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REVIEW

Insights into lncRNAs in Alzheimer's disease mechanisms

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common dementia among the elderly. The pathophysiology of AD is characterized by two hallmarks: amyloid plaques, produced by amyloid β (Aβ) aggregation, and neurofibrillary tangle (NFT), produced by accumulation of phosphorylated tau. The regulatory roles of non-coding RNAs (ncRNAs), particularly long noncoding RNAs (lncRNAs), have been widely recognized in gene expression at the transcriptional and posttranscriptional levels. Mounting evidence shows that lncRNAs are aberrantly expressed in AD progression. Here, we review the lncRNAs that implicated in the regulation of Aβ peptide, tau, inflammation, cell death, and other aspects which are the main mechanisms of AD pathology. We also discuss the possible clinical or therapeutic utility of lncRNA detection or targeting to help diagnose or possibly combat AD.

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Introduction

Alzheimer's disease (AD) was initially described as a 'peculiar severe disease process of the cerebral cortex', by Dr. Alois Alzheimer in 1906 at a conference in Tubingen, Germany [1]. AD is now characterized as a progressive degenerative disease with cognitive dysfunction, memory loss, and emotional disorder [2]. More than 50 million people are currently affected by dementia worldwide, and AD is the most common form of dementia and may contribute to up to 70% of the dementia cases [3]. The majority of AD cases are sporadic with a late-onset (LOAD), which usually occurs in people older than 65 years; whereas a small portion of AD cases are familial with early-onset AD (EOAD), which commonly affects people under 65 years of age and has a genetic predisposition [4].

Long non-coding RNAs (lncRNAs) comprise a class of non-coding RNAs (ncRNAs) that are longer than 200 nucleotides (nt) in length, and account for one of the largest proportions of the non-coding transcriptome in number of transcripts. Given their diverse structural and biochemical features, lncRNAs impact AD pathogenesis via a variety of regulatory mechanisms, including transcriptional, posttranscriptional and translational regulation [5].

AD pathophysiology

The pathophysiology of AD is characterized by two hallmarks: amyloid plaques resulting from abnormal proteolytic processing of amyloid precursor protein (APP) in the extra neuronal environment; and neurofibrillary tangle (NFT) resulting from accumulation of hyperphosphorylated tau protein in neurons [6]. Amyloid plaques are mainly comprised of amyloid β (Aβ) peptide, particularly Aβ42 isoform, which is a hydrophobic peptide that is considered to have pronounced toxicity [7]. Given its insoluble properties, Aβ peptide has a tendency to aggregate and forms the core of the amyloid plaque by acquiring the configuration of a β-pleated sheet [8–11]. Aβ production is a consequence of the sequential proteolytic cleavage of amyloid precursor protein (APP) by a β-secretase (BACE1) and γ-secretase [12], wherein APP is a type I transmembrane glycoprotein of with three major isoforms arising from alternative splicing [13]. Under normal conditions APP is cleaved by α-secretase, leading to the release of a soluble molecule called sAPPα, and a fragment of the carboxyl terminal portion (CTF83) [14,15]. In contrast to Aβ, sAPPα functions in neuronal protection against toxicity [16,17], and is found at a lower level in AD patients compared to controls. When APP is cleaved by BACE1, a shorter amino-terminal portion (sAPPβ) and a longer carboxyl terminal fragment (CTF99) are

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generated [18,19]. APP CTFs are further processed by γ-secretase to produce Aβ, which is secreted, aggregated and accumulated in extracellular plaques, leading to the formation of amyloid neurotic plaques [20]. In addition to Aβ production, dysregulation of Aβ metabolism also contributes substantially to AD pathology, including Aβ degradation and transportation [3,21].

Neurofibrillary lesions are hallmarks of AD and other tauopathic neurodegenerative diseases. NFTs are mainly aggregations of hyperphosphorylated microtubule-associated protein tau, which mainly exists in the cytoplasm of the neuronal axon, synaptic regions and cerebrospinal fluid (CSF) [22]. Hyperphosphorylated tau forms aberrant aggregations with cytoskeletal proteins and shows a lower grade of interaction with microtubules, leading to dysfunction of axonal transport [23]. The phosphorylation levels of tau are significantly increased in AD patients, compared to age-matched controls, supporting that tau phosphorylation contributes to AD pathology. In addition to the amyloid and tau hypothesis of AD, many other hypotheses including inflammatory mechanism, mitochondrial dysfunction, oxidative stress and cholinergic hypothesis have also been raised [6,24,25]. Altogether, AD is a complex and multifaceted disease influenced by genetics, environment, and lifestyle.

Long-noncoding RNAs

LncRNAs are a class of endogenous regulatory RNA molecules longer than 200 nucleotides. These transcripts typically contain no obvious open reading frame (ORF) and thus lack protein-coding capacity [26–28]. LncRNAs have been discovered predominantly by high-throughput sequencing technologies, including microarrays and next-generation sequencing (NGS) [29]. The estimated number of lncRNAs ranges from around 59,000 to 102,000 listed in the NONCODE database [30,31,32]. Like protein-coding genes, lncRNAs are commonly transcribed by RNA polymerase II and are often post-transcriptionally modified by 5′ capping, 3′ polyadenylation, and RNA splicing. However, lncRNAs have features distinct from protein-coding genes, such as being shorter in length and having lower sequence conservation across species [33]. LncRNAs are involved in a variety of biological functions including development, differentiation, and metabolism [34,35]. Moreover, lncRNAs affect many cellular processes, including chromatin and DNA modification, RNA transcription, pre-RNA splicing, mRNA stability, and translation [36,37].

LnRNAs involved in Alzheimer's disease (AD)

Mammalian genomes encode tens of thousands of lncRNAs, and up to 40% of these lncRNAs are specifically expressed in the brain [34]. Aberrant lncRNA expression has been associated with many neurodegenerative diseases [38–41]. Particularly, several hundreds of lncRNAs are found differentially expressed in 3xTg-AD model mice, compared to age-matched control animals [42]. In addition, 99 lncRNAs are down-regulated and 150 lncRNAs are up-regulated in the hippocampus of APP/PS1 transgenic mice, compared to controls [43]. Transcriptome analyses on post-mortem human brains also identify that levels of multiple lncRNAs are altered significantly in AD patient brains [38,44,45]. Collectively, lncRNAs are differentially expressed in AD patients or animal models, therefore can serve as biomarkers even potential treatment target for AD.

LncRNA and mRNA transcription

Transcription begins with the binding of RNA polymerase to the promoter region of a gene with the assistance of transcription factors (TFs). Gene expression changes have been identified during AD progression in a cell-type specific manner. Particularly, AD risk genes, such as ApoE, BACE1 and TREM2, show aberrant expression levels during AD progression [46,47]. Gene expression control primarily occurs at the level of transcription [46]. Importantly, an increasing number of lncRNAs have been identified as transcriptional regulators. LncRNAs, participate in AD pathology via modulating RNA transcription, are summarized below.

NDM29

Neuroblastoma differentiation marker 29 (NDM29), an ncRNA transcribed by RNA pol III in human, drives the neuroblastoma (NB) cell differentiation process towards a non-malignant neuron-like phenotype [48–50]. Notably, NDM29 expression is enhanced in the cerebral cortex of AD patients, as compared to age-matched controls, demonstrating that NDM29 is linked to AD pathology. Additionally, NDM29 biosynthesis is sensitive to pro-inflammatory molecules, such as interleukin 1α (IL-1α) and TNFα (tumour necrosis factor α); both are considered landmarks of AD onset. NDM29 significantly increases both *APP* mRNA and protein levels, and subsequently enhances production of the two major Aβ isoforms, Aβ42 and Aβ40. Aβ42 (42 residues long) contains two more residues than Aβ40 (40 residues long) on the C-terminus. Aβ42, but not Aβ40, is the major component of amyloid plaques in AD brains [51]. NDM29 preferentially enhances the ratio of Aβ42/Aβ40 [52], leading to accumulation of toxic Aβ.

LRP1-AS

Low-density lipoprotein (LDL)-related protein (LRP1) belongs to the LDL receptor family. LRP1 is abundantly expressed in the brain. LRP1 and its ligand apolipoprotein E (ApoE) have been identified in senile plaques in AD brains [53], suggesting a role of LRP1 in Aβ accumulation. In addition, numerous studies have demonstrated that LRP1 is deeply involved in APP trafficking and Aβ processing. Receptor-associated protein (RAP)-mediated blocking of LRP1 function increases APP levels on the cell surface and decreases Aβ production [54]. Transmembrane domain on the C-terminus of LRP1 reduces Aβ production by competing with APP for cleavage mediated by β- and γ-secretase [55]. LRP1 also facilitates heparan sulphate proteoglycan (HSPG) dependent Aβ uptake into cells [56]. Moreover, LRP1 also modulates ApoE levels and lipid metabolism by altering the stability of ApoE mRNA [57]. Altogether, LRP1 participates in AD pathogenesis via a variety of mechanisms.

LRP1-AS, a 1387 nt lncRNA, is transcribed from the opposite strand of mouse *LRP1* gene. There is a 395 bp overlap of exon2 of LRP1-AS and exon5 and exon6 of LRP1, and this location of LRP1/LRP1-AS has been maintained throughout evolution. RNAi silencing of LRP1-AS leads to increased LRP1 expression, whereas overexpression of LRP1-AS results in decreased LRP1 levels. Thus, LRP1-AS negatively regulates LRP1 expression at both RNA and protein levels [58]. In addition to direct sequence pairing, LRP1-AS also reduces LRP1 transcription via decreasing LRP1 promoter activity induced by Hmgb2 and Srebp1. Srebp1 is a transcription factor that regulates LRP1 transcription, and Hmgb2 interacts with Srebp1 and forms a transcriptional complex to regulate LRP1 levels. Conflicting conclusions have been obtained concerning the link between LRP1 levels and AD pathogenesis. Some groups reported that LRP1 levels are increased in the AD brain [59], whereas others reported that LRP1 levels are decreased compared to age-matched controls. Importantly, the levels of LRP1-AS are significantly increased [58]. Altogether LRP1-AS could serve as a diagnostic marker and a potential therapeutic target for AD treatment.

LncRNA and pre-mRNA splicing

Alternative splicing, allowing a single gene coding for multiple proteins, is an important regulatory mechanism for gene expression. Dysregulation of mRNA splicing is considered a key feature of AD, particularly genes related to hallmarks of AD such as Aβ burden and neurofibrillary tangles [60]. LncRNAs can regulate alternative splicing through interacting with specific splicing factors or form RNA-RNA duplex with mRNAs. LncRNAs, participate in AD pathology via modulating RNA splicing, are summarized below.

51A

Sortilin-related receptor (SORL1, also known as LR11), a member of the low-density lipoprotein receptor (LDLR) family, is abundantly and specifically expressed in neurons [61,62]. SORL1 levels are significantly reduced in neurons in AD brains [63,64], suggesting a role in AD pathogenesis. Importantly, SORL1 affects APP trafficking and proteolytic processing by directly interacting with APP, leading to reduced Aβ production in the brain. By contrast, reduction of SORL1 expression preferentially guides APP into the β-secretase cleavage pathway, instead of the retromer recycling pathway, resulting in increased production of neurotoxic Aβ [65].

51A, a lncRNA around 300 nt in length, is transcribed by RNA polymerase III from the antisense configuration to intron 1 of the *SORL1* gene in human. In contrast to SORL1, lncRNA 51A levels are upregulated in post-mortem AD brains. Mechanistically, 51A pairs with intron 1 of SORL1 pre-mRNA, where an alternative splicing event occurs, and leads to reduced production of canonical SORL1 protein and increased production of an alternative variant. Consequently, as an upstream regulator of APP processing and Aβ production, 51A promotes Aβ secretion [66].

GDNFOS

Glial cell line-derived neurotrophic factor (GDNF) was initially reported to promote the survival of dopamine neurons and dopamine uptake in the midbrain [67]. Given its role in protecting dopamine neurons and rescuing motor neurons, it has the potential to be developed as a therapeutic agent for Parkinson's disease (PD) [68], wherein the major pathological landmark is progressive loss of dopaminergic neurons. Additionally, GDNF is also involved in extensively regulating neuronal populations, neurite branching, and synaptic plasticity, but is not specific to dopamine neurons [69]. Two GDNF mRNAs are produced by alternative splicing of exon2 of the *GDNF* gene, pre-(α) long pro-GDNF and pre-(β) short pro-GDNF [70,71], resulting in the production of two secreted proteins in neurons. Notably, secretion of long GDNF is constitutive, whereas short GDNF is activity-dependent [72]. In AD patients, the levels of GDNF are significantly up-regulated in cerebrospinal fluid (CSF), whereas levels are down-regulated in serum compared to control patients [73]. However, this conclusion remains controversial, as another study showed that GDNF mRNA is significantly increased in the middle temporal gyrus of AD brains, whereas the peptide was decreased in comparison with age-matched normal brains [69].

GDNFOS is a *cis*-natural antisense transcript, transcribed from the opposite strand of the *GDNF* gene in human. Three GDNFOS isoforms have been identified – GDNFOS1, GDNFOS2, and GDNFOS3. Both GDNFOS1 and GDNFOS2 are lncRNAs, with no obvious ORF. GDNFOS1 is reverse complementary to the 5′-UTR of the GDNF, and GDNFOS2 has no pairing sequence to the GDNF transcript. GDNFOS3 transcript contains an ORF and has potential for protein translation [69]. GDNFOS1 is abundantly expressed in the brain but has lower expression than GDNF isoform containing exon 1 and exon 4 transcripts. GDNFOS1 levels are similar between AD and control brains, however, alteration of the GDNFOS isoform ratio may contribute to AD pathogenesis [69]. Given that levels of GDNFOS and GDNF are closely correlated, where GDNF is proved to be involved in neurite branching and synaptic plasticity [69]. Therefore, it is fair to speculate that GDNFOS may play a role in regulating synaptic plasticity. Clearly, more evidence is required to demonstrate the implication of GDNFOS in AD pathogenesis.

LncRNA and mRNA stability

The steady-state level of an mRNA is determined by the rate of synthesis and degradation; therefore, mRNA degradation is an essential point to control gene expression. Previous study has demonstrated that destabilization of mRNAs encoding for synaptic transmission proteins contributes to synaptic function loss in AD pathology [74]. Additionally, AD risk genes exhibit aberrant mRNA decay rate in AD patients [75]. LncRNAs, participate in AD pathology via modulating mRNA stability, are summarized below.

BACE1-AS

The extracellular plaque deposition of the Aβ peptide is one of the hallmark pathologies in AD patients. Aβ production requires sequential proteolytic cleavage of APP by β-secretase and γ-secretase. Beta-site APP-cleaving enzyme 1 (BACE1) is a protease that increases the amount of β-secretase cleavage products [76]. BACE1 is highly expressed in the brain, and both the expression and enzymatic activity are enhanced in AD brains [77,78]. BACE1 deficiency substantially reduces the Aβ burden in APP transgenic mice [79].

BACE1-AS and BACE1 mRNA are two transcripts from the same locus in chromosome 11 (11q 23.3) in human; BACE1 mRNA is transcribed from the sense strand and BACE1-AS from the antisense strand. BACE1-AS pairs to BACE1 and forms an RNA duplex, resulting in an altered structure of BACE1 and enhanced mRNA stability, therefore BACE1-AS not only increases the mRNA levels but also the protein levels of BACE1 [80]. BACE1-AS is heavily involved in Aβ metabolism, as deficiency of *BACE1-AS* not only reduces BACE1 levels, but further suppresses production of Aβ40 and Aβ42 [80]. BACE1-AS levels are sensitive to multiple cell stressors, such as serum starvation, Aβ42, and hydrogen peroxide (H_2O_2) [80]. RNAi-mediated BACE1-AS inhibition reduces BACE1-mediated APP cleavage in human SH-SY5Y cell [81]. BACE1-AS is also stabilized by HuD, a neuronal RNA-binding protein that is implicated in AD pathogenesis [82]. BACE1-AS is increased not only in APP transgenic mice, but also in AD brains [80]; the ratio of BACE1-AS to BACE1 is particularly enhanced. *BACE1-AS* and the ratio of BACE1-AS to BACE1 have even been proposed as a new biomarker of AD diagnosis. Knockdown of BACE1 or BACE1-AS transcript by continuous infusion of siRNAs into the third ventricle of APP transgenic mice, not only downregulates BACE1 protein levels, but also significantly reduces insoluble Aβ [83]. These findings raise the possibility of BACE1-AS as a promising treatment regime for AD patients.

BDNF-AS

Brain-derived neurotrophic factor (BDNF) is involved in synaptic function, neurogenesis and cognitive function [84]. In addition, BDNF protects neurons from injuries, prevents neuronal function loss and facilitates the regeneration of damaged neurons [85,86]. BDNF is also linked to the core pathological features of AD and may serve as a biomarker for disease diagnosis. BDNF regulates APP processing by provoking the non-amyloidogenic processing pathway, therefore reducing the production of Aβ [87,88]. Pretreatment of BDNF protects cells against the toxicity induced by Aβ42 in cultured neurons and in mouse brain [89]. Interestingly, Aβ42 also promotes BDNF production in astrocytes, which in turn rescues neurite degeneration in neuroblastoma cells [90]. The AD mouse model produces more aggregated and insoluble Aβ42 and shows significant reduction of BDNF levels [91]. Moreover, BDNF administration reverses the neurodegenerative changes in AD mouse brains, such as synapse loss, learning and memory impairment [92], and therefore merits exploration as a potential therapy for AD.

BDNF-AS is a natural antisense transcript to BDNF. Human *BDNF-AS* gene is located on the positive strand of chromosome 11, and the transcription start site is approximately 200 kb downstream from the *BDNF* gene promoter. BDNF-AS negatively modulates BDNF levels *in vitro* and *in vivo* [93]. Aβ treatment not only decreases BDNF, but also promotes BDNF-AS levels in PC12 cells. Silencing BDNF-AS significantly increases BDNF levels, and alleviates cell apoptosis and ROS intensity induced by Aβ treatment; cell viability is also enhanced [94]. Other study also reported that BDNF-AS-mediated decrease of BDNF down-regulates levels of activity-regulated cytoskeleton-associated protein (ARC), which is an immediate-early gene and involved in synaptogenesis and synaptic plasticity [95].

EBF3-AS

Early B cell factor 3 (EBF3, also known as olf) is expressed in the olfactory receptor neurons and their precursors [96]. As a DNA binding TF, it is involved in apoptosis, cell cycle arrest and neurogenesis [97,98]. Notably, the expression of EBF3 is elevated in the hippocampus of AD mice.

EBF3-AS is an 842 nt non-coding RNA that is transcribed from the opposite strand of the protein-coding gene *EBF3*; its levels are up-regulated in the hippocampus of APP/PS1 mice. LncRNA EBF3-AS deficiency not only reduces EBF3 levels but also inhibits apoptosis induced by okadaic acid (OA) or Aβ in human SH-SY5Y cell. These lines of evidence indicate that EBF3-AS may serve as a new therapeutic target for the treatment of AD [99].

Sox2OT

Sox2 is a key TF for the regulation of stem cell pluripotency and neuronal genesis [100]. Sox2 overlapping transcript (Sox2OT) is a lncRNA transcribed from the intron of the *Sox2* gene [101]. Sox2OT is roughly 3.4 kb in length and is an evolutionarily conserved transcript between human and mouse [102]. Sox2OT plays a key role in the induction and/or maintenance of Sox2 expression [103]. Moreover, Sox2OT is expressed in the cerebral cortex of the developing mouse brain, where it promotes neuronal differentiation and neurogenesis by repressing Sox2 [104]. Furthermore, Sox2OT is differentially expressed in the AD model mouse and is involved in early and late disease stages, suggesting a role of Sox2OT as a biomarker of AD [105].

SNHG1

Small nucleolar RNA host gene 1 (SNHG1), a lncRNA located at 11q12.3 in human, promotes neuroinflammation and neuronal toxicity in PD [106,107]. In AD pathology, Aβ treatment increases the expression of SNHG1, while repression of SNHG1 in Aβ treated cells attenuates the effect of Aβ on cell viability, and mitochondrial membrane potential (MMP). This is achieved via targeting kringle containing

transmembrane protein 1 (KREMEN1), a transmembrane receptor that has an intrinsic pro-apoptotic activity, via a mechanism of SNHG1 mediated miR-137 sponge, that selectively targets the untranslated region of KREMEN1 in SH-SY5Y and human primary neuron (HPN) cells [108].

NAT-RAD18

NAT-RAD18 is a lncRNA that is 509 nt in length, also a natural antisense transcript against Rad18. It contains an ORF of 225 bases, a 5′-untranslated region of 93 bases and a poly(A) containing 3′-untranslated region of 188 bases. NAT-RAD18 shows 78% homology with Rad18 genomic sequence and the reverse-complement sequence of Rad18 transcript in adult rat brain [109].

NAT-RAD18 is specifically expressed in neurons, as demonstrated by co-localization of NAT-Rad18 with NeuN, which is a neuronal marker. At the cellular level, the expression of Rad18 was counterbalanced by that of NAT-Rad8 in both mRNA and protein level. Expression of NAT-RAD18 is up-regulated, whereas Rad18 is down-regulated in response to cell stressor Aβ40 [109]. Rad18, a member of the structural maintenance of chromosome (SMC) family, is responsible for repair of multiple types of DNA damage [110], and its dysregulation makes cells more sensitive to DNA lesions [111]. Defective DNA repair has been linked to neurodegenerative disorders; therefore, it is worth further determining the function of NAT-Rad18 in AD pathogenesis.

NEAT1

Nuclear paraspeckles assembly transcript 1 (NEAT1) is a lncRNA that is enriched in the nucleus and serves as an essential architectural component of paraspeckle nuclear bodies [112,113]. NEAT1 regulates gene expression by influencing the nuclear retention of structured or edited RNAs, such as RNA containing inverted Alu repeat element [114].

Levels of NEAT1 are significantly reduced in AD mouse brains and AD patients [115]. Mechanistically, NETA1 knockdown decreases Aβ degradation via altering the levels of endocytosis-related genes, such as CAV2, TGFB2 and TGFBR1 in the human astrocytic U251 cell line [115]. Aβ also induces production of NEAT1, and knockdown of NEAT1 attenuates apoptosis and p-tau levels caused by Aβ. Additionally, NEAT1 acts as a sponge for miR-107, which is known to reduce Aβ-induced injuries, leading to the aggravation of Aβ-induced neuronal damage in human SH-SY5Y and SK-N-SH cells [116]. These findings show that NEAT1 regulates AD pathogenesis via a variety of mechanisms.

MALAT1

LncRNA MALAT1 (also known as NEAT2), a long intergenic non-coding RNA, is around 7 kb in human and 6.7 kb in mouse. MALAT1 is a highly conserved lncRNA that is preferentially localized to nuclei [117]. MALAT1 is abundantly expressed at a level comparable to, or even higher than, housekeeping protein-coding genes, such as GAPDH or β-actin [118]. MALAT1 is also highly expressed in neurons, and it regulates synaptogenesis via modulating levels of neuroligin1 and synaptic cell adhesion molecule 1 (SynCAM1) [119].

Lower MALAT1 levels are detected in the CSF collected from AD patients, compared to controls [120], suggesting that CSF MALAT1 could serve as a diagnostic marker. Nonetheless, lncRNA MALAT1 inhibits neuronal apoptosis and inflammation and promotes neurite outgrowth in AD. Additionally, lncRNA MALAT1 reversely regulates the expression of miR-125b, which increased Prostaglandin-Endoperoxide Synthase 2 (PTGS2) and Cyclin Dependent Kinase 5 (CDK5) expression levels and decreased Forkhead Box Q1 (FQXQ1) expression in AD pathologies, all three are predicted regulatory targets by miR-125 [121].

LncRNA and protein translation

Translational control is another important step in gene expression. The global reduction of polysomal mRNA translation and impaired ribosome function have been identified in AD patient brains [122,123]. LncRNAs, which are involved in AD pathology via modulating protein translation, are summarized below.

BC200

Synaptic plasticity is widely accepted as an essential neurochemical foundation of learning and memory [124]. Dendritic protein synthesis is critical to maintaining long-term synaptic plasticity [125–130]. Synaptic impairment is related to AD-related memory deficits [131]. BC200 is a 200 nt lncRNA that is structurally subdivided into three domains. The 5′ region of BC200 contains Alu repetitive elements, the central part is rich with A-residues, and the 3′ region is unique to BC200. Cytoplasmic BC200 is almost exclusively expressed in neurons, and transported to dendritic processes [132]. BC200 represses translation by directly interacting with dendritic mRNA, and this repression is reversed by Poly(A)-binding protein (PABP), a protein component of the BC200 ribonucleoprotein (RNP) complexes [133,134]. Protein synthesis at the synapses of neurons contribute to neuronal plasticity; therefore, BC200 is speculated to regulate synaptic plasticity at translational level.

BC200 expression is decreased in cortical tissue in normal ageing, between the ages of 49 and 86, in addition, its levels are significantly increased in AD brains compared with age-matched normal brains. Importantly, the extent of increase is associated with the severity of the disease [135]. Mislocalization and overexpression of BC200 RNA results in dendritic regression and clogging in AD neurons. Moreover, the distribution of BC200 appeared reduced in neuropil areas in AD brains, compared with normal brains. Importantly, this altered BC200 distribution is associated with dendritic loss in AD neurons [135]. Alteration of BC200 levels is a potential drug target to rescue memory loss in AD [135–137].

BC200 also regulates BACE1 expression: knockdown of BC200 RNA significantly suppresses BACE1 levels and overexpression of BC200 increases BACE1 levels. This may lead to altered Aβ metabolism [138]. Additionally, reduction of BC200 promotes cell viability and decreases cell apoptosis

via targeting BACE1 [138]. However, more evidence is required to demonstrate an interaction between BC200 and local protein translation and its implications in AD pathogenesis.

LoNA

Ribosomes and protein biosynthesis are altered in the cerebral cortex in AD brains. Levels of ribosomal RNA (rRNA), the major component of ribosomes, particularly rRNA 28 S/18 S, are decreased during the progression of AD [139,140]. Mechanistically, the nuclear organizer region (NOR) surface, where rDNA is located in the nucleolus, is reduced in AD patients [141]. Additionally, rDNA promoter is hypermethylated [142], suggesting that epigenetic silencing occurs in AD patients. We have previously identified a long nucleolar noncoding RNA (LoNA), which is transcribed by RNA polymerase II and specifically enriched in nucleoli. The mature form of mouse LoNA is 1.5 kb in length, it contains two exons but no obvious ORF. Structurally it contains a poly(A) signal at the 3′ end, but no cap at the 5′ end. LoNA regulates rRNA transcription by binding directly to nucleolin (NCL) and reducing its activity. In addition to that, LoNA also alters rRNA methylation via interacting with fibrillarin (FBL). Consequently, LoNA regulates protein translation by modulating essential components of the ribosome and its assembly. Protein translation primarily takes place at neuronal soma but also occurs at synapses. Local protein translation has an important role in synaptic development and plasticity [130,143,144]. We have demonstrated that LoNA regulates synaptic plasticity by altering ribosomal RNA and protein levels at synapses. Subsequently, the levels of synaptic proteins, including PSD95, Synaptophysin and Snap25, are significantly increased in LoNA deficient mice. Moreover, polysome binding mRNAs of these genes are also enhanced in N2a cells lacking LoNA. In support of this, the dendrite spine density is profoundly increased in LoNA deficient mice, as demonstrated by Golgi staining. Conversely, LoNA administered mice show reduced levels of synaptic proteins, and LoNA expressing N2a cells exhibit decreased polysome binding mRNAs of same synaptic genes. Importantly, LoNA administered mice display severe LTP deficits, and behaviourally, these mice exhibit impaired cognitive functions as demonstrated by the Morris water maze task [145].

During the early stages of AD pathology, silencing of the rDNA appears to account for AD-related ribosomal deficiency [142]. Moreover, the ratio of rRNA 28 S/18 S is significantly suppressed in AD. Notably, LoNA levels are significantly increased in the hippocampus of AD mice, compared to age-matched controls, accompanied by decreased rRNA levels. Knockdown of LoNA not only partially restores rRNA levels but also rescues the cognitive deficits in AD mice [145], potentially providing an approach for AD treatment. A table (Table 1) summarizes lncRNAs discussed in this review, their biological function and roles in AD pathology have provided.

Discussion and perspectives

Many lncRNAs have been discovered by sensitive, precise high-throughput genomic transcriptome sequencing, and up to 40% of these lncRNA are preferentially expressed in mammalian brains [28]. These lncRNAs also exhibit exquisitely spatiotemporally specific expression patterns, suggesting that they are biologically meaningful. As the most common type of dementia, AD is a tremendous challenge around the world. Given the advancements in transcriptome-wide profiling, numerous lncRNAs have been discovered to be associated with AD. Furthermore, levels of multiple lncRNAs are dysregulated in AD patients [42,153]. Indeed, some of the lncRNAs have demonstrated their roles in AD pathology. Although most of these studies focus on the effect of lncRNAs on Aβ metabolism, deeper and more insightful investigations are necessary. Schematic mechanisms of AD associated LncRNAs are summarized in Fig. 1.

In addition to deepening the understanding of AD pathology, there is also an increasing focus on the need to develop novel biomarkers to facilitate early clinical diagnosis of diseases. In the past, the diagnosis of AD has relied heavily on dementia symptoms, when the disease typically has reached a late stage. Biomarkers that show abnormal concentrations in the pre-clinical stage of AD thus allow early diagnosis of AD. LncRNAs have been considered desirable candidates for AD biomarkers. Indeed, the plasma lncRNA BACE1-AS has shown potentials as a biomarker

Table 1. Key features of AD associated lncRNAs.

LncRNA	Species	Length(nt)	5′Cap	Poly(A) tail	Splicing pattern	Protein binding partners	References
LoNA	M	1516	No	Yes	CS	NCL,FBL	[145]
LRP1-AS	H/M	645/1387	Yes	Yes	CS,ES	Hmgb2	[58]
BACE1-AS	H/M	840/2025	Yes	Yes	CS,A5′SS,A3′SS	HuD	[82]
Sox2OT	H/M/R	3132/2998/722	Yes	Yes	CS,ES,A5′SS,MECE	FUS,YY1	[103–105146]
NEAT1	H/M	3756/3190	Yes	Yes	IR,A5′SS,A3′SS	NONO,SFPQ,PSF,Ezh2	[113,116,147,148]
MALAT1	H/M	8545/6983	Yes	No	IR,A5′SS,A3′SS,MECE	SRSF1,SFPQ	[121,149]
SNHG1	H/M	1137/476	Yes	Yes	IR,ES,A5′SS,A3′SS,MECE	MATR3,Ezh2	[108,150,151]
BDNF-AS	H	1437	Yes	Yes	IR,ES,A5′SS,A3′SS,MECE	PABPC1	[93,152]
BC200	H	200	No	No	N/A	PABP	[133,134,138]
51A	H/M	300	No	No	N/A	unknow	[66]
GDNFOS	H	1550	Yes	Yes	IR,ES,MECE	unknow	[69]
EBF3-AS	H/M	842	Yes	Yes	CS	unknow	[99]
NAT-RAD18	R	509	No	No	N/A	unknow	[109]
NDM29	H	1584	No	No	N/A	unknow	[51,52]

H:human, M:mouse, R:rat, ES: exon skipping, IR: intron retention, A5′SS: alternative 5′ splice sites, A3′SS: alternative 3′ splice sites, CS: constitutive splicing, MECE: mutually exclusive exon

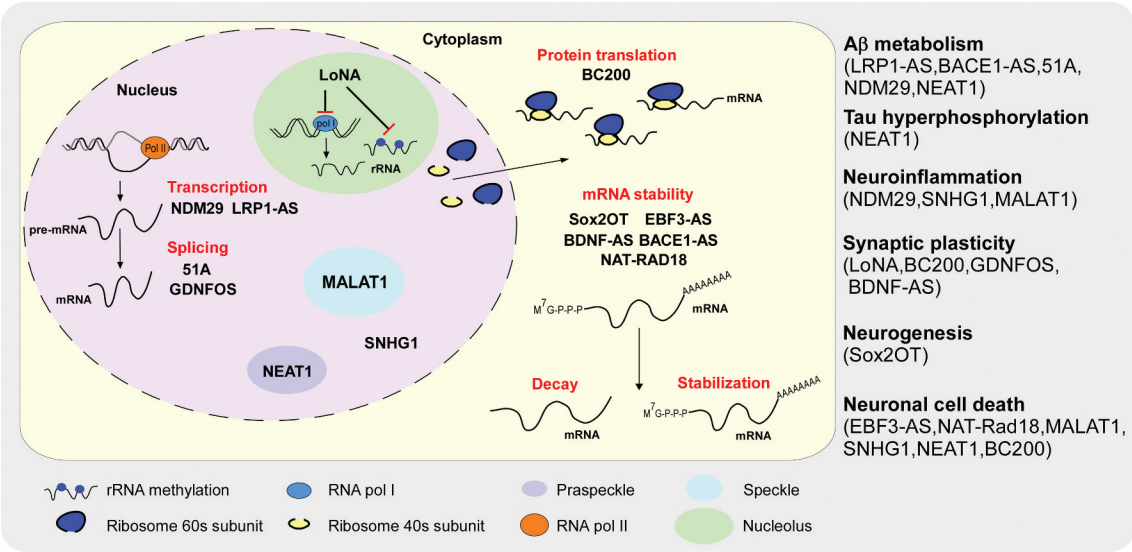

Figure 1. Schematic of LncRNAs and their regulatory mechanisms in AD. LncRNAs modulate cellular process such as mRNA transcription (NDM29 and LRP1-AS), mRNA splicing (51A and GDNFOS), mRNA stability (Sox2OT, EBF3-AS, BDNF-AS, BACE1-AS and NAT-RAD18), and protein translation (LoNA and BC200). LncRNAs participate in AD pathology via having impact on Aβ metabolism (LRP1-AS, BACE-AS, 51A, NDM29 and NEAT1), tau hyperphosphorylation (NEAT1), neuroinflammation (NDM29, SNHG1 and MALAT1), synaptic plasticity (LoNA, BC200, GDNFOS and BDNF-AS), neurogenesis (Sox2OT), and neuronal cell death (EBF3-AS, NAT-Rad18, MALAT1, SNHG1, NEAT1 and BC200).

for AD diagnosis [154]. CSF biomarkers are, however, regarded as preferential biomarkers over plasma, as the brain (interstitial fluid) is in a direct contact with the CSF, which may more accurately reflect the metabolism and pathology in the brain. Some of the exosome vectored miRNAs derived from CSF have demonstrated the possibilities of serving as biomarkers [155], however, more investigations on lncRNAs and their potential roles in AD diagnosis are still lacking.

LncRNAs could also become a novel therapeutic target for AD treatment. Antisense oligonucleotide (ASO)-based lncRNA knockdown has demonstrated a promising therapeutic effect in patients with Angelman syndrome, a single-gene disorder characterized by intellectual disability [156,157]. Although no ASOs targeting lncRNA have been developed in the treatment of neurodegenerative diseases, ASOs targeting mRNAs indeed have been approved by Food and Drug Administration (FDA) for the treatment of Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) [158]. Additionally, ASOs also have demonstrated promising efficacy in treatment of Huntington's disease (HD) by targeting huntingtin gene (HTT), in treatment of amyotrophic lateral sclerosis (ALS) by targeting SOD1 and C9ORF72, in treatment of AD by targeting MAPT (TAU) [159]. Multiple lncRNAs have shown differential expression in AD and control animals/patients, and most of them are tightly related to Aβ metabolism, thus lncRNAs could also serve as a novel therapeutic target for AD treatment.

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