REVIEW

Long noncoding RNAs and Alzheimer's disease

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Abstract: Long noncoding RNAs (lncRNAs) are typically defined as transcripts longer than 200 nucleotides. lncRNAs can regulate gene expression at epigenetic, transcriptional, and posttranscriptional levels. Recent studies have shown that lncRNAs are involved in many neurological diseases such as epilepsy, neurodegenerative conditions, and genetic disorders. Alzheimer's disease is a neurodegenerative disease, which accounts for >80% of dementia in elderly subjects. In this review, we will highlight recent studies investigating the role of lncRNAs in Alzheimer's disease and focus on some specific lncRNAs that may underlie Alzheimer's disease pathophysiology and therefore could be potential therapeutic targets.

Keywords: lncRNA, Alzheimer's disease, ncRNAs, amyloid β peptide, BACE1, BC200, BACE1-AS

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disease and accounts for >80% of dementia cases in people aged older than 65 years.[1] The disease is characterized by devastating symptoms such as apraxia, agnosia, aphasia, and emotional disturbance because of progressive mental and behavioral function decline.[2–4] The 2015 Alzheimer's Association report predicts that, by 2050, there will be a new diagnostic case every 33 seconds, corresponding to 1 million new AD patients every year.[5] Given the disability and dependence of these patients, the increasing prevalence of AD will impose huge burdens on families and society. Long noncoding RNAs (lncRNAs) comprise a subgroup of noncoding RNAs (ncRNAs) longer than 200 nucleotides (nt), accounting for the largest proportion of the mammalian noncoding transcriptome. lncRNAs impact AD pathogenesis because of their diverse biochemical and functional effects such as chromatin modulation, posttranscriptional and posttranslational regulation, and protein complex organization.[6,7]

AD pathophysiology

Since the time of Dr Alois Alzheimer, neuropathologists have known that brain tissue of patients with AD contains extracellular senile plaques and intracellular neurofibrillary tangles composed of amyloid beta (Aβ) protein and hyperphosphorylated tau protein, respectively.[8–15] Amyloid precursor protein (APP) is sequentially cleaved by β-site APP cleaving enzyme-1 (BACE1), and γ-secretase during Aβ biosynthesis, with γ-secretase initiating the "amyloid-cascade".[16] Aβ peptides aggregate into soluble oligomers that are proposed to be the activator of N-methyl-D aspartate receptor endocytosis, mitochondrial dysfunction, oxidative damage, excessive calcium influx, lipid dysregulation, synaptic dysfunction, neuronal stress, apoptosis, aberrant neurogenesis, and neuroinflammation. However, whether or not Aβ induces tau aggregation is still being debated.[17–21] But most recent studies suggest that Aβ oligomer formation may

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be the essential step in the pathophysiology underpinnings of AD.[17,22–24]

lncRNA

ncRNAs can be divided on the basis of size into short ncRNAs (<200 nt in length) and lncRNAs.[17,25] lncRNAs vary from 200 nt to over 100 kb and usually lack an obvious open reading frame.[26–30] lncRNAs secondary structure connected to specific functions are evolutionarily conserved.[31,32] They regulate dynamically, localizing at specific cell types and in subcellular compartments.[26,33,34] lncRNAs regulate gene expression at different levels.[35] Most lncRNAs are located in the nucleus, which is consistent with their major function of epigenetic regulation.[26,36] lncRNAs are not considered to be the "dark matter", rather they have essential roles in controlling transcription and translation, as well as during genetic imprinting, genome rearrangement, chromatin modification regulation of the cell cycle, transcription, splicing, messenger RNA (mRNA) decay, and translation.[27,30,37] The pathomechanism and genetic factors of AD have been investigated for nearly 100 years. Research is ongoing, many studies have demonstrated that dysregulation of lncRNAs involved in cancer; epilepsy; and cardiovascular, neurodegenerative, and genetic diseases. Some have posited that lncRNAs may also have a major role in AD[35,38,39] (Table 1; Figure 1).

BACE1-AS

β-site amyloid precursor protein cleaving enzyme-1 antisense transcript (BACE1-AS) is a conserved RNA transcribed from the positive strand of chromosome 11 on the opposite strand of the BACE1 locus (11q 23.3).[16,17] BACE1-AS regulates BACE1 (β-site APP cleaving enzyme-1) expression at both the mRNA and protein levels. BACE1 is essential for the production of the toxic Aβ.[40,41]

AD pathogenesis has been implicated in many different cell stressors. Following exposure to high temperature, serum starvation, staurosporine, Aβ1–42, high glucose, BACE1-AS, and BACE1 mRNA are both upregulated. This suggests that cell stressors may alter BACE1-AS expression and subsequently BACE1 enzyme activity.[16,42] Regardless of whether BACE1-AS is knocked down or overexpressed, both BACE1 mRNA and BACE1 protein are regulated in parallel, thereby reducing Aβ production and plaque deposition.[16,17,42] In animals, loss of BACE1 results in numerous behavioral and physiological deficits, including memory loss, reduced synaptic plasticity,[43] emotional deficits,[44] and peripheral myelination defects.[45–49] The delicate physiologic and pathologic boundaries indicate that BACE1 expression should be tightly regulated.[16,49]

In summary, cell stress increases BACE1-AS levels, which in turn stimulates BACE1 expression, which could enhance APP processing and Aβ1–42 production. Elevated Aβ1–42 levels can further promote BACE1-AS overexpression and the APP processing cascade in a feedforward manner.[16,42,50] By forming an RNA duplex, BACE1-AS increases BACE1 mRNA stability.[42,51,52] So, BACE1 and BACE1-AS may be potential biomarkers and treatment targets for AD.[46,50,53,54]

51A

The neuronal sortilin-related receptor gene (SORL1, also known as SORLA and LR11) has long been hypothesized to be involved in AD pathogenesis.[55–58] Recent studies have posited that SORL1, as a sorting receptor for APP holoprotein, interacts with APP in endosomes and the trans-Golgi network where it affects trafficking and proteolytic processing.[59] Decreased SORL1 expression might shift APP from the retromer recycling pathway to the β-secretase cleavage pathway, increasing secreted APP production and subsequent

Table 1 Dysregulated lncRNAs in Alzheimer's disease

lncRNAs	Target	Role	References
BACE1-AS↑	Upregulation BACE1 mRNA stability	Aβ↑	16
51A↑	Downregulating SORL1 variant A	Aβ↑	59,61
17A↑	Impairing the GABA B signaling	Aβ↑, Aβx-42/Aβx-40↑	62,63
NDM29↑	Promoting the cleavage activity of BACE and γ-secretase	Aβ↑, Aβx-42/Aβx-40↑	12
BC200 ↑/↓	Targeting at eIF4A to decouple ATP hydrolysis	Modulators of local protein synthesis to maintain the long-term synaptic plasticity	65
NAT-Rad18 ↑	Controlling the expression of DNA repair protein Rad18	Making the neuron more sensitive to apoptosis	68

Notes: The arrows next to lncRNAs indicates up/down regulation. The arrows next to Aβ indicates up/down expression.
Abbreviations: Aβ, amyloid β peptide; BACE1, β-site APP cleaving enzyme-1; BC200, brain cytoplasmic 200 RNA; GABA, gamma-aminobutyric acid; eIF4A, eukaryotic initiation factor 4A; lncRNAs, long noncoding RNAs; mRNA, messenger RNA; NDM29, neuroblastoma differentiation marker 29; SORL1, sortilin-related receptor gene; ATP, adenosine triphosphate.
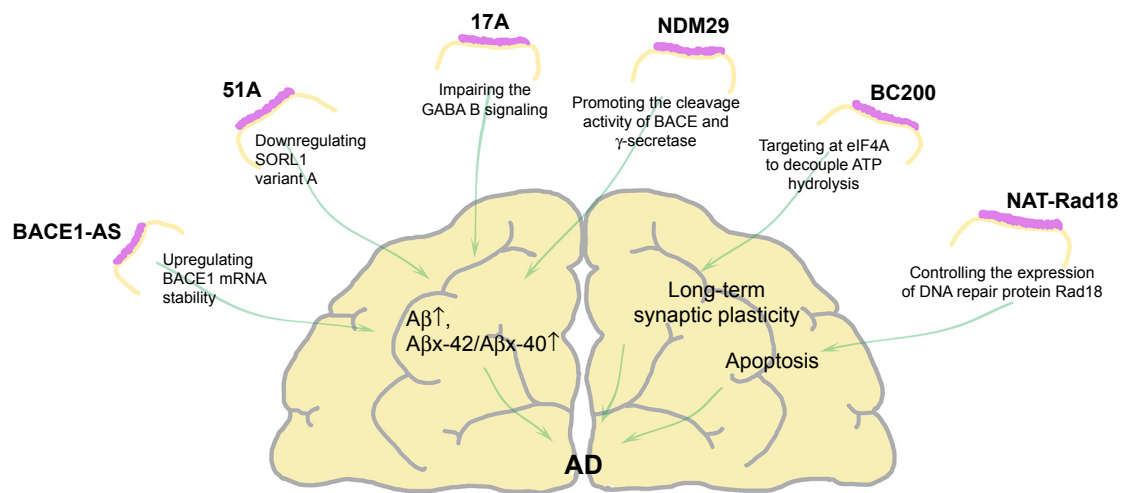
Figure 1 Dysregulated lncRNAs in AD.
Notes: BACE1-AS, 17A, 51A, and NDM29 directly or indirectly increase Aβ formation and/or the Aβx-42/Aβx-40 ratio. BC200 modulates local protein synthesis to maintain long-term synaptic plasticity. NAT-Rad18 is implicated in apoptosis. The arrows next to Aβ indicates up/down expression.
Abbreviations: Aβ, amyloid β peptide; AD, Alzheimer's disease; BACE1, β-site APP cleaving enzyme-1; BC200, brain cytoplasmic 200 RNA; eIF4A, eukaryotic initiation factor 4A; lncRNAs, long noncoding RNAs; NDM29, neuroblastoma differentiation marker 29; SORL1, sortilin-related receptor gene; mRNA, messenger RNA.

Aβ formation.[59,60] 51A is a novel ncRNA that maps in an antisense configuration to intron 1 of the SORL1 gene, the synthesis of which promotes the expression of alternatively spliced SORL1 variants. Notably, 51A is overexpressed in in vitro models and the AD brain. One possible mechanism by which 51A might increase AD susceptibility is by increasing amyloid formation via downregulating SORL1 variant A through alternative splicing.[59,61]

17A

17A is a 159-nt lncRNA synthesized by RNA polymerase III and maps in intron 3 of G-protein-coupled receptor 51 gene (GPR51); it undergoes alternative splicing, increasing the number of GABA B2 receptor isoforms. GABA B R2 splice variant B may affect GABA B biological function by regulating intracellular 3′–5′-cyclic adenosine monophosphate accumulation and the activation of specific potassium channels. These events would impair GABA B signaling, enhance Aβ secretion, and increase the Aβx-42/Aβx-40 ratio. 17A RNA is upregulated in AD compared with control tissues, suggesting that it could directly or indirectly be involved in the mechanism of AD.[52,62,63]

NDM29

Neuroblastoma differentiation marker 29 (NDM29) is an RNA polymerase III-transcribed ncRNA. NDM29 synthesis is dose-dependently induced by inflammatory stimulation. The upregulation of NDM29 RNA is accompanied by altered APP modulation. Meanwhile, it can promote the cleavage

activities of BACE that, in turn, generates an enhanced amount of APP C-terminal fragments for further processing by the γ-secretase cleavage complex to increase Aβ formation and the Aβx-42/Aβx-40 ratio.[12,63,64]

Brain cytoplasmic 200 RNA (BC200)

BC200 is a translational regulator that targets eukaryotic initiation factor 4A, thus decoupling adenosine triphosphate hydrolysis from RNA duplex unwinding, modulating local protein synthesis in postsynaptic dendritic microdomains, and contributing to the maintenance of long-term synaptic plasticity.[65]

One postmortem study found that BC200 RNA levels in cortical areas are reduced by >60% between the ages of 49 and 86 years. Compared with age-matched normal brains, BC200 RNA is significantly upregulated in the AD brain. Moreover, the relative BC200 RNA levels in AD-involved brain areas increase in parallel with disease progression. Still, at least one study reported BC200 downregulation.[66] The contradiction between studies may be due to differences in brain regions and varying disease severity, but aberrant BC200 RNA expression in AD is a possibility.[67]

Relative BC200 RNA levels decrease in dendrites but increase in somata. This divergent expression affects microtubule-dependent transport and could contribute to axonal and dendritic blockage that may be early events in AD. It could eventually contribute to local Aβ generation and subsequent amyloid deposition.[24,68] Another group found that BC200 RNA is not affected under apoptotic conditions

in vitro and hypothesized that BC200 is only involved in necrosis rather than apoptosis.[22]

NAT-Rad18

Apoptosis is the main form of programmed cell death, and excessive apoptosis causes progressive cell loss that contributes to many neurodegenerative disorders, including AD. Rad18 is a member of the Rad6 epistasis group, which is responsible for postreplication repair. NAT-Rad18 genes encode for natural antisense transcripts against Rad18, encoding a spectrum of DNA-damaging agents. There is a counterbalanced relationship between Rad18 and NAT-Rad18 in both mRNA and protein level, with Rad18 showing a low expression level. NAT-Rad18 is differentially up-regulated expressed in brain tissues especially cortical neurons following exposure to Aβ. Collectively, this evidence indicates that NAT-Rad18 may be involved in AD via its effects on DNA repair system.[69]

Conclusion

Almost all lncRNAs related to AD have been listed in this review, but investigation into this field is in the early stage. Since AD was first reported, a century passed before the discovery of basic molecular mechanism. Unquestionably, new information about lncRNAs may light a new beacon in the search for AD treatments. Depending on the mechanism of AD, BACE1-AS, 17A, 51A, and NDM29 directly or indirectly increase Aβ formation and/or the Aβx-42/Aβx-40 ratio. The roles of BC200 and NAT-Rad18 are different. BC200 modulates local protein synthesis to maintain long-term synaptic plasticity. NAT-Rad18 is implicated in apoptosis, while BC200 is only involved in necrosis. As the lncRNA field continues to develop, we still need to elucidate how lncRNAs operate at the molecular and cellular levels. Most recent studies suggest that lncRNAs are desirable candidates in the ongoing quest for AD biomarkers and could help identify rational therapeutic strategies. An enhanced understanding of lncRNA biology could open more avenues to early AD diagnosis and treatment.

Disclosure

The authors report no conflicts of interest in this work.

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