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Progress on the Long Non-coding RNAs Involved in Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is terminal and is considered the most common neurodegenerative disease characterized by progressive memory loss and cognitive impairment, accounting for 60% of all dementia cases. AD has been widely studied, but its pathological mechanism is still unclear. Noncoding RNAs (ncRNAs) are a class of RNAs that do not encode proteins. Increasing evidence has indicated that long noncoding RNAs (lncRNAs) play essential roles in protein coding processes, biological activities and various diseases, including AD. This study aims to highlight the emerging roles of lncRNAs in AD by summarizing current studies about lncRNAs as potential biomarkers, the roles of lncRNAs involved in Aβ plaque formation, tau hyperphosphorylation, microglia and astrocyte activation, NLRP3 inflammation and oxidative stress. Finally, we tried to elucidate the possible mechanisms by which lncRNAs function and provide new ideas for the diagnosis and treatment of AD.

Keywords: Long noncoding RNA; Alzheimer's disease; Biomarker; Biological roles

Introduction

The Telomere-to-telomere (T2T) Consortium contains a complete 3.055 billion base pair (bp) sequence of a human genome called T2T-CHM13, which includes gapless assemblies for all chromosomes except Y. To date, T2T-CHM13 is the newest and most complete sequence and was published in "Science" in 2022. However, T2T-ChM13 still does not represent the entire human genome. It was reported that 63,494 of the presently annotated human genes and 233,615 transcripts. Among them, 19,969 genes (86,245 transcripts) were predicted to be protein-coding genes, while the rest consisted of introns, regulatory sequences, noncoding RNAs, and unknown and uncertain protein-coding genes [1]. There are many noncoding sequences, including various ncRNAs, introns and other sequences. In recent decades, protein-coding mRNAs and microRNAs have been widely studied, while reports about lncRNAs are still relatively rare.

In recent years, increasing evidence has proven the significant roles of *lncRNAs* in cellular processes and various diseases, such as cancer, the cardiovascular system rheumatoid arthritis ischemia and Alzheimer's Disease (AD) [2-10]. For instance, the *lncRNA* XIST is upregulated in colon cancer tissues and cell lines, and its knockdown can inhibit tumor growth. Further study investigated whether the *lncRNA* X-inactive Specific Transcript (XIST) promotes colon cancer tumor growth by targeting *miR-34a* and the Wnt/β-catenin pathway [11]. Exosomal *lncRNA* Psoriasis Susceptibility-related RNA Gene Induced by Stress (PRINS) in peripheral blood serum in Monoclonal Gammopathy of Undetermined Significance (MGUS) patients has potential as a biomarker with a sensitivity and specificity of 84.9% and 83.3%, respectively, when compared to that in healthy donors [12]. *Lnc-SOX6-1* expression was elevated in pediatric Acute Myeloid Leukemia (AML) patients and in various AML cells. This finding correlates with the outcomes of treatments and a worse risk of stratification [13]. The *lncRNA SNHG20* has also been shown to play a vital role in Epithelial Ovarian Cancer (EOC) since it is highly expressed in EOC tissues of patients, and its knockdown can inhibit EOC cell proliferation, migration and invasion. Therefore, the *lncRNA* Small Nucleolar RNA Host Gene 20 (*SNHG20)* has potential as a diagnostic marker and treatment target [14].

LncRNA-HOTAIR affects ovarian cancer susceptibility in an Iranian population [15]. *LncRNA H19* in the Iranian population was reported to be an important factor that increases the risk of breast cancer [16]. *LncRNA MEG3* is a tumor suppressor. It was reported to be a predictive and prognostic marker for patients with breast cancer, while *lncRNA-NEF* has been found to be involved in intrahepatic cholangiocarcinoma (IHCC), a liver cancer, as a tumor suppressor [17]. Intrahepatic Cholangiocarcinoma (IHCC) patients with high plasma levels of *lncRNA*-Neighboring Enhancer of FoxA2 *(NEF)* had significantly better survival conditions than IHCC patients with low plasma levels [18]. The *lncRNAs TINCR* and *CARLo-7* participate in bladder cancer and play a critical role in mediating bladder cancer through the Wnt/β-catenin and *JAK2/STAT3* signaling pathways [19,20].

Noncoding RNAs (*ncRNAs*) are a class of genes that do not encode proteins. *NcRNAs* longer than 200 nucleotides (nt) are called long noncoding RNAs (*lncRNAs*), while *ncRNAs* shorter than 200 nt are known as small or short *ncRNA*s. Noncoding RNAs reported in the literature are classified as *lncRNAs*, microRNAs (*miRNAs*), transfer RNAs (*tRNAs*), ribosomal RNAs (*rRNAs*), small nuclear RNAs (*snRNAs*), piwi-associated RNAs (*piRNAs*), endogenous short-interfering RNAs (*siRNAs*) and circular RNAs (*circRNAs*) [10]. However, the type and number of human *ncRNAs* currently annotated by the HUGO Gene Nomenclature Committee (HGNC, www.genenames.org) are long noncoding RNAs (4514), microRNAs (1914), transfer RNAs (587), small nuclear RNAs (568), ribosomal RNAs (60), small nuclear RNAs (50), small *NF90* (*IRF3*) (50)-associated RNAs, Y RNAs (4) and vault RNAs (4). The HUGO is the only group with the authority to approve symbols for human genes. Long noncoding RNAs consist of most noncoding RNAs [21]. MiRNAs have been widely studied as a group of small *ncRNAs*. In contrast, scientific research on *lncRNAs* is emerging. Here, we focused mainly on the recent emerging roles of *lncRNAs* in Alzheimer's disease.

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Long noncoding RNAs (*lncRNAs*)

LncRNAs are a group of highly heterogeneous regulatory *ncRNAs* lacking a significant open reading frame. More than 50,000 *lncRNAs* are estimated to exist in the human genome. The majority of *lncRNAs* have a similar but different structure than *mRNAs*. In terms of similarity, they have a similar biological origin and are also transcribed by RNA polymerase II, 5-capped, spliced and polyadenylated. The difference is that *lncRNAs* are shorter and have fewer weakly encoded but longer exons, typically lower expression and poor conservation of primary sequences [22]. Another distinguishing characteristic of *lncRNAs* is strong tissue-specific expression patterns. Brain tissues are more conservative in the expression of *lncRNAs* than other tissues, and it is estimated that approximately 40% of *lncRNAs* are expressed specifically in brain tissues. Hence, *lncRNAs* are potentially involved in many important physiological processes in the nervous system, such as neuronal differentiation, neurite outgrowth, synaptogenesis and synaptic plasticity [23,24]. *LncRNAs* include linear *lncRNAs* and circular RNAs (*circRNAs*). Some studies have investigated circular long noncoding RNAs that also play vital roles in AD, such as *ciRS-7*, *ciRS-7*, *circNF1-419*, *circHDAC9*, *circ_0000950* and *circA*β [25].

LncRNAs have been implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis and Huntington's diseases [26-31]. For example, the *lncRNA NONMMUG014387* promotes Schwann Cells (SCs) after peripheral nerve injury [32]. The *lncRNA GAS5* affects neuron death and neuronal function in ischemic stroke. The apoptosis of neurons can be inhibited, and neuronal injury can be improved by inhibiting *DNMT3B*-dependent *MAP4K4* methylation when *lncRNA GAS5* is silenced [33]. Additionally, *lncRNA SPRY4* was found to be dysregulated in Non-small Cell Lung Cancer (NSCLC) cells. NSCLC patients with low levels of *lncRNA SPRY4 Intronic Transcript 1* (*SPRY4-IT1*) might have relatively shorter survival times. Hence, *lncRNA SPRY4* also has biomarker potential [34]. In addition, *lncRNA MEG3* was also found to be involved in nerve injury and injured nerve regeneration in rats with sciatic nerve defects through regulating the proliferation and migration of SCs [35]. A comprehensive profile of *lncRNAs* in a transgenic mouse model of Alzheimer's disease was generated, and a total of 4622 *lncRNAs* were analyzed. Among them, 205 *lncRNAs* were significantly different. *MAPT-AS1*, a *lncRNA*, may play an important role in breast cancer [36].

The *lncRNA linc00657* was found to induce neuropathic pain by mediating the *miR-136/ZEB1* axis in a rat model. The reduction in *linc00657* can inhibit neuroinflammation in CCI rats by targeting the expression of cyclooxygenase-2, tumor necrosis factor-α and interleukin-1β, and these outcomes were reversed by miR-136 inhibitors [37]. *LncRNA* embryonic stem cells expressed 1 (*Lncenc1*) is also a *lncRNA* involved in neuropathic pain. *Lncenc1* interacts with *EZH2* and downregulates *BAI1* gene expression to affect neuropathic pain in mouse microglia [38]. Recently, downregulation of *lncRNA ZEB1-AS1* was found in peripheral blood mononuclear cells of Sporadic amyotrophic lateral sclerosis (SALS) patients. *ZEB1-AS1* was implicated in the pathology of neuronal differentiation [39]. Here, we emphasize linear long noncoding RNAs involved in AD.

Alzheimer's disease

Alzheimer's Disease (AD) is the most common neurodegenerative disease characterized by progressive memory loss and cognitive impairment. It is a disease that threatens human health worldwide. However, research into the mechanisms of AD is lagging far behind expectations [40]. Although the exact causes of the disease are not understood, it is believed that the main pathological features of AD are the dysregulation of two proteins in brain tissue, extracellular protein amyloid β (Aβ) deposition and intracellular type 2 microtubule-associated protein (tau) aggregation or insoluble Neurofibrillary Tangle (NFT) formation [41]. The plaques caused by Aβ aggregation play a major role in cognitive decline and cell death by disrupting cellular communication and causing microglial activation and inflammation [42]. In addition to Aβ deposition, dysregulation of the protein tau also leads to AD. Hyperphosphorylated tau protein aggregates to form NFTs, which block synaptic transmission and are thought to be closely linked to cognitive decline in AD [43].

While Aβ plaques and NFTs in neurons are key features of AD, neuroinflammation has emerged as another major cause. In the pathogenesis of AD, aggregates of Aβ and NFTs trigger an inflammatory response in the nervous system, termed neuroinflammation, mediated by central Nervous System (CNS) resident glial cells such as microglia and astrocytes, inflammasomes, and inflammatory mediators including cytokines, chemokines and reactive oxygen species. Conversely, neuroinflammation leads to the deterioration of Aβ plaques and tau hyperphosphorylation, which further potentiate AD progression and contribute to AD pathology [44-46].

Many studies have shown that neuroinflammation and oxidative stress are inextricably linked and lead to most neurodegenerative pathologies, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease. Inflammatory cells secrete excess oxygen free radicals, leading to oxidative stress, and some Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) can further promote intracellular signaling cascades to increase the secretion of proinflammatory factors, ultimately leading to neuroinflammation. Thus, neuroinflammation and oxidative stress can be mutually stimulating, especially in the disease state [47].

Dementia is diagnosed by core clinical criteria, including the appearance of interference with the ability to work or function; decline from previous levels of functioning and performing; not explained by delirium or major psychiatric disorder; and cognitive impairment is detected and diagnosed, which is related to impaired abilities in daily activities. The possible AD dementia diagnosis meets the cognitive deficits for AD, and etiologically mixed presentation meets all AD dementia clinical criteria. Currently, well-known biomarkers for judging the pathological process of AD are Aβ Positron Emission Tomography (PET) of the brain, the Aβ42/Aβ40 ratio in Cerebrospinal Fluid (CSF), low Cerebrospinal Fluid (CSF) Aβ42, increased CFS tau, including total and phosphorylated tau, and decreased Fluorodeoxy Glucose (FDG) uptake on PET in the brain [48].

For the diagnosis of AD, cognitive testing is the most common way to check for AD symptoms. If the cognitive test has difficulty determining the disease, Magnetic Resonance Imaging (MRI) and other tests mentioned above will be performed. However, there are some disadvantages. For instance, PET and MRI are not easy to widely use due to their high cost. Additionally, CSF collection requires an invasive lumbar puncture procedure with general anesthetics. It causes side effects of headache [49]. Therefore, investigating other biomarkers in blood, such as the plasma Aβ42/Aβ40 ratio, tau and Neurofilament Light (NFL), has become a topic of interest in recent years. The aims for biomarkers such as other proteins, *miRNAs*, metabolites and exosomes have been reported [50]. In this mini-review, we mainly summarize the comprehensive role of various *lncRNAs* involved in AD, including Aβ deposition, tau protein hyperphosphorylation and neuroinflammation-related pathological processes, such as microglia and astrocyte

activation, the *NLRP3* inflammasome and oxidative stress.

LncRNAs as potential biomarkers or therapeutic targets in Alzheimer's Disease (AD)

LncRNAs have been investigated to have great potential as diagnostic biomarkers and therapeutic targets in AD. *LncRNAs* might be a new focus for AD biomarker studies, which are critical for early-stage screening and timely prevention of AD. One of the most studied *lncRNAs* is *BACE1-AS*. The expression level of *lncRNA BACE1-AS* in whole plasma samples was lower in pre-AD subgroup patients and higher in full-AD patients than in healthy people. Additionally, the level of *lncRNA BACE1-AS* in plasma can accurately reflect pre-AD, full-AD and healthy people with good sensitivity and specificity [30,51].

LncRNA 51A in plasma, an antisense transcript of the *SORL1* gene *SORL1-AS* (*51A*), has been implicated as a potential biomarker. The expression of *lncRNA 51A* can cause aggregation in AD patients in both the brain and plasma. The plasma 51A level has a negative correlation with Mini-Mental State Examination (MMSE) scores in AD patients [52,53]. The results from a study enrolled 120 AD patients, 120 Parkinson's Disease (PD) patients and 120 controls and showed that *lncRNA MALAT1* and its target are potential biomarkers for AD management involving *FOXQ1, PTGS2* and *CDK5* [54]. The *lncRNA EBF3-AS* promotes neuronal apoptosis in AD model mice and affects *EBF3* expression, indicating that *EBF3-AS* has the potential as a new therapeutic target for the treatment of AD [55].

LncRNA NEAT1, reported to be a novel target for Alzheimer's disease progression *via* the *miR-124/BACE1* axis as mentioned above, can Mediate Microtubule (MT) stabilization by the FZD3/GSK3β/p-tau pathway in *SH-SY5Y* cells and APP/PS1 mice. Specifically, *lncRNA NEAT1* mediates the phosphorylation of tau protein through *FZD3* [54, 56].

LncRNAs involved in Aβ plaque formation

Aβ plays a critical role in the pathophysiology of AD by causing the death of neurons due to its insoluble and neurotoxic characteristics. Aβ usually has two isoforms, Aβ40 and Aβ42, which are generally released from amyloid precursor protein (APP) by β-secretase 1 (*BACE1*) and γ-secretase. The Aβ42 peptide is more toxic and has faster growth of Aβ42 aggregates. The expression of *BACE1* was upregulated in the brain enzymes of patients with AD [57]. It should be noted that BACE1 transcripts are upregulated by the *lncRNA BACE1-AS*, which is transcribed from the opposite strand of the *BACE1* gene and shares complementary sequences, and its expression is mediated in brain and vascular homeostasis [30]. In other words, *lncRNA BACE1-AS* expression could increase *BACE1 mRNA*, which in turn increases the production of Aβ [58]. Therefore, *lncRNABACE1-AS* plays an important role in Aplaque formation.

In addition, *LncRNA* X-inactive Specific Transcript (XIST) is a functional *lncRNA*. Yue et al., found that *lncRNA* XIST expression was upregulated *in vivo* and *in vitro* in AD models. The molecular mechanism of *lncRNA* XIST in AD models showed that silencing of *lncRNA* XIST downregulated Aβ protein-related *BACE1* through *miR-124/BACE1* signaling pathways [59]. Similarly, *lncRNA MAGI2-AS3* has been acknowledged as an important factor for Aβ deposition. Studies have shown direct interactions between *MAGI2-AS3* and *miR-374b-5p* and between *BACE1* and *miR-374b-5p*. Specifically, when *SH-SY5Y* and *BV2* cells were stimulated with Aβ25-35, *MAGI2-AS3* expression increased, while *miR-374b-5p* expression decreased. Reduction of *MAGI2-AS3* and overexpression of *miR-374b-5p* can cause the same effect: enhancement of neuronal survival and impairment of neuroinflammation in AD cell models. These effects can be reversed by inhibiting *miR-374b-5p*. Furthermore, in AD patients, *MAGI2-AS3* and *miR-374b-5p* blood levels were also negatively correlated. *LncRNA MAGI2-AS3* can interact with *miR-374b-5p*, indicating its critical role in attenuating neurotoxicity and neuroinflammation [60]. On the other hand, *lncRNAs 17A, 51A*, and *NDM29* were reported to increase Aβ formation and/or the Aβx-42/Aβx-40 ratio directly or indirectly, although they may play other roles [61].

LncRNAs involved in tau hyperphosphorylation

AD is also characterized by the hyperphosphorylation of tau protein or Neurofibrillary Tangles (NFTs) in cells. Activated kinases add phosphate groups to tau proteins, which leads to their hyperphosphorylation and NFT formation [62]. These steps are regulated by multiple kinases, primarily Glycogen Synthase Kinase 3 (*GSK3β*) and Cyclin-Dependent Kinase 5 (*CDK5*) [63]. *LncRNAs*, such as the *lncRNAs linc-00507*, *RP11-543N12.1* and *SOX21-AS1*, participate in tau hyperphosphorylation. The level of *linc00507* was significantly increased in both animal and cell models of AD. *Linc00507* sponges *miR-181c-5p* to regulate the Microtubule-associated Protein Tau (*MAPT*) or Tau-Tubulin Kinase-1 (*TTBK1*) pathway, which activates the *P25/P35/GSK3β* signaling pathway. Consequently, *linc-00507* mediates tau protein hyperphosphorylation [64].

LncRNAs RP11-543N12.1 and *SOX21-AS1* are highly expressed in *SH-SY5Y* cells following Aβ25-35 treatment and act as a *lncRNA/miRNA* axis to promote phosphorylation of tau protein and cell apoptosis during AD progression. *LncRNA RP11543N12.1* inhibits proliferation and enhances apoptosis by targeting *miR3243p*, indicating that *RP11543N12.1* and *miR3243p* may be potential biomarkers and therapeutic targets in AD. *LncRNA SOX21-AS1* has been found to sponge *miR-107* in *SH-SY5Y* and *SK-N-SH* cells. The upregulation of tau protein phosphorylation and apoptosis and the viability decrease can be inhibited by *miR-107* in Aβ1-42-treated *SH-SY5Y* cells. However, *lncRNA SOX21-AS1* can reverse this effect of *miR-107* [65,66]. The *lncRNA NEAT1*, reported to be a novel target for Alzheimer's disease progression *via* the *miR-124/BACE1* axis above, can mediate Microtubule (MT) stabilization by the FZD3/GSK3β/p-tau pathway in *SH-SY5Y* cells and APP/PS1 mice [54, 56].

LncRNAs involved in Microglia (MG) and astrocyte activation

Neuroinflammation is largely mediated by glial cells, including microglia and astrocytes. Activated microglia and astrocytes have been implicated as key players in the progression of AD [67]. Microglia are the major immune cells of the CNS. In response to stimuli, microglia are activated into two phenotypes, M1 and M2. The M1 type is a neurotoxic phenotype, secreting pro-inflammatory cytokines (TNF-α, IL-16, etc.) and chemokines (CCL2, IL-18, etc.) that promote neuroinflammation and induce neuronal damage and oxidative stress, thereby triggering synaptic loss and accelerating the disease process, the M2 type is a neuroprotective phenotype, releasing arginase 1, *IGF-1* and *Fzd1*, which are involved in neuroprotection and tissue repair. Astrocytes are the most abundant glial cells in the brain, and similar to microglia, which have two phenotypes, neurotoxic and neuroprotective activation states (A1/A2), astrocytes in Alzheimer's disease have both protective and inflammatory effects on neurons [68].

Some *lncRNAs* have been found to regulate AD progression by modulating the ratio of neurotoxic and neuroprotective activation states of microglia and astrocytes. The expression of *lncRNA MALAT1* was significantly reduced in AD cells, animal models and human AD

brain tissues. This occurred possibly through interacting with *miRNAs miRs*-200a, -26a and -26b, which are generally increased in AD [69]. In addition, *lncRNA MALAT1* was dysregulated in Acute Spinal Cord Injury (ASCI) rat models, and its knockdown reduced ASCI possibly through inhibiting the inflammatory response of microglia [70].

Likewise, in AD rats, the expression of *lncRNA MEG3* was downregulated. Conversely, upregulation of the *lncRNA MEG3* improved cognitive impairment and neuronal damage and prevented astrocyte activation in hippocampal tissues in AD rats by impeding the *PI3K/Akt* signaling pathway [71]. In addition, several *lncRNAs* XIST and *NEAT1* act as sponges of *miR-124*, which is specifically expressed in microglia, and switch microglia to an anti-inflammatory state by imbalancing the M1/M2 ratio in CNS macrophages, so these *lncRNAs* may also be involved in the activation states of microglia [10]. The *lncRNA LEF1-AS1* can attenuate apoptosis and improve the viability of LPS-treated Spinal Cord Injury (SCI) microglia, while the *lncRNA SNHG14* promotes microglial activation by regulating *miR-145-5p/PLA2G4A* in cerebral infarction in a Middle Cerebral Artery Occlusion (MCAO) mouse model and microglia [72,73]. Similarly, *lncRNA SNHG5* can promote astrocyte and microglial viability [74]. In addition, LPS-induced microglial neurotoxicity can be decreased by silencing *lncRNA* nostrill [75]. *LncRNA-Cox2* induced from astrocyte-derived Extracellular Vesicles (EVs) involves the impairment of microglial phagocytic activity in mice.

Importantly, *lncRNA-11496* was found to contribute to microglial apoptosis in chronic T. gondii-infected mice by targeting *Mef2c*, which is related to neuronal differentiation, survival, and synapse formation, by binding to *Histone Deacetylase 2* (*HDAC2*) [76]. On the other hand, *lncRNA-11496* positively regulated the expression of its target. The overexpression of *lncRNA* uc.80 improves depression in rats by promoting M2 polarization of microglia [77]. These findings indicate that *lncRNA-11496* might be used as a therapeutic target for treating T. gondii-induced mental and behavioral disorders in the brain. Further study on the mechanism is needed. The increase in *lincRNA-Cox2* expression led to a reduction in microglial phagocytic activity, which was restored by inhibiting the expression of *lincRNA-Cox2 via siRNA* interference [78]. *LincRNA-EPS* can reduce Cerebral Ischemia Reperfusion (CIR) injury, inflammation and oxidative stress by maintaining High Temperature Requirement Factor A1 *Htra1* stability through recruiting *HNRNPL* [79]. *LncRNA AK148321* also reduces neuroinflammation in LPS-stimulated BV2 microglia *via* the *miR-1199-5p/HSA5* axis [80].

LncRNAs involved in the *NLRP3* inflammasome

The formation of inflammation is a key aspect of inflammatory responses. Nucleotide-binding Oligomerization domain-like Receptor containing Pyrin Domain 3 (*NLRP3*) is one of the most studied inflammasomes and is present in microglia and astrocytes in the CNS. Studies have shown that the *NLRP3* inflammasome plays an important role in neurodegenerative diseases, particularly Alzheimer's disease. The *NLRP3* inflammasome is a multiprotein complex containing *NLRP3*, *ASC* and *procaspase-1*. Activation of the *NLRP3* inflammasome leads to the release of caspase-1, which mediates the production of the proinflammatory cytokines IL-1β and IL-18 and induces several downstream inflammatory factors, thereby initiating inflammatory responses. These inflammatory mediators are closely linked to Aβ deposition and tau aggregation, contributing to the pathogenesis of AD [81].

The *lncRNA SNHG14* expression is higher in the cytoplasm than in the nucleus of astrocytes, suggesting that the *lncRNA SNHG14* may downregulate gene expression by sponging specific *miRNAs*. Bioinformatics analysis predicted a binding site between *miR-223-3p* and *SNHG14* as well as between *miR-223-3p* and *NLRP3*. The direct interactions between *miR-223-3p* and *SNHG14*, as well as *miR-223-3p* and *NLRP34*, were further confirmed by using a luciferase reporter assay. Altogether, it could be concluded that *SNHG14* might sponge *miR-223-3p* and thus regulate *NLRP3* expression at the posttranscriptional level in the AD study [82].

The *lncRNA NONRATT004344.2* is a *lncRNA* that is highly expressed in the brain and is also known as *lncRNA 4344*. Researchers found that *lncRNA 4344* regulates the activated *NLRP3* inflammasome in microglia, which contributes to brain function decline and neurodegenerative diseases. The results of the animal experiments showed that *lncRNA 4344* sponges *miR-138-5p* to upregulate the expression of the inflammasome *NLRP3*. Conclusively, the *lncRNA-4344/miR-138-5p/NLRP3* axis plays an essential role in regulating neuroinflammation and cognitive decline by acting as a sponge of *miR-138-5p* to downregulate *NLRP3* expression [83].

LncRNAs involved in oxidative stress

Oxidative stress plays an important role in the pathogenesis of AD. Oxidants and oxidative products can regulate APP and the associated secretase. This increases the expression of APP, leading to the aggregation of Aβ. In turn, irreversibly deposited Aβ disrupts the activity of N-Methyl-D-Aspartate NMDA receptors to promote the production of oxygen free radicals and excessive calcium influx into neurons, thereby inducing neuronal damage. Oxidative stress also directly interacts with the tau protein kinases *GSK-3* and *CDK5* to promote their hyperphosphorylation. Similar to Aβ protein, free p-tau protein aggregates to form *NTFs,* leading to significant oxidative stress and neurological impairment [84].

In Aβ25-35-stimulated PC12 cells, silencing of *lncRNA H19* and *BDNF-AS* resulted in significantly increased Superoxide Dismutase (SOD) and Catalase (CAT) expression and decreased Malondialdehyde (MDA) expression, leading to a reversal of the Aβ25-35-induced oxidative stress response, suggesting that *lncRNA H19* and *BDNF-AS* may be involved in AD development and progression *via* oxidative stress [85]. *LncRNA SOX21-AS1* plays an important role in tau hyperphosphorylation and cell apoptosis during AD progression. In another study, scientists also found that silencing the *lncRNA SOX21-AS1* alleviated oxidative stress and inhibited apoptosis in hippocampal neurons of AD mice by upregulating *FZD3/5 via* the Wnt signaling pathway. In other words, the *lncRNA SOX21-AS1* can also regulate oxidative stress to participate in cell cycle distribution and apoptosis during AD pathology [86].

Other long noncoding RNAs involved in AD

There are many other very important *lncRNAs* involved in AD, but their specific biological roles and mechanisms still need to be further investigated. The expression of the long noncoding RNA *MALAT1* was previously found to inhibit Cyclic AMP Response Element-binding Protein (CREB) dephosphorylation, a transcription factor that regulates cell proliferation, by PP2A. Furthermore, lower levels of *MALAT1* were measured in the CSF of AD patients than in the CSF of control patients. In addition, dysregulated *MALAT1* was also found in neurodegenerative and neuro-oncological disorders, indicating an important role of *lncRNA MALAT1* in neurodegenerative diseases, including AD [87]. A *lncRNA* activated by TGF-beta, called *lncRNA*-ATB, was elevated in the CSF and serum of patients with AD. Prohibiting *lncRNA-ATB* can protect *PC12* cells from neurotoxicity induced by Aβ25-35 through regulating the *miR-200/ZNF217* axis [88]. In addition, *lncRNAs RP11-*

462G22.1 and *PCA3* were also upregulated in the CSF exosomes of both PD and AD patients. Some *lncRNAs*, such as *lncRNA BC200* and *NAT-Rad18*, were discovered as early as 2007. The *lncRNA BC200* found in the AD patient brain may play a critical role in maintaining long-term synaptic plasticity during AD progression by regulating local protein synthesis [89]. NAT-Rad18 expressed in rat cortical neurons was previously shown to be involved in apoptosis [90] (Figure 1).

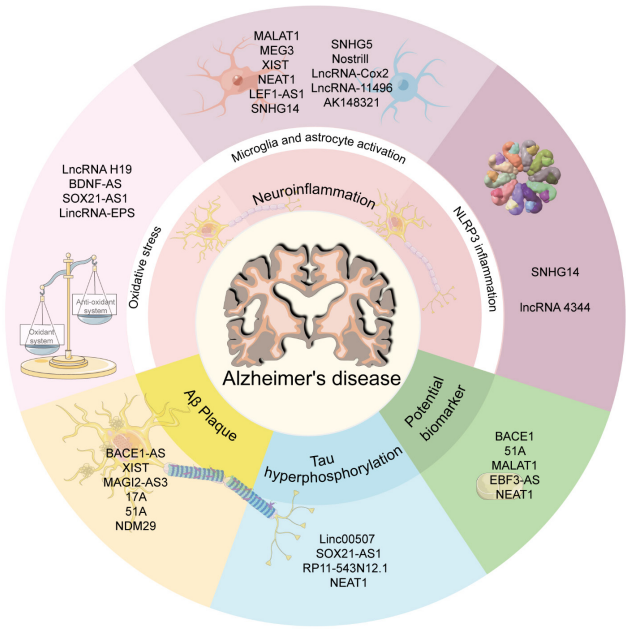

Figure 1: *LncRNAs* as potential biomarkers or therapeutic targets in Alzheimer's Disease (AD).

A systematic study on the *lncRNA* profile investigated a total of 14 upregulated *lncRNAs* and 20 downregulated *lncRNAs* in Peripheral Blood Mononuclear Cells (PBMCs) of AD patients compared with those in the control groups (fold change ≥ 2.0, $p<0.05$). Among them, *lncRNAs TTC39C-AS1*, *lnc-AL445989.1-2*, *LINC01420*, *lnc-CSTB-1* and *LOC401557* may play critical roles in AD pathogenesis. Notably, the most significant one is the antisense transcript of the *TTC39C-AS1* gene, which is closely related to neurogenic atrophy [91,92]. In addition, hippocampal *lncRNA* profiles in AD rats were reported. A total of 315 *lncRNAs* were found to be significantly dysregulated in the AD model rats (≥ 2.0-fold, $p<0.05$). The expression profiles of *lncRNAs* in the hippocampus of intranasal LPS-induced AD model mice were determined by microarray analysis. A total of 395 *lncRNAs* were differentially expressed in AD rat and mouse models compared with controls (>2.0-fold, $p<0.05$) [93, 94].

Other *lncRNAs* reported in AD patients, mice, rat or cells are *BDNF-AS*, upregulated in peripheral blood of AD patients; *ANRIL*, knockdown of it reduces Aβ-induced apoptosis, inflammation and autophagy in *PC12* cells; *HOTAIR*, downregulated in the brain by exercise in rat model; *N336694*, upregulated in the brain of AD model mice; *PART1*, increased by Aβ in endothelial cells; *SNHG1*, increased by *A25-35* in *SH-SY5Y* cells; *SOX2-OT*, *lincRNA-p21*, upregulated in AD model mice; Rpph1, upregulated in the cortex of AD model mice [95-97]. There are still deregulated *lncRNAs*, such as *TTC39C-AS1*, *LOC401557*, *CH507-513H4.4*, *CH507-513H4.6*, *CH507-513H4.3*, *RP11-462G22.1*, and *PCA3*, in AD patients [52].

Conclusion

Over the past two decades, the role of *miRNAs* has been comprehensively studied. *LncRNAs* account for the majority of *ncRNAs* and have been found to be involved in various biological processes and diseases. *lncRNA* XIST is involved in colon cancer, *lncRNA PRINS* in Monoclonal Gammopathies (MGUS), *lnc-SOX6-1* in Acute Myeloid Leukemia (AML), *lncRNA SNHG20* in Epithelial Ovarian Cancer (EOC), *lncRNA-HOTAIR* in ovarian cancer, *lncRNA H19*, *lncRNA MEG3* and *lncRNA MAPT-AS1* in breast cancer, *lncRNA-NEF* in liver cancer, *lncRNAs TINCR* and *lncRNAs CARLo-7* in bladder cancer, and *lncRNA SPRY4* in lung cancer. There are certainly more unknown *lncRNAs* that contribute to cancers.

In this review, we focused on summarizing *lncRNAs* and their critical potential roles in key pathological features of AD, such as Aβ plaques, tau hyperphosphorylation and neuroinflammation, as well as their interactions. As described above, these *lncRNAs* directly or indirectly regulate vital genes or proteins that may play an important role in the development of AD. Therefore, studying these *lncRNAs* and their disease-related regulatory mechanisms may provide new ideas for identifying effective treatments for AD. Seventy-five percent of AD patients worldwide have not been diagnosed, mostly in underdeveloped countries. Further study on *lncRNAs* as biomarkers or intervention targets may provide new insights into diagnosing and treating AD.

Notably, some *lncRNA* studies have only been carried out in the brains of laboratory animals and or cell models, but these models have not been able to accurately recapitulate the various features of AD. Therefore, there may be significant difficulties in translating results from AD models to humans. In-depth studies investigating more *lncRNAs* that have essential biological roles in the development of AD and studying their mechanism are still the major topic in the future. Furthermore, research on *lncRNA* biomarkers and *lncRNA*-targeted drugs is also very important. However, the application of regulatory *lncRNAs* in AD still has many challenges to overcome. For example, due to insufficient research, unexpected risks and inappropriate pathological effects may occur when *lncRNA*-targeted drugs are used clinically. Nevertheless, we believe that with continued innovation in experimental methods and techniques, the application of safe and effective *lncRNA*-associated biomarkers or drugs for the treatment of AD is possible.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Authors' contributions

Aodeng Qimuge contributed in writing-original draft preparation, Su D, Bai Y and Yang X. X. assisted in literatures, Wuhan Qimuge mainly completed designing, reviewing and editing, and supervision.

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References

1. Nurk S, Koren S, Rhie A, Rautiainen M, Bzikadze AV, et al. (2022) The complete sequence of a human genome. Science 376: 44-53.
2. Saw PE, Xu X, Chen J, Song EW (2021) Non-coding *RNAs*: The new central dogma of cancer biology. Sci China Life Sci 64:22-50.
3. Yan H, Bu P (2021) Non-coding *RNA* in cancer. Essays Biochem 65:625-639.
4. Fasolo F, Di Gregoli K, Maegdefessel L, Johnson JL (2019) Non-coding *RNAs* in cardiovascular cell biology and atherosclerosis. Cardiovasc Res 115:1732-1756.
5. Wang J, Yan S, Yang J, Lu H, Xu D, et al. (2020) Non-coding *RNAs* in rheumatoid arthritis: From bench to bedside. Front Immunol 10:3129.
6. Wang Y, Luo Y, Yao Y, Ji Y, Feng L, et al. (2020) Silencing the *lncRNA* Maclpil in pro-inflammatory macrophages attenuates acute experimental ischemic stroke via *LCP1* in mice. J Cereb Blood Flow Metab 40:747-759.
7. Jia H, Ma H, Li Z, Chen F, Fang B, et al. (2019) Downregulation of *LncRNA TUG1* inhibited *TLR4* signaling pathway-mediated inflammatory damage after spinal cord ischemia reperfusion in rats *via* suppressing *TRIL* expression. J Neuropathol Exp Neurol 78:268-282.
8. Wang J, Cao B, Zhao H, Gao Y, Luo Y, et al. (2019) Long noncoding *RNA H19* prevents neurogenesis in ischemic stroke through *p53/Notch1* pathway. Brain Res Bull 150:111-117.
9. Ghafouri-Fard S, Shoorei H, Taheri M (2020) Non-coding *RNAs* participate in the ischemia-reperfusion injury. Biomed Pharmacother 129:110419.
10. Liu Y, Cheng X, Li H, Hui S, Zhang Z, et al. (2022) Non-coding rnas as novel regulators of neuroinflammation in alzheimer's disease. Front Immunol 13:908076.
11. Sun N, Zhang G, Liu Y. (2018) Long non-coding *RNA XIST* sponges *miR-34a* to promotes colon cancer progression *via* Wnt/β-catenin signaling pathway. Gene 665:141-148.
12. Sedlarikova L, Bollova B, Radova L, Brozova L, Jarkovsky J, et al. (2018) Circulating exosomal long noncoding *RNA PRINS*—First findings in monoclonal gammopathies. Hematol Oncol 36:786-791.
13. Guan X, Wen X, Xiao J, An X, Yu J, et al. (2019) *Lnc-SOX6-1* upregulation correlates with poor risk stratification and worse treatment outcomes, and promotes cell proliferation while inhibits apoptosis in pediatric acute myeloid leukemia. Int J Lab Hematol 41:234-241.
14. Wang D, Dai J, Hou S,Qian Y (2019) *LncRNA SNHG20* predicts a poor prognosis and promotes cell progression in epithelial ovarian cancer. Biosci Rep 39:BSR20182186.
15. Saeedi N, Ghorbian S (2020) Analysis of clinical important of *LncRNA-HOTAIR* gene variations and ovarian cancer susceptibility. Mol Biol Rep 47:7421-7427.
16. Safari MR, Rezaei FM, Dehghan A, Noroozi R, Taheri M, et al. (2019) Genomic variants within the long non-coding *RNA H19* confer risk of breast cancer in Iranian population. Gene 701:121-124.
17. Bayarmaa B, Wu Z, Peng J, Wang Y, Xu S, et al. (2019) Association of *LncRNA MEG3* polymorphisms with efficacy of neoadjuvant chemotherapy in breast cancer. BMC cancer 19:1-8.
18. Liang Z, Zhu B, Meng D, Shen X, Li X, et al. (2019) Down-regulation of *lncRNA-NEF* indicates poor prognosis in intrahepatic cholangiocarcinoma. Biosci Rep 39:BSR20181573.
19. Huang H, Fan X, Zhang X, Xie Y, Ji (2020) *LncRNA CARLo-7* facilitates proliferation, migration, invasion, and EMT of bladder cancer cells by regulating Wnt/β-catenin and *JAK2/STAT3* signaling pathways. Transl Androl Urol 9:2251.
20. Xu C, Liu M, Jia D, Tao T, Hao D (2021) *lncRNA TINCR SNPs* and expression levels are associated with bladder cancer susceptibility. Genet Test Mol Biomarkers 25:31-41.
21. Seal RL, Chen LL, Griffiths-Jones S, Lowe TM, Mathews MB, et al. (2020) A guide to naming human non-coding *RNA* genes. EMBOJ39:e103777.
22. Stojic L (2020) Tuning the Expression of Long Noncoding *RNA* Loci with *CRISPR* Interference. RNA-Chromatin Interactions: Methods Mol Biol 1-6.
23. Zhou S, Yu X, Wang M, Meng Y, Song D, et al. (2021) Long non-coding *RNAs* in pathogenesis of neurodegenerative diseases. Front Cell Dev Biol 9:719247.
24. Srinivas T, Mathias C, Oliveira-Mateos C, Guil S (2023) Roles for *lncRNAs* in brain development and pathogenesis: emerging therapeutic opportunities. Mol Ther.
25. Ghafouri-Fard S, Safari M, Taheri M, Samadian M (2022) Expression of linear and circular *lncRNAs* in Alzheimer's disease. J Mol Neurosci 72:187-200.
26. Zhang H, Liu X, Liu Y, Liu J, Gong X, et al. (2022) Crosstalk between regulatory non-coding *RNAs* and oxidative stress in Parkinson's disease. Front Aging Neurosci 14:975248.
27. Ruffo P, De Amicis F, Giardina E, Conforti FL. (2023) Long-noncoding *RNAs* as epigenetic regulators in neurodegenerative diseases. Neural Regen Res 18:1243.
28. Tan X, Liu Y, Liu Y, Zhang T, Cong S (2021) Dysregulation of long non-coding *RNAs* and their mechanisms in Huntington's disease. J Neurosci Res 9:2074-2090.
29. Sivagurunathan N, Ambatt AT, Calivarathan L. (2022) Role of Long Non-coding *RNAs* in the Pathogenesis of Alzheimer's and Parkinson's Diseases. Curr Aging Sci 15:84-96.
30. Fotuhi SN, Khalaj-Kondori M, Hoseinpour Feizi MA, Talebi M (2019) Long non-coding *RNA BACE1-AS* may serve as an Alzheimer's disease blood-based biomarker. J Mol Neurosci 69:351-359.
31. Wang D, Gao H, Li Y, Jiang S, Yong Y, et al. (2020) Genome-scale expression pattern of long non-coding *RNAs* in Chinese Uyghur patients with Parkinson's disease. Med Sci Monit 26:e925888-1.
32. Pan B, Shi ZJ, Yan JY, Li JH, Feng SQ (2017) Long non-coding *RNA NONMMUG014387* promotes Schwann cell proliferation after peripheral nerve injury. Neural Regen Res 12:2084.
33. Deng Y, Chen D, Gao F, Lv H, Zhang G, et al. (2020) Silencing of long non-coding *RNA GAS5* suppresses neuron cell apoptosis and nerve injury in ischemic stroke through inhibiting *DNMT3B*-dependent *MAP4K4* methylation. Transl Stroke Res 950-966.
34. Sun M, Liu XH, Lu KH, Nie FQ, Xia R, et al. (2014) *EZH2*-mediated epigenetic suppression of long noncoding *RNA SPRY4-IT1* promotes *NSCLC* cell proliferation and metastasis by affecting the epithelial–mesenchymal transition. Cell Death Dis 5:e1298.
35. Ma Y, Zhai D, Zhang W, Zhang H, Dong L, et al. (2020) Down-regulation of long non-coding *RNA MEG3* promotes Schwann cell proliferation and migration and repairs sciatic nerve injury in rats. J Cell Mol Med 24:7460-7469.
36. Wang D, Li J, Cai F, Xu Z, Li L, et al. (2019) Overexpression of *MAPT-AS1* is associated with better patient survival in breast cancer. Biochem Cell Biol 97:158-164.
37. Shen F, Zheng H, Zhou L, Li W, Zhang Y et al. (2019) *LINC00657* expedites neuropathic pain development by modulating *miR-136/ZEB1* axis in a rat model. J Cell Biochem 120:1000-1010.
38. Zhang Z, Sun X, Zhao G, Ma Y, Zeng G. (2021) *LncRNA* embryonic stem cells expressed 1 (*Lncenc1*) is identified as a novel regulator in neuropathic pain by interacting with *EZH2* and downregulating the expression of *Bai1* in mouse microglia. Exp Cell Res 399:112435.
39. Rey F, Maghraby E, Messa L, Esposito L, Barzaghini B, et al. (2023) Identification of a novel pathway in sporadic Amyotrophic Lateral Sclerosis mediated by the long non-coding *RNA ZEB1-AS1*. Neurobiol Dis 178:106030.
40. Breijyeh Z, Karaman R (2020) Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules 25:5789.
41. Busche MA, Hyman BT (2020) Synergy between amyloid-β and tau in Alzheimer's disease. Nat Neurosci 23:1183-1193.
42. Moujalled D, Strasser A, Liddell JR (2021) Molecular mechanisms of cell death in neurological diseases. Cell Death Differ 28(7):2029-2044.
43. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M (2019) Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine19:5541-5554.
44. Rajesh Y, Kanneganti TD (2022) Innate immune cell death in neuroinflammation and Alzheimer's disease. Cells 11:1885.
45. Cai Y, Liu J, Wang B, Sun M, Yang H (2022) Microglia in the neuroinflammatory

pathogenesis of Alzheimer's disease and related therapeutic targets. Front Immunol 13:856376.13.

46. Whitson HE, Colton C, El Khoury J, Gate D, Goate A, et al. (2022) Infection and inflammation: New perspectives on Alzheimer's disease. Brain Behav Immun Health 22:100462.

47. Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladâcenco O, et al. (2022) An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. Int J Mol Sci 23(11):5938.

48. Jack Jr CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, et al. (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:257-262.

49. Swarbrick S, Wragg N, Ghosh S, Stolzing A (2019) Systematic review of *miRNA* as biomarkers in Alzheimer's disease. Mol Neurobiol 56:6156-6167.

50. Zetterberg H, Burnham SC (2019) Blood-based molecular biomarkers for Alzheimer's disease. Mol Brain 12:1-7.

51. Feng L, Liao YT, He JC, Xie CL, Chen SY, et al. (2018) Plasma long non-coding *RNA BACE1* as a novel biomarker for diagnosis of Alzheimer disease. BMC Neurol 18:1-8.

52. Garofalo M, Pandini C, Sproviero D, Pansarasa O, Cereda C, et al. (2021) Advances with long non-coding *rnas* in alzheimer's disease as peripheral biomarker Genes 12:1124.

53. Deng Y, Xiao L, Li W, Tian M, Feng X, et al. (2017) Plasma long noncoding *RNA 51A* as a stable biomarker of Alzheimer's disease. Int J Clin Exp Pathol 10(4):4694-4699.

54. Zhuang J, Cai P, Chen Z, Yang Q, Chen X, et al (2020). Long noncoding *RNA MALAT1* and its target *microRNA-125b* are potential biomarkers for Alzheimer's disease management *via* interactions with *FOXQ1*, *PTGS2* and *CDK5*. Am J Transl Res 12(9):5940.

55. Gu C, Chen C, Wu R, Dong T, Hu X, et al. (2018) Long noncoding *RNA EBF3-AS* promotes neuron apoptosis in Alzheimer's disease. DNA Cell Biol 37:220-226.

56. Zhao Y, Wang Z, Mao Y, Li B, Zhu Y, et al. (2020) *NEAT1* regulates microtubule stabilization *via* FZD3/GSK3β/P-tau pathway in *SH-SY5Y* cells and *APP/PS1* mice. Aging (Albany NY) 12:23233-23250.

57. Zeng T, Ni H, Yu Y, Zhang M, Wu M, et al. (2019) *BACE1-AS* prevents *BACE1 mRNA* degradation through the sequestration of *BACE1*-targeting *miRNAs*. J Chem Neuroanat 98:87-96.

58. Sayad A, Najafi S, Hussen BM, Abdullah ST, Movahedpour A, et al. (2022) The emerging roles of the beta-secretase *BACE1* and the long non-coding *RNA BACE1-AS* in human diseases: A focus on neurodegenerative diseases and cancer. Front Aging Neurosci 14:853180.

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

60. Zhang J, Wang R (2021) Deregulated *lncRNA MAGI2-AS3* in Alzheimer's disease attenuates amyloid-beta induced neurotoxicity and neuroinflammation by sponging *miR-374b-5p*. Exp Gerontol 144:111180.

61. Luo Q, Chen Y (2016) Long noncoding RNAs and Alzheimer's disease. Clin Interv Aging 11:867-872.

62. Roda AR, Serra-Mir G, Montoliu-Gaya L, Tiessler L, Villegas S (2022) Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease. Neural Regen Res 17:1666-1674.

63. Hisanaga SI, Krishnankutty A, Kimura T (2022) *In vivo* analysis of the phosphorylation of tau and the tau protein kinases *Cdk5-p35* and *GSK3*beta by using Phos-tag *SDS-PAGE*. J Proteomics 262:104591.

64. Yan Y, Yan H, Teng Y, Wang Q, Yang P, et al. (2020) Long non-coding *RNA 00507/miRNA-181c-5p/TTBK1/MAPT* axis regulates tau hyperphosphorylation in Alzheimer's disease. J Gene Med 22:e3268.

65. Cai M, Wang YW, Xu SH, Qiao S, Shu QF, et al. (2018) Regulatory effects of the long noncoding *RNA RP11543N12.1* and *microRNA3243p* axis on the neuronal apoptosis induced by the inflammatory reactions of microglia. Int J Mol Med 42:1741-1755.

66. Xu W, Li K, Fan Q, Zong B, Han L. (2020) Knockdown of long non-coding *RNA SOX21-AS1* attenuates amyloid-beta-induced neuronal damage by sponging *miR-107*. Biosci Rep 40:BSR20194295.

67. Merighi S, Nigro M, Travagli A, Gessi S (2022) Microglia and Alzheimer's disease. Int J Mol Sci 23:12990.

68. Jiang H, Zhang Y, Yue J, Shi Y, Xiao B, et al. (2022) Non-coding *RNAs*: The neuroinflammatory regulators in neurodegenerative diseases. Front Neurol 13:929290.

69. Chanda K, Jana NR, Mukhopadhyay D (2022) Long non-coding *RNA MALAT1* protects against Abeta(1-42) induced toxicity by regulating the expression of receptor tyrosine kinase *EPHA2 via* quenching *miR-200a/26a/26b* in Alzheimer's disease. Life Sci 302:120652.

70. Zhou HJ, Wang LQ, Wang DB, Yu JB, Zhu Y, et al. (2018) Long noncoding *RNA MALAT1* contributes to inflammatory response of microglia following spinal cord injury *via* the modulation of a *miR-199b/IKKbeta/NF-kappaB* signaling pathway. Am J Physiol Cell Physiol 315:C52-C61.

71. Yi J, Chen B, Yao X, Lei Y, Ou F, et al. (2019) Upregulation of the *lncRNA MEG3* improves cognitive impairment, alleviates neuronal damage, and inhibits activation of astrocytes in hippocampus tissues in Alzheimer's disease through inactivating the *PI3K/Akt* signaling pathway. J Cell Biochem 120:18053-18065.

72. Cui SY, Zhang W, Cui ZM, Yi H, Xu DW, et al. (2021) Knockdown of long non-coding *RNA LEF1-AS1* attenuates apoptosis and inflammatory injury of microglia cells following spinal cord injury. J Orthop Surg Res 16:6.

73. Qi X, Shao M, Sun H, Shen Y, Meng D, et al. (2017) Long non-coding *RNA SNHG14* promotes microglia activation by regulating *miR-145-5p/PLA2G4A* in cerebral infarction. Neuroscience 348:98-106.

74. Jiang ZS, Zhang JR (2018) *LncRNA SNHG5* enhances astrocytes and microglia viability *via* upregulating *KLF4* in spinal cord injury. Int J Biol Macromol 120:66-72.

75. Mathy NW, Burleigh O, Kochvar A, Whiteford ER, Behrens M, et al. (2021) A novel long intergenic non-coding *RNA*, nostrill, regulates *iNOS* gene transcription and neurotoxicity in microglia. J Neuroinflammation 18:16.

76. Sun X, Wang T, Wang Y, Ai K, Pan G, et al (2020) Downregulation of *lncRNA-11496* in the brain contributes to microglia apoptosis *via* regulation of *Mef2c* in chronic T. gondii infection mice. Front Mol Neurosci 13:77.

77. Gu XH, Xu LJ, Zheng LL, Yang YJ, Tang ZY, et al (2020) Long non-coding *RNA* uc. 80-overexpression promotes M2 polarization of microglias to ameliorate depression in rats. IUBMB life. 72:2194-203.

78. Hu G, Liao K, Niu F, Yang L, Dallon BW, et al (2018) Astrocyte EV-induced *lincRNA-Cox2* regulates microglial phagocytosis: Implications for morphine-mediated neurodegeneration. Mol Ther Nucleic Acids 13:450-63.

79. Guo H, Guo X, Jiang S (2022) Long non-coding RNA *lincRNA*-erythroid prosurvival (*EPS*) alleviates cerebral ischemia/reperfusion injury by maintaining high-temperature requirement protein A1 (*Htra1*) stability through recruiting heterogeneous nuclear ribonucleoprotein L (*HNRNPL*). Bioengineered 13:12248-60.

80. Gao S, Cheng QC, Hu YG, Tan ZZ, Chen L, et al (2021) *LncRNA AK148321* alleviates neuroinflammation in LPS-stimulated *BV2* microglial cell through regulating *microRNA-1199-5p/HSPA5* axis. Life Sci 266:118863.

81. Barczuk J, Siwecka N, Lusa W, Rozpędek-Kamińska W, Kucharska E, et al. (2022) Targeting *NLRP3*-mediated Neuroinflammation in Alzheimer's disease treatment. Int J Mol Sci 23:8979.

82. Duan R, Wang SY, Wei B, Deng Y, Fu XX, et al. (2021) Angiotensin-(1–7) analogue *AVE0991* modulates astrocyte-mediated neuroinflammation *via lncRNA SNHG14/miR-223-3p/NLRP3* pathway and offers neuroprotection in a transgenic mouse model of Alzheimer's disease. J Inflamm Res 18:7007-19.

83. Feng X, Zhan F, Luo D, Hu J, Wei G, et al. (2021) *LncRNA 4344* promotes *NLRP3*-related neuroinflammation and cognitive impairment by targeting *miR-138-5p*. Brain Behav Immun 98:283-98.

84. Bai R, Guo J, Ye XY, Xie Y, Xie T (2022) Oxidative stress: The core pathogenesis and mechanism of Alzheimer's disease. Ageing Res Rev 77:101619.

85. Xu X, Zhang Y (2022) Regulation of oxidative stress by long non-coding *RNAs* in central nervous system disorders. Front Mol Neurosci 15:931704.

86. Zhang L, Fang Y, Cheng X, Lian YJ, Xu HL (2019) Silencing of long noncoding *RNA SOX21-AS1* relieves neuronal oxidative stress injury in mice with Alzheimer's disease by upregulating *FZD3/5 via* the Wnt signaling pathway. Mol Neurobiol 56:3522-37.

87. Yao J, Wang XQ, Li YJ, Shan K, Yang H, et al. (2016) Long non-coding *RNA MALAT 1* regulates retinal neurodegeneration through *CREB* signaling. EMBO Mol Med 8:346-62.

88. Wang J, Zhou T, Wang T, Wang B (2018) Suppression of *lncRNA-ATB* prevents amyloid-β-induced neurotoxicity in *PC12* cells *via* regulating *miR-200/ZNF217* axis. Biomed Pharmacother 108:707-15.

89. Mus E, Hof PR, Tiedge H (2007) Dendritic *BC200 RNA* in aging and in Alzheimer's disease. Proc Natl Acad Sci U S A 104:10679-84.

90. Parenti R, Paratore S, Torrisi A, Cavallaro S (2007) A natural antisense transcript against *Rad18*, specifically expressed in neurons and upregulated during β-amyloid-induced apoptosis. Eur J Neurosci 26:2444-57.

91. Kurt S, Tomatir AG, Tokgun PE, Oncel C (2020) Altered expression of long non-coding *RNAs* in peripheral blood mononuclear cells of patients with Alzheimer's disease. Molecular neurobiology 57:5352-5361.

92. Gui Y, Liu H, Zhang L, Lv W, Hu X (2015) Altered *microRNA* profiles in cerebrospinal fluid exosome in Parkinson disease and Alzheimer disease. Oncotarget 6:37043.

93. Aquino R, de Concini V, Dhenain M, Lam S, Gosset D, et al. (2023) Intrahippocampal Inoculation of Aβ1–42 Peptide in Rat as a Model of Alzheimer's Disease Identified *MicroRNA-146a-5p* as Blood Marker with Anti-Inflammatory Function in Astrocyte Cells. Cells 12:694.

94. Tang L, Liu L, Li G, Jiang P, Wang Y, et al. (2019) Expression profiles of long noncoding *RNAs* in intranasal LPS-mediated Alzheimer's disease model in mice. Biomed Res Int.

95. Canseco-Rodriguez A, Masola V, Aliperti V, Meseguer-Beltran M, Donizetti A, et al. (2022) Long Non-Coding *RNAs*, Extracellular Vesicles and Inflammation in Alzheimer's Disease. Int J Mol Sci 23:13171.

96. Chen Y, Li Z, Chen X, Zhang S (2021) Long non-coding *RNAs*: From disease code to drug role. Acta Pharm Sin B 11:340-354.

97. Chen ZY, Zhang Y (2022) Animal models of Alzheimer's disease: Applications, evaluation, and perspectives. Zool Res 43:1026-1040.