated in hippocampus of APP/PS1 transgenic mice (Gu et al., 2018). They reported that EBF3-AS knockdown by siRNA could inhibit the apoptosis induced by A $\beta$ 25-35 and okadaic acid (OA) in mouse model of AD. A $\beta$ 25-35 and okadaic acid increased the expression of EBF3. They observed that lncRNA EBF3-AS stimulated the EBF3 expression and promoted neuron apoptosis in AD brain (Gu et al., 2018). These evidences suggested that

EBF3-AS might be considered as a new therapeutic target for the treatment of AD.

### OTHER RELATED LNCRNAS

Lee and colleagues identified 47 upregulated and 158 downregulated lncRNAs in rat model of AD compared with healthy controls using microarray analysis (Lee et al., 2015). Moreover, it was reported that lncRNAs AD-linc1, AD-linc2 and HAO2-AS are upregulated in the hippocampus of the patients with AD, which indicated that these lncRNAs might have key functions in AD (Magistri et al., 2015). Another notable lncRNA associated with AD is n336934, which is involved in the cholesterol homeostasis pathway. Disruption of cholesterol metabolism is a feature of AD pathogenesis (Hannaoui et al., 2014). Moreover, lncRNA NAT-Rad18 is upregulated in rat cortical neurons after A $\beta$  treatment. Therefore, the highly upregulated lncRNA NAT-Rad18 may reduce the ability of neurons to respond to DNA damage stressors in AD pathogenesis (Parenti et al., 2007).

### MICRORNAS IN AD

MicroRNAs (miRNAs) are endogenous ~22 nucleotide non-coding RNAs, responsible for direct posttranscriptional regulation of gene expression, either by targeting mRNA degradation or by inhibition of protein translation at both mRNA and protein levels (Kou et al., 2020). After transcription, the primary microRNA transcripts are cleaved to precursor (pre) microRNAs by Drosha (Denli et al., 2004), and following their export to the cytoplasm, the pre-microRNAs are processed by Dicer to generate mature microRNAs (Okada et al., 2009). The microRNAs that now are incorporated into a ribonucleoprotein complex named RNA-induced silencing complex (RISC), guides the complex to the target mRNAs (O'Brien et al., 2018; Zhang et al., 2004). Recent studies have indicated that miRNAs are involved in the most critical biological processes, including proliferation, differentiation, development, and apoptosis

(Bartel, 2009; Esquela-Kerscher and Slack, 2006). Specifically, miRNAs are widely found within the nervous system where they play key roles during neuronal differentiation, synaptogenesis, and plasticity (Goodall et al., 2013). This has been the clue for considering miRNAs as crucial molecules to be studied in AD, and nowadays, dysfunction of miRNAs in AD is increasingly recognized (Ramakrishna and Muddashetty, 2019). miRNAs that contribute to the A $\beta$  plaque production and tau phosphorylation as the main pathologic hallmarks of AD, could play crucial roles in the AD pathobiology. Specifically, some miRNAs that have been known to be implicated in the regulation of BACE1, APP and tau expression and processing, and in the tau phosphorylation, have been outlined in Table 2 and will be discussed in more details through the following sections.

#### *miRNAs involved in regulation of the BACE1 expression*

$\beta$ -site amyloid precursor protein-cleaving enzyme1 (BACE1), a rate-limiting enzyme involved in the formation of A $\beta$ , plays a crucial role in AD progression (Maoz et al., 2017; Zong et al., 2011). Several miRNAs that are potentially involved in the regulation of BACE1 expression appeared to be downregulated in AD. For instance, miR-9, miR-29c, miR-29a/b-1, miR-101, miR-107, miR-298, and miR-15b exhibit reduced expression in patients or model animals with AD and contribute to the elevated A $\beta$  formation (Gong et al., 2017; Hébert et al., 2008; Wang et al., 2008; Yang et al., 2015; Zhang et al., 2021). On the other hand, miR-339-5p was found to be significantly downregulated in the brain of AD patients compared with the age-matched healthy controls. Further analysis indicated that miR-339-5p negatively regulates BACE1 level by targeting the 3'-UTR region of the BACE1 to reduce A $\beta$  accumulation, which makes it as a novel drug target (Long et al., 2014). Similarly, both miR-195 and miR-135b negatively regulate expression level of BACE1 by binding to the 3'-UTR of

**Table 2:** A list of miRNAs that are involved in the regulation of BACE1, APP and tau processing

miRNAs	Expression	Source	Result	Target gene	References
miR-9	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Hébert et al., 2008
miR-29c	down	brains of AD cases and hippocampus of SAMP8	increase of A $\beta$ formation	BACE1	Yang et al., 2015
miR-29a/b-1	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Hébert et al., 2008
miR-31	up	3xTg- AD mice	promote APP production	APP	Barros-Viegas et al., 2020
miR-101	down	brain of AD cases and hippocampus of mice	promote APP production	APP	Barbato et al., 2020
miR-107	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Wang et al., 2008
miR-298	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Chopra et al., 2021
miR-15b	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Gong et al., 2017
miR-339-5p	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Long et al., 2014
miR-195	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Zhu et al., 2012
miR-135b	down	brains of AD cases	increase of A $\beta$ formation	BACE1	Zhang et al., 2016
miR-188-3p	down	brains of AD cases and hippocampus of 5 x FAD TG mice	increase of A $\beta$ formation	BACE1	Zhang et al., 2014
miR-149	down	brains of AD cases and SH-SY5Y cells	increase of A $\beta$ formation	BACE1	Du et al., 2021
hsa-mir-520c	down	HEK-293 cells	promote APP production	APP	Kou et al., 2020
hsa-mir-106a	down	HEK-293 cells	promote APP production	APP	Kou et al., 2020
miR-16	down	SAMP8 model mice	promote APP production	APP	Liu et al., 2012
miR17	down	SAMP8 model mice	promote APP production	APP	Liu et al., 2012
miR-132/212	down	3xTg- AD mice	increase Tau expression hyperphosphorylation	Tau	Hernandez-Rapp et al., 2016
miR-106b	down	sporadic AD patients and SH-SY5Y cells	increase Tau hyperphosphorylation	Tau	Kou et al., 2020
miR-125b	up	CSF of AD patients	increase Tau hyperphosphorylation	SphK1	Ma et al., 2017
miR-15 a	down	Neuro2a cells	increase Tau hyperphosphorylation	ERK1	Kou et al., 2020

the BACE1 mRNA (Zhang et al., 2016; Zhu et al., 2012). Other miRNA that was found to be involved in the A $\beta$  regulation is miR-188-

3p. It was negatively correlated with the BACE1 abundance and A $\beta$  production, and improved the long-term synaptic plasticity in

an APP transgenic mice (Zhang et al., 2014). Furthermore, Hébert et al. reported that expression of the miR-29a/b-1 was significantly low in AD brain but the BACE1 protein level was significantly high, and the decreased level of the miR-29a/b-1 in human cell culture could promote the A $\beta$  production (Hébert et al., 2008). In another study, Yang et al. found that miR-29c, a member of the miR-29 family, plays a role in the regulation of BACE1 abundance by targeting its 3'-UTR both in human and mouse cell lines. Interestingly, up-regulation of miR-29c in the hippocampus of SAMP8 mice improved spatial memory (Yang et al., 2015). Du et al. observed a decreased expression of the miRNA cluster miR-149 in individuals with AD as well as in an AD cell model. This study identified BACE1 as a direct target of miR-149, and showed that the miR-149 deficiency in mice could lead to the increased A $\beta$  accumulation. Furthermore, the overexpression of miR-149 in A $\beta$ -treated SH-SY5Y cells inhibited the A $\beta$  accumulation and promoted the neuronal viability (Du et al., 2021). In summary, several miRNAs play important roles in regulating BACE1 protein levels and comprehensive understandings of the complex network of regulatory microRNAs that suppress the BACE1 production may lead to the discovery of breakthrough treatment strategies for AD.

#### ***miRNAs in regulation of APP expression***

Mounting evidence has shown that the regulation of APP expression by miRNAs could affect production and accumulation of A $\beta$ , resulting in neurotoxicity and synaptic failure (Improta-Caria et al., 2020; Patel et al., 2008). Different miRNAs have been reported to be involved in the regulation of APP gene expression and thus the accumulation of fibrillar A $\beta$ . For example, hsa-mir-106a and hsa-mir-520c were negatively correlated with the endogenous APP levels in HEK-293 cells and showed regulatory effects by binding to the 3'-UTR of APP (Kou et al., 2020; Patel et al., 2008). Moreover, miR-16 was also found to target APP mRNA and suppress APP pro-

duction, and cause accumulation of APP protein in SAMP8 model mice (Liu et al., 2012). Additionally, another study demonstrated that inhibition of miR-16 in primary hippocampal neurons decreased the cell viability in a cellular AD model (Zhang et al., 2015a). Similarly, the binding of miR-101, miR-31, and miR-17 to the 3'-UTR of the APP mRNA resulted in decreased level of APP in patients with AD (Barros-Viegas et al., 2020; Kou et al., 2020). Interestingly, the high level of miR-31 reduced the levels of APP and BACE1 mRNAs in the hippocampus of 17-months-old AD triple-transgenic (3xTg-AD) female mice, and improved memory deficits and cognitive inflexibility (Barros-Viegas et al., 2020).

#### ***miRNAs in tau expression and tau phosphorylation***

Abnormal accumulation of intraneuronal filaments formed by tau proteins is the most common pathological feature in AD (Muralidar et al., 2020). Several miRNAs have been reported to be related to tauopathy. For instance, the miR-132/212 cluster is frequently downregulated in AD and has been shown to regulate tau *in vitro* and *in vivo* (Hernandez-Rapp et al., 2016). Smith et al. reported that miR-132/212 deficiency in mice leads to increased tau expression, phosphorylation and aggregation (Smith et al., 2015). It has been reported that miRNAs can affect tau phosphorylation and subsequently modulate tangle formation. miR-15 may induce tau hyperphosphorylation through ERK1 in Neuro2a cells (Hébert et al., 2010). Studies have demonstrated that miR-106b is downregulated in sporadic AD patients as well as in the human neuroblastoma SH-SY5Y cells, and it can inhibit A $\beta$ 42-induced tau phosphorylation at the site of Tyr18 (Liu et al., 2016). Moreover, one study has found that overexpression of miR-125b could lead to cell apoptosis and tau hyperphosphorylation by activating the cyclin-dependent kinase 5 (Banzhaf-Strathmann et al., 2014).

## CONCLUSIONS AND PERSPECTIVES

In this review, we summarized the relationship between ncRNAs and AD pathogenesis based on recent evidence. Multiple studies have shown the critical role of ncRNAs in various biological processes, including cell growth, apoptosis, and differentiation, indicating that they might be involved in the occurrence and progress of neurodegenerative diseases including AD (Barbato et al., 2020; Zhou et al., 2019). Recent progress in biotechnologies such as high-throughput sequencing, mouse modeling, cell lines treated with different A $\beta$  peptides, and human biological samples such as brain, CSF, and serum have provided important insights into the biological function and clinical relevance of ncRNAs in AD (Bruno et al., 2020; Zhao et al., 2019). These ncRNAs were associated with diverse processes in the brain underlying the pathogenesis of AD, including formation of A $\beta$  plaques, the phosphorylation of Tau, synaptic dysfunction, and neuroinflammation (Zhang et al., 2021). It is necessary and urgent to seek reliable and effective biomarkers for early diagnosis of AD, and timely detection of the disease can offer the opportunities for early intervention to potentially delay or prevent the pathological process of AD. In recent years, most studies suggest that ncRNAs are desirable candidates as diagnostic markers of preclinical or clinical AD due to their easy accessibility and stability throughout storage and handling. Understanding the regulatory function and molecular mechanisms of ncRNAs in AD pathophysiology will allow the development of new therapies and diagnostic markers for AD. In conclusion, although the role and impact of ncRNAs in the pathogenesis of AD remain partially unknown, but promise to open more avenues to early diagnosis and treatment of AD.

### Highlights

- Non-coding RNAs play crucial roles in the pathogenesis of Alzheimer's disease.
- Non-coding RNAs (ncRNAs) can be used as potential therapeutic targets and biomarkers.

- Reliable biomarkers for early diagnosis are required to halt the disease development and improve the effects of therapeutic strategies.

### Acknowledgments

Authors appreciate the Cognitive Sciences and Technologies Council of Iran for supporting this work.

### Funding

This work was supported by the Cognitive Sciences and Technologies Council of Iran, grant number 6300.

### Competing interests

The authors have no relevant financial or non-financial interests to disclose.

### Author contributions

Majid Khodayi-Shahrak performed research and wrote the manuscript; Mohammad Khalaj-Kondori supervised research, reviewed and edited the manuscript; Mohammad Ali Hosseinpour Feizi reviewed and edited the manuscript; Mahnaz Talebi reviewed and edited the manuscript.

## REFERENCES

- Ahmadi S, Zobeiri M, Bradburn S. Molecular mechanisms underlying actions of certain long noncoding RNAs in Alzheimer's disease. *Metab Brain Dis.* 2020; 35:681-93.
- Airaksinen MS, Saarma M. The GDNF family: signaling, biological functions and therapeutic value. *Nat Rev Neurosci.* 2002;3:383-94.
- Airavaara M, Pletnikova O, Doyle ME, Zhang YE, Troncoso JC, Liu Q-R. Identification of novel GDNF isoforms and cis-antisense GDNFOS gene and their regulation in human middle temporal gyrus of Alzheimer disease. *J Biol Chem.* 2011;286:45093-102.
- Amaral PP, Neyt C, Wilkins SJ, Askarian-Amiri ME, Sunkin SM, Perkins AC, et al. Complex architecture and regulated expression of the Sox2ot locus during vertebrate development. *RNA.* 2009;15:2013-27.

- Amid C, Bahr A, Mujica A, Sampson N, Bikar S-E, Winterpacht A, et al. Comparative genomic sequencing reveals a strikingly similar architecture of a conserved syntenic region on human chromosome 11p15.3 (including gene ST5) and mouse chromosome 7. *Cytogenet Genome Res.* 2001;93:284-90.
- Andersen OM, Reiche J, Schmidt V, Gotthardt M, Spoelgen R, Behlke J, et al. Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein. *Proc Natl Acad Sci.* 2005;102:13461-6.
- Annese A, Manzari C, Lionetti C, Picardi E, Horner DS, Chiara M, et al. Whole transcriptome profiling of Late-Onset Alzheimer's Disease patients provides insights into the molecular changes involved in the disease. *Sci Rep.* 2018;8(1):1-15.
- Arisi I, D'Onofrio M, Brandi R, Felsani A, Capsoni S, Drovandi G, et al. Gene expression biomarkers in the brain of a mouse model for Alzheimer's disease: mining of microarray data by logic classification and feature selection. *J Alzheimer's Dis.* 2011;24:721-38.
- Asadi MR, Hassani M, Kiani S, Sabaie H, Moslehian MS, Kazemi M, et al. The perspective of dysregulated LncRNAs in Alzheimer's disease: a systematic scoping review. *Front Aging Neurosci.* 2021;13:709568.
- Auderset L, Cullen CL, Young KM. Low density lipoprotein-receptor related protein 1 is differentially expressed by neuronal and glial populations in the developing and mature mouse central nervous system. *PLoS One.* 2016;11(6):e0155878.
- Azizi Aghali R, Khalaj M, Zeinalzadeh N, Feizi H, Farhoudi M, Talebi M. Comparison between the plasma levels of long noncoding RNA BDNF-as in patients with Alzheimer's disease and healthy subjects. *J Babol Univ Med Sci.* 2018;20(4):24-9.
- Banzhaf-Strathmann J, Benito E, May S, Arzberger T, Tahirovic S, Kretschmar H, et al. Micro RNA-125b induces tau hyperphosphorylation and cognitive deficits in Alzheimer's disease. *EMBO J.* 2014;33:1667-80.
- Barbato C, Giacobozzo G, Albiero F, Scardigli R, Scopa C, Ciotti M, et al. Cognitive decline and modulation of Alzheimer's disease-related genes after inhibition of microRNA-101 in mouse hippocampal neurons. *Mol Neurobiol.* 2020;57:3183-94.
- Barros-Viegas AT, Carmona V, Ferreira E, Guedes J, Cardoso AM, Cunha P, et al. miRNA-31 improves cognition and abolishes amyloid- $\beta$  pathology by targeting APP and BACE1 in an animal model of Alzheimer's disease. *Mol Ther Nucleic Acids.* 2020;19:1219-36.
- Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell.* 2009;136:215-33.
- Bhat SA, Ahmad SM, Mumtaz PT, Malik AA, Dar MA, Urwat U, et al. Long non-coding RNAs: Mechanism of action and functional utility. *Non-Coding RNA Res.* 2016;1(1):43-50.
- Bruno DCF, Donatti A, Martin M, Almeida VS, Geraldini JC, Oliveira FS, et al. Circulating nucleic acids in the plasma and serum as potential biomarkers in neurological disorders. *Braz J Med Biol Res.* 2020;53(10):e9881.
- Bruno E, Quattrocchi G, Nicoletti A, Le Pira F, Maci T, Mostile G, et al. Lack of interaction between LRP1 and A2M polymorphisms for the risk of Alzheimer disease. *Neurosci Lett.* 2010;482:112-6.
- Buchman AS, Yu L, Boyle PA, Schneider JA, De Jager PL, Bennett DA. Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology.* 2016;86:735-41.
- Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. *Genes Dev.* 2011;25:1915-27.
- Chen L, Guo X, Li Z, He Y. Relationship between long non-coding RNAs and Alzheimer's disease: a systematic review. *Pathol Res Practice.* 2019;215(1):12-20.
- Cheng L, Doecke JD, Sharples RA, Villemagne VL, Fowler CJ, Rembach A, et al. Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment. *Mol Psychiatry.* 2015;20:1188-96.
- Chopra N, Wang R, Maloney B, Nho K, Beck JS, Pourshafie N, et al. MicroRNA-298 reduces levels of human amyloid- $\beta$  precursor protein (APP),  $\beta$ -site APP-converting enzyme 1 (BACE1) and specific tau protein moieties. *Mol Psychiatry.* 2021;26:5636-57.
- Ciarlo E, Massone S, Penna I, Nizzari M, Gigoni A, Dieci G, et al. An intronic ncRNA-dependent regulation of SORL1 expression affecting A $\beta$  formation is upregulated in post-mortem Alzheimer's disease brain samples. *Dis Models Mech.* 2013;6:424-33.
- Crist AM, Hinkle KM, Wang X, Moloney CM, Matchett BJ, Labuzan SA, et al. Transcriptomic analysis to identify genes associated with selective hippocampal vulnerability in Alzheimer's disease. *Nat Commun.* 2021;12:2311.

- Deng Y, Xiao L, Li W, Tian M, Feng X, Feng H, et al. Plasma long noncoding RNA 51A as a stable biomarker of Alzheimer's disease. *Int J Clin Exp Pathol.* 2017;10:4694-9.
- Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary microRNAs by the Microprocessor complex. *Nature.* 2004;432(7014):231-5.
- Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res.* 2012;22:1775-89.
- Ding Y, Luan W, Wang Z, Cao Y. LncRNA BDNF-AS as ceRNA regulates the miR-9-5p/BACE1 pathway affecting neurotoxicity in Alzheimer's disease. *Arch Gerontol Geriatr.* 2022;99:104614.
- Doxtater K, Tripathi MK, Khan MM. Recent advances on the role of long non-coding RNAs in Alzheimer's disease. *Neural Regen Res.* 2020;15:2253-4.
- Du W, Lei C, Dong Y. MicroRNA-149 is downregulated in Alzheimer's disease and inhibits  $\beta$ -amyloid accumulation and ameliorates neuronal viability through targeting BACE1. *Genet Mol Biol.* 2021;44 (1):e20200064.
- Ecker JR, Bickmore WA, Barroso I, Pritchard JK, Gilad Y, Segal E. ENCODE explained. *Nature.* 2012;489(7414):52-4.
- Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer.* 2006;6:259-69.
- Faghihi MA, Modarresi F, Khalil AM, Wood DE, Sahagan BG, Morgan TE, et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of  $\beta$ -secretase. *Nat Med.* 2008;14:723-30.
- Faghihi MA, Zhang M, Huang J, Modarresi F, Van der Brug MP, Nalls MA, et al. Evidence for natural antisense transcript-mediated inhibition of microRNA function. *Genome Biol.* 2010;11(5):R56.
- Fantes J, Ragge NK, Lynch S-A, McGill NI, Collin JRO, Howard-Peebles PN, et al. Mutations in SOX2 cause anophthalmia. *Nat Genet.* 2003;33:462-3.
- Feng L, Liao Y-T, He J-C, Xie C-L, Chen S-Y, Fan H-H, et al. Plasma long non-coding RNA BACE1 as a novel biomarker for diagnosis of Alzheimer disease. *BMC Neurol.* 2018;18(1):4.
- Fotuhi SN, Khalaj-Kondori M, Feizi MAH, Talebi M. Long non-coding RNA BACE1-AS may serve as an Alzheimer's disease blood-based biomarker. *J Mol Neurosci.* 2019;69:351-9.
- Fotuhi SN, Khalaj-Kondori M, Feizi MAH, Talebi M. Memory-related process in physiological status and Alzheimer's disease. *Mol Biol Rep.* 2020;47:4651-7.
- Gao Y, Zhang N, Lv C, Li N, Li X, Li W. LncRNA SNHG1 knockdown alleviates amyloid- $\beta$ -induced neuronal injury by regulating ZNF217 via sponging miR-361-3p in Alzheimer's disease. *J Alzheimers Dis.* 2020;77:85-98.
- Gavazzo P, Vella S, Marchetti C, Nizzari M, Cancedda R, Pagano A. Acquisition of neuron-like electrophysiological properties in neuroblastoma cells by controlled expression of NDM29 ncRNA. *J Neurochem.* 2011;119:989-1001.
- Gavazzo P, Vassalli M, Costa D, Pagano A. Novel ncRNAs transcribed by Pol III and elucidation of their functional relevance by biophysical approaches. *Front Cell Neurosci.* 2013;7:203.
- Goff LA, Rinn JL. Linking RNA biology to lncRNAs. *Genome Res.* 2015;25:1456-65.
- Gong G, An F, Wang Y, Bian M, Yu L-J, Wei C. miR-15b represses BACE1 expression in sporadic Alzheimer's disease. *Oncotarget.* 2017;8(53):91551.
- Goodall EF, Heath PR, Bandmann O, Kirby J, Shaw PJ. Neuronal dark matter: the emerging role of microRNAs in neurodegeneration. *Front Cell Neurosci.* 2013;7:178.
- Gu C, Chen C, Wu R, Dong T, Hu X, Yao Y, et al. Long noncoding RNA EBF3-AS promotes neuron apoptosis in Alzheimer's disease. *DNA Cell Biol.* 2018;37:220-6.
- Guo C-C, Jiao C-h, Gao Z-M. Silencing of LncRNA BDNF-AS attenuates A $\beta$ 25-35-induced neurotoxicity in PC12 cells by suppressing cell apoptosis and oxidative stress. *Neurol Res.* 2018;40:795-804.
- Hannaoui S, Shim SY, Cheng YC, Corda E, Gilch S. Cholesterol balance in prion diseases and Alzheimer's disease. *Viruses.* 2014;6:4505-35.
- Hébert SS, Horré K, Nicolai L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, et al. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/ $\beta$ -secretase expression. *Proc Natl Acad Sci.* 2008;105:6415-20.
- Hébert SS, Papadopoulou AS, Smith P, Galas M-C, Planel E, Silahtaroglu AN, et al. Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyperphosphorylation and neurodegeneration. *Hum Mol Genet.* 2010;19:3959-69.

- Hernandez-Rapp J, Rainone S, Goupil C, Dorval V, Smith PY, Saint-Pierre M, et al. microRNA-132/212 deficiency enhances A $\beta$  production and senile plaque deposition in Alzheimer's disease triple transgenic mice. *Sci Rep*. 2016;6:30953.
- Holsinger RD, Schnarr J, Henry P, Castelo VT, Fahnestock M. Quantitation of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease. *Mol Brain Res*. 2000;76:347-54.
- Hombach S, Kretz M. Non-coding RNAs: Classification, biology and functioning. *Adv Exp Med Biol*. 2016;937:3-17.
- Hoogmartens J, Cacace R, Van Broeckhoven C. Insight into the genetic etiology of Alzheimer's disease: A comprehensive review of the role of rare variants. *Alzheimers Dement (Amst)*. 2021;13(1):e12155.
- Huang W, Meng F, Cao J, Liu X, Zhang J, Li M. Neuroprotective role of exogenous brain-derived neurotrophic factor in hypoxia-hypoglycemia-induced hippocampal neuron injury via regulating Trkb/MiR134 signaling. *J Mol Neurosci*. 2017;62:35-42.
- Huang Z, Zhao J, Wang W, Zhou J, Zhang J. Depletion of lncRNA NEAT1 rescues mitochondrial dysfunction through NEDD4L-dependent PINK1 degradation in animal models of Alzheimer's disease. *Front Cell Neurosci*. 2020;14:28.
- Idda ML, Munk R, Abdelmohsen K, Gorospe M. Noncoding RNAs in Alzheimer's disease. *Wiley Interdisciplinary Reviews: RNA*. 2018;9(2):e1463.
- Improta-Caria AC, Nonaka CKV, Cavalcante BRR, De Sousa RAL, Aras Júnior R, Souza BSdF. Modulation of microRNAs as a potential molecular mechanism involved in the beneficial actions of physical exercise in Alzheimer disease. *Int J Mol Sci*. 2020;21(14):4977.
- Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, et al. The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet*. 2015;47:199-208.
- Jandura A, Krause HM. The new RNA world: growing evidence for long noncoding RNA functionality. *Trends Genet*. 2017;33:665-76.
- Jiao S, Shen L, Zhu C, Bu X, Liu Y, Liu C, et al. Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. *Transl Psychiatry*. 2016;6(10):e907.
- Kazemzadeh M, Safaralizadeh R, Orang AV. lncRNAs: emerging players in gene regulation and disease pathogenesis. *J Genet*. 2015;94:771-84.
- Khajehdehi M, Khalaj-Kondori M, Ghasemi T, Jahanghiri B, Damaghi M. Long noncoding RNAs in gastrointestinal cancer: Tumor suppression versus tumor promotion. *Dig Dis Sci*. 2021;66:381-97.
- Khodayi M, Khalaj-Kondori M, Feizi MAH, Bonyadi MJ, Talebi M. Plasma lncRNA profiling identified BC200 and NEAT1 lncRNAs as potential blood-based biomarkers for late-onset Alzheimer's disease. *EXCLI J*. 2022;21:772-85.
- Khorkova O, Hsiao J, Wahlestedt C. Basic biology and therapeutic implications of lncRNA. *Adv Drug Deliv Rev*. 2015;87:15-24.
- Kim Y-K, Song J. The role of long noncoding RNAs in diabetic Alzheimer's disease. *J Clin Med*. 2018;7(11):461.
- Knauss JL, Miao N, Kim S-N, Nie Y, Shi Y, Wu T, et al. Long noncoding RNA Sox2ot and transcription factor YY1 co-regulate the differentiation of cortical neural progenitors by repressing Sox2. *Cell Death Dis*. 2018;9:799.
- Kou X, Chen D, Chen N. The regulation of microRNAs in Alzheimer's disease. *Front Neurol*. 2020;11:288.
- Kwok ZH, Tay Y. Long noncoding RNAs: links between human health and disease. *Biochem Soc Transact*. 2017;45:805-12.
- Labzin LI, Heneka MT, Latz E. Innate immunity and neurodegeneration. *Annu Rev Med*. 2018;69:437-49.
- Laurent GS, Wahlestedt C, Kapranov P. The Landscape of long noncoding RNA classification. *Trends Genet*. 2015;31:239-51.
- Lee DY, Moon J, Lee S-T, Jung K-H, Park D-K, Yoo J-S, et al. Distinct expression of long non-coding RNAs in an Alzheimer's disease model. *J Alzheimer's Dis*. 2015;45:837-49.
- Li G-D, Bi R, Zhang D-F, Xu M, Luo R, Wang D, et al. Female-specific effect of the BDNF gene on Alzheimer's disease. *Neurobiol Aging*. 2017;53:192.e11-9.
- Li H, Zheng L, Jiang A, Mo Y, Gong Q. Identification of the biological affection of long noncoding RNA BC200 in Alzheimer's disease. *Neuroreport*. 2018;29:1061-7.
- Li L, Xu Y, Zhao M, Gao Z. Neuro-protective roles of long non-coding RNA MALAT1 in Alzheimer's disease with the involvement of the microRNA-30b/CNR1 network and the following PI3K/AKT activation. *Exp Mol Pathol*. 2020a;117:104545.

- Li X, Wang SW, Li XL, Yu FY, Cong HM. Knock-down of long non-coding RNA TUG1 depresses apoptosis of hippocampal neurons in Alzheimer's disease by elevating microRNA-15a and repressing ROCK1 expression. *Inflamm Res*. 2020b;69:897-910.
- Lin D, Pestova TV, Hellen CU, Tiedge H. Translational control by a small RNA: dendritic BC1 RNA targets the eukaryotic initiation factor 4A helicase mechanism. *Mol Cell Biol*. 2008;28:3008-19.
- Lin LF, Doherty DH, Lile JD, Bektesh S, Collins F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science*. 1993;260(5111):1130-2.
- Liu T, Huang Y, Chen J, Chi H, Yu Z, Wang J, et al. Attenuated ability of BACE1 to cleave the amyloid precursor protein via silencing long noncoding RNA BACE1-AS expression. *Mol Med Rep*. 2014;10:1275-81.
- Liu W, Liu C, Zhu J, Shu P, Yin B, Gong Y, et al. MicroRNA-16 targets amyloid precursor protein to potentially modulate Alzheimer's-associated pathogenesis in SAMP8 mice. *Neurobiol Aging*. 2012;33:522-34.
- Liu W, Zhao J, Lu G. miR-106b inhibits tau phosphorylation at Tyr18 by targeting Fyn in a model of Alzheimer's disease. *Biochem Biophys Res Commun*. 2016;478:852-7.
- Long JM, Ray B, Lahiri DK. MicroRNA-339-5p down-regulates protein expression of  $\beta$ -site amyloid precursor protein-cleaving enzyme 1 (BACE1) in human primary brain cultures and is reduced in brain tissue specimens of Alzheimer disease subjects. *J Biol Chem*. 2014;289:5184-98.
- Luo Q, Chen Y. Long noncoding RNAs and Alzheimer's disease. *Clin Intervent Aging*. 2016;11:867.
- Ma L, Bajic VB, Zhang Z. On the classification of long non-coding RNAs. *RNA Biol*. 2013;10:924-33.
- Magistri M, Velmeshev D, Makhmutova M, Faghihi MA. Transcriptomics profiling of Alzheimer's disease reveal neurovascular defects, altered amyloid- $\beta$  homeostasis, and deregulated expression of long noncoding RNAs. *J Alzheimer's Dis*. 2015;48:647-65.
- Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol*. 2010;9:702-16.
- Maoz R, Garfinkel BP, Soreq H. Alzheimer's Disease and ncRNAs. *Adv Exp Med Biol*. 2017;978:337-61.
- Mardokh Rohani N, Khalaj-Kondari M, Khodayi-Shahrak M, Talebi M, Hoseinpour Feizi MA. Association of TOMM40, CHAT and SORL1 polymorphisms with the Alzheimer's disease in the Turkish-speaking Azeri population in Northwest of Iran. *J Cell Mol Res*. 2020;12(1):41-8.
- Massone S, Vassallo I, Fiorino G, Castelnuovo M, Barbieri F, Borghi R, et al. 17A, a novel non-coding RNA, regulates GABA B alternative splicing and signaling in response to inflammatory stimuli and in Alzheimer disease. *Neurobiol Dis*. 2011;41:308-17.
- Massone S, Ciarlo E, Vella S, Nizzari M, Florio T, Russo C, et al. NDM29, a RNA polymerase III-dependent non coding RNA, promotes amyloidogenic processing of APP and amyloid  $\beta$  secretion. *Biochim Biophys Acta*. 2012;1823:1170-7.
- Matsui T, Ingelsson M, Fukumoto H, Ramasamy K, Kowa H, Frosch MP, et al. Expression of APP pathway mRNAs and proteins in Alzheimer's disease. *Brain Res*. 2007;1161:116-23.
- Mattson MP. Pathways towards and away from Alzheimer's disease. *Nature*. 2004;430(7000):631-9.
- Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, et al. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. *Nat Biotechnol*. 2012;30:453-9.
- Mufson EJ, Mahady L, Waters D, Counts SE, Perez SE, DeKosky S, et al. Hippocampal plasticity during the progression of Alzheimer's disease. *Neuroscience*. 2015;309:51-67.
- Muralidar S, Ambi SV, Sekaran S, Thirumalai D, Palaniappan B. Role of tau protein in Alzheimer's disease: The prime pathological player. *Int J Biol Macromol*. 2020;163:1599-617.
- Mus E, Hof PR, Tiedge H. Dendritic BC200 RNA in aging and in Alzheimer's disease. *Proc Natl Acad Sci*. 2007;104:10679-84.
- Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, et al. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat Med*. 2009;15:331-7.
- Nagahara AH, Mateling M, Kovacs I, Wang L, Eggert S, Rockenstein E, et al. Early BDNF treatment ameliorates cell loss in the entorhinal cortex of APP transgenic mice. *J Neurosci*. 2013;33:15596-602.

- Nicolas G, Acuña-Hidalgo R, Keogh MJ, Quenez O, Steehouwer M, Lelieveld S, et al. Somatic variants in autosomal dominant genes are a rare cause of sporadic Alzheimer's disease. *Alzheimer's Dement.* 2018;14:1632-9.
- O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. *Front Endocrinol.* 2018;9:402.
- Okada C, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, et al. A high-resolution structure of the pre-microRNA nuclear export machinery. *Science.* 2009;326(5957):1275-9.
- Parenti R, Paratore S, Torrisi A, Cavallaro S. A natural antisense transcript against Rad18, specifically expressed in neurons and upregulated during  $\beta$ -amyloid-induced apoptosis. *Eur J Neurosci.* 2007;26:2444-57.
- Patel N, Hoang D, Miller N, Ansaloni S, Huang Q, Rogers JT, et al. MicroRNAs can regulate human APP levels. *Mol Neurodegener.* 2008;3:10.
- Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet.* 2016;17:47-62.
- Ramakrishna S, Muddashetty RS. Emerging role of microRNAs in dementia. *J Mol Biol.* 2019;431:1743-62.
- Reitz C. The role of intracellular trafficking and the VPS10d receptors in Alzheimer's disease. *Future Neurol.* 2012;7:423-31.
- Roberts TC, Morris KV, Wood MJ. The role of long non-coding RNAs in neurodevelopment, brain function and neurological disease. *Philos Trans R Soc Lond B Biol Sci.* 2014;369(1652):20130507.
- Sarlak G, Htoo H, Hernandez J-F, Iizasa H, Checler F, Konietzko U, et al. Sox2 functionally interacts with  $\beta$ APP, the  $\beta$ APP intracellular domain and ADAM10 at a transcriptional level in human cells. *Neuroscience.* 2016;312:153-64.
- Scherzer CR, Offe K, Gearing M, Rees HD, Fang G, Heilman CJ, et al. Loss of apolipoprotein E receptor LR11 in Alzheimer disease. *Arch Neurol.* 2004;61:1200-5.
- Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, et al. Amyloid- $\beta$  protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med.* 2008;14:837-42.
- Singer O, Marr RA, Rockenstein E, Crews L, Coufal NG, Gage FH, et al. Targeting BACE1 with siRNAs ameliorates Alzheimer disease neuropathology in a transgenic model. *Nat Neurosci.* 2005;8:1343-9.
- Singh R, Gupta S, Peng W, Zhou N, Pochampally R, Atfi A, et al. Regulation of alternative splicing of Bcl-x by BC200 contributes to breast cancer pathogenesis. *Cell Death Dis.* 2016;7(6):e2262.
- Smith PY, Hernandez-Rapp J, Jolivet F, Lecours C, Bisht K, Goupil C, et al. miR-132/212 deficiency impairs tau metabolism and promotes pathological aggregation in vivo. *Hum Mol Genet.* 2015;24:6721-35.
- Straten G, Eschweiler GW, Maetzler W, Laske C, Leyhe T. Glial cell-line derived neurotrophic factor (GDNF) concentrations in cerebrospinal fluid and serum of patients with early Alzheimer's disease and normal controls. *J Alzheimer's Dis.* 2009;18:331-7.
- Strobel S, Grünblatt E, Riederer P, Heinsen H, Arzberger T, Al-Sarraj S, et al. Changes in the expression of genes related to neuroinflammation over the course of sporadic Alzheimer's disease progression: CX3CL1, TREM2, and PPAR $\gamma$ . *J Neural Transm (Vienna).* 2015;122:1069-76.
- Sun M, Kraus WL. From discovery to function: the expanding roles of long noncoding RNAs in physiology and disease. *Endocrine Rev.* 2015;36:25-64.
- Talebi M, Delpak A, Khalaj-Kondori M, Sadigh-Eteghad S, Talebi M, Mehdizadeh E, et al. ABCA7 and EphA1 genes polymorphisms in late-onset Alzheimer's disease. *J Mol Neurosci.* 2020;70:167-73.
- Tang L, Liu L, Li G, Jiang P, Wang Y, Li J. Expression profiles of long noncoding RNAs in intranasal LPS-mediated Alzheimer's disease model in mice. *Biomed Res Int.* 2019;2019:9642589.
- Van Gool B, Storck SE, Reekmans SM, Lechat B, Gordts PL, Pradier L, et al. LRP1 has a predominant role in production over clearance of A $\beta$  in a mouse model of Alzheimer's disease. *Mol Neurobiol.* 2019;56:7234-45.
- von Einem B, Schwanzar D, Rehn F, Beyer A-S, Weber P, Wagner M, et al. The role of low-density receptor-related protein 1 (LRP1) as a competitive substrate of the amyloid precursor protein (APP) for BACE1. *Exp Neurol.* 2010;225:85-93.
- Wan P, Su W, Zhuo Y. The role of long noncoding RNAs in neurodegenerative diseases. *Mol Neurobiol.* 2017;54:2012-21.
- Wang H, Iacoangeli A, Popp S, Muslimov IA, Imataka H, Sonenberg N, et al. Dendritic BC1 RNA: functional role in regulation of translation initiation. *J Neurosci.* 2002;22:10232-41.

- Wang J, Zhou T, Wang T, Wang B. Suppression of lncRNA-ATB prevents amyloid- $\beta$ -induced neurotoxicity in PC12 cells via regulating miR-200/ZNF217 axis. *Biomed Pharmacother.* 2018a;108:707-15.
- Wang W-X, Rajeev BW, Stromberg AJ, Ren N, Tang G, Huang Q, et al. The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of  $\beta$ -site amyloid precursor protein-cleaving enzyme 1. *J Neurosci.* 2008;28:1213-23.
- Wang X, Zhang M, Liu H. LncRNA17A regulates autophagy and apoptosis of SH-SY5Y cell line as an in vitro model for Alzheimer's disease. *Biosci Biotechnol Biochem.* 2019;83:609-21.
- Wang Z, Qin W, Wei C, Tang Y, Zhao L, Jin H, et al. The microRNA-1908 up-regulation in the peripheral blood cells impairs amyloid clearance by targeting ApoE. *Int J Geriatr Psychiatry.* 2018b;33:980-6.
- Wei C-W, Luo T, Zou S-S, Wu A-S. The role of long noncoding RNAs in central nervous system and neurodegenerative diseases. *Front Behav Neurosci.* 2018;12:175.
- Wu P, Zuo X, Deng H, Liu X, Liu L, Ji A. Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. *Brain Res Bull.* 2013;97:69-80.
- Yamanaka Y, Faghihi MA, Magistri M, Alvarez-Garcia O, Lotz M, Wahlestedt C. Antisense RNA controls LRP1 Sense transcript expression through interaction with a chromatin-associated protein, HMGB2. *Cell Rep.* 2015;11:967-76.
- Yang B, Xia Z-a, Zhong B, Xiong X, Sheng C, Wang Y, et al. Distinct hippocampal expression profiles of long non-coding RNAs in an Alzheimer's disease model. *Mol Neurobiol.* 2017;54:4833-46.
- Yang G, Song Y, Zhou X, Deng Y, Liu T, Weng G, et al. MicroRNA-29c targets  $\beta$ -site amyloid precursor protein-cleaving enzyme 1 and has a neuroprotective role in vitro and in vivo. *Mol Med Rep.* 2015;12:3081-8.
- Yao R-W, Wang Y, Chen L-L. Cellular functions of long noncoding RNAs. *Nat Cell Biol.* 2019;21:542-51.
- Yi J, Chen B, Yao X, Lei Y, Ou F, Huang F. Upregulation of the lncRNA MEG3 improves cognitive impairment, alleviates neuronal damage, and inhibits activation of astrocytes in hippocampus tissues in Alzheimer's disease through inactivating the PI3K/Akt signaling pathway. *J Cell Biochem.* 2019;120:18053-65.
- Yin R-H, Yu J-T, Tan L. The role of SORL1 in Alzheimer's disease. *Mol Neurobiol.* 2015;51:909-18.
- Zagrebelsky M, Gödecke N, Remus A, Korte M. Cell type-specific effects of BDNF in modulating dendritic architecture of hippocampal neurons. *Brain Struct Funct.* 2018;223:3689-709.
- Zhang B, Chen C, Wang A, Lin Q. MiR-16 regulates cell death in Alzheimer's disease by targeting amyloid precursor protein. *Eur Rev Med Pharmacol Sci.* 2015a;19:4020-7.
- Zhang H, Kolb FA, Jaskiewicz L, Westhof E, Filipowicz W. Single processing center models for human Dicer and bacterial RNase III. *Cell.* 2004;118:57-68.
- Zhang J, Hu M, Teng Z, Tang Y-P, Chen C. Synaptic and cognitive improvements by inhibition of 2-AG metabolism are through upregulation of microRNA-188-3p in a mouse model of Alzheimer's disease. *J Neurosci.* 2014;34:14919-33.
- Zhang J, Wang R. Deregulated lncRNA MAGI2-AS3 in Alzheimer's disease attenuates amyloid- $\beta$  induced neurotoxicity and neuroinflammation by sponging miR-374b-5p. *Exp Gerontol.* 2021;144:111180.
- Zhang L, Fang Y, Lian Y, Chen Y, Wu T, Zheng Y, et al. Brain-derived neurotrophic factor ameliorates learning deficits in a rat model of Alzheimer's disease induced by  $\text{A}\beta$ 1-42. *PLoS One.* 2015b;10(4):e0122415.
- Zhang W, Zhao H, Wu Q, Xu W, Xia M. Knockdown of BACE1-AS by siRNA improves memory and learning behaviors in Alzheimer's disease animal model. *Exp Ther Med.* 2018;16:2080-6.
- Zhang Y, Xing H, Guo S, Zheng Z, Wang H, Xu D. MicroRNA-135b has a neuroprotective role via targeting of  $\beta$ -site APP-cleaving enzyme 1. *Exp Ther Med.* 2016;12:809-14.
- Zhang Y, Zhao Y, Ao X, Yu W, Zhang L, Wang Y, et al. The role of non-coding RNAs in Alzheimer's disease: from regulated mechanism to therapeutic targets and diagnostic biomarkers. *Front Aging Neurosci.* 2021;13:654978.
- Zhang Z. Long non-coding RNAs in Alzheimer's disease. *Curr Top Med Chem.* 2016;16:511-9.
- Zhao J, Yue D, Zhou Y, Jia L, Wang H, Guo M, et al. The role of microRNAs in  $\text{A}\beta$  deposition and tau phosphorylation in Alzheimer's disease. *Front Neurol.* 2017;8:342.
- Zhao Y, Zhang Y, Zhang L, Dong Y, Ji H, Shen L. The potential markers of circulating microRNAs and long non-coding RNAs in Alzheimer's disease. *Aging Dis.* 2019;10(6):1293.

Zhou H, Mangelsdorf M, Liu J, Zhu L, Wu JY. RNA-binding proteins in neurological diseases. *Sci China Life Sci.* 2014;57:432-44.

Zhou M, Zhao H, Wang X, Sun J, Su J. Analysis of long noncoding RNAs highlights region-specific altered expression patterns and diagnostic roles in Alzheimer's disease. *Brief Bioinform.* 2019;20:598-608.

Zhou X, Xu J. Identification of Alzheimer's disease-associated long noncoding RNAs. *Neurobiol Aging.* 2015;36:2925-31.

Zhu H-C, Wang L-M, Wang M, Song B, Tan S, Teng J-F, et al. MicroRNA-195 downregulates Alzheimer's disease amyloid- $\beta$  production by targeting BACE1. *Brain Res Bull.* 2012;88:596-601.

Zhu J, Fu H, Wu Y, Zheng X. Function of lncRNAs and approaches to lncRNA-protein interactions. *Sci China Life Sci.* 2013;56:876-85.

Zong Y, Wang H, Dong W, Quan X, Zhu H, Xu Y, et al. miR-29c regulates BACE1 protein expression. *Brain Res.* 2011;1395:108-15.