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Relationship between long non-coding RNAs and Alzheimer's disease: a systematic review

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ABSTRACT

Alzheimer disease (AD), is a typical progressive and destructive neurodegenerative disease. It is the leading cause of senile dementia that is mainly represented as neurocognitive symptoms, including progressive memory impairment, cognitive disorder, personality change and language barrier, etc. The pathogeny and nosogenesis of AD have not been clearly explained. AD is characterized by extracellular senile plaques (SP) formed by beta amyloid (Aβ) deposition and neurofibrillary tangles in neuronal cells formed by hyperphosphorylation of tau, as well as the deficiency of neuronal with gliosis. However, the complete spectrum of regulating factors in molecular level that affect the pathogenesis of AD is unclear. Long non-coding RNAs (lncRNAs) are involved in numerous neurodegenerative diseases, such as Parkinson's disease (PD) and AD. It is increasingly recognized that lncRNAs is tightly related to the pathogenesis and prevention and cure of AD. In the review, we highlighted the roles of lncRNAs in AD pathways and discussed increasing interest in targeting and regulating lncRNAs for the therapeutics of AD.

1. Introduction

Alzheimer disease (AD) is one of the commonest neurodegenerative and multifactorial disease worldwide with genetic(70%) and environmental(30%) causes [1], accounting for more than 80% of all dementia cases and affects about 6% of the population aged older than 65 years (late-onset AD), while 2-10% of patients were subjected to early-onset AD [2,3]. Two distinctive pathologies, senile plaques (SP) and neurofibrillary tangles (NFTs), are believed to have a bearing on the incidence of AD. Moreover, AD is characterized by the irreversibly and progressively loss of neuronal structure and function within the hippocampus and neocortical brain, etc., leading to cognitive impairment and dementia [4]. Currently, there are no effective therapies for AD, and only the symptoms can be improved by drugs. Therefore, it is necessary to further explore the pathogenesis of AD and improve the early diagnosis level of AD to intervene and treat as soon as possible. Meanwhile, studies have revealed that non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), short-interfering RNAs (siRNAs), and circular RNAs (circRNAs) that have been involved in AD pathogenesis [5]. Furthermore, lncRNAs affects the pathogenesis of AD were contributed by they have a variety of biochemical and functional activities, which regulated the diseases from epigenetic, transcriptional, post-transcriptional, and translational levels [5,6]. The relationship of lncRNAs between AD and related research progress was the main focus of this review.

Abbreviations: AD, Alzheimer disease; SP, senile plaques; Aβ, beta amyloid; lncRNAs, long non-coding RNAs; PD, Parkinson's disease; NFTs, neurofibrillary tangles; ncRNAs, non-coding RNAs; miRNAs, microRNAs; siRNAs, short-interfering RNAs; circRNAs, circular RNAs; OS, oxidative stress; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme-1; MAPT, microtubule-associated protein Tau; CSF, cerebrospinal fluid; PHF, paried helical filaments; SF, straight filament; FAD, familial Alzheimer disease; SAD, sporadic Alzheimer disease; PS, presenilin; CDK5, cyclin-dependent kinase 5; GSK3β, glycogen synthase kinase 3β; TREM2, receptor expressed in myeloid cell 2; PANDAR, promoter of CDKN1A antisense DNA damage-activated RNA; EMT, epithelial-mesenchymal transition; CNS, central nervous system; GAS5, growth arrest-specific 5; APOE, apolipoprotein E; BACE1-AS, β-site amyloid precursor protein cleaving enzyme-1 antisense transcript; SORL1, sortilin-related receptor 1; AβPP, amyloid-β protein precursor; qRT-PCR, real-time quantitative reverse transcriptase PCR; NATs, natural antisense transcripts; LRP1, low density lipoprotein receptor-related protein 1; HMGB2, high mobility group box 2; BC200, brain cytoplasmic RNA 1; EBF3, early B cell factor 3; OA, okadaic acid; Sox2OT, Sox2 overlapping transcript; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; EPHB2, ephrin receptor B2; NDM29, neuroblastoma differentiation marker 29; PPR, pentatricopeptide repeat

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1.1. Pathogenesis of AD

AD is a multifactorial and multigenic disease, which associated with different pathogenic mechanisms. Moreover, beta amyloid (Aβ) cascade theory, hyperphosphorylation of tau protein, aging and oxidative stress (OS), and neurotransmitter channels hold major roles [7–9]. First of all, the precipitation of Aβ was one of the main pathological mechanisms of AD. Amyloid precursor protein (APP) is a transmembrane protein of 770 amino acid residues. APP produced Aβ by proteolysis, sequentially degradated by β-site APP cleaving enzyme-1 (BACE1), and γ-secretase promote Aβ biosynthesis, which is the "amyloid-cascade" [10,11]. Seriously, the agglutinated Aβ generated and aggregated excessively in the brain and oligomeric Aβ1-42 can cause neurotoxicity, forming a circular or elliptical SP, which closely related to the pathogenesis of AD, destroying the multiple neurotransmitter systems. However, the above changes were mainly caused by the abnormalities of Aβ anabolism, the decrease of Aβ catabolism level and the imbalance of Aβ transportation [9,12].

NFTs were the aggregates of hyperphosphorylated microtubule-associated protein (MAP) → tau, which mainly existences in the cytoplasm of neuronal axons, as well as in the synaptic regions and cerebrospinal fluid (CSF) [8]. NFTs were mainly aggregated by paried helical filaments (PHF) and straight filament (SF), the number of which can be used as the marker for the clinical detection of AD. Hyperphosphorylated tau was bankrupted in the ability to coalescent microtubules and becomes unstable, coming into being filaments that aggregate into NFTs. Loss of balance between phosphorylation and dephosphorylation of tau bring about NFT formation and pathogenesis of AD [13].

Interestingly, Aβ peptides aggregate into soluble oligomers that were proposed to be the activator of N-methyl-d aspartate receptor endocytosis, dysfunction in mitochondria, oxidative damage, calcium ion overload, lipodystrophy, synaptic dysfunction, neuronal stress, apoptosis, aberrant neurogenesis, and neuroinflammation. However, whether or not Aβ could induce tau aggregation remains being deliberate [14–17]. However, recent studies declared that the Aβ formation of oligomer may be the inevitable step in the pathophysiology underpinnings of AD [18–20]. The detailed pathogenesis of AD was generality shown in Fig. 1.

Furthermore, AD is clinically classified into early-onset AD when it occurs in persons below the age of 65. This is also called as familial AD (FAD) and late-onset or sporadic AD(SAD) when it occurs after the age of 65. The two key biochemical features postulated are extracellular Aβ plaques and intracellular NFTs. APP is normally cleaved by α and β secretase to sAPPα or sAPPβ, which promote neuronal growth [21]. In patients with AD, the APP is sequentially cut by α and γ secretase and converted to insoluble product which circulates in blood and promotes the same in more cells [22]. There is abundance in β sheets as against alpha helices normally. Atypical hyperphosphorylation of tau protein, a microtubule-associated protein that supports the cytoskeleton structures and regulates functions, causes the NFTs [21]. This leads to the activation of protein kinases and cellular apoptosis [23].

1.1.1. FAD

FAD, in which the disease is inherited in an autosomal-dominant fashion with nearly 100% penetrance, accounts for only 1-5% of cases [24], which is related to a genetic predisposition, including mutations in the APP gene on chromosome 21, presenilin 1 (PS1) gene on chromosome 14, as well as presenilin 2 (PS2) gene on chromosome 1 [25]. Mutations in such genes directly impact Aβ by increasing either the total peptide levels, the relative amount of Aβ1-42, or the aggregation propensity of Aβ [24,26]. Thus far, there have been more than 230 reported mutations in APP or the presenilins that cause FAD. Interestingly, although the symptoms occur earlier and are more severe in FAD than SAD, the general memory and cognitive changes, as well as the hallmark Aβ and tau pathologies, are remarkably similar in both forms of the disease. Porquet et al. [27] established FAD model in a senescence phenotype mouse, and investigated the main AD brain molecular markers, such as alterations in amyloid pathway, neuroinflammation, and hyperphosphorylation of tau in these mice along their lifetimes. Results demonstrated that a senescence-accelerated background exacerbated the amyloid pathology and maintained the cognitive dysfunction present in APP/PS1 mice. Moreover, tau pathology also changed, including the activity of cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3β (GSK3β).

1.1.2. SAD

Most forms of AD are SAD or inherited in a non-Mendelian fashion, and less than 1% of cases are autosomal-dominant. In addition to FAD genetics, in which AD is elicited by mutations in specific genes, genetic associations have been found for SAD. The apolipoprotein E4(APOE 4) allele has been shown to exhibit high-avidity binding to Aβ, and increasing in vitro and in vivo data indicate that APOE 4 is an Aβ-binding molecule that influences soluble Aβ clearance as well as its tendency to accumulate [24]. With reference to SAD-APOE, triggering receptor expressed in myeloid cell 2 (TREM2) and CD33 which are related to tau modification and microglial phagocytosis of Aβ are considered responsible [28]. Furthermore, there is also abnormality in the metabolism of proteins, glucose, cholesterol and proteostasis failure in ubiquitin protease pathway which triggers cell death and increases NFT formation [29]. Inability to process gangliosides causes conversion of APP precursor to insoluble toxic Aβ. Aberrant synthesis of tau occurs due to abnormal glucose metabolism as well as increase in cytokines, reactive oxygen and neuroinflammation. The tangles and β-pleated fibrillar Aβ and tau containing NFTs directly activate the classical complement pathway [30]. This in turn results in molecules of cytopathic relevance, resulting in clustering of microglia and astrocytes. There are also membrane attack complex, upregulation of complex defence proteins and probably opsonization. The believed cascade of mechanism is amyloid which leads to inflammation, phosphorylation of tau, oxidative stress, altered calcium homoeostasis, loss of synapses, cholinergic dysfunction, apoptosis with additional disturbance, other neurotransmitters such as serotonin and norepinephrine [31].

1.2. LncRNAs

LncRNAs are novel RNA molecules over 200 nucleotides in length, located in the nucleus or cytoplasm, which demonstrate a conserved secondary structure and a functional roles in molecular biology by multifaceted mechanisms at various levels in spite of that they have no potential for protein-coding. In comparison to small ncRNAs, such as miRNAs and siRNAs, the functions of lncRNAs are little understood [32,33]. Fortunately, a growing number of evidences have indicated that lncRNAs play a pivotal role in maintaining cell physiological function but also in a train of human diseases, such as degenerative disorders, cardiovascular diseases, and cancer, etc. For example, Zhou et al. identified AD associated lncRNAs by re-annotation of microarray data based on postmortem tissue samples of AD patients and matched elderly controls, and found 24 up-regulated and 84 down-regulated lncRNAs in AD patients as compared to controls, most being intergenic [20]. Ma et al. [34] demonstrated that elevated lncRNA-nuclear-enriched abundant transcript (Neat1) expression aggravated myocardial ischemia reperfusion injury via activation of apoptosis and autophagy in diabetic rats. More recently, well described tumor suppressive lncRNA, GAS5, was described to suppress malignancy of glioma stem cells via a miR-196a-5p/FOXO1 feedback loop and proliferation, migration, and invasion of glioma cells by negative regulation of miR-18a-5p [35]. There is evidence showing that the dysregulation of lncRNAs promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR) leads to the development and progression in several cancers including colorectal cancer, via p53-dependent manner [36]. This suggests that these lncRNAs may be of value as prognostic indices and a therapeutic

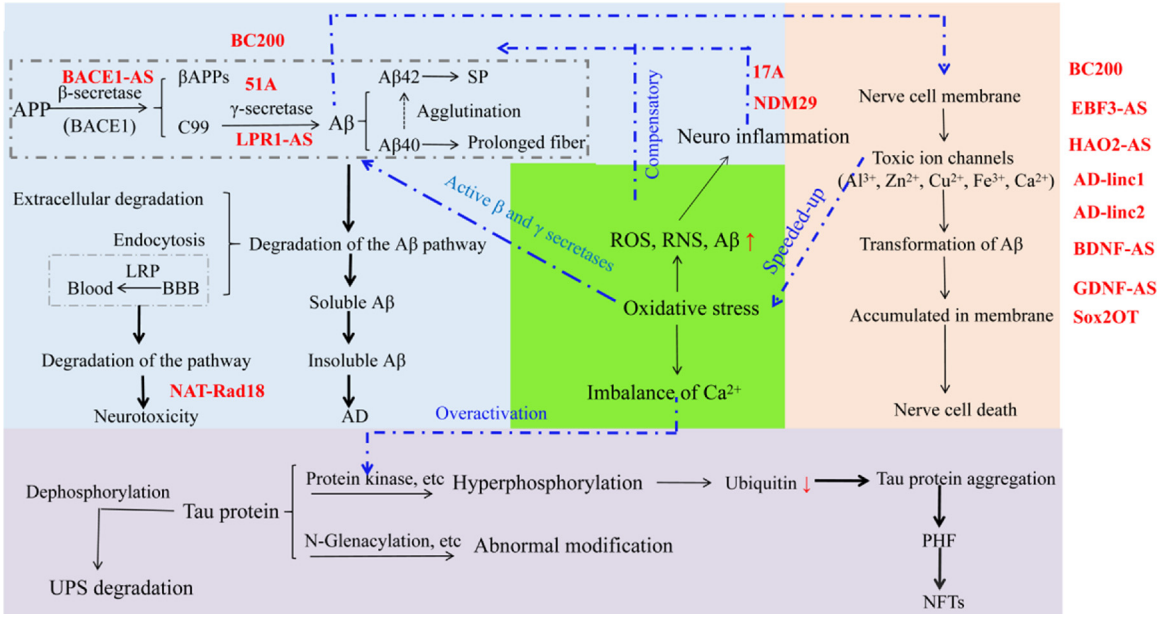

Fig. 1. The pathogenesis of Alzheimer disease(AD) and involved lncRNAs. Beta amyloid (Aβ) cascade theory, hyperphosphorylation of tau protein, oxidative stress (OS), and neurotransmitter channels hold major players in pathogenic mechanisms of AD. β-site APP cleaving enzyme-1 antisense transcript (BACE1-AS), 51 A and low density lipoprotein receptor-related protein 1 antisense transcript (LRP1-AS) were contributed to the accumulation of Aβ peptide. brain cytoplasmic RNA 1(BC200), early B cell factor 3 antisense transcript(EBF3-AS), Sox2 overlapping transcript (Sox2OT), AD-linc1, AD-linc2 and HAO2-AS were involved in synaptic and neuron exhaustion. Antisense transcript of brain-derived neurotrophic factor (BDNF-AS) and antisense transcript of glial-derived neurotrophic factor (GDNF-AS) played important roles in the decreasing of neurotrophin. 17 A and neuroblastoma differentiation marker 29(NDM29) can be triggered by inflammatory response to deprave the development of AD. Antisense transcript against Rad18 (NAT-Rad18) can promote neuron apoptosis via implicating DNA damage.

target, as a high expression of lncRNAs PANDAR is associated with poor prognosis. Furthermore, modulating lncRNAs PANDAR has been reported to induce apoptosis and inhibit the tumor growth through modulation of cell cycle and epithelial-mesenchymal transition (EMT) pathway.

Particularly, lncRNAs are trapped in regulating the development of central nervous system (CNS) through such approaches as histone modification, transcriptional co-factor, messenger RNA (mRNA) decay and alternative splicing [37–39]. These approaches are closely related to a variety of principal diseases of human beings, including AD, autism spectrum disorder and schizophrenia, and so on. It was reported that a novel lncRNA, lncRNA-IFI6, regulates antiviral innate immunity in the JFH1 HCV infection model. LncRNA-IFI6 regulates HCV infection independently of the JAK-STAT pathway. LncRNA-IFI6 exerts its regulatory function via promoter activation and histone modification of IFI6 through its spatial domain [40]. LncRNA growth arrest-specific 5(GAS5) accumulates in growth arrested cells and plays a crucial role in progression of multiple cancers, including glioma. Yuan et al. [41] indicated that lncRNA GAS5 indel polymorphism might alert the binding of transcriptional factor TFAP2A and activation of its expression, and highlight the highlight the importance and potential of the biological relevance of the GAS5 indel genetic variant in glioma predisposition. Moreover, alternative splicing is a central component of human brain complexity. Preview study demonstrated that the stable expression of lnc17 A in SHSY5Y neuroblastoma cells induces the synthesis of an alternative splicing isoform that abolish GABA B2 intracellular signaling [42](i.e., inhibition of cAMP accumulation and activation of K(+) channels). Furthermore, 17 A expression in neuroblastoma cells enhances the secretion of amyloid β peptide (Aβ) and the Aβ x-42/Aβ x-40 peptide ratio and that its synthesis is induced in response to inflammatory stimuli.

2. Evidences for the involvement of lncRNAs in AD

Increasing evidences also revealed the manifold functions of lncRNAs in neurodevelopment, brain function and aging, and the disorders of lncRNA expression was implicated in numerous types of neurological diseases included AD [43]. Recent studies have further revealed that lncRNAs may act on the pathogenesis of AD at the epigenetic and translational levels [42,44]. Moreover, compared with healthy population, 315 lncRNAs were significantly dysregulated in the brain of AD patients, of which 238 lncRNAs were up-regulated and 77 were down-regulated [45]. Nevertheless, the expression profiles, targets, and functions of lncRNAs were implicated in the pathogenesis of AD[46]. The roles of lncRNAs in AD have attracted widespread interest, and considerable lncRNAs associated AD have been unveiled [42,44]. Compared with healthy controls, some of lncRNAs as BACE1-AS, 51 A, BC200 and NDM29 were differentially expressed in AD, and which were correlated with AD pathogenesis[47]. Hundreds of lncRNAs aberrantly expressed between AD samples and healthy controls in human and rat models were identified by expression profiles analysis [45], which forcefully demonstrated the relevance between altered expression pattern of lncRNA and AD. Therefore, lncRNAs are the potential biomarkers and therapeutic targets for early AD. Several specific lncRNAs were dysregulated in AD, some of which have been implicated in the regulation of critical genes related to AD, including APP and beta-site BACE1. As shown in Table 1, we summarized the lncRNAs trapped in regulating key factors in AD.

3. LncRNAs implicated in the pathophysiology of AD

3.1. LncRNAs in Aβ peptide accumulation

3.1.1. BACE1-AS

Previous studies reported that beta-secretase 1(BACE1) is the rate-limiting enzyme that contributed to the formation of Aβ peptides and the amyloid deposition [48]. Aβ, the major constituent of SP, is closely interlocked with the pathological process of AD. Aβ-42 and Aβ-40 coexist in the amyloid plaques, which are two main subtypes of Aβ. Aβ-42 has two extra residues at C-terminus, is the major component of SP even

Table 1
Summary of lncRNAs in AD

Name	Aliases	Type	Target protein/Process/Mechanism	Roles in AD
BACE1-AS	BACE1AS; BACE1-AS1	Antisense lncRNA	Post-transcriptional level	Regulates the APP cleaving and Aβ production
BC200	BCYRN1; BC200a	Protomer-associated RNA	Translational level	Increasing synapse loss
GDNF-AS	GDNFOS	Antisense lncRNA	Epigenetic level	Aggravating neurotrophin depletion
17A		Intronic lncRNA	Post-transcriptional leve	Triggering with inflammation response in AD
51A			Downregulating SORLI variant A	Resulting the abnormality of APP processing
Sox2OT		Antisense lncRNA	Translational level	Regulation neurogenesis
BDNF-AS	BDNFOS; BDNF-AS1	Antisense lncRNA	Epigenetic level	Aggravating neurotrophin depletion
NDM29			Promoting the cleaving of BACE and γ-secretase	Triggering with inflammation response in AD
NAT-Rad18		Antisense lncRNA	Controlling the expression of Rad18	Promoting neuron apoptosis
LRP1-AS		Antisense lncRNA	low-density receptor-related protein 1	Accelerating the APP endocytic trafficking and Aβ processing
EBF3-AS		Antisense lncRNA	Possibly involved in nuclear processes	Promoting neuron apoptosis
HAO2-AS		Antisense lncRNA	Possibly involved in nuclear processes	Increasing expressions in AD
AD-linc1, AD-linc2			Unknown	Increasing expressions in AD

though the levels of Aβ-40 are much more than Aβ-42, suggesting that which plays a more important role in the pathogenesis of AD. Besides, the soluble Aβ-42 level in the CSF intimated cortical Aβ deposition [49]. Nonetheless, it was recorded as an increased in Aβ-42 at early-onset AD. In addition, the total Aβ levels and the radio of Aβ-42/Aβ-40 are significantly increased in the brains of sporadic AD patients. Accumulating evidences suggested that insoluble Aβ oligomers forming a circular or elliptical SP, causing neurotoxicity, destroying the multiple neurotransmitter systems, thereby aggravating AD [50]. This suggests that the inhibition of BACE1 and subsequent reduction of Aβ may cure or prevent AD.

BACE1 antisense transcript (BACE1-AS), is a conserved RNA transcribed from the positive strand of chromosome 11 on the opposite strand of the BACE1 locus, regulated the expression of BACE1 at mRNA and protein levels [11,14]. By regulating the expression of BACE1, lncRNA BACE1-AS plays an important role in the AD control at the physiological and pathological boundaries. LncRNA BACE1-AS can positively regulate BACE1 mRNA and protein expression in vitro and vivo, and Aβ1-42 stimulation also can elevate the expression of lncRNA BACE1-AS, increasing BACE1 mRNA stability and generating additional Aβ1-42 through a post-transcriptional feed-forward mechanism [11]. In addition, silencing lncRNA BACE1-AS expression with short interfering RNA(siRNA) in SP AD SH-SY5Y cells attenuates the ability of BACE1 to cleave APP and reduce the production of Aβ1-42 oligomers [51]. Furthermore, the knockdown of lncRNA BACE1-AS by siRNA can improve disease symptoms in AD animal models, including memory and learning behaviors [52]. Therefore, it is possible that BACE1 and lncRNA BACE1-AS turn into biomarkers and therapeutic targets for AD. In addition, the expression of the lncRNA BACE1-AS was significantly promoted by external stimulus such as Aβ.

However, lncRNA BACE1-AS does not directly inhibit the transcription of BACE1 mRNA by forming a dimer with the coding gene like the common natural antisense transcripts (NATs). Conversely, lncRNA BACE1-AS masked the binding site of miR-485-5p on BACE1 mRNA, thereby suppressing the inhibition effect of miR-485-5p on BACE1 mRNA and increasing the stability of BACE1 mRNA, and then resulting in high expression of BACE1 protein [53]. Meanwhile, Aβ-42 and Aβ-40 would be increasingly generated by BACE1 protein effecting on APP. In addition, the continuously generated Aβ can in turn affect the up-regulation of BACE1-AS, thus forming a positive feedback loop, which increased the formation of SP in the brain of AD patients and aggravates the development of the disease [11,54]. In addition to increasing the production of Aβ, BACE1-AS can also promote the aggregation of Aβ. Furthermore, we also discovered that BACE1-AS can also increase the cytotoxicity of DHAl3, promote cell apoptosis, and even promote the phosphorylation of tau protein. As we known, phosphorylation of tau protein is closely related to NFT which is another important pathological marker for AD. It is demonstrated that lncRNA BACE1-AS is likely to be a vital regulating factor in the morbidity of AD [55].

3.1.2. 51A

Sortilin-related receptor 1(SORL1) is one of candidate genes involved in the processing of amyloid-β protein precursor (AβPP), as a potential genetic factors of AD[56]. SORL1 encodes a SORLA protein, thereby preventing the transporting of AβPP from the Golgi to endosomal compartments with Aβ secretases reside[57]. Large number of international studies have demonstrate that down-regulation of SORL1 enhances the amyloidogenic process, significantly increases the risk of FAD and SAD [58,59]. Meanwhile, 51 A, a fresh lncRNA, is the antisense transcript of SORL1. Ciarlo et al. [44] reported that lncRNA 51 A expression leads to accumulation of Aβ-42 by driving the splicing form of SORL1 mRNA, resulting in the decreasing of SORL1 variant A synthesis, which is related to the abnormality of APP processing, and made the further step of increasing Aβ formation. Furthermore, they suggested that lncRNA 51 A expressed in human brains, particularly outstanding up-regulated in cerebral cortices of AD cases. In addition, Lv et al. [60] measured the plasma levels of lncRNA 51 A by real-time quantitative reverse transcriptase PCR (qRT-PCR), found that the levels of 51 A in plasma were significantly increased in AD patients ($p < 0.001$). The result indicated that the levels of 51 A in plasma might reflect the extent of cognitive impairment in AD patients.

3.1.3. LRP1-AS

Low density lipoprotein receptor-related protein 1(LRP1) is involved in the molecular pathways leading to the deposition of Aβ by interacting APOE[61]. Expression of APOE is positively correlated with APP density in AD patients. Meanwhile, LRP1 and APP interaction accelerated APP endocytic trafficking and processing to Aβ [62]. Furthermore, LRP1 is a receptor involved in several cellular processes including intracellular signaling, lipid homeostasis, and APP trafficking and processing, which is highly expressed in CNS, hippocampus, cortical neurons and activated astrocytes [63]. Studies also showed that lower level of LRP1 associated with AD risk. However, little is known about the mechanisms of LRP1 expression regulation. Interestingly, LRP1-AS is the natural antisense transcript of LRP1, which can suppress LRP1 expression. It is clearly indicated that LRP1-AS negatively regulates LRP1 gene expression, which prompt us the elevated LRP1-AS in the AD patients brains might repress LRP1 expression [61]. Concretely, the LRP1-AS directly binds to high mobility group box 2 (HMGB2) and inhibits the activity of HMGB2 to increase the transcription of LRP1, thereby aggravating the development of AD. LRP1-AS function is in turn regulated by LRP1 mRNA that can base pair with LRP1-AS forming an RNA duplex, which prevents the interaction between LRP1-AS and HMGB2 [64,65].

3.2. LncRNAs in synaptic and neuron exhaustion

3.2.1. BC200

One of the neuropathological features of AD is the progressive loss of synapses, and persistent disruption of synaptic plasticity may initially manifested as the number of synapses decreased and finally turns into the neurons loss in the later period of disease. Therefore, it is believed that synaptic failure is the foundation of memory impairment in AD patients. Brain cytoplasmic RNA 1 (BCYRN1 or BC200), a long non-coding RNA, has been reported with substantially higher levels and plays momentous role in human breast, skin, lung, esophagus, and cervix tumors[66,67]. It was a small but stable RNA species, universally expressed in rat neurons and involved in the synthesis of synapse-related protein. Studies suggested that BC200 may play various roles in different brain areas [5]. It was certain that BC200 was human or primate-specific and about half of them were found in the brain at all of the lncRNAs (Table 1) related to AD [68,69]. LncRNAs were differentially expressed across various cerebral regions, as well as in astrocytes, oligodendrocytes, glia, and neurons. Evidence for lncRNA regulated the synaptic plasticity and cell cycle is consist with the postulate association in senescence and neurodegenerative disorders. Studies have demonstrated BC200 RNA was significantly up-regulated in AD brains, and this up-regulation in AD was specific [70]. Synapse loss and dendritic regression are substantial in AD, but these degenerative changes are accompanied by significant dendritic sprouting and remodeling, often in the same neuron. Such reactive developments may be of a compensatory nature, directed at maintaining connectivity and plasticity [70].

However, the research on the role of BC200 in AD pathogenesis have only recently been initiated, the precise biological role and mechanism of BC200 remain largely unclear and need to be investigated. Recently, Li et al. [71] established an AD cell model overexpressing Aβ1-42, found that BC200 and BACE1 were increased upon treatment with Aβ1-42, and inhibition of BC200 rescued this Aβ1-42-mediated dysfunction, as indicated by the interaction of BC200 directly targeting BACE1. Taken together, the data showed that BC200 might be a potent positive regulator of BACE1 in AD cells. Still, the specific function and mechanism will be reveled in the near future.

3.2.2. EBF3-AS

Recently, Magistri et al. [72] used RNA sequencing to observe significant alterations in the lncRNA expression profile of AD brains and found that lncRNA EBF3-AS was significantly up-regulated in the brain of SAD compared to control individuals. In this context, a research demonstrated that the expressions of early B cell factor 3 (EBF3) and lncRNA EBF3-AS and were up-regulated in hippocampus of APP/PS1 mice (AD model mice) [73]. EBF3-AS knockdown by siRNA inhibited the apoptosis induced by Aβ25-35 and okadaic acid (OA) in SH-SY5Y. The expression of EBF3 was down-regulated in Aβ25-35- and OA-treated SH-SY5Y, which was reversed by EBF3-AS knockdown. EBF3 knockdown can reverse the Aβ25-35-induced apoptosis in SHSY5Y. These results revealed that lncRNA EBF3-AS promoted neuron apoptosis in SAD, and involved in regulating EBF3 expression.

3.2.3. Other related lncRNAs

Furthermore, Wang and colleagues discovered that lncRNAs H19 and PVT1 might be associated with AD using the network analysis [73]. Moreover, it was reported that Sox2 overlapping transcript (Sox2OT) is a stable transcript in mouse embryonic stem cells associated with embryo differentiation [36]. Interestingly, Sox2OT overlaps with Sox2 gene which is an important regulator of neurogenesis. Studies reported that the expression levels of AD-linc1, AD-linc2 and HAO2-AS in AD patients were increased [72], which indicated that those factors might be associated with AD.

3.3. Roles of lncRNAs in neurotrophin depletion

Neurotrophins is contributes to the proliferation, differentiation, and survival of neurons and glia, which could mediate learning, memory, and behavior. Neurotrophins are believed to the potential drug targets for several neurologic disorders.

3.3.1. BDNF-AS

Brain-derived neurotrophic factor (BDNF), is a protein synthesized in the brain and expressed in the CNS, which can prevent neuron function loss and death, improve the pathological state of neurons, and regulate the regeneration and differentiation of damaged neuron [74,75]. Research pointed out that BDNF regulates the APP processing by stimulating the non-amyloidogenic processing pathway, the expression of which in astrocytes may be considered as a compensatory event to keep adequate neurotrophic support to neurons in the initial stages of AD pathology [76,77]. BDNF-AS is an antisense lncRNA of BDNF, which plays an important role in the regulation of BDNF expression. The expression of BDNF was suppressed by BDNF-AS, as a result of silencing BDNF-AS could improve the levels of BDNF mRNA, promote BDNF production, and induce neuronal differentiation. Therefore, the inhibition effect of BDNF-AS emerges a drift strategy for specifically advancing BDNF levels, which has great potential to AD treatment. Furthermore, suppression of BDNF-AS enhanced the expression of mRNAs encoding glial-derived neurotrophic factor (GDNF) and ephrin receptor B2 (EPHB2), both implicated in AD pathogenesis [78,79].

3.3.2. GDNF-AS

GDNF is an important biologically active trophic factor, has a nutritional effect on a variety of cells, such as dopaminergic neuron [80], neural stem cells [81] and mesenchymal stem cells [82]. Meanwhile, GDNF has incomparable functions than other growth factors, such as implicated in programmed death of cell [83], promoted the survival of neuronal [84], and involved in the repair of axonal damage [85]. However, GDNF-AS is transcribed by the antisense strand of GDNF gene, the expression levels of which are defective in neurodegenerative diseases and only in primates [86,87]. The GDNF-AS gene are spliced into different isoforms, consisted of lncRNAs GDNF-AS1, lncRNAs GDNF-AS2 and GDNF-AS3. Particularly, GDNF-AS3 is not lncRNA, which has a potential open reading frame that encodes a protein with no known homologs in GenBank. The mature GDNF peptide was down-regulated in AD patients. Further studies and analysis of novel isoforms about GDNF and GDNF-AS in AD brains may uncover the function of endogenous GDNF in human brain diseases [36]. However, more evidence is demanded to elucidate the relevance between GDNF-AS and GDNF mRNA as well as the relationship with AD pathogenesis.

3.4. LncRNAs and inflammation

Scientific data demonstrated that lncRNAs were responsible for the differentiation of immune cell in mammalian and corresponding immune response. When the innate immune system and inflammatory signals were overactivated, a large number of free radicals and proinflammatory cytokines would be produce, bringing about the inflammatory cascade and leading to neurodegeneration, which may be a cause of AD [88].

3.4.1. 17A

LncRNA 17A, is one of pol III-dependent lncRNAs which have the potential to regulate pol II-transcribed protein coding genes maps into intron 3 of GPR51 gene (coding GABA B2 receptor, GABAB R2) [36,89]. Massone et al. [42] reported that overexpression of 17 A suppressing the expression of GABABR2 variant A, thereby enhancing the levels of variant B and the accumulation of Aβ-40 and Aβ-42. Interestingly, the expression of 17 A was triggered by inflammation response in the brains

of AD patients. Moreover, compared with control group, 17 A was up-regulated in AD cases, insinuating that it could directly or indirectly implicated in the progression of AD[89].

3.4.2. NDM29

Neuroblastoma differentiation marker 29 (NDM29), a RNA polII-transcribed lncRNA which was frequently transcribed in cells of the central nervous system [90]. It was showed that the expression of NDM29 might influence also key player of neurodegenerative pathways. Recent studies have implicated that NDM29 can induce APP synthesis, resulting in the level of Aβ and the ratio of Aβ-42/Aβ-40 both increased [90–92]. Meanwhile, inflammatory stimuli can promote the expression of NDM29 RNA and the formation of Aβ, which can be inhibited by anti-inflammatory drugs. Furthermore, high levels of NDM29 detected in patients who affected by neurodegenerative diseases. Therefore, the expression of NDM29 may induce the formation of Aβ in AD.

3.5. LncRNAs in mitochondrial impairment and oxidative stress

Mitochondria are the main site of Aβ deposition. Aβ deposition leads to the decreasing of metabolic rate in brain, the changing of enzyme activities which related to energy metabolism in mitochondria, the barrier of electron transfer, the reducing of ROS clearance, and the increasing of super-oxygen ion production. However, oxygen free radicals can cause protein cross-linking, promote the aggregation and deposition of Aβ, and form a vicious circle as a result of mitochondrial dysfunction, reduced ATP production, and decreased neuronal function. Even triggers mitochondria to release proapoptotic factors that cause apoptosis [93]. Moreover, several mitochondrial lncRNAs which get trapped in the regulation of mitochondrial gene have been identified by RNA-seq, such as lncND5, lncND6 and lncCYTB [94,95]. These three lncRNAs were 58, 34, and 14% as abundant as their complementary coding ND5, ND6, and CYTB mRNAs, respectively. These mitochondrial DNA-encoded lncRNAs primarily form intermolecular duplexes with their respective complementary mRNAs. This suggested that they may have a functional role in mitochondria to either stabilize their partner mRNAs or regulate their expression. LncND5 RNA was the most abundant of the three mitochondrial DNA-encoded lncRNAs. The expressions of lncND5, lncND6, and lncCYTB were regulated by nuclear-encoded mitochondrial processing proteins, such as the penta-tricopeptide repeat (PPR) protein family. However, the roles of lncRNAs related to AD are required for further investigation.

3.6. lncRNAs in DNA damage

Rad18 is an enzyme involved in the DNA damage repair system. Meanwhile, NAT-Rad18 is a natural antisense transcript against Rad18 encoding a DNA repair protein. NAT-Rad18 is transcribed from the antisense Rad18 gene. It is specifically demonstrated that the gene expression of Aβ-stimulated NAT-Rad18 was up-regulated, which led to the down-regulation of Rad18 at the posttranscriptional level. These results suggested that NAT-Rad18 can reduce the impact of DNA damage stress to neurons and increase neuron apoptosis [36].

4. Inner connections between lncRNAs with miRNAs

It's generally believed that lncRNAs lack a conventional Open Reading Frame, are promoter-driven, can be alternatively spliced and are often polyadenylated. LncRNAs may overlap with protein-coding genes, or be found in their intronic regions because which often further defined in relate to nearby protein-coding genes [96]. LncRNA affects histone markers and acts as scaffold proteins to affect chromatin organization and gene transcription, which may be attributed to the multi-function combination of DNA, nuclear and cytosolic proteins. Moreover, lncRNAs also interact with various classes of RNA and influence mRNA nuclear retention, transport, stability and cytosolic translation [93,94].

A great part of human genes can be transcribed, but the vast majority of transcriptions are ncRNAs, which play an important regulatory role in many vital activities by affecting gene expression and epigenetics. LncRNAs and miRNAs were two important types of ncRNAs that have be found as key roles in regulating the development of many diseases such as AD[33]. LncRNAs can be the host of miRNAs in competition for mRNA with miRNA or as miRNAs sponges to regulate miRNAs. While miRNAs can down-regulate lncRNA by directly binding it or regulate lncRNA indirectly with medial factors. Their regulatory roles were mutual and jointly form a complex regulatory network [97].

Many reports revealed that miRNAs involved in several regulations of secretases, for example, β-secretase (BACE1), γ-secretase, and α-secretase [98–101]. Moreover, the expressions of APP, Tau protein, and APOE4 were regulated by miRNAs [102–105]. Studies found that lncRNAs regulated miRNAs mainly in three ways. The first, lncRNAs could be as a precursor or host of miRNAs. According to reports, a part of lncRNAs can form the precursor of miRNAs by intracellular shearing [106]. Second, miRNA "sponge" is one of the pathways. The lncRNAs with this effect was called competitive endogenous RNA (ceRNA) [107]. Recently, a mechanism model has been proposed to explore the function of lncRNA interact with miRNA, that was, lncRNA can act as a ceRNA [108]. Third, lncRNAs competed with miRNAs to combine with mRNAs. LncRNAs indirectly inhibited the negative regulation of target genes by miRNAs, and that was the result of lncRNAs competed with miRNAs to combine with the target mRNAs of 3'UTR. As mentioned above, the coding gene of β-secretase can transcribe the antisense lncRNA(BACE1-AS). The up-regulation of BACE1-AS would be increase the stability of BACE1 mRNA and promote the production of Aβ by a feed-forward mechanism at the post-transcriptional level. It is closely related to the pathogenesis of AD [11]. Faghihi and colleagues [53] demonstrated that a miRNA (miR-485-5p) was also involved in the regulation of BACE1 by in vitro experiments. BACE1 mRNAs not only can bind to the open reading frame of BACE1-AS, but also miR-485-5p. However, BACE1-AS can competitively combine with BACE1 mRNA to reduce the inhibition by miR-485-5p.

5. Conclusion

In summary, the pathogenesis of AD is extremely complex, involving multiple molecular signaling pathways. More and more lncRNAs were identified that responsible for the pathogenesis and development of AD. So far, almost all lncRNAs involved in AD have been overviewed in this review, but the exploration of this field is still in its infancy. In the review, we highlighted the roles of different lncRNAs in AD pathways. BACE1-AS, 51 A and LRP1-AS were contributed to the accumulation of Aβ peptide. In addition, BC200, EBF3-AS, Sox2OT, AD-linc1, AD-linc2 and HAO2-AS were the risk factors for AD may through exacerbating synaptic and neuron exhaustion. Moreover, BDNF-AS and GDNF-AS played important roles in AD via decreasing neurotrophin. 17 A and NDM29 can be triggered by inflammatory response in AD, and then depraving the development of AD. NAT-Rad18 can promote neuron apoptosis via implicating DNA damage. Besides, there were other lncRNAs were abnormally expressed in AD patients, and may be related to mitochondrial impairment and oxidative stress, such as lncND5, lncND6 and lncCYTB. Nevertheless, in-depth studies of the roles and underlying mechanism of lncRNAs in AD are still needed.

6. Perspectives

With the increasing synaptic of the aging population, the prevention and treatment of AD is particularly urgent. At present, the treatment strategies for AD are mainly aimed at effectively inhibiting the Aβ decomposition and tau protein dephosphorylation, regulating the production of reactive oxygen species and the formation of toxic ion

channels destruction, etc. Those methods tend to have significant experimental results but limited clinical efficacy. If further studies can confirm the usefulness of certain lncRNAs as diagnostic markers of preclinical or clinical AD, highly sensitive RNA analysis can be used for AD diagnosis. It is conceivable that the diagnosis will be more efficient, sensitive and accurate. Meanwhile, AD is considered to be a disease that involving many factors such as genetics, environment, metabolism, and age. If further researches can identify and prove which lncRNAs are associated with the FAD and which are involved in the SAD development, which will provide new directions for the precise treatment of AD. Prevention and treatment of AD should be based on the comprehensive measures, including improving diagnostic methods to detect patients in early stage, effectively controlling the risk factors to reduce the incidence of disease, identifying the inter-relationships and interactions between various pathogenesis, and fully revealing the pathogenesis to simultaneously block signaling pathways, exploiting potential therapeutic targets, and developing natural Chinese herbal medicines with multi-target effects and no toxic side effects, and so on. Meanwhile, in order to obtain better therapeutic effects, we should be engaged in to explore and broaden the treatment channels of AD.

In recent years, more and more lncRNAs have been discovered with the development of genome wide sequencing, and the studies about lncRNAs which involved in human neurodegenerative diseases have also made great breakthroughs. Undoubtedly, mimics or inhibitor of lncRNAs will most possibly become a potential and fresh strategy for the treatment of AD. However, it is impossible to predict their functions according to their sequence, because of its large number, variety, and various regulatory pathways, which brings considerable difficulties to further study. Therefore, accelerating the development of bioinformatics, establishing the blameless corresponding lncRNA libraries and the developing of new experimental techniques are indispensable.

Meanwhile, lncRNAs have a dual role of physiological regulation and pathological changes in nerve cells. The question is how to regulate the expression and role of lncRNA and use it to treat AD, providing a potential therapeutic target of lncRNA-related pathogenesis for the AD treatment, of which further researches are needed. Only through more in-depth studies to understand the specific mechanisms of lncRNAs and AD, can we explore the possibility of treating AD etiology by regulating ncRNA. At the same time, the comparative and standardized study designs of more large-scale samples are needed to re-examine the results of previous researches between lncRNAs and AD. We need to optimize the processing and detection methods of lncRNAs in the experiment if we want to apply lncRNAs to the clinical diagnosis of AD.

Researchers have made efforts to explore the approaches developing lncRNAs-based therapeutics: lncRNAs mimics and lncRNAs antagonists. It is possible to find sensitive and specific lncRNAs in the AD diagnostic tests and expand its potential application value. Furthermore, lncRNAs would be used in conjunction with other techniques for clinically assisted diagnosis, as an early biomarker for the diagnosis of AD, providing new methods and targets for the treatment of AD patients.

Conflict of interest

The authors have no conflict of interest to declare.

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