Long Non-coding RNA: Insight Into Mechanisms of Alzheimer’s Disease

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Alzheimer’s disease (AD), a heterogeneous neurodegenerative disorder, is the most common cause of dementia accounting for an estimated 60–80% of cases. The pathogenesis of AD remains unclear, and no curative treatment is available so far. Increasing evidence has revealed a vital role of non-coding RNAs (ncRNAs), especially long non-coding RNAs (lncRNAs), in AD. LncRNAs contribute to the pathogenesis of AD via modulating amyloid production, Tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, synaptic impairment and neuroinflammation. This review describes the biological functions and mechanisms of lncRNAs in AD, indicating that lncRNAs may provide potential therapeutic targets for the diagnosis and treatment of AD.

Keywords: long non-coding RNA, Alzheimer's disease, amyloid beta, tau phosphorylation, mitochondrial dysfunction, oxidative stress, synaptic dynamics, biomarker

INTRODUCTION

Alzheimer’s disease (AD), a main cause of dementia and one of the most costly and lethal diseases (2021), is clinically characterized by progressive memory deterioration or other cognitive dysfunction, which ultimately needs full-time medical care. A cross-sectional study has shown that the overall prevalence of dementia achieves 6.0% in 2020 (3.9% for AD), representing 15.07 million individuals aged over 60 years suffered dementia in China (Jia et al., 2020). Moreover, dementia has become the second largest cause of death in individuals aged more than 70 years after ischemic heart disease (Collaborators, 2019). AD is generally divided into two groups, namely the late onset of AD (LOAD) and the early onset of AD (EOAD). EOAD, also called familial AD, is closely correlated to mutations in amyloid precursor protein (APP) and the presenilin1/2 genes. The mutations lead to the dysfunction of APP processing and induce the excessive production of amyloid-beta (Aβ). However, these genes account only for near 11% of EOAD and 0.6% of all cases of AD (Karch and Goate, 2015). LOAD, also called sporadic AD, is the majority of AD cases. The most well-known genes correlating with LOAD are apolipoprotein genotype E4 (APOE4) and triggering receptor expressed on myeloid cells 2 gene (TREM2) (Ulland and Colonna, 2018; Zhao et al., 2018).

With the recent advancement of transcriptome-wide profiling approach, numerous of non-coding RNAs (ncRNAs) have been identified. The long non-coding RNAs (lncRNAs), which are long transcripts (>200 nucleotides in length) without apparent protein-coding capacity, have received increasing attention and are expected to be novel epigenetic regulators of gene expression at transcriptional and post-transcriptional levels (Mercer et al., 2009; Briggs et al., 2015; Zhang et al., 2019b; Karakas and Ozpolat, 2021). LncRNAs modulate chromatin functions by interaction with DNA, RNA and protein, and regulate the transcription of target genes in cis or in trans in...
the nucleus. In addition, lncRNAs function as miRNA sponges to suppress the miRNA availability to mRNAs in the cytosol (Statello et al., 2021). LncRNAs are widely expressed in brains and affect the proliferation, survival, metabolism and differentiation of neuronal cells, which is considered to contribute to the pathogenesis of AD (Wu et al., 2013). Mounting evidence has shown that lncRNAs are aberrantly expressed in AD progression, and modulate Aβ plaque formation, tau hyperphosphorylation, neuroinflammation and neuronal apoptosis (Luo and Chen, 2016; Zhou et al., 2021). However, the underlying mechanisms of lncRNAs in AD have not yet been elucidated. Herein, we will summarize the well-characterized lncRNAs in AD (Figure 1), highlighting their potential roles in the disease pathogenesis.

**LncRNAs and Aβ Accumulation**

**Aβ and AD**

Although the causality between Aβ and AD remains controversial, it is generally considered that Aβ may be the trigger of AD pathogenesis. In the amyloidogenic pathway, Aβ is produced through sequential cleavage of APP by β-secretase (β-site APP cleaving enzyme 1, BACE-1) and γ-secretase to produce Aβ1−42. In non-amyloidogenic pathway, APP is cleaved by α-secretase and γ-secretase to produce secreted amyloid precursor protein α (sAPPα), p3 and APP intracellular domain (AICD) (Morris et al., 2014; Soria Lopez et al., 2019). Aβ oligomers may trigger secondary or downstream events, such as the hyperphosphorylation of tau, synapse dysfunction and loss, inflammation, oxidative stress, and excitotoxicity, while Aβ plaques alone are not responsible for memory impairments observed in AD (Thal and Fandrich, 2015; Scheltens et al., 2016). Interestingly, recent research shows Aβ may work as an anti-microbial peptide and therefore potentially acts to combat infiltrating infectious agents (Moir et al., 2018). On June 7, 2021, aducanumab, a monoclonal antibody targeting amyloid protein, is approved to treat AD by the US Food and Drug Administration (FDA), which has sparked global debate, and further clinical trials are needed in the future (Alexander et al., 2021; Kuller and Lopez, 2021; Mullard, 2021).

**Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1 Antisense Transcript Promotes Aβ Production**

BACE1-AS is a conserved 2 KB non-coding antisense transcript that is transcribed from the antisense strand of the BACE1 gene locus on chromosome 11 (11q23. 3), and includes 104 nucleotides of full complementarity to human BACE1 mRNA (Faghihi et al., 2008; Kandalepas and Vassar, 2014). BACE1-AS promotes BACE1 expression at both mRNA and protein levels, which enhances APP cleavage and alters the pattern of Aβ aggregation (Li et al., 2019; Zeng et al., 2019). BACE1-AS is upregulated in peripheral blood samples and brain regions including cerebellum, hippocampus and entorhinal cortex in AD patients (Faghihi et al., 2008; Fotuhi et al., 2019). Interestingly, the accumulation of Aβ1−42 further increases BACE1-AS expression, driving APP processing cascade in a feed-forward manner (Faghihi et al., 2008; Li et al., 2019). The neuronal RNA-binding protein HuD interacts with BACE1-AS and increases its level, and subsequently promotes BACE1 expression and Aβ production (Kang et al., 2014). Cellular stimuli, including serum starvation, Aβ42 and H2O2 treatment, induce the upregulation of BACE1-AS under high glucose concentration (Boland et al., 2008; Faghihi et al., 2008; Liu et al., 2014). Knockdown of BACE1-AS by siRNA promotes the survival of primary neurons, and improves learning and memory function.

**FIGURE 1 | LncRNAs in the mechanisms of AD.**
memory functions of AD mice through inhibiting the expression of BACE1, APP and p-tau (Zhang et al., 2018b; Li et al., 2019).

51A Enhances Aβ Formation
LncRNA 51A maps in antisense configuration to the sortilin-related receptor 1 (SORL1) gene, which induces a splicing shift of SORL1 from the synthesis of SORL1 variant A to an alternatively spliced protein form. SORL1 participates in the trafficking of APP through endocytic and secretory compartments (Willnow et al., 2010; Barthelson et al., 2020), and decreased SORL1 shifts APP from the retromer-recycling endosome pathway to the β-secretase cleavage pathway, leading to increased production and accumulation of Aβ (Sager et al., 2007; Verheijen et al., 2016). Recent studies reveal that 51A is increased in the plasma and brains of AD patients compared that in controls, and indicate a negative correlation with the Mini-Mental State Examination (MMSE) scores (Luo and Chen, 2016; Garofalo et al., 2021).

17A Increases the Ratio of Aβx-42 vs. Aβx-40
LncRNA 17A is a 159 nucleotides lncRNA synthesized by RNA polymerase III, and localizes to intron 3 of the human G-protein-coupled receptor 51 gene (GPR51, GABA B2 receptor). The synthesis of 17A leads to the maturation of GABAB R2 mRNA, which induces alternative GPR51 splicing and eventually impairs GABA B-mediated signaling. The level of 17A is increased in the cerebral tissues derived from AD patients with an increased ratio of Aβx-42 vs. Aβx-40 (Massone et al., 2011). Overexpression of 17A in cultured neuronal cells amplifies the Aβ42 to Aβ40 ratio and promotes apoptosis (Wang et al., 2019b). All these data indicate that 17A overexpression may lead to an altered Aβ secretion and play a vital role in AD progression.

Brain Cytoplasmic 200 Promotes Aβ Accumulation
BC200 is a polyadenylated 200 nucleotides primate neuron-specific ncRNA that is transcribed by RNA polymerase III. BC200 acts as a local translational modulator by inhibiting translation in postsynaptic dendritic microdomains, which eventually maintains the plasticity of neuron. BC200 is upregulated in specific brain areas and is increased with disease progression in AD, while it shows a steady decline in normal aging (Sosińska et al., 2015). Moreover, the overexpression of BC200 in AD is accompanied with distribution changes, including dendritic mislocalization of the transcript and accumulation of BC200 in the perikaryon (Sosińska et al., 2015; Shin et al., 2017), which has been proposed to be a starting point for the neurodegenerative changes, and eventually leads to Aβ production and amyloid deposition. In addition, BC1, a potential analog of BC200 in mice, induces APP mRNA translation through fragile X syndrome protein (FMRP), and the dysfunction of BC1 or BC1-FMRP association in AD mice impedes the aggregation of Aβ in the brain and protects against spatial learning and memory deficits (Mus et al., 2007).

Neuroblastoma Differentiation Marker 29 Promotes Aβ Secretion
NDM29 is a lncRNA transcribed by RNA Pol III, and promotes neuroblastoma cell differentiation to a non-malignant neuron-like phenotype (Castelnuovo et al., 2010; Zhang et al., 2018a). NDM29 is upregulated in postmortem cerebral cortex from AD patients (Massone et al., 2012). NDM29 overexpression promotes the amyloidogenic processing of APP and leads to the increase of Aβ secretion and Aβx-42/Aβx-40 ratio (Massone et al., 2012).

LncRNA AND TAU HYPERPHOSPHORYLATION
Tau Hyperphosphorylation and AD
Tau protein is encoded by the microtubule-associated protein tau (MAPT) gene that is located on chromosome 17 in human and chromosome 11 in mice (Andreadis, 2006; Barbier et al., 2019), and plays a pivotal role in binding and stabilizing microtubules by promoting tubulin assembly to regulate the function of neurons. The abnormal hyperphosphorylation of tau alters its charge and conformation and exposes the microtubule-binding domain, leading to self-oligomerization of tau protein and forming the paired helical filaments (PHF). The aggregation of tau and PHF eventually results in the formation of neurofibrillar tangles (NFTs) (Iqbal et al., 2016; Duan et al., 2017; Guo et al., 2017). Beyond hyperphosphorylation, tau protein is also post-translationally modified through truncation, glycosylation, glycation, ubiquitination, nitration, methylation, lipoperoxidation, sumoylation, and acetylation, all of which are involved in the etiology of AD and other tauopathies (Iqbal et al., 2016). On the other hand, tau phosphorylation is regulated by a balance between phosphatase activity and tau kinase (Massone et al., 2012; Martin et al., 2013a). The number of NFTs rather than Aβ are correlated with the severity of cognitive impairment in AD patients (Giannakopoulos et al., 2003). Moreover, the distribution and accumulation of tau within synapse impairs synaptic transport and signaling pathways, leading to dysfunction and even loss of synapses in AD patients (Pooler et al., 2014; Dejanovic et al., 2018; John and Reddy, 2021). Similarly, tau oligomers are toxic to synapses and can cause synaptic impairment prior to the NFTs (Dejanovic et al., 2018). Notably, there is an intense crosstalk between Aβ and tau. Aβ exerts its toxicity at least in part through tau and the Aβ-dependent pathologies can be greatly amplified by tau expression (Bloom, 2014; Nisbet et al., 2015). Removing endogenous tau prevents Aβ-associated cognitive impairments (Guerrero-Muñoz et al., 2015). Aβ-induced upregulation of intracellular calcium levels is a key upstream event for the formation of tauopathy and dislocation in the dendritic compartment (Bloom, 2014; Zempel and Mandelkow, 2015). Furthermore, pyroglutamylated Aβ, an important form of Aβ, induces tau-dependent toxicity and propagates in a prion-like manner (Nussbaum et al., 2012).
**Nuclear Paraspeckles Assembly Transcript 1 Induces Tau Dephosphorylation**

NEAT1 is vital for nuclear paraspeckles, and it regulates nuclear bodies, chromatin remodeling, microtubules (MTs) stability and gene expression (Martin et al., 2013b). Recent studies have demonstrated that NEAT1 is correlated to neuronal loss and neurodegenerative disorders (Lo et al., 2016; Sunwoo et al., 2017). Knockdown of NEAT1 increases the expression of p-tau and dysfunction of MTs through Frizzled Class Receptor 3 (FZD3)/CSK3β/p-tau pathway (Kickstein et al., 2010). Interestingly, metformin increases NEAT1 expression, and leads to decreased FZD3 expression and dephosphorylation of tau (Zhong et al., 2017). Additionally, NEAT1 modulates Aβ via regulating miR-124/BACE1 axis (Zhao et al., 2020b).

**Linc00507 Induces Tau Hyperphosphorylation**

Linc00507, first described in the Mammalian Gene Collection Program, is expressed in a cortex-specific manner in non-human primates and humans (Strausberg et al., 2002; Ransohoff et al., 2018). Linc00507 is upregulated in the hippocampus and cerebral cortex of APP/PS1 mice, which subsequently triggers the p25/p35/GSK3β activation and leads to tau-pathology. In addition, linc00507 functions as an endogenously competing RNA (ceRNA) that directly binds to mir-181c-5p, inducing the upregulation of MAPT and tau tubulin kinase 1 (TTBK1) (Strausberg et al., 2002; Mills et al., 2016).

**LncRNA AND LOSS OF SYNAPTIC HOMEOSTASIS**

**Loss of Synaptic Homeostasis and AD**

An analysis of post-mortem brain tissues from AD patients has revealed significant synapse loss (Hendrige et al., 2015; de Wilde et al., 2016). Restoring excitatory synaptic transmission in the hippocampus can effectively ameliorate the cognitive deficits in animal models with AD (Nisticò et al., 2012). The synaptic pathology correlates with clinical manifestations of AD and parallels the cognitive decline (Selkoe, 2002; Kashyap et al., 2019). In addition, dramatic synaptic loss is the first indicator of AD progression even in the earliest stages of AD. Increasing evidence reveals that synaptic dysfunction may be due to soluble Aβ, phosphorylated tau accumulation and mitochondrial free radicals at synapses (John and Reddy, 2021; Pereira et al., 2021). The physiological levels of Aβ may enhance neuronal activity by presynaptic potentiation and further facilitate Aβ production, and ultimately induces negative postsynaptic regulation of excitatory synaptic transmission (Palop and Mucke, 2010). However, excessive Aβ may lead to the dysfunction of pre-synapses consisting of axonal transport, synaptic vesicle cycling and neurotransmitter release. The interaction of Aβ oligomers and postsynaptic compartment of excitatory synapses with high affinity leads to synaptic plasticity impairment (Selkoe, 2002; Palop and Mucke, 2010; Chen et al., 2019). The abnormal accumulation and mislocalization of tau disrupts the microtubule-based cellular transport and impedes the trafficking of essential cargo, leading to decreased mitochondrion-dependent ATP production, calcium buffering and synapse loss (Forner et al., 2017; John and Reddy, 2021). In addition, ApoE and its receptor regulate synaptic functions at both pre- and postsynaptic sites, amongst which ApoE4 induces neuronal dysfunction at the earliest stages of AD (Lane-Donovan and Herz, 2017; Zhao et al., 2020a). Furthermore, the dysfunction of AMPA receptors (AMPA) trafficking impairs neuronal circuit formation and causes long-term depression, which contributes to the symptoms of AD (Jurado, 2017; Ma et al., 2020).

**BC200 Impairs Synaptic Functions**

BC200 is selectively expressed in neurons and delivered to the dendrites to regulate the synthesis of local proteins (Yan et al., 2020), and maintains the long-term plasticity (Muslimov et al., 1997). The mislocalization and overexpression of BC200 contributes to dendrites impairment in AD. The level of BC200 in affected brain areas closely correlates with the synaptic impairment and the severity of AD (Muddashetty et al., 2002; Bassell and Twiss, 2006). In addition, the somatodendritic distribution of BC200 is altered in severe AD (Muddashetty et al., 2002; Bassell and Twiss, 2006). Furthermore, BC200 binds to eukaryotic initiation factor 4A (eIF4A) and other RNA-binding proteins to regulate the levels of post-synaptic dendritic microdomains, including FMRP, synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP) and poly (A)-binding protein (PABP) (Zalfa et al., 2005; Mus et al., 2007; Duning et al., 2008).

**BDNF-AS Damages Synaptic Plasticity**

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuronal survival and synaptic plasticity and promotes the synapse growth, which consequently regulates learning and memory function (Lu et al., 2014; Petukhova et al., 2019). BDNF-AS is a conserved non-coding antisense RNA transcript, and modulates synaptic structure and functions via interacting with BDNF mRNA (Alsina et al., 2001). BDNF is decreased in most neurodegenerative disorders (Ji et al., 2010), however, some studies show increased BDNF in the post-mortem brain tissue with AD (Ventriglia et al., 2013). BDNF-AS forms an in vivo RNA-RNA duplex with BDNF mRNA and decreases the protein level of BDNF, while BDNF-AS inhibition upregulates the level of BDNF (Alsina et al., 2001). Moreover, BDNF-AS downregulates the level of BDNF mRNA through interfering chromatin at its locus (Alsina et al., 2001).

**LncRNA AND MITOCHOONDRIAL DYSFUNCTION**

**Mitochondrial Dysfunction and AD**

Mitochondrial dysfunction is revealed as one of the earliest features of AD (Sery et al., 2013). The brain consumes nearly 20% of the total basal oxygen budget to support ATP demands, and it is susceptible to oxidative stress and energy shortage due to mitochondrial dysfunction (Galluzzi et al., 2012; Perez Ortiz and Swerdlov, 2019). Several studies suggest that bioenergetic deficits precede the accumulation of Aβ and tau, and are exacerbated...
with these aggregated proteins (Galluzzi et al., 2012; Tyumentsev et al., 2018). Moreover, it is found that restoration of the activity of phosphatase and tensin homolog (PTEN) induced putative kinase 1 (PINK1) improves the cognitive functions and lowers Aβ production in AD mice (Tyumentsev et al., 2018; Lim et al., 2020).

**Nuclear Enriched Abundant Transcript 1 Induces Mitochondrial Impairment**

NEAT1 is a lncRNA transcribed from the multiple endocrine neoplasia type 1 (MEN1) gene, known as a scaffold for paraspeckles. NEAT1 plays a vital role in the formation and maintenance of paraspeckles (Cadonic et al., 2016). NEAT1 is upregulated during aging in the APP/PS1 transgenic mouse model and in the temporal cortex and hippocampus of AD mice (Liu et al., 2014; Huang et al., 2020). Knockdown of NEAT1 ameliorates cognitive impairments and improves hippocampal memory formation, and its overexpression exacerbates the progression of AD pathology and cognitive impairment in AD mice (Zhou et al., 2018b; Cao et al., 2019). The underlying mechanisms of NEAT1 in AD remain undefined. Recent studies show that NEAT1 interferes with mitochondria through PINK1 in AD models (Zhou et al., 2018b). NEAT1 promotes the degradation of PINK1 and impairs PINK1-dependent autophagy, leading to the dysfunction of autophagy signaling and inducing the amyloid accumulation and mitochondrial impairment (Zhou et al., 2018b; Lim et al., 2020). In addition, NEAT1 regulates Aβ accumulation in AD mice through interacting with miR-124 and miR-107, and knockdown of NEAT1 attenuates Aβ-induced neuronal damage (Zhou et al., 2018b; Butler et al., 2019; Ke et al., 2019).

**LncRNA AND NEURONAL APOPTOSIS**

**Neuronal Apoptosis and AD**

Neuronal apoptosis plays an important role in central nervous system, and the perturbation of apoptosis is involved in the neurodegenerative diseases including AD (Gu et al., 2018). Caspases act as both initiator and executor of apoptosis, and at least 7 caspases have been involved in AD including caspase-1, 2, 3, 6, 8, 9, and 12. For instance, the level of caspase-1 mRNA is upregulated in AD brain extracts (Qian et al., 2015). The deficiency of caspase-2 protects several neuronal subtypes from Aβ-induced apoptotic death in vitro (Desjardins and Ledoux, 1998), and caspase-3 is increased in AD brain and is activated in Aβ-treated neuronal cultures (Gervais et al., 1999). Previous reports have shown that many DNA fragmentation in post-mortem brains of AD patients, which indicates the activity of apoptosis in AD (Lassmann et al., 1995). All these data suggest that neuronal apoptosis dysregulation mediates the pathogenesis of AD.

**Early B Cell Factor 3 Antisense RNA Induces Neuronal Apoptosis**

EBF3-AS, a 2-exon RNA transcribed from the opposite strand of the protein-coding gene Early B cell factor 3 (EBF3), is abundantly expressed in brain (Zhao et al., 2019). EBF3 is thought to be a target gene of EBF3-AS and is potentially associated with age in LOAD (Magistri et al., 2015). Previous studies have revealed that EBF3 homologs are essential for survival and dysfunction of EBF3 correlates to a range of nervous system developmental defects including perturbation of neuronal development and migration (Belbin et al., 2011). EBF3-AS and EBF3 are upregulated in the hippocampus of AD mice, and knockdown of EBF3-AS and EBF3 inhibits the apoptosis induced by Aβ (Chao et al., 2017). These results suggest that EBF3-AS induces neuronal apoptosis in AD, supporting EBF3-AS as a new target for AD treatment.

**Natural Antisense Transcript Against Rad18 Promotes Neuronal Apoptosis**

NAT-Rad18, with a length of 509 nucleotides, plays a crucial role in DNA repair, and is directly responsible for the specific mono-ubiquitylation of the polymerase adapter PCNA (Lloyd et al., 2006; Parenti et al., 2007). NAT-Rad18 is universally expressed in the brain, especially in the cerebellum, brainstem, spinal cord, olfactory bulb, cortex, hippocampus and striatum (Flores et al., 2018). The upregulation of NAT-Rad18 renders cells more sensitive to a wide spectrum of DNA-damaging agents (Harvey et al., 2004), which may be part of a complex transcriptional and post-transcriptional genomic program underlying Aβ-neurotoxicity.

**Metastasis-Associated Lung Adenocarcinoma Transcript 1 Reduces Neuronal Apoptosis**

MALAT1 is a long intergenic non-coding RNA that is located on chromosome 11q13 and consists of 8,828 nucleotides (Tateishi et al., 2000). Emerging evidence suggests a neuroprotective function of MALAT1 via inhibiting neuroinflammation. MALAT1 is decreased in Aβ1–42 treated neurons, and induces the neurite outgrowth (Ji et al., 2003; Ma et al., 2019). Overexpression of MALAT1 reduces neuronal apoptosis and alleviates neuronal injury (Zhuang et al., 2020), and knockdown of MALAT1 promotes neuronal apoptosis and represses neurite growth (Ji et al., 2003). Additionally, MALAT1 modulates miR-125b expression and consequently suppresses neuronal apoptosis and inflammation (Ji et al., 2003; Ma et al., 2019).

**Taurine Upregulated Gene 1 Facilitates Neuronal Apoptosis**

TUG1 is a novel lncRNA with 6.7-kb nucleotides located on the chromosome 22q12, and is involved in neuronal apoptosis, proliferation, cell cycle and metastasis (Li et al., 2020a). Recent studies have revealed the important role of TUG1 in AD through controlling the neuronal apoptosis. TUG1 silencing decreases cellular apoptosis in Aβ25–35-treated hippocampal neurons, and consequently improves spatial learning and memory of AD mice (Guo et al., 2020). In addition, TUG1 acts as miR-15a sponge and regulates neuronal apoptosis via the proteolytic cleavage of crucial proteins (Guo et al., 2020; Li et al., 2020b).
**TABLE 1 | Potential lncRNA biomarkers in AD patients.**

| Related lncRNA | Regions of AD patients | Biological function | References |
|----------------|------------------------|---------------------|------------|
| BACE1-AS↑↓† | Brain, plasma | Upregulating BACE1 mRNA stability; Altering Aβ aggregation pattern increasing Aβ expression. | Faghihi et al., 2008; Fotuhi et al., 2019 |
| NDM29† | Cerebral cortex | Promoting the cleavage activity of BACE amyloid-β secretase; Increasing Aβ secretion and Aβ42/Aβ40 ratio. | Massone et al., 2012 |
| 51A↑ | Cerebral cortex and plasma | Downregulating SOX5; Increasing production and accumulation of Aβ. | Massone et al., 2011; Ciarlo et al., 2013 |
| 17A† | Cerebral cortex | Impairing the GABAB signaling pathway | Massone et al., 2011 |
| BC200† | Cerebral cortex | Inducing Aβ production and amyloid deposition; Maintaining the long-term synapse plasticity | Mus et al., 2007 |

The arrows next to lncRNA indicates up/down-regulation in AD patients.

**Wilms Tumor 1 Homolog Antisense RNA Inhibits Neuronal Apoptosis**

WT1-AS, a lncRNA located on chromosome 11p13, is important in regulating transcription, apoptosis and RNA metabolism (Zhang et al., 2019a; Wu et al., 2021). WT1-AS is downregulated in Aβ25–35 treated SH-SYSY cells, and overexpression of WT1-AS inhibits WT1 expression and reverses the deleterious effects of Aβ25–35 (Toska and Roberts, 2014). In addition, WT1-AS inhibits apoptosis via reducing WT1 expression or suppressing miR-375 expression (Toska and Roberts, 2014).

**LncRNA AND NEUROINFLAMMATION**

**Neuroinflammation and AD**

Neuroinflammation is a response to various stimuli and consists of glia cells, lymphocytes, monocytes and macrophages, which directly contributes to the pathogenesis and progression of AD (Maccioni et al., 2020). Neuroinflammation acts as a “double-edged sword” in the central nerve system (Cortés et al., 2018; Maccioni et al., 2020). The balance between neuronal damage and inflammation is mainly regulated by glia cells (Maccioni et al., 2020). Microglia functions as resident phagocytes to dynamically monitor the environment, and contributes to the brain development and synaptic pruning (Frost and Schafer, 2016; Colonna and Butovsky, 2017). Astrocytes are shown to maintain brain homeostasis, protect neural circuits and repair injuries (Sofroniew and Vinters, 2010; Cai et al., 2017b). Dysfunction of astrocytes induces tau hyperphosphorylation and NFT formation and failure of Aβ clearance (Yan et al., 2013; Leyns and Holtzman, 2017). Moreover, astrocytes are the most important energy regulators in CSF, and astrocyte metabolic dysfunction is considered as an initiating factor in AD (Yan et al., 2013).

**Maternally Expressed Gene 3 Reduces Neuroinflammatory Injury**

MEG3 locates on chromosome 14 in humans and acts as a mediator in inflammation. MEG3 plays a key role in various biological processes including microglia activation and inflammatory response (Kobayashi et al., 2000; Meng et al., 2021). Upregulation of MEG3 inactivates astrocyte through inhibiting the PI3/Akt pathway, and improves the spatial memory in AD rats (Yi et al., 2019). MEG3 is also a direct target of miR-7a-5p, and overexpression of MEG3 reduces miR-7a-5p and promotes microglia activation (Meng et al., 2021).

**MALAT1 Attenuates Neuroinflammation**

Accumulating evidence indicates the neuroprotective and anti-inflammatory role of MALAT1 in neurodegenerative diseases (Zhou et al., 2018a; Masoumi et al., 2019). MALAT1 inhibits the inflammation-associated miRNAs levels, and attenuates neuroinflammation in AD (Ma et al., 2019). MALAT1 is also decreased in Aβ1–42 treated cells and inhibits neuronal apoptosis (Ma et al., 2019).

**Other LncRNA With AD**

Glia cell line-derived neurotrophic factor (GDNF) is a neurotrophic peptide, and is known as a neurotropin to promote the survival and differentiation of midbrain dopaminergic neurons (Ledda et al., 2007; Airavaara et al., 2011). Glial cell line-derived neurotrophic factor opposite strand (GDNFOS) is a cis-natural antisense transcribed from the opposite strand of GDNF gene (Cortini et al., 2019). In patients with AD, the level of mature GDNF is increased in CSF and decreased in serum, while GDNFOS is upregulated in cerebellum (Straten et al., 2009; Airavaara et al., 2011). MAGI2-AS3 is significantly increased in Aβ25–35 induced neuronal cells and in AD patients, and knockdown of MAGI2-AS3 attenuates neurotoxicity and neuroinflammation (Wang et al., 2020). LncRNA X-inactive specific transcript (XIST) is a functional lncRNA which plays an important role in the development and progression of many malignant tumors (Yi et al., 2019). The expression of XIST is significantly increased in AD models and silencing XIST negatively regulates the expression of miR-124 and promotes BACE1 expression (Du et al., 2017). Ribonuclease P RNA component H1 (RPPH1) is an RNA component of the RNase P ribonucleoprotein, which cleaves tRNA precursor molecules to generate the mature tRNA (Yue et al., 2020). Overexpression of RPPH1 increases the density of dendritic spine in hippocampal neuron (Cai et al., 2017a), which suggests a protective role of RPPH1 in the early stage of AD. Small nucleolar RNA host gene 1 (SNHG1) is upregulated in Aβ25–35 treated cells and knockdown of SNHG1 attenuates Aβ25–35 induced mitochondrial dysfunction and cell apoptosis (Cai et al., 2017b).
et al., 2017a; Wang et al., 2019a). Recent studies have shown that knockdown of the LncRNA antisense non-coding RNA in the INK4 locus (lnc-ANRIL) inhibits apoptosis and promotes neurite outgrowth in a cellular model of AD (Zhou et al., 2020).

**LncRNA in Clinical AD Management and Perspective**

LncRNAs are relatively stable, which indicates that the serum or CSF LncRNAs might be promising biomarkers and therapeutic targets for AD diagnosis and treatment (Table 1). The concentration of BACE1 in CSF and plasma shows a good diagnostic value in AD patients (Shen et al., 2018; Lopez-Font et al., 2019). Therapeutic strategies targeting BACE1 have been extensively developed but discontinued due to futility or safety reasons (Ghosh and Osswald, 2014; Hampel et al., 2021). However, it is also shown that the plasma concentration of BACE1 in CSF and plasma shows a good diagnostic value in AD patients (Fotuhi et al., 2019). Overexpression of NMD29 is observed in AD postmortem cerebral cortex samples (Massone et al., 2012). 51A is overexpressed in AD post-mortem samples and shows an active role in altering SORL1 expression in AD patients and a positive correlation with Aβ production compared with that in healthy controls (Ciarlo et al., 2013). 17A is upregulated in cerebral cortices in AD patients and is specifically overexpressed in AD patients rather than other neurodegenerative diseases (Massone et al., 2011). The level of BC200 in cortical areas is increased in brains from AD patients, and is reduced in normal aging individuals (Mus et al., 2007). However, it is also shown that the plasma levels of 17A, 51A and, BC200 are not significantly affected in AD patients compared with those in age-matched controls (Feng et al., 2018). These inconsistent results may be attributed to relative smaller sample size and different disease stages.

Larger-scale trials are needed to elucidate the LncRNA profile in AD.

**CONCLUSION**

Up to now, numerous LncRNAs have been identified to be associated with AD, but it is only a tip of the iceberg. LncRNAs play a critical role in the AD pathogenesis including amyloid production, Tau hyperphosphorylation, mitochondrial dysfunction, synaptic impairment and neuroinflammation. However, how LncRNAs function at molecular and cellular levels remains a huge challenge, and the biological characteristics and underlying mechanisms of LncRNAs in AD still need to be elucidated. Undoubtedly, further investigation of LncRNAs lights a new beacon for clinical diagnosis and treatment of AD.

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**

ZL, YC, JJ, YX, and XZ wrote the paper. All authors read and approved the final manuscript.

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**REFERENCES**

(2021). 2021 Alzheimer’s disease facts and figures. *Alzheimers. Dement.*, 17, 327–406. doi: 10.1002/azd.12328

Airavaara, M., Pletnikova, O., Doyle, M. E., Zhang, Y. E., Troncoso, J. C., and Liu, Q. R. (2011). Identification of novel GDNF isoforms and cis-antisense GDNFOS gene and their regulation in human middle temporal gyrus of Alzheimer disease. *J. Biol. Chem.* 286, 4593–45102. doi: 10.1074/jbc.M111.310250

Alexander, G. K., Knopman, D. S., Emerson, S. S., Ovbiagele, B., Kryscio, R. J., Perlmutter, J. S., et al. (2019). Revisiting FDA approval of aducanumab. *N. Engl. J. Med.* 385, 769–771. doi: 10.1056/NEJMmp2110468

Alisina, B., Vu, T., and Cohen-Cory, S. (2001). Visualizing synapse formation in arboring optic axons in vivo: dynamics and modulation by BDNF. *Nat. Neurosci.* 4, 1093–1101. doi: 10.1038/nn735

Andreadis, A. (2006). Misregulation of tau alternative splicing in neurodegeneration and dementia. *Prog. Mol. Subcell. Biol.* 64, 89–107. doi: 10.1007/978-3-540-34449-0_5

Barthelson, K., Newman, M., and Lardelli, M. (2020). Sorting out the role of the sortilin-related receptor 1 in Alzheimer’s disease. *J. Alzheimers Dis. Rep.* 4, 123–140. doi: 10.3233/ADR-200177

Bassell, G. J., and Twiss, J. L. (2006). RNA exodus to Israel: RNA controlling function in the far reaches of the neuron. *Workshop on RNA control on neuronal function. EMBO Rep.* 7, 31–35. doi: 10.1038/sj.embor.7400616

Belbin, O., Carrasquillo, M. M., Crump, M., Culley, O. J., Hunter, T. A., Ma, L., et al. (2011). Investigation of 15 of the top candidate genes for late-onset Alzheimer's disease. *Hum. Genet.* 129, 273–282. doi: 10.1007/s00439-010-0924-2

Bloom, G. S. (2014). Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.* 71, 505–508. doi: 10.1001/jamaneurol.2013.5847

Boland, B., Kumar, A., Lee, S., Platt, F. M., Wegiel, J., Yu, W. H., et al. (2008). Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer’s disease. *J. Neurosci.* 28, 6926–6937. doi: 10.1523/JNEUROSCI.0800-08.2008

Briggs, J. A., Wolvevtang, E. J., Mattick, J. S., Rinn, J. L., and Barry, G. (2015). Mechanisms of long non-coding RNAs in mammalian nervous system development, plasticity, disease, and evolution. *Neuron* 88, 861–877. doi: 10.1016/j.neuron.2015.09.045

Butler, A. A., Johnston, D. R., Kaur, S., and Lubin, F. D. (2019). Long noncoding RNA NEAT1 mediates neuronal histone methylation and age-related memory impairment. *Sci. Signal.* 12:eaaw9277. doi: 10.1126/scisignal.aaw9277
Muddashetty, R., Khanam, T., Kondrashov, A., Bundman, M., Iacoangeli, A., Kremerskothen, J., et al. (2004). Poly(A)-binding protein is associated with neuronal NC1 and BC200 ribonucleoprotein particles. J. Mol. Biol. 321, 433–445. doi: 10.1016/S0022-2836(02)00655-1

Mullard, A. (2021). Landmark Alzheimer’s drug approval confounds research community. Handb. Clin. Neurol. 167, 231–255. doi: 10.1016/B978-0-12-804766-8.00013-3

Sordincek, P., Mikula-Pietraska, J., and Kusiak, K. (2015). The double-edged sword of long non-coding RNA: The role of human brain-specific BC200 RNA in translational control, neurodegenerative diseases, and cancer. Mutat. Res. Rev. Mutat. Res. 766, 58–67. doi: 10.1016/j.mrrev.2015.08.002

Statel, O., Guo, C. J., Chen, L. L., and Huarte, M. (2021). Gene regulation by long non-coding RNAs and its biological functions. Nat. Rev. Mol. Cell Biol. 22, 96–118. doi: 10.1038/s41580-020-00315-9

Straten, G., Eischweiler, G. W., Maetzel, W., Laske, C., and Leyhe, T. (2009). Glial cell-line derived neurotrophic factor (GDNF) concentrations in cerebrospinal fluid and serum of patients with early Alzheimer’s disease and normal controls. J. Alzheimers. Dis. 18, 331–337. doi: 10.3233/JAD-2009-1146

Straubage, R. L., Feingold, E. A., Grouse, L. H., Derge, J. G., Klausner, R. D., Collins, F. S., et al. (2002). Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proc. Natl. Acad. Sci. U. S. A. 99, 16899–16903. doi: 10.1073/pnas.242603899

Sunwoo, J. S., Lee, S. T., Im, W., Lee, M., Byun, J. I., Jung, K. H., et al. (2017). Altered expression of the long noncoding RNA NEAT1 in Huntington’s disease. Mol. Neurobiol. 54, 1577–1586. doi: 10.1007/s12035-015-9928-9

Tatschini, S., Sakuraba, Y., Masuyama, S., Inoue, H., and Yamaizumi, M. (2000). Dysfunction of human Rad18 results in defective postreplication repair and hypersensitivity to multiple mutagens. Proc. Natl. Acad. Sci. U. S. A. 97, 7927–7932. doi: 10.1073/pnas.97.14.7927

Thal, D. R., and Fandrich, M. (2015). Protein aggregation in Alzheimer’s disease: abeta and tau and their potential roles in the pathogenesis of AD. Acta Neuropathol. 129, 163–165. doi: 10.1007/s00401-015-1387-2

Toska, E., and Roberts, S. G. (2014). Mechanisms of transcriptional regulation by WT1 (Wilms’ tumour 1). Biochim. J. 461, 15–32. doi: 10.1042/BJ20131587

Tyumyntsev, M. A., Stefanova, N. A., Muraveva, N. A., Rumyantseva, Y. V., Kiseleva, E., Vavlin, V. A., et al. (2018). Mitochondrial dysfunction as a predictor and driver of Alzheimer’s disease-like pathology in OXYS rats. J. Alzheimers. Dis. 63, 1075–1088. doi: 10.3233/JAD-180065

Ulland, T. K., and Colonna, M. (2018). TREM2 - a key player in microglial biology and disease. Nat. Rev. Neuro. 14, 667–675. doi: 10.1038/s41586-018-0072-1

Ventriglia, M., Zanardini, R., Bonomini, C., Zanetti, O., Volpe, D., Pasqualetti, P., et al. (2013). Serum brain-derived neurotrophic factor levels in different neurological diseases. Biomed. Res. Int. 2013:901082. doi: 10.1155/2013/901082

Verheijen, J., Van den Bosche, T., Van der Zee, J., Engelborghs, S., Sanchez-Valle, R., Lladó, A., et al. (2016). A comprehensive study of the genetic impact of rare variants in SORL1 in European early-onset Alzheimer’s disease. Acta Neuropathol. 132, 213–224. doi: 10.1007/s00401-015-1566-9

Wang, H., Lu, B., and Chen, J. (2019a). Knockdown of IncRNA SNHG1 attenuated AR(25-35)-induced neuronal injury via regulating KREME1 by acting as a ceRNA of miR-137 in neuronal cells. Biochem. Biophys. Res. Commun. 518, 438–444. doi: 10.1016/j.bbrc.2019.08.033

Wang, Q., Ge, X., Zhang, J., and Chen, L. (2020). Effect of IncRNA WT1-AS regulating WT1 on oxidative stress injury and apoptosis of neurons in Alzheimer’s disease via inhibition of the miR-375/SI4X axis. Aging 12, 23974–23995. doi: 10.18632/aging.104077

Wang, X., Zhang, M., and Liu, H. (2019b). LncRNAAT17 regulates autophagy and apoptosis of SH-SYSY cell line as an in vitro model for Alzheimer’s disease. Biosci. Biotechnol. Biochem. 83, 699–621. doi: 10.1007/s10529-018-51627-4

Willnow, T. E., Carlo, A. S., Rohe, M., and Schmidt, V. (2010). SORLA/SORL1, a neuronal sorting receptor implicated in Alzheimer’s disease. Rev. Neurosci. 21, 315–329. doi: 10.1515/REVNEURO.2010.21.4.315

Wu, C., Yang, J., Liu, X., Wu, J., and Wu, J. (2021). LncRNA WT1-AS/miR-494-3p regulates cell proliferation, apoptosis, migration and invasion via PTEN/PDK1/AKT signaling pathway in non-small cell lung cancer. Onco. Targets. Ther. 14, 991–904. doi: 10.2147/OTT.S27833

Wu, P., Zuo, X., Deng, H., Liu, X., Liu, L., and Ji, A. (2013). Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. Brain Res. Bull. 97, 69–80. doi: 10.1016/j.brainresbull.2013.06.001
Zhao, J., Fu, Y., Yamazaki, Y., Ren, Y., Davis, M. D., Liu, C. C., et al. (2020a). Long non-coding RNA 00307/miRNA-181c-5p/TTBK1/MAPT axis regulates tau hyperphosphorylation in Alzheimer's disease. *J. Gene Med.* 22:e5326. doi: 10.1002/jgm.3368.

Yan, L. J., Xiao, M., Chen, R., and Cai, Z. (2015). Metabolic dysfunction of astrocyte: an initiating factor in beta-amyloid pathology? *Aging Neurodegener* 1, 7–14.

Yi, J., Chen, B., Yao, X., Lei, Y., Ou, F., and Huang, F. (2019). Upregulation of the lncRNA MEG3 improves cognitive impairment, alleviates neuronal loss, and inhibits activation of microglia in hippocampal tissue in Alzheimer's disease through inactivating the PI3K/Akt signaling pathway. *J. Cell. Biochem.* 120, 18053–18065. doi: 10.1002/jcb.29108.

Yue, D., Guaqunin, G., Jingxin, L., Sen, S., Shuang, L., Yan, S., et al. (2020). Silencing of long noncoding RNA XIST attenuated Alzheimer's disease-related BACE1 alteration through miR-124. *Cell Biol. Int.* 44, 630–636. doi: 10.1002/cbi.11263.

Zalfa, F., Adinolfi, S., Napoli, I., Kühn-Hölsken, E., Urlaub, H., Achsel, T., et al. (2005). Fragile X mental retardation protein (FMRP) binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA-binding motif. *J. Biol. Chem.* 280, 33403–33410. doi: 10.1074/jbc.M504286200.

Zempel, H., and Mandelkow, E. M. (2015). Tau mis-sorting and spastin-induced microtubule disruption in neurodegeneration: Alzheimer disease and hereditary spastic paraplegia. *Mol. Neurodegener.* 10:68. doi: 10.1186/s13024-015-0064-1.

Zeng, T., Ni, H., Yu, Y., Zhang, M., Wu, M., Wang, Q., et al. (2019). BACE1-AS prevents BACE1 mRNA degradation through the sequestration of BACE1-targeting miRNAs. *J. Chem. Neuroanat.* 98, 87–96. doi: 10.1016/j.jchemneu.2019.04.001.

Zhang, Q., Hu, C., Huang, J., Liu, W., Lai, W., Leng, F., et al. (2019a). ROCK1 induces dopaminergic nerve cell apoptosis via the activation of Drp1-mediated aberrant mitochondrial fission in Parkinson's disease. *Exp. Mol. Med.* 51, 1–13. doi: 10.1038/s41277-019-0318-z.

Zhang, T., Pang, P., Fang, Z., Guo, Y., Li, H., Li, X., et al. (2018a). Expression of BC1 impairs spatial learning and memory in Alzheimer's disease via APP translation. *Mol. Neurobiol.* 55, 6007–6020. doi: 10.1007/s12035-017-0820-z.

Zhang, W., Zhao, H., Wu, Q., Xu, W., and Xia, M. (2018b). Knockdown of BACE1-AS by siRNA improves memory and learning behaviors in Alzheimer's disease animal model. *Exp. Ther. Med.* 16, 2080–2086. doi: 10.3892/etm.2018.6359.

Zhang, X., Wang, Z., Zhu, W., Dong, J., Cheng, Y., Yin, Z., et al. (2019b). Mechanisms and functions of long non-coding RNAs at multiple regulatory levels. *Int. J. Mol. Sci.* 20:5573. doi: 10.3390/ijms2025573.

Zhao, J., Fu, Y., Yamazaki, Y., Ren, Y., Davis, M. D., Liu, C. C., et al. (2020a). APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat. Commun.* 11:5540. doi: 10.1038/s41467-020-19264-0.

Zhao, M. Y., Wang, G. Q., Wang, N. N., Yu, Q. Y., Liu, R. L., and Shi, W. Q. (2019). The long-non-coding RNA NEAT1 is a novel target for Alzheimer's disease progression via miR-124/BACE1 axis. *Neurol. Res.* 41, 489–497. doi: 10.1080/01616412.2018.1548747.

Zhao, N., Liu, C. C., Qiao, W., and Bu, G. (2018). Apolipoprotein E receptors, and modulation of Alzheimer's disease. *Biol. Psychiatry* 83, 347–357. doi: 10.1016/j.biopsych.2017.03.003.

Zhou, Y., Wang, Z., Mao, Y., Li, B., Zhu, Y., Zhang, S., et al. (2020b). NEAT1 regulates microtubule stabilization via EZF3/ASK3/JB-p-tau pathway in SH-SY5Y cells and APP/PS1 mice. *Aging* 12, 23233–23250. doi: 10.18632/aging.104098.

Zhong, J., Jiang, L., Huang, Z., Zhang, H., Cheng, C., Liu, H., et al. (2017). The long non-coding RNA Neat1 is an important mediator of the therapeutic effect of bexarotene on traumatic brain injury in mice. *Brain Behav. Immun.* 65, 183–194. doi: 10.1016/j.bbi.2017.05.001.

Zhou, B., Li, L., Qiu, X., Wu, J., Xu, L., and Shao, W. (2020). Long non-coding RNA ANRIL knockdown suppresses apoptosis and pro-inflammatory cytokines while enhancing neurite outgrowth via binding microRNA-125a in a cellular model of Alzheimer's disease. *Med. Mol. Rep.* 22, 1489–1497. doi: 10.3892/mmr.2020.11203.

Zhou, H. J., Wang, L. Q., Wang, D. B., Yu, J. B., Zhu, Y., Xu, Q. S., et al. (2018a). Long noncoding RNA MALAT1 contributes to inflammatory response of microglia following spinal cord injury via the modulation of a miR-199b/IKKβ/NF-kB signaling pathway. *Am. J. Physiol. Cell Physiol.* 315, C52–C61. doi: 10.1152/ajpcell.00278.2017.

Zhou, K., Zhang, C., Yao, H., Zhang, X., Zhou, Y., Che, Y., et al. (2018b). Knockdown of long non-coding RNA NEAT1 inhibits glioma cell migration and invasion via modulation of SOX2 targeted by miR-132. *Mol. Cancer* 17:105. doi: 10.1186/s12943-018-0849-2.

Zhou, S., Yu, X., Wang, M., Meng, Y., Song, D., Yang, H., et al. (2021). Long non-coding RNAs in pathogenesis of neurodegenerative diseases. *Front. Cell Dev. Biol.* 9, 1219–1231. doi: 10.3389/fcell.2021.719247.

Zhuang, J., Cai, P., Chen, Z., Yang, Q., Chen, X., Wang, X., et al. (2020). Long noncoding RNA MALAT1 and its target microRNA-125b are potential biomarkers for Alzheimer's disease management via interactions with FOXQ1, PTGS2 and CDK5. *Am. J. Transl. Res.* 12, 5940–5954. doi: 10.3389/fncel.2020.587747.

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