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Role Of Lncrna In Alzheimer's Diseases

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Abstract

Long noncoding RNA (lncRNA) are a family of RNA molecules with over 200 nucleotides in size. They cannot code for proteins but still have biological activities. lncRNAs are abundantly expressed in the pathogenic process of neurological diseases like Alzheimer's. The lncRNA EBF3-AS is more expressed in the brains of older Alzheimer's disease patients called late onset Alzheimer's disease. NAT-Rad18, a lncRNA over synthesized in specific areas of the brain in AD rats. The lncRNA n336694 targets miR-106b which increases its expression. MiR-106b leads to apoptosis markers in cells. oxidative stress-induced injury to the neurons is caused by the lncRNA SOX21-AS1. The lncRNA-ATB is involved in AD pathophysiology and reducing its expression helps with oxidative stress-induced injury. lncRNA MEG3 inhibits inflammatory injury and oxidative stress in individuals suffering from AD. The increase of lncRNA 17A in cerebral tissues of AD patients affects Aβ secretion. BACE1-AS suppression reduces Aβ and BACE1 levels and inhibits tau protein phosphorylation (3). The lncRNA BC200, also known as BCYRN1 upregulates Aβ production through BACE1 modulation which leads to AD pathogenesis. NEAT1 regulates the miR-124/BACE1 axis and plays a role in AD development. Reduced SORL1 expression increases neurotoxic Aβ formation in AD brains. LRP1-AS negatively regulates systemic Aβ clearance during AD progression. GAS5 regulates insulin signaling, neuronal survival, tau phosphorylation, and neuroinflammation. MAGI2-AS3-miR-374b-5p axis modulates neuroinflammation and neurotoxicity caused by Aβ fragment. Upregulation of WT1-AS inhibits the miR-375/SIX4 axis, OSI, and neuronal apoptosis in AD. BDNF-AS is found to be important in AD though the mechanism has yet to be determined. This review study aims to enhance comprehension of the disease progression of Alzheimer's disease (AD) in relation to various long non-coding RNAs (lncRNA).

Keywords: Long noncoding RNA (lncRNA, Alzheimer's disease (AD), Apoptosis, Micro RNA, Neuroinflammation, Okadaic acid (OA)

INTRODUCTION

Alzheimer's disease (AD) is a neurological disease characterized by a gradual decline in memory function, language abilities, and cognitive deficits, including challenges in problem-solving, spatial reasoning, and mood fluctuations. By symptoms manifestation age it is charecterised by two types Early-onset Alzheimer's disease (EOAD) (Muhs et al., 2006, Zhang et al., 2021) in individuals younger than 65 years old) and is characterized by a more pronounced hereditary component, and late onset Alzheimer's disease (load) (Muhs et al., 2006, Zhang et al., 2021). The disease's genetic and etiological aspects revolve around distinct genes, such as presenilin-1 (PSEN1), amyloid precursor protein (APP) and presenilin-2 (PSEN2). Long non-coding RNAs (lncRNAs) are a distinct category of non-coding RNAs, characterized by their size ranging from 200 nucleotides to several kilobases. These lncRNAs exhibit selectivity in their expression patterns across different tissues and play a significant role in gene expression regulation.

lncRNAs exert significant influence at the molecular level by participating in biological processes such as transcription, translation, gene expression control, chromatin remodeling, and genomic imprinting. Around 40% of these lncRNAs exhibit distinct expression patterns in brain tissue. Numerous studies have established a correlation between expression abnormalities and several neurodegenerative illnesses, including Alzheimer's disease (AD) (Muhs et al., 2006).

Research conducted on both animals and humans substantiates the probable contribution of lncRNAs in AD. Numerous investigations have been conducted into Alzheimer's disease and its underlying pathophysiological mechanisms, but there has been a greater emphasis on long non-coding RNAs (lncRNAs) specifically regarding their structural characteristics and their influence on the onset, progression, or treatment of AD. This work aims to conduct a comprehensive summary of these studies and validate the correlation between the Alzheimer's disease (AD) effects of lncRNAs.

lncRNAs are found to be very significant for the regulation of Alzheimer's disease. During progression of Alzheimer's disease some of them upregulated or downregulated in the patient's physiology. Here we tried to make a comprehensive study to find out the important lncRNAs whose dysregulation causes Alzheimer's disease.

Lnc RNAs which are upregulated in AD.

EBF3-AS

The fragment of Aβ peptide (25-35) has neurotoxic capabilities. ebf3as is the two axon RNA transcription of ebf3 gene. EBF3 is important in the nervous system and has been linked with age at the onset of LOAD. Aβ 25–35 and Okadaic Acid trigger the synthesis of EBF3 in SH-SY5Y cells (Gu et al., 2018). EBF3-AS knockdown reversed the upregulation of EBF3. EBF3-AS synthesis increases in response to Aβ 25–35. EBF3-AS blocking causes reversal of the apoptosis resulted by Aβ 25–35 and OA. EBF3-AS plays a key role in neuron apoptosis and is involved in AD.

Nat Rad 18

NAT-Rad18 is a 509 nucleotide-long natural antisense. NATs are a type of long natural antisense that make up 15-20% of the mouse and human genome. They regulate gene expression by silencing sense RNAs at different levels, like transport, translation, maturation, stability, and transcription. Rad18 is involved in repairing various DNA lesions (Brooks, 2002). When it is downregulated, cells become vulnerable to DNA-damaging agents and patients with hereditary diseases linked to DNA repair defects may experience neurological abnormalities. Silencing Rad18 through its NAT may be part of a complex genomic program that contributes to Aβ -neurotoxicity. A NAT correspond to Rad18 has been found in cerebral cortex of human brain. In summary, NAT-Rad18 is important for the repair of DNA and is expressed in different brain regions, including the hippocampus, striatum, brainstem, cortex, olfactory bulb, spinal cord, and cerebellum (Parenti et al., 2007).

lncRNA n336694

The study on bioinformatics predictions, carried out by Target Scan, has identified miR-106b as a potential target of lncRNA n336694. This conclusion was drawn based on the putative target sequences that were discovered in the miR-106b 3'UTR. Moreover, a quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed to assess the messenger RNA (mRNA) levels of miR-106b in SH-SY5Y cells that

underwent transfection with the lncRNA n336694 mimic and the lncRNA n336694 inhibitor (Parenti et al., 2007). It was discovered that the over expression of long non-coding RNA (lncRNA) n336694 can significantly elevate the messenger RNA (mRNA) levels of miR-106b. When comparing the two, it shows that the suppression of long non-coding RNA n336694 resulted in a reduction in the synthesis of miR-106b (Huang et al., 2017; Canseco-Rodriguez et al., 2022). They indicate that miR-106b is a specific target of the long non-coding RNA n336694.

lncRNA17a

About 50 million of the world's population are suffering from AD (Lee et al., 2023). lncRNAs are regulatory molecules involved in neurodegenerative diseases and are a potential therapeutic target. It is found that specific epigenetic modifications are reversed or promoted by lncRNAs c. lncRNA17A up-regulates in response to the Aβ1-42 peptide and its overexpression-induced apoptosis, migration, and invasion in cells (Wang et al., 2019). the upregulation of 17A inhibited neurogenesis, while its depletion promoted neurogenesis.

Bace1-as

Aβ is a key player in AD (Muhs et al., 2006). BACE1 is a crucial factor in its pathogenesis, with upregulation and downregulation affecting its expression and stability. In Alzheimer's patients, the cortex exhibits elevated levels of Aβ, HuD, APP, and other biomarkers (Hampel et al., 2012). Upregulation prevents miRNA binding, while downregulation increases miRNA levels (He et al., 2020). Downregulation improves memory and learning behaviors, inhibits tau protein phosphorylation and APP production in human brain hippocampus (Asadi et al., 2021).

Neat1

The long non-coding RNA known as nuclear enriched abundant transcript 1 (NEAT1) has significant evolutionary conservation between humans and rodents. Increased expression levels of NEAT1 have been linked with neurodegenerative and several cognitive illnesses, including AD. The involvement of NEAT1 in neuroplasticity and epigenetic control mechanisms within the context of AD pathology is significant. Previous studies have demonstrated that NEAT1 engages in interactions with the P300/CBP complex. Suppression of NEAT1 expression has been seen to result in the downregulation of H3K27Ac and the overexpression of H3K27Cro levels. The involvement of NEAT1 in the establishment of long-term memory in the hippocampus has been shown, with its suppression resulting in alterations in histone H3 lysine-9 demethylation and gene expression 3. The expression of NEAT1 is raised in transgenic mice carrying the APP/PS1 mutation, resulting in the modulation of the interaction between NEDD4L and PINK1 (Asadi et al., 2021). This modulation subsequently affects autophagy signaling, leading to elevated amyloid buildup and impaired cognitive function. In SH-SY5Y and SK-N-SH cells exposed to Aβ, the expression of NEAT1 is upregulated (Dong et al., 2021). Conversely, the downregulation of NEAT1 hinders the Aβ-induced decrease in cell viability and p-Tau levels, while concurrently boosting apoptosis. The potential therapeutic applications of NEAT1 regarding AD are promising and warrant further investigation.

Sox21-as1

It has been long observed that lncRNAs confer a significant role in gene expression regulation. Down-regulation of miR-107 in Alzheimer's disease may suppress SYK expression and inactivate NF-KB signaling pathway, leading to a decline in spatial memory. SOX21-AS1 functions as a sponge for mRNAs in SH-SY5Y and SK-N-SH cells, mediating neuronal damage through Aβ-induced neuronal damage caused by Aβ1-42 (Xu et al., 2020). Its inhibition may mitigate neuronal damage and enhance CDK5 activity, providing a potential therapeutic strategy for the treatment of Alzheimer's. Inhibition reverses inhibition of p-Tau levels, viability, and apoptosis, indicating potential therapeutic benefits for the disease.

BC 200

The non-coding RNA BC-200, which is produced from the BCYRN1 gene, functions as a translational regulator by specifically targeting eIF4A (eukaryotic initiation factor 4A) (Muhs et al., 2006). It also maintains long-term synaptic plasticity (Muhs et al., 2006). In the context of AD, findings suggest that there is an elevation in BC-200 levels. However, research conducted in 2007 revealed a decline in the expression of this phenomenon. This decline was attributed to variations in brain areas and the severity of the condition. The control group's post-mortem exams revealed a decrease in BC-200 levels, while an AD cell model induced by Aβ1-42 exhibited an increase in BC-200 and BACE1 expression (Khodayi et al., 2022). The

downregulation of BCAE1 expression by targeted inhibition of BC-200 resulted in a reduction in apoptosis and an enhancement of cell viability in cells affected by AD. The use of BC-200 has promised to generate innovative insights into the field of gene therapy for AD.

LRP1-AS

In Alzheimer's disease the pathogeny is the accumulation of the Aβ protein. The lncRNA LRP1-as transcribed from antisense of LRP gene. The lrp1 plays a significant role of systematic elimination Aβ in AD. The expression of lrp1 is negatively regulated by lrp1-as.as a result influences the progression of ad pathology (Li et al., 2021).

lncRNA 51A

SORL1 is important in preventing Alzheimer's disease. A reduction in its expression leads to increased amyloid-beta production and aggregation. lncRNA 51A, an antisense configuration, inhibits its expression and promotes Aβ generation. It is frequently upregulated in AD patients and alters splicing, leading to impaired APP processing and increased Aβ formation. 51A may contribute to the progression of AD by reducing SORLA levels. Further investigations are needed to validate this hypothesis (Lan et al., 2022).

lncRNA which are downregulated in AD

MEG3

Necroptosis is an outcome caused by the accumulation of pathogenic tau protein, which is believed to be initiated by the upregulation of the lncRNA MEG3 (Canseco-Rodriguez et al., 2022). This upregulation is hypothesized to occur via the signaling pathway associated with TNF-induced inflammation. Long non-coding RNAs (lncRNAs) are known to exert a pivotal influence on gene expression regulation, hence exerting a substantial influence on several biological phenomena, including brain aging and neurodegenerative disorders. Additional investigation is necessary considering the considerable quantity of non-coding RNAs that demonstrate variable expression in the distinctive forms of Alzheimer's disease.

Other lncRNA

lncRNA, including SNHG1, XIST, RPPH1, LoNA, lnc-ANRIL, and ATB, play crucial roles in various diseases, including Alzheimer's disease. SNHG1 is involved in cell injury and can induce ZFN217 expression (Gao et al., 2020), while XIST is involved in malignant tumor development and AD (Yue et al., 2020). RPPH1 enhances cdc45 expression, causing neuronal apoptosis and targeting miR-326 (Gu et al., 2021). LoNA decreases rRNA production and 2′-O-methylation, enhancing rRNA and ribosome levels, translation, long-term memory, synapse flexibility, and AMPA/NMDA receptors (Bhattacharyya et al., 2021). lncRNA ATB regulates inflammation as well as neuronal functions, potentially acting as a therapeutic target for Alzheimer's disease (Wang et al., 2018). MALAT1 plays a crucial role in synaptic density, Schwann cell proliferation, and regenerative responses (Li et al., 2020). WT1-AS, a lncRNA linked to Alzheimer's disease causes the downregulation of miR-375 and the upregulation of SIX4 expression have been shown to effectively inhibit neuronal apoptosis and mitigate oxidative stress-induced damage (Wang et al., 2020).

CONCLUSION

Long non-coding RNAs (lncRNAs) exert a significant influence in the regulation of gene expression. Moreover, it also contributes by interacting with miRNAs within the competing endogenous RNA (ceRNA) network. Their specificity of expression in various tissues renders them more susceptible to disorders, particularly neurodegenerative ailments such as Alzheimer's disease (AD).AD is considered the most critical member of this group, with 40% of its tissue expression specificity related to the brain. The expression of lncRNAs in AD has been done extensively, but this review aims to provide a comprehensive summary of validated molecular methods and the contribution of lncRNAs in AD pathogenesis. Further research on existing pathways for each lncRNA has potential. However, limitations to the study include the searching process, which focused on selecting keywords, and the lack of full text for some studies. Further research on these pathways could provide valuable insights into the role of lncRNAs in neurodegenerative diseases.

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CONFLICT OF INTEREST

None

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