Review.

Long non-coding RNAs, extracellular vesicles and inflammation in Alzheimer's disease.

Ania Canseco-Rodríguez[1#], Valeria Masola[1,2#], Vicenza Aliperti[2], Maria Meseguer-Beltran[1], Aldo Donizetti[2], Ana María Sanchez-Perez[*1]

[1]*Neurobiotecnology group. Faculty of Health Science and Institute of Advanced Materials (INAM). University of Jaume I, Castellon (Spain)*

[2]*Department of Biology, University of Naples Federico II, Napoli, Italy*

First authorship

*** Correspondence:** Ana María Sánchez-Pérez, sanchean@uji.es

Abstract: Alzheimer´s Disease (AD) has currently no effective treatment; however, preventive measures can significantly delay the progress/onset of the disease. Thus, accurate and early prediction of risk is an important strategy to alleviate the AD burden. Neuroinflammation is a major factor prompting the onset of the disease. Inflammation exerts its toxic effect via multiple mechanisms. Amongst others, it is affecting gene expression via modulation of non-coding RNAs (ncRNAs), such as miRNAs. Recent evidence supports that inflammation can also affect long non-coding RNAs (lncRNAs) expression. While the association between miRNAs and inflammation in AD has been extensively studied, the role of lncRNAs in neurodegenerative diseases has been less explored. In this review, we focus on lncRNAs and inflammation in the context of AD. Furthermore, since plasma-isolated extracellular vesicles (EVs) are increasingly recognized as an effective monitoring strategy of brain pathologies, we have focused on the studies reporting dysregulated lncRNAs in EVs isolated from AD patients and controls. The revised literature shows a positive association between pro-inflammatory lncRNAs and AD. However, the reports evaluating lncRNAs alterations in EVs isolated from plasma of patients and controls, although still limited confirm the value of specific lncRNAs associated with AD as reliable biomarkers. This is an emerging field that will open new avenues to improve risk prediction, patients' stratification and may lead to the discovery of potential novel therapeutic targets for AD

Keywords: Alzheimer's disease, inflammation, non-coding RNAs, exosomes vesicles.

1. Alzheimer's disease and inflammation

Acute inflammation, as part of the innate immune system, plays a protective role when injury or damage occurs. However, chronic inflammatory response has the opposite effects, and it is recognized as a decisive mechanism underlying several human pathologies [1]. Neuroinflammation is characterized by the hyperactivation of microglia (the brain resident macrophages) and astrocytes. Accumulated evidence indicates that neuroinflammation in different brain areas is a

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common denominator in several degenerative disorders of various etiology, e.g. Huntington's disease [2], Parkinson's disease (PD) [3] and Alzheimer's disease (AD) [4], [5]. In AD, the association of amyloid plaques (Aβ) deposits and tau neurofibrillary tangles (NFT) with neuroinflammation has been extensively acknowledged [6][7] [8]–[10] to the point that immunotherapies have been proposed to ameliorate AD [11]. Aβ oligomers, among other harmful stimuli, accumulated through a lifetime, and can continuously stimulate microglial cells [12]–[14]. The sustained activation of the immune response leads to chronic production of pro-inflammatory cytokines that, in turn, are toxic to neurons. Damaged neurons undergo different pathological processes that lead to an increment of amyloid precursor protein and increased Aβ secretion, thus worsening the inflammatory response [15]–[18]. This negative cycle leads to impaired brain function and finally massive neuronal death. Targeting neuroinflammation has been proposed in several clinical trials to prevent the progress of the disease (reviewed in [19]).

2. Non-coding RNAs in the brain.

Most of the human genome is transcribed into non-coding RNAs (ncRNAs). ncRNAs are classified into structural and regulatory ncRNAs. The first class includes ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs). The second group is further classified into different categories according to their size: **short ncRNAs**, including microRNAs (miRNAs, 22-23 nucleotides, nts) and piwiRNAs (piRNAs, 26-31 nts); **medium ncRNAs** (50-200 nts) and **long ncRNAs** (lncRNAs, > 200 nts) [20]–[22]. ncRNAs can regulate gene expression either positively or negatively through different molecular mechanisms and at different levels, from chromatin remodeling to mRNA translation [23]–[26]. Moreover, different ncRNAs can interact with each other in an intricate network to regulate their stability and abundance [27]. ncRNAs are highly expressed in the brain, and their expression pattern is finely regulated [28], [29]. Brain function and development are widely affected by ncRNAs action [30], [21], thus dysregulation of ncRNAs expression and/or function may lead to brain disorders ranging from neurological and neuropsychiatric diseases to tumorigenesis [31], [32].

2.1 Long non-coding RNAs

LncRNAs are typically transcribed by Polymerase II, and their structure resembles mRNAs since they are 5'-capped, polyadenylated, and spliced [32] [33]. However, unlike mRNAs, lncRNAs are

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shorter, less stable, and show lower expression levels with a tissue-specific expression pattern [32].

LncRNAs are dynamically expressed during development, playing a key role in the regulation of a wide range of cellular processes, acting both as chromatin regulators and by regulating gene expression at the transcriptional and post-transcriptional levels [34]. Also, lncRNAs fold into thermodynamically stable secondary structures characterized by different functional domains (DNA-binding domains, RNA-binding domains, protein-binding domains, conformational switch) [35]. In this way, lncRNAs can physically and functionally interact with the other biomolecules (DNA, RNA, and proteins) both by base-pairing with complementary nucleic acid sequences or through these functional domains [36]. They can be classified into several major categories based on their position relative to neighboring protein-coding genes (sense, antisense, bidirectional, intergenic transcripts), their subcellular localization, and their mechanism of action (*cis*- or *trans*-acting lncRNAs) [22], [32]. *Cis*-acting lncRNAs influence the expression of nearby genes located in the same chromosome as their own sites of transcription [37]in contrast with *trans*-acting lncRNAs, that can operate in distant regions, in different chromosomes [26].

3. Long Non-Coding RNAs in Alzheimer's disease related to inflammation.

The dysregulation of ncRNAs associated with AD is well acknowledged [38] [39], and lncRNAs in association with AD have been extensively reviewed [40]-[41]–[43]. Some studies focus on the role of lncRNAs as potential AD biomarkers [44] others focus on lncRNAs showing *competing endogenous RNA network* (ceRNA) mechanisms [45]. More recently, a group of lncRNAs has been suggested as potential therapeutic targets for AD [46].

Since neuroinflammation is a central mechanism of AD, attention has focused on the possible immune-modulatory activities of lncRNAs, revealing that they can positively and/or negatively regulate innate immune genes expression through their general mechanisms of action (miRNA sponge, chromatin remodeling, transcriptional activation/inhibition, post-transcriptional modification) and even regulation of protein activity [47]–[49]. Transcriptomics studies have highlighted the role of different lncRNA-associated ceRNA networks in the APP/S mice model, mainly involved in synaptic plasticity, memory, and neuroinflammation [50], [51]. In the brain, inflammatory stimuli (e.g. LPS) regulate the expression of genes via the upregulation of several lncRNAs [52]. Furthermore, the lncRNA modulation of neuroinflammation is increasingly acknowledged

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as a key mechanism underlying nervous system disorders [53]. Here, we review updated literature that, experimentally, has demonstrated the association of specific lncRNAs with inflammatory processes in the context of AD. According to their reported effect in cellular, animal models, and patients, we classify lncRNAs as pro-inflammatory or anti-inflammatory (table 1).

3.1 Pro-inflammatory lncRNAs, evidence from cellular, animal models, and human studies.

Up to date, the majority of neuroinflammation-associated lncRNAs reported regarding AD progression have a pro-inflammatory role.

Lnc-ANRIL is mapped at the INK4 locus and has been identified in several diseases that are related to inflammation and nerve dysfunction [54]. INK4 proteins are cell-cycle inhibitors and are generally lost or inactivated in some types of cancer, and thus considered tumor suppressors [55]. In PC12 cells, a well-known neuronal cellular model, lnc-ANRIL was upregulated by incubating the cells with Aβ1-42 oligos. Moreover, the lnc-ANRIL knockdown decreased inflammatory cytokine expression, inhibited Aβ-induced apoptosis, and autophagy, and led to increased neurite outgrowth, by binding and downregulating miR-125a [56]. In models of coronary disease, lnc-ANRIL can increase NF*k*B expression via miR-181b modulation [57], but whether miR-181b is targeted in neuronal cells is yet unknown. Moreover, whether these changes are reflected in humans or in animal models of AD remains elusive.

LncRNA BACE1-AS, the antisense of BACE1 (β-secretase), improves BACE mRNA stability, preventing the binding of miR-485-5p, thus increasing BACE levels [58]. In a neuronal cellular model, the neuroblastoma cell line SH-SY5Y, BACE1-AS can regulate apoptosis, inflammatory response, and oxidative stress, through direct regulation of the miR-214-3p/CDIP1 signaling axis [59]. Interestingly, BACE1-AS/BACE1 dysfunction underlies several human diseases with strong inflammatory component, including multiple tumors and degenerative diseases [60]. In addition, BACE1-AS, is upregulated in serum samples of AD patients and brain tissues of AD transgenic (Tg) mice [61], suggesting that BACE-AS could be a direct link between inflammation and AD development.

LncRNA BDNF antisense (**BDNF-AS**) has been reported as a target of anti-inflammatory treatments. Specifically, lithium treatment decreased inflammation via decreasing BDNF-AS levels, and increasing its target miR-9-5p, in a rat model of spinal cord injury [62]. According to this putative role in facilitating inflammation, increased levels of BDNF-AS can impair cognition in

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neurodegenerative preclinical models. Moreover, elevated levels of BDNF-AS are found in AD patients' blood [63]. Despite this evidence, the direct role of BDNF-AS on inflammation in AD models has not yet been reported.

Brain cytoplasmic 200 (BC200) is a lncRNA located in dendrites where it regulates local protein synthesis. BC200 decreases with normal aging, but not in AD; thus, BC200 is higher in the prefrontal cortex and hippocampus of AD patients compared to age-matched controls [64]. The mechanism of action of BC200 involves the PI3K/AKT axis found both in cancer cells [65] and in an AD model, associated with inflammation [66]. Interestingly, plasma BC200 has been found to be able to discriminate healthy controls from preclinical cases [67].

LncRNA HOX antisense intergenic RNA (HOTAIR) is highly expressed in inflammatory conditions, e.g. tumors, traumatic brain injury mice model, and LPS-treated microglial (BV2) cells. Accordingly, silencing HOTAIR suppresses microglial activation and the release of inflammatory factors [53]. Supporting a pro-inflammatory role of HOTAIR, sulfasalazine (used for the treatment of autoimmune diseases) reduces HOTAIR expression and prevents the increment of microglia M1-like in a mice model of cuprizone-induced demyelination [68]. Furthermore, the HOTAIR/miR-130a-3p axis is downregulated by exercise in rat models of AD. In this study, treadmill exercise exerts neuroprotection by reducing inflammatory microglia and oxidative stress, and consequently, improving cognitive function [69]. In humans, aerobic exercise can attenuate the white matter hyperintensities associated with AD and aging [70]. Not surprisingly, exercise has been proposed as a useful strategy to prevent AD [71], under the well-known anti-inflammatory effect of exercise [72]. However, whether HOTAIR mediates some of those exercise-induced effects has not been demonstrated.

Lnc 17A is a 159-nts antisense transcript controlling $GABA_B$ alternative splicing, leading to impaired $GABA_B$ signaling [73]. Importantly, 17A synthesis is regulated by inflammatory processes, and it is upregulated in the cerebral cortex of AD patients [73]. Impaired GABAergic function plays a major role in AD [74], thus, this lncRNA represents an interesting link between inflammation and AD.

MAGI2-AS3 acts as a ceRNA of miR-374b-5p and its expression correlates with AD disease severity [75]. Although no studies on human neuroinflammation have been reported, MAGI2-AS3 appears in a screening of the ceRNA network in asthma studies [76], thus suggesting a pro-inflammatory role of MAG12-AS3.

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LncRNA N336694 is found up-regulated in APP/PS1 mice brain tissue, supporting a pro-inflammatory role [77]. In accordance, simvastatin treatment that ameliorates cognition and reduces inflammation downregulates lncRNA n336694/miR-106b [77].

NDM29 (Neuroblastoma differentiation marker 29) is a lncRNA transcribed by RNA pol III, embedded in the first intron of the ASCL3 (*achaete scute-like homolog* 3) gene in humans. NDM29 expression is enhanced in the cerebral cortex of AD patients, its biosynthesis responds to pro-inflammatory molecules, and it is downregulated by anti-inflammatory drugs in different neuroblastoma cell lines [78].

Nuclear paraspeckles assembly transcript 1 (**NEAT1**) is upregulated in the temporal cortex and hippocampus of AD patients compared to controls [79], and it is reported to modulate inflammatory processes via activating or inhibiting miRNAs, in the AKT, TLR4, TRAF6, and NF-κB signaling pathways [80]**.**

Prostate androgen-regulated transcript 1 (PART1) is a lncRNA with a key role in a variety of biological processes. Using Aβ (1-42)-incubated endothelial cells as a model of the blood-brain barrier (BBB), lncRNA PART1 appeared to be implicated in BBB permeability regulation via binding NOVA2. The higher expression of PART1 in endothelial cells incubated with Aβ(1-42) led to PPP2R3A mRNA decrease and subsequent higher NFkB-p65 phosphorylation. This signaling contributes to the alteration of BBB proteins (e.g., occludin, claudin-5, and ZO-1), leading to increased permeability. Although this could be a potential mechanism aggravating AD pathogenesis, more studies are needed to unravel the function of this lncRNA in AD, as a diagnostic and therapeutic [81].

Ribonuclease P RNA component H1 (**Rpph1**) is a lncRNA that participates in the maturation of tRNA [82]. This lncRNA is upregulated in the cortex of APPswe/PS1deltaE9 mice compared to wild-type controls [83]. In addition, it was shown that Rpph1 enhances CDC42 levels and promotes dendritic spine formation through the competition with endogenously expressed miR-330-5p and this represents a regulatory loop of potential compensatory mechanisms in the early stage of AD [83]. Over-expression of Rpph1 promotes inflammation in mesangial cells, a model of diabetic nephropathy, via the Gal-3/Mek/Erk axis [84], leading to the hypothesis of a potential inflammatory role in AD.

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LncRNA maternally expressed gen 3 (MEG3) expression declined in the hippocampus of AD model rats, and over-expressing MEG3 inhibited the activation of the astrocytes, reducing neuronal damage via the PI3K/AKT pathway [85]. No data on humans have been reported yet.

SOX21-antisense transcript 1 (SOX21-AS1) represses the expression of SOX21 gene, a member of the large SOX (*SRY*-related HMG-box genes) family of transcription factors involved in development regulation [86]. Knocking down SOX21-AS1, thus increasing SOX21 levels**,** prevents neuronal oxidative stress, and inhibits apoptosis in AD mice through the upregulation of the FZD3-5/Wnt signaling pathway [87]. Thus, considering the close relationship between oxidative stress and inflammation [88]. SOX21-AS1 can be classified as pro-inflammatory lncRNA, since its silencing-alleviates oxidative stress.

SRY-box transcription factor 2 overlapping transcript (**SOX2-OT)** is a lncRNA transcribed from the intron of the Sox2 gene [89] with a key role in maintaining SOX2 expression [90]. SOX2-OT is involved in neural embryonic development and adult mouse neurogenesis. Although adult neurogenesis is impaired in AD mice models [91] it is not known whether SOX2-OT dysfunction may contribute to the progress of the disease. However, SOX2-OT has been shown to mediate inflammation, oxidative stress as well as neuronal apoptosis in PD cellular models, acting via miR-942-5p/Nuclear apoptosis-inducing factor 1 (NAIF1) axis [92]. Although there is no experimental evidence in AD cellular or animal models, a Logic Mining method used for the analysis of a microarray expression dataset shows SOX2-OT as one of the 5 genes common to both early and late AD states of the *anti-NGF AD11* transgenic mouse model [91]. Further studies are required to validate this gene in human transcriptional studies.

Small nucleolar RNA host gene 1 (SNHG1) is a lncRNA that belongs to the Small Nucleolar RNA host gene (SNHG) family, comprising more than 20 members, many of which have been found associated with cancer progression [93]. In SH-SY5Y and human primary neuron cells, Aβ incubation increased the expression of SNHG1, while the silencing of this lncRNA attenuated Aβ-induced cellular death and alterations in mitochondrial membrane potential. In this study, SNGH1 was shown to act as a miR-137 sponge targeting KREMEN1 *(kringles* containing transmembrane protein 1) [94]. KRMEN1 is a transmembrane receptor that blocks the WNT/catenin pathway but can induce apoptosis independently [95]. Interestingly, silencing of KREMEN1 (by miR-431 overexpression) prevented Aβ-mediated synapse loss in primary cultures from a mice

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model of AD, suggesting that KREMEN1 may facilitate AD progression [96]. Another pathway modulated by SNHG1 is the miR-361-3p/ZNF217 axis, reported in Aβ25-35-treated neuroblastoma cell lines (SK-N-SH and CHP 92 212), where increasing SNHG1 reduced miR-361-3p, increasing its target ZNF217 (zinc finger gene 217 transcription factor) levels. ZNF217 is also the target of miR-212-3p [97] and miR-200 [98] in the context of Aβ25-35 induced inflammation, where ZNF217 upregulation is associated with increased neurotoxicity.

Small Nucleolar RNA Host Gene 14 (SNHG14) is another member of the SNHG family and has an essential role in promoting pro-inflammatory microglia activation [99]. In astrocytes from the transgenic APP/PSEN mice model, SNHG14 was reported to sponge miR-223-3p, which directly targets and restrains NLRP3 inflammasome. In this model, angiotensin analogs inhibit inflammation and prevent cognitive impairment by inhibiting SNHG14, thus restoring miR-223-3p function [99]. Exercise that improves cognition and reduces inflammation markers, can also reduce SNG14 levels, in mice models and AD patients [100].

3.2 Anti-inflammatory lncRNAs.

Although less studied than the pro-inflammatory, some lncRNAs have an anti-inflammatory action in AD.

LincRNA-p21 was found upregulated by *Bilobalide* (the effective component of EGb76, extract of Ginkgo biloba), decreasing neuroinflammation, and promoting autophagy in a mice model of AD [101]. Another example is represented by **MALAT1** (metastasis-associated lung adenocarcinoma transcript 1) which is downregulated in the cerebral-spinal fluid (CSF) in AD patients compared to controls [102], [103]. MALAT1 levels correlate positively with alleviated AD severity, as evaluated by the Mini-mental Status examination (MMSE) score, and biomarkers Aβ42, t-tau, and p-tau. MALAT1 reduction and miR125b increase correlate with AD, but not with PD; suggesting that lnc-MALAT1/miR-125b are potential biomarkers for AD diagnosis. Consistently, in two cellular models of AD MALAT1 was found to inhibit inflammation by sponging miR-125b [102]. Intriguingly, MALAT1 can promote neuroinflammation by NRF2 inhibition in a PD mouse model [104]. Further research is required to unveil the putative opposite role of MALAT1 in the inflammatory process underlying PD and AD.

4. Extracellular vesicles in neurodegenerative diseases, a link between lncRNAs, inflammation, and AD.

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Extracellular vesicles (EVs) are heterogeneous membranous structures released into the extracellular space by all cell types. The main function of EVs is the intercellular communication underlying various physiological, but also pathological processes [105].

EVs are generally classified into three groups according to their origin, content, and size [106]. A**poptotic bodies** are the largest size vesicles (around 5000 nm in diameter) and are released during apoptosis; **microvesicles,** the middle size group (100-1000 nm in diameter), are formed by plasma membrane outward invaginations; the smallest size vesicles, **exosomes** (30-150 nm in diameter), are released from the endosome system forming multivesicular bodies inside the cells before release.

EVs are characterized by a lipidic bilayer that contains cell organelles, DNA, cytosolic and membrane proteins, coding transcripts, and ncRNAs [107], [108], including lncRNAs [109]. Once released into the interstitial spaces and body fluids, the secreted vesicles can be internalized by other cells, acting both on self and neighboring cells (autocrine and paracrine communication) and over long distances (endocrine communication) [110], [111]. EVs can be internalized by recipient cells following receptor-ligand interactions without undergoing any structural and functional changes [112], [113], and their cargos function as effector molecules in recipient cells [114]. All cell types in the central nervous system (CNS) (neurons, astrocytes, oligodendrocytes, microglia, and embryonic neural stem cells) can release EVs [115]. Their cargos are involved in the regulation of various biological processes, such as cell proliferation, differentiation [116], [117] and synaptic plasticity [118], facilitating the communication within the CNS and between the CNS with other systems [116]. In pathological conditions, EVs undergo significant changes in their quantity, size, and cargo composition, thus reflecting the inflammatory condition of the brain [119]. For this reason, they have been considered excellent biomarkers for the early detection of neurodegenerative and inflammatory processes. Moreover, EVs properties (low immunogenicity, biological barrier permeability, and ability to transport a range of different biomolecules) have led to considering them for potential therapeutic intervention as a vehicle for effective drug delivery [120], [121].

4.1 Dysregulated extracellular vesicular lncRNAs in AD

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Since EVs cargo reflects cellular status, the discovery of neuronal-derived EVs in blood and ~~(~~CSF~~)~~ revolutionized the field of brain biomarkers, providing a non-invasive strategy that allows the evaluation of brain physio-pathological state.

As a good reflection of cellular status, the ncRNA profiles contained in plasma EVs (particularly, microvesicles and exosomes) are altered in pathological situations, mostly cancer, metabolic and cardiovascular disease [121]. Specifically, in neuronal-derived EVs isolated from AD patients altered expression profiles of several miRNAs have been found [122], [123]. However, to date, few studies have characterized lncRNAs in EVs directly involved in AD, including **lncRNA BACE1-AS**, up-regulated in exosomes isolated from plasma of AD patients [124], and **PCA3** and **RP11-462G22.1**, up-regulated in AD EVs isolated from CSF [125]. PCA3 is known for its involvement in prostate cancer [126], whereas RP11-462G22.1 was originally found as a muscular dystrophy-associated lncRNA [127]. However, their biological function in AD is still unknown. Interestingly, in another study, plasma exosomal BACE1-AS, 51A, BC200, and BACE1 mRNA were determined but only BACE1-AS was found different in AD from control [128], suggesting that BACE1-AS can be used as biomarkers (moreover if combined with imaging data of entorhinal cortex thickness).

Further studies are warranted to ascertain the relationship between lncRNAs in neuronal-derived EVs as indicative of the neuroinflammatory process leading to neurodegeneration in AD

5. Concluding remarks

In this study, we have reviewed the literature showing the association between lncRNAs and inflammation in the context of AD. The revised evidence supports that the lncRNAs that are found increased in AD pathology (patients, animals, and/or *in vitro* models) may participate in the pro-inflammatory process. Moreover, given the importance of EVs in cellular communication, we aimed to understand whether and which lncRNAs are found in plasma or CSF EVs in AD models, thus understanding their potential role as reliable biomarkers of disease. Interestingly, only a few studies have been found that address that issue in the context of AD, in remarkable contrast with the studies addressing miRNAs in EVs. Further studies are required to confirm if the lncRNAs studied in inflammatory conditions are present in EVs. In addition, the function of lncRNAs found either in plasma or within EVs remains unknown, and whether EVs in CSF and plasma carry different lncRNAs as cargo, is still elusive. The field of lncRNAs in AD and EVs is an emerging field that may open new routes to identify biomarkers, with potential applications for prediction of the

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risk to develop the disease, and/or patients' stratification that will afford better and effective intervention

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Table 1. Long non-coding RNAs related to inflammation and Alzheimer's disease. LncRNAs are described in alphabetical order. In red the putative pro-inflammatory lncRNAs and in blue putative anti-inflammatory lncRNAs.

Lnc	Relation to Inflammation (model) (ref)	Regulation in AD (Model) (ref)	Mechanism of action (ref)
17A	Upregulated by inflammatory processes (AD patients) (Massone *et al.*, 2011)	Upregulated in cerebral cortex (AD patients) (Massone *et al.*, 2011)	Proinflammatory/Regulation of **GABA$_B$** alternative splicing, leading to impaired GABA$_B$ signaling. (Massone *et al.*, 2011)
ANRIL	Decrease inflammatory cytokine expression. (P12 cells) (Zhou *et al.*, 2020)	Upregulated by Aβ1–42 (NGF-stimulated PC12 cells) (Zhou *et al.*, 2020)	Downregulates **miR-125a**/NF-KB (Zhou *et al.*, 2020; Guo *et al., 2018)*
BACE1-AS	Knocking-down of BACE1-AS alleviates neuronal injury by repressing autophagy in vivo through **miR-214-3p/ATG5** axis. (Mice model) (Zhou *et al.*, 2021)	Upregulated Serum (AD patients) Upregulated brain (mice model) (Zhou *et al.*, 2021)	Increases the stability of BACE1 mRNA **miR-485-5p** miRNA sponge (Faghihi *et al.*, 2010) Regulates **miR-214-3p/CDIP**1 axis. (Li *et al.*, 2022)
BC200	Increase the inflammation (NSCLC metastasis in patients and LC cells) (Gao *et al.*, 2019)	Upregulated in the prefrontal cortex and hippocampus (AD patients) (Mus *et al.*, 2007) Increased in plasma (AD patients) (Khodayi M *et al* 2022)	Modulates **PI3K/AKT** pathway. (Liu *et al.*, 2020)
BDNF-AS	Promotes inflammation (rat model) (Wang *et al.*, 2021)	Upregulated in peripheral blood (AD patients). (Ding *et al.*, 2022)	Downregulates **miR-9-5p.** (Wang *et al.*, 2021)
HOTAIR	Upregulated in (LPS-treated microglial BV2 cells). (Chen *et al.*, 2021). Sulfasalazine inhibits HOTAIR, suppresses inflammatory microglia and cytokine release. (Mice model of cuprizone-induced demyelination) (Duan *et al.*, 2018)	Exercise may attenuate cognitive impairment (rat model) (Lu *et al.*, 2022)	Exercise downregulates **HOTAIR/miR-130a-3p** axis. (Lu *et al.*, 2022) Sulfasalazine downregulates **HOTAIR/miR-5p-AKT2-NF-kB** axis preventing demyelination. (Duan *et al.*, 2018)
LincRNA-p21	Reduces neuroinflammation (BV-2 microglial cells). (Qin *et al.*, 2021)	Upregulating lincRNA-p21 (Bilobalide) improved function. (Mice model) (Qin *et al.*, 2021)	Binds directly to **STAT3** and blocks the **JAK2/STAT3** signaling, while STAT3 phosphorylation could inhibit autophagy (Jin *et al.*, 2019)
MEG3	Reduces the inflammation (rat model) (Yi *et al.*, 2019)	Downregulated in hippocampus. (Rat model). (Yi *et al.*, 2019)	Inactivate **PI3K/AKT** pathway/(Yi *et al.*, 2019)

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N336694	Reduces inflammation (mouse model) (Huang *et al*., 2017)	Upregulated in brain. (Mice model). (Huang *et al*., 2017)	**miR-106a** (incrementing IL-10 levels)/(Huang *et al*., 2017)
NDM29	Upregulated by pro-inflammatory cytokines (Massone *et al*., 2012)	Upregulated in the cerebral cortex (AD patients). (Massone *et al*., 2012)	Increases **APP** synthesis and actively promotes Aβ x-42 secretion/ (Massone *et al*., 2012)
NEAT1	Increase inflammation (H9c2 cells) (Chen X *et* al, 2020)	Upregulated in the temporal cortex and hippocampus. (AD patients) (Spreafico *et al*., 2018). Increased in plasma lof AD patients (Khodayi M *et al* 2022	**miR-15/107** sponge; Activating or inhibiting microRNAs, AKT, TLR4, TRAF6, and NF-κB signaling pathways. (Zhan *et al*., 2019; Pan *et al*., 2022)
NEAT2 (MALAT1)	Suppress inflammatory cytokines in AD (Cai *et al*., 2020)	Downregulated in the CSF (AD patients). (Ma *et al*., 2019)	**miR-125b** sponge**,** increases anti-inflammatory **miR-155.** (Zhuang *et al*., 2020; Ma *et al*., 2019)
NNT-AS1	NNT-AS1 correlates with inflammation (HBE cells). (Geng *et al*., 2021; Mei *et al*., 2020)	Upregulated (AD patients) (Geng *et al*., 2021)	**miR-214-5p** sponge. (Geng *et al*., 2021)
PART1	Promotes **NFκB-p65 higher phosphorylation** (Endothelial cells). (Ning *et al*., 2022)	Increased by Aβ (endothelial cells) (Ning *et al*., 2022)	Upregulates PPP2R3A mRNA (Responsible for **NFκB-p65)** (Ning *et al*., 2022)
Rpph1	Its overexpression promotes inflammation under low glucose conditions (mesangial cells). (Zhang P. *et al*., 2019)	Upregulated in the cortex. (AD mice model). (Cai *et al*., 2017)	Regulates **Gal-3/Mek/Erk** pathways. (Zhang P. *et al*., 2019)
SNHG1	Promotes inflammation (PD cell models). (Cao *et al*., 2018)	Increased by Aβ (SH-SY5Y cells) (Cao *et al*., 2018)	Regulates **miR-7/NLRP3** pathway. (Cao *et al*., 2018) Regulates KREMEN1 via **miR-137** (Wang *et al*., 2019)
SNHG14	Promotes inflammation (astrocytes) (Duan *et al*., 2021)	Upregulated (AD patients) (He *et al*., 2021)	Regulates **miR-233-3p/NLRP3.** (Duan *et al*., 2021)
SOX2-OT	Promotes inflammation, apoptosis and oxidative stress (SH-SY5Y cell) (Guo *et al*., 2021)	Upregulated in (AD mice model) (Guo *et al*., 2021)	Repression of Sox2 via **miR-942-5p/NAIF1.** (Guo *et al*., 2021)
SOX21-AS1	Antisense, reduces lncSOX21 level	Upregulated in AD mice model (Zhan L *et al*, 2019)	Upregulates **FZD3-5Wnt** signaling pathway (Zhan L *et al*, 2019). Sponge of **miR-107** (Xu *et al* 2020)

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

AMSP and AD drafted the idea of the manuscript. AC, AD, AMSP, MMSB, VA, and VM reviewed the literature. All authors contributed to writing the original draft and editing. AMSP conducted the final editing. All authors approved the submitted version.

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