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REVIEW PAPER

LncRNAs Orchestrating Neuroinflammation: A Comprehensive Review

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Abstract
CNS diseases account for a major part of the comorbidity and mortality of the human population; moreover, neuroinflammation has become an indication for different CNS diseases, for instance, Parkinson's and Alzheimer's disease. Microglia and astrocytes are the two main glial cells that can be found in the CNS. Each of these plays an important role in mediating immune responses like inflammation. There are many studies suggesting the role of LncRNAs in mediating neuroinflammation. Indeed, LncRNAs orchestrate neuroinflammation through various mechanisms, namely miRNA sponge, and transcriptional activation/inhibition. In addition, LncRNAs regulate different downstream pathways like NF-κB, and PI3K/AKT. In this study, we gathered the existing studies regarding the mechanisms of action of LncRNAs in the pathogenesis of different CNS diseases like neurodegenerative diseases and traumatic injuries through regulating neuroinflammation. We aim to elaborate on the regulatory roles of LncRNAs in neuroinflammation and bring a more profound understanding of the etiology of CNS diseases in terms of neuroinflammation.

Keywords Long non-coding RNAs · Neuroinflammation · Neurodegenerative diseases · Central nervous system

Abbreviations

AD	Alzheimer's disease
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
ANRIL	Antisense non-coding RNA in the INK4 locus
APP	Amyloid precursor protein
Aβ	Amyloid-beta
BACE1	β-Site amyloid precursor protein cleaving enzyme 1
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
ceRNAs	Competing endogenous RNAs
CNS	Central nervous system
DGCR5	DiGeorge syndrome critical region gene 5
EAE	Experimental autoimmune encephalomyelitis
TBI	Traumatic Brain Injury
EZH2	Enhancer of zester homolog 2
GAS5	Growth arrest-specific 5
GBP9	LncRNA guanylate binding protein-9
I/R	Ischemia and reperfusion
IFN-γ	Interferon-gamma
IL-1β	Interleukin-1β
IL-6	Interleukin-6
LncRNAs	Long non-coding RNAs
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
miRNAs	MicroRNAs
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Multiple sclerosis
ncRNAs	Non-coding RNAs
NEAT1	Nuclear paraspeckle assembly transcript 1
NF-κB	Nuclear factor-k-gene binding
NLRP3	Nod-like receptor protein 3
OGD/R	Oxygen–glucose deprivation/reoxygenation
PD	Parkinson's disease
PI3K	Phosphoinositide 3-kinase
ROS	Reactive oxygen species

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SCI	Spinal cord injury
siRNAs	Small interfering RNAs
TGF-β	Transforming growth factor
TLE	Temporal lobe epilepsy
TNF-α	Tumor necrosis factor-α
TUG1	Taurine-upregulated gene 1
XIST	X inactive specific transcript
STAT	Signal transducer and activator of transcription

Background

Commencing with the advent of methods for human gene sequencing, new classes of genes were revealed (Robinson et al. 2020). One of the most profound discoveries was that over 85% of the genome is transcribed, but only 1.5% to 2% of which encodes protein-coding genes. Many of the non-coding genes were initially considered to be non-functional due to their low protein-coding potential. However, they are now perceived to play a robust role in regulating the biological processes (Bridges et al. 2021). One of the newly identified types of genes is called long non-coding RNAs (LncRNAs). LncRNAs constitute a vast group of transcribed RNAs. To distinguish them from smaller non-coding RNAs, LncRNAs are defined as transcripts which have more than 200 nucleotides in length (Choi et al. 2019). LncRNAs are synthesized by RNA polymerase II (Pol II) and then are capped and polyadenylated. LncRNAs were considered to be unstable, but emerging studies demonstrated that the majority of LncRNAs are stabilized mostly via polyadenylation, while other LncRNAs are stabilized via secondary structures like triple-helical structures (Bridges et al. 2021). LncRNAs are the cornerstone of many aspects of biology, as they have been proven to have critical roles in various biological processes ranging from cell differentiation, proliferation, or apoptosis, and gene expression to immune responses (McDonel and Guttman 2019). Besides, targeting LncRNAs with miRNAs and siRNAs has opened promising windows in the treatment and diagnosis of different diseases (Khan et al. 2022). Neuroinflammation is a type of inflammation within the brain and spinal cord. Inflammation is an immune response of the body to an insult or injury. The degree of neuroinflammation varies within the context of disease, stress, injury, or infection. The duration, context, and course are important terms of an inflammatory response in understanding the behavioral, biochemical, and pathophysiological consequences. Different cytokines, chemokines, Reactive Oxygen Species (ROS), and secondary messengers that are produced by resident CNS glia (microglia and astrocyte) and endothelial cells cause neuroinflammation (DiSabato et al. 2016). Neuroinflammation can have both positive and detrimental effects. Peripheral immune cell translocation through the blood–brain barrier (BBB) promotes glial activation, increasing BBB permeability, and contributing to chronic neuroinflammation (Tripathi et al. 2021), which might lead to various types of diseases such as neurodegenerative diseases (DiSabato et al. 2016; Singh 2022). Microglia and astrocytes are the two major glial cells in the nervous system. They have various functions in the nervous system, including mediating innate immune responses in the brain; moreover, they both have two opposing phenotypes, neurotoxic, and neuroprotective (Kwon and Koh 2020). They are key players in neuroinflammation by releasing different cytokines, chemokines, and growth factors. Astrocytes can have a role in building BBB which distinguishes the peripheral immune system from the brain (Abbott et al. 2006). Microglia cells are the resident cells of the innate immune system in the central nervous system and the first responder to pathological insults (Singh 2022). LncRNAs play a pivotal role in orchestrating neuroinflammation, as suggested by recent studies. However, the role of LncRNAs and the downstream regulatory process in neuroinflammation modulation are less studied and need more research. In this literature review, the relation between neuroinflammation and LncRNAs is comprehensively discussed by gathering the existing studies in terms of the roles of LncRNAs in neuroinflammation that occurs in neurodegeneration, traumatic diseases, neuropathic pain, and infections.

Neurodegenerative Diseases

Alzheimer

Alzheimer's disease (AD) is a neurodegenerative disease caused by the accumulation of the extracellular amyloid β (Aβ) plaques and the hyperphosphorylated tau protein-making intracellular aggregations of neurofibrillary tangles (NFT) (Tiwari et al. 2019). In neurodegenerative diseases' pathogenicity, neuroinflammation can be attributed to the propagation of neurodegenerative diseases (Rajesh and Kanneganti 2022). It has been suggested that the synthesis of human amyloid-β peptides (Aβ) leads to the secretion of cytokines and neuronal cell death (Hashioka et al. 2021). In addition, mitochondrial dysfunction is a crucial player in the pathogenesis of AD; in fact, mitochondrial dysfunction accompanied by mitophagy is a major contributor to the accumulation of amyloid-β peptides (Rai et al. 2020). High levels of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6 have been found in patients suffering from Alzheimer's disease compared with healthy patients (Rajesh and Kanneganti 2022). NF-κB can exert an important role in AD since many AD-associated genes like *BIN1*, *APP*, *COX2*, and others are target genes of NF-κB (Kaltschmidt et al. 2022). Despite copious amounts of research conducted

on therapeutic techniques in AD, there is no solid therapy for AD; however, traditional medicinal plants have obtained attention in the management of AD (Tripathi et al. 2024). With the advent of evidence in genomic, transcriptomic, and small RNA sequencing, several studies have suggested the role of LncRNA in AD (Chanda and Mukhopadhyay 2020). *XIST* was remarkably upregulated in the hippocampus of AD mice compared with control mice. The XIST, miR-124, and BACE1 expression levels were detected by real-time PCR; In addition, *XIST* could interact with miR-124, leading to its decreased expression in AD, which exerts a considerable role in the control of *BACE1* gene expression. Therefore, there is LncRNA *XIST*/miR-124/*BACE1* signaling pathway playing a pivotal role in AD (Yue et al. 2020). LncRNA *XIST* binds to EZH2 to epigenetically regulate NEP which mediates neuroinflammation and injury (Yan et al. 2022). The transcription of two different LncRNAs is altered in cerebral tissue. *LncRNA00507* and *17A* were upregulated in patients with AD, and they are attributed to contribute to alternative splicing in tau phosphorylation and Gamma-Aminobutyric Acid B (GABA B), respectively (Varesi et al. 2022). Plasma LncRNA *BACE1* was upregulated significantly in patients with AD (Wang et al. 2020a). However, in a case–control study between 45 AD and 36 control patients, the level of plasma LncRNA *BACE1* was low in the pre-AD stage, while the levels increased dramatically in the full AD stage (Fotuhi et al. 2019). Therefore, the level of LncRNA *BACE1* can open new doors to the early diagnosis of AD but needs more studies to be conducted (Varesi et al. 2022). LncRNA *NEAT 1* has also been suggested to exert a key role in exacerbating AD conditions. Furthermore, Micro-27a-3p is the target gene of LncRNA *NEAT1*. The role of *NEAT1* in terms of inflammation has become clear which can activate NF-κB signaling (Pan et al. 2022). The downregulation of micro-27a-3p could demonstrate the upregulation of *NEAT 1* leading to an increase in the synthesis of Amyloid-beta Precursor Protein (APP) protein, tau protein, and BACE 1 protein (Dong et al. 2021a). Also, there are target-binding sites between miR-29c-3p and *BACE1* (Cao et al. 2021a). LncRNA 17A is over-expressed in AD; in fact, LncRNA 17A is identified to play a key role in autophagy, neurodegeneration, and deactivating GABA signaling. Besides, LncRNA 17A can have therapeutic and diagnostic potentials (Wang et al. 2019a). *LncRNA ANRIL* can be upregulated by Aβ1–42, and it regulates miR-125a and NF-KB; therefore, an overexpression of *ANRIL* can increase inflammation. In the methodology of this study, LncRNA ANRIL is knocked down via transfecting lnc-ANRIL knockdown plasmid; moreover, in terms of inflammation, TNF-α, (IL)−1β, IL-6, and IL-17 were significantly reduced (all $P < 0.01$) in knocked down group (Zhou et al. 2020a). LncRNA *HOTAIR* was upregulated in AD patients, and it could be exerted as a diagnostic marker in AD patients (Lu et al. 2022a). MiR-130a-3p mediated the regulation of *HOTAIR* on inflammation and cognitive ability (Lu et al. 2022b). *LncRNA MAGI2-AS3* could sponge miR-374b-5p; furthermore, *MAGI2-AS3* was upregulated in AD patients, whereas miR-374b-5p expression was reduced in AD patients. The downregulation of *MAGI2-AS3* lowered the severity of neuroinflammation and improved neuronal viability (Zhang and Wang 2021). AVE0991 alleviated neuronal and synaptic damage and recovered spatial cognitive impairment in AD mice. AVE0991 reduced astrocytic NLRP3 inflammasome-mediated neuroinflammation by LncRNA *SNHG14*. NLRP3 is a target of miR-223-3p in astrocytes while *SNHG14* acts as a sponge of miR-223-3p (Duan et al. 2021) (Fig. 1). LncRNA BDNF-AS is recognized to regulate gene expression at an epigenetic level by chromatin modification. BDNF-AS is the anti-strand of the *BDNF* gene, which is responsible for coding the neurotrophic factor needed for neurodevelopment and stability; moreover, BDNF protein level is significantly reduced in AD and Huntington's disease (HD). Knockdown of BDNF-AS leads to an increase in BDNF protein level, in fact, BDNF-AS interacts with PRC2 complex, thereby increasing the suppressive chromatin mark in the *BDNF* promoter region (Policarpo et al. 2021).

Parkinson

The activation of inflammasomes and G1 and subsequent secretion of pro-inflammatory cytokines exert an important role in neurodegeneration and neuroinflammation in Parkinson's disease (PD) (Haque et al. 2020). The accumulation of the aberrant protein of α-synuclein (α-syn) which is a pathologically relevant protein of PD can activate the NLRP3 inflammasome in microglia leading to a cascade of neuroinflammation (Li et al. 2021a). In addition, other factors like iNOS play a key role in the pathogenesis of PD (Yadav et al. 2017). The levels of some LncRNAs are reported to change in patients (Taghizadeh et al. 2021). Indeed, LncRNAs finetune several pathways regulating neuroinflammation like Wnt/β-catenin which is considered to be a critical player in signaling pathways for maintenance and cellular hemostasis (Ramakrishna et al. 2023). *LncRNA MALAT1* expression was increased in patients with PD leading to more severe inflammation (Table 1) (Cai et al. 2020a). Moreover, *LncRNA IL6ST-AS* is upregulated in PD patients causing microglia activation (Table 1) (Lin et al. 2023). *LncRNA NEAT1* was over-expressed in MPTP-induced PD mice while the level of miR-374c-5p was downregulated. The inhibition and suppression of *NEAT1* increased the cell viability, and repressed cell apoptosis and autophagy. The viability and apoptosis of SH-SY5Y were analyzed by MTT assay and flow cytometry, respectively (Table 1) (Dong et al. 2021b). LncRNA *TUG1* was significantly expressed in the serum of PD patients, and a positive relation was found

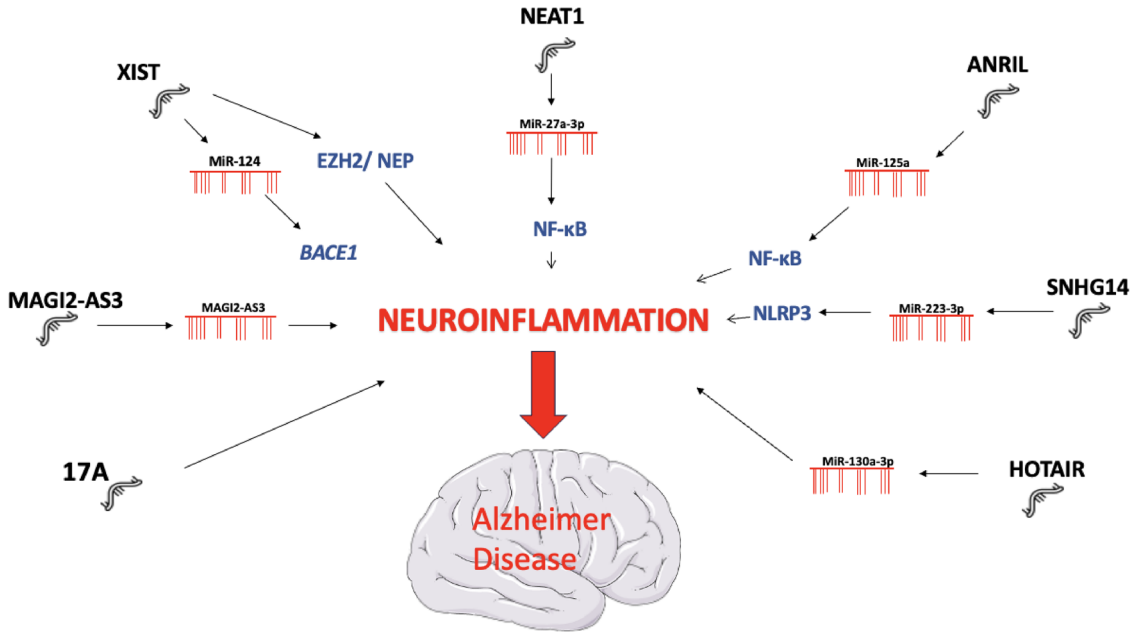

Fig. 1 A summary of the regulatory roles of LncRNAs in Alzheimer's Disease (AD) pathogenicity. LncRNAs mediate neuroinflammation through different mechanisms one of which is via sponging miRNAs, thereby regulating the downstream pathways and expression of targeted genes

between *TUG1* and pro-inflammatory cytokines. In fact, the downregulation of *TUG1* leads to the decrease of TNF-α, IL-6, and IL-1β, and inhibits cell proliferation (Cheng et al. 2021a). LncRNA *DLX6-AS1* has a pivotal role in promoting Neuropilin 1 (*NRP1*) expression by acting as ceRNA of miR-223-3p. Throughout this pathway, *DLX6-AS1* increases the inflammatory response caused by microglia (Liu et al. 2022a). *HOTAIR* was upregulated in PD sponging miR-221-3p which targets α-synuclein causing the regulation of α-synuclein expression; moreover, the knockdown of *HOTAIR* reduced inflammatory cytokines, cell apoptosis, and oxidative stress reaction (Sun et al. 2022). In a study with the animal experiment, the knockdown of *MIR17HG* expression decreased neuronal apoptosis, microglial activation, and α-synuclein; furthermore, LncRNA *Mir17hg* sponges miR-153-3p and increased the expression of α-synuclein causing microglial inflammation and neuronal apoptosis in PD (Zhang et al. 2022a). *BACE1-AS* is upregulated in MPP^+-stimulated SH-SY5Y cells while miR-214-3p is downregulated in PD patients. MiR-214-3p targets *R* and is over-expressed in patients suffering from PD. Throughout this pathway, *LncRNA BACE1-AS* mediates inflammation, apoptosis, and cell proliferation in SH-SY5Y cells (Li et al. 2022a). LncRNA *RMST* can be used as the diagnostic biomarker for PD since the level of LncRNA *RMST* in serum is at high levels in both PD patients and PD cell models; moreover, LncRNA *RMST* correlates positively with the level of inflammatory cytokines like TNF-α (Chen et al. 2022a). LncRNA *H19* can exert a role in the expression of *PIK3R3* by mediating miR-585-3p. In PD model mice, upregulation of *H19* leads to the attenuation of cell apoptosis (Zhang et al. 2020a). LncRNA *XIST* has been reported to have a role in the progression of PD. *XIST* which is upregulated in PD exacerbates the condition of PD through sponging miR-199a-3p to mediate *Sp1* expression and *LRRK2* (Zhou et al. 2021). In another case–control study, 78 patients and 78 gender-aged matched were collected. The results depicted that a negative association exists between LncRNA ANRIL and miR-34a and miR-125a in PD patients compared to the control group. To be more specific, LncRNA ANRIL levels were detected by ROC curve analyses which *LncRNA ANRIL* demonstrated the highest AUC (AUC: 0.879, 95% CI: 0.824–0.934). Moreover, the negative correlation among ANRIL, miR-34a, and miR-125a was statistically significant with miR-34a ($p = 0.016$) and miR-125a ($p = 0.005$) in PD patients but not in controls (Yang et al. 2022). In addition to LncRNAs, miRNAs are another class of non-coding RNAs with diverse biological functions. miRNAs could serve as potential regulators in different pathways such as TLR signaling in the pathogenesis of PD (Singh and Khatri 2024; Uppala et al. 2023). Moreover, miRNAs have untapped potential in the treatment (Tryphena et al. 2023).

Multiple Sclerosis

LncRNA *GAS5* has been recognized to be altered in multiple sclerosis (MS). The expression of *GAS5* has been elevated in MS which has downregulated the expression of *IRF4* by

Table 1 LncRNAs regulating neuroinflammation in Parkinson's disease (PD)

LncRNA	Mechanism	Function	Effects on inflammation	References
MALAT1	Inhibiting Nrf2 via regulating EZH2-mediated epigenetic repression	Increasing ROS levels and inflammasome activation	+	Cai et al. (2020a)
IL6ST-AS	JAK-STAT3 pathway is activated by the IL-6/IL6ST complex which is the target for IL-6	Stimulating an excessive immune response in glial cells, and neuronal necrosis	+	Lin et al. (2023)
MEG3	Regulating the expression of LRRK2	Improving cell viability and preventing apoptosis	−	Huang et al. (2021a)
NEAT1	NEAT1 binds to miR-374c-5p and downregulate miR-374c-5p in PD	Impacting in SH-SY5Y cells viability by regulating apoptosis and autophagy	+	Dong et al. (2021b)
TUG1	TUG1 sponges and mediate the expression of the miR-152-3p	Activating inflammation and cell apoptosis. Mediating miR-152-3p/PTEN pathway	+	Zhai et al. (2020)
DLX6-AS1	Function through the ceRNA mechanism of miR-223-3p/NRP1	Activation of microglial inflammatory response	+	Liu et al. (2022a)
HOTAIR	Sponging miR-221-3p which targets α-synuclein	Cell apoptosis and secretion of inflammatory cytokines	+	Sun et al. (2022)
MIR17HG	MIR17HG sponges miR-153-3p and regulates the secretion of α-synuclein	Neuronal apoptosis and microglial inflammation	+	Zhang et al. (2022a)
BACE1-AS	LncRNA BACE1-AS regulates the expression of miR-21IT24-3p which mediates CDIP1	Inflammatory responses, cell apoptosis, cell proliferation	+	Li et al. (2022a)
RMST	MiR-150-5p binds to *RMST*	By targeting miR-150-5p, RMST mediates inflammatory responses and cell apoptosis	+	Chen et al. (2022a)
H19	H19 sponges miR-585-3p which increases the expression of PIK3R3	Attenuation of neuron apoptosis	−	Zhang et al. (2020a)
SNHG1	Binding to miR-181a-5p, and regulating the expression of CXCL12	Elevating MPP^+ induced neuronal injury, and apoptosis	+	Wang et al. (2021a)
JHDM1D-AS1	Sponging miR-134-5p to increase the expression of PIK3R3	Attenuating neuronal apoptosis, inflammation, and oxidative stress	−	Wang et al. (2021b)
BDNF-AS	Sponging miR-125b-5p	Promoting cell apoptosis, and inflammatory responses	+	Fan et al. (2020)
XIST	Binding to miR-199a-3p to mediate the expression of Sp1 and LRRK2	Promoting the progression of PD by cell apoptosis	+	Zhou et al. (2021)
ANRIL	MiR-125a and miR-34a are the target genes of ANRIL	Cell apoptosis and neuronal injury	+	Yang et al. (2022)

binding with EZH2; thus, it can suppress the M2 polarization (Table 2) (Chen et al. 2021b). Moreover, LncRNA *Gm13568* regulates inflammatory cytokines secretion such as IL-6, TNF-α, and IP-10 through the expression of *NOTCH1* and phosphorylation of signal transducer and activator of transcription 3 (p-STAT3) (Table 2) (Liu et al. 2021a). LncRNA *NEAT1* and *KCNQ1OT1* were upregulated in MS patients. They exert an indispensable role in the $CD4^+$ T differentiation cells into Th17 cells which causes the upregulation of IL-17 and downregulation of TGF-β inflammatory cytokines (Karimi et al. 2022). *MALAT1* expression is decreased in the spinal cord of EAE mice by specific siRNA which improves the polarization of M1. Downregulation of *MALAT1* can induce changes in the T-cell differentiation which derives Tregs phenotypes from T-cells instead of Th1/Th17 cells (Masoumi et al. 2019).

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that is characterized by motor dysfunction following the death of motor neurons which manifests in muscle stiffness (Karimi et al. 2022). Human imaging studies and rodent studies suggest the role of neuroinflammation in the progression of ALS (McCauley and Baloh 2019). Although there have been many studies conducted on ALS pathogenesis, ALS remains an unknown disease in many aspects, and the molecular mechanism inducing neurodegeneration in ALS has not been completely discovered (Ruffo et al. 2023). Several paraspeckles have been identified to induce neurotoxicity in ALS patients, one of which is LncRNA *NEAT1-2* which forms a specific paraspeckle in ALS patients. LncRNA *NEAT1-2* is upregulated in ALS

Table 2 The role of LncRNAs mediating neuroinflammation in Multiple Sclerosis (MS)

LncRNA	Mechanism of action	Functions	Animal/cell	Models	Effect on inflammation	References
GAS5	Binding with EZH2 to mediate the expression of *IRF4*	It regulates microglial activation and M2 polarization	Animal/mice	EAE	+	Chen et al. (2021b)
Gm1358	Regulating the expression of *NOTCH1*, and phosphorylation of STAT3	Mediating inflammatory cytokines and chemokines synthesis in active astrocytes	Animal/mice	EAE	+	Liu et al. (2021a)
NEAT1 and KCNQ1OT1	Increasing RORC, and decreasing in the expression of FOXP3	Upregulation of IL-17, and downregulation of TGF-β inflammatory cytokines	Th17 cells in MS patients	–	+	Karimi et al. (2022)
MALAT1	*MALAT1* is downregulated by specific siRNA	Increasing the T-cell proliferation, and differentiation of Tregs phenotypes from T-cell	Mice	EAE	–	Masoumi et al. (2019)
HOTAIR	No accessible data	It was upregulated in VD-deficient serum compared to normal serum. It affects the expression of VD-related genes and inflammation	Mice	EAE	+	Pahlevan Kakhki et al. (2018)
GSTT1-AS1	Recruiting EZH2 enzyme to facilitate *H3K27* methylation	A significant and positive association was found with *TNF* genes	Patients	–	+	Ganji et al. (2019)

patients increasing the formation of paraspeckle and inducing neurotoxicity (Suzuki et al. 2019). LncRNA *MALAT1* is reported to exert a pivotal role in the pathogenesis of ALS. *MALAT1* regulates the expression of *SYNRG*, *ITSN2*, *PICALM*, *AP3131*, and *AAK1* genes which are potentially important in the pathogenesis of ALS (Liu et al. 2021b). Another LncRNA reported to have a major role in ALS is *C9Orf72-AS* which has the reverse repeat sequence of the causative hexanucleotide of ALS disease; in addition, this LncRNA can cause an indirect regulation of gene expression and RBPs sequester (Ruffo et al. 2023).

Frontotemporal Dementia

Frontotemporal Dementia (FTD) is considered to be a neurodegenerative disease impairing the frontal and temporal lobes of the brain (Rasmussen et al. 2019). *C9ORF72* is reported to be the most significant gene in ALS/FTD with a hexanucleotide (GGGGCC) expansion within the first intronic region of the *C9ORF72* gene (Douglas 2018). The repetition of this specific hexanucleotide expansion goes through translation producing five dipeptide repeat proteins (DPRs). Poly-Proline-Arginine (Poly-PR), the extremely toxic DPR, binds and upregulates *NEAT1* which induces neurotoxicity in FTD (Suzuki et al. 2019). *NEAT1-1* upregulation can induce protection in TDP-43 proteinopathies, and it can attenuate TDP-43 toxicity in FTD (Matsukawa et al. 2021). *NEAT1* is suggested to be mediating neuroinflammation during FTD pathogenesis (Serpente et al. 2024).

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disease manifested by dyskinesia, cognitive impairment, and neuropsychological dysfunction. LncRNA *NEAT1* and *MEG3* can regulate and alter the expression of p53 which leads to the repression of specific genes in HD. LncRNA *NEAT1* is downregulated in mice models with HD, and upregulation of LncRNA *NEAT1* can have a protective role against neuronal damage and attenuate neuroinflammation (Tan et al. 2021a); furthermore, CREB and p53 can stimulate and alter the expression of *MEG3* which can play a role in neurotoxicity (Chanda et al. 2018). Repression of *MEG3* which acts as a ceRNA can attenuate neurological impairment and protect against neuronal ischemic injury (Luo et al. 2020). Also, it is suggested that the *BDNF-AS* level is changed in HD resulting in the regulation of *BDNF* which has been reported to be playing an important role in the pathogenesis of HD (Corey-Bloom et al. 2014). *TUG1* expression which is regulated by p53 is elevated in HD; moreover, it plays a protective role against the cytotoxic effects induced by mHTT (Johnson 2012). LncRNA *DNM3OS* is upregulated in patients with HD which can sponge miR-196b-5p and decrease its expression. LncRNA *DNM3OS* downregulation reduces cell apoptosis and increases cell viability (Ghafouri-Fard et al.

2022). LncRAN *DGCR5*, which is also known as *linc00037*, expression level has been altered in HD which implies that *DGCR5* is tightly correlated with transcriptional regulation in the progression of HD (Ni et al. 2022).

Epilepsy

Epilepsy is a neuro-related disease which is characterized by neuronal network dysfunction. Neuroinflammation has been suggested to be exerting a fundamental role in the progression of epilepsy (Soltani Khaboushan et al. 2022). LncRNAs are aberrantly expressed in both patients and animal models which brings the potential mechanism of LncRNAs in epileptogenesis and progression of epilepsy (Kuang et al. 2023). LncRNA *MALAT1* expression is altered in patients with epilepsy. Knockdown of *MALAT1* may have a protective role against epilepsy via the activation of the PI3K/Akt signaling pathway, which prevents the apoptosis and autophagy of hippocampal neurons (Fig. 1) (Wu and Yi 2018). LncRNA *TUG1* expression level is elevated during epilepsy; moreover, *TUG1* sponges miR-199a-3p leading to the regulation of hippocampal neuron cell activity and apoptosis (Fig. 2) (Li et al. 2021b). LncRNA *ZFAS1* serum levels are higher in patients suffering from temporal lobe epilepsy (TLE). LncRNA *ZFAS1* increases neuronal apoptosis and inflammation which implies the diagnostic biomarker of *ZFAS1*; furthermore, LncRNA *ZFAS1* mediates neuroinflammation by regulating the release of cytokines such as TNF-α, IL-1, and IL-6, and boosting NF-κB activation (He et al. 2021a). LncRNA *ZNF883* regulates the development of epilepsy by mediating NLRP3 inflammasome activation. *ZNF883* targets miR-138-5p which negatively regulates ubiquitin-specific peptidase 47 (USP47), which reverses the ubiquitination of NLRP3 (Gong et al. 2022). The serum level of *UCA1* is elevated in epileptic patients. *UCA1*, which regulates the autophagy gene expression, constitutes a complex formation with miR-132-3p and the transcriptional factor of EZH2. MiR-132-3p is negatively correlated with *ATG16L1*; in addition, LncRNA UCA1 exacerbates the epilepsy condition by promoting autophagy gene expression by epigenetic regulation via *ATG16L1* and miR-132-3p (Wen et al. 2022). LncRNA *ZFAS1* plays a pivotal regulatory role in epilepsy development. LncRNA *ZFAS1* sponges miR-15a-5p which upregulates the expression of oxidative stress responsive (*OXSR1*). To put it simply, throughout the *ZFAS1*/miR-15a-5p/*OXSR1* pathway, the NF-κB pathway is activated and a neuroinflammatory response is induced (Wang et al. 2022a). LncRNA *PVT1* has been proven to exert an important role in regulating inflammatory response and neuronal

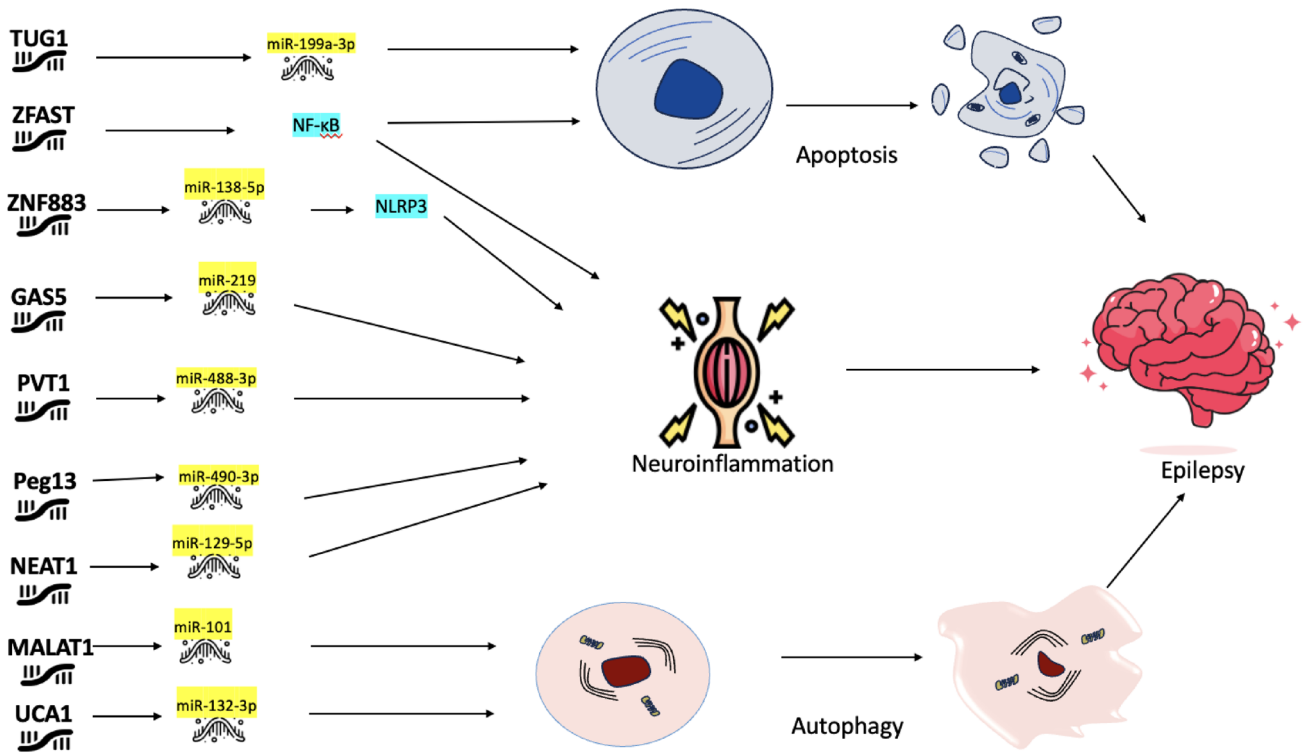

Fig. 2 A synopsis of the mechanisms of actions of LncRNAs in epilepsy. LncRNAs regulate many mechanisms of the cell. Indeed, LncRNAs orchestrate neuroinflammation, apoptosis, and autophagy in the pathogenesis of Epilepsy through sponging miRNAs and, thus, regulating downstream pathways

cell injury. LncRNA *PVT1* sponges miR-488-3p to mediate the *FOXD3*/*SCN2A* pathway causing neuronal cell injury and inflammatory responses in epilepsy (Fig. 2) (Wen et al. 2023). LncRNA *GAS5* regulates the expression of inflammatory cytokines and inflammatory responses by binding to EZH2 which inhibits miR-219 causing cell apoptosis and exacerbation of inflammation. Moreover, LncRNA *GAS5* regulates the CaMKIIγ/*NMDAR* pathway (Fig. 2) (Zhao et al. 2022b). LncRNA *NEAT1* is over-expressed in epilepsy and plays a pivotal role in neuroinflammation regulation. *NEAT1* sponges miR-129-5p, causing an elevation in the expression of IL-6, *COX2*, TNF-α, and *Notch1*; indeed, *NEAT1* regulates the *Notch1* signaling pathway in the IL-1β-induced epilepsy cell model (Fig. 1) (Wan and Yang 2020). LncRNA *H19* is over-expressed after status epilepticus which is probably caused by epileptic seizure-induced hypoxia. LncRNA *H19* targets let-7b through the ceRNA to suppress the overexpression of *H19*. Overexpression of let-7b inhibits hippocampal glial cell activation, inflammatory response, and epileptic seizure by targeting Stat3 (Han et al. 2020). LncRNA *SNHG1* sponges miR-154-5p to maintain the expression of Toll-like receptor (TLR)−5. The serum level of *SNHG1* which is elevated during epilepsy promotes neuronal injury in SH-SY5Y (Zhao et al. 2020a). LncRNA *Peg13* regulates the expression of *Psmd11* by sponging miR-490-3p. *Peg13* suppressed the progression of epilepsy by upregulating *Psmd11* which suppresses the Wnt/β-catenin pathway. *Psmd11* overexpression inhibits cell apoptosis and suppresses the microglia and astrocytes activation which leads to the reduction of inflammatory response in epilepsy (Fig. 2) (Feng et al. 2020). LncRNA *XIST* expression is elevated during epilepsy causing an increase in the expression level of IL-1β, IL-6, and TNF-α. LncRNA *XIST* sponges miR-29c-3p which maintains the expression of *NFAT5*. LncRNA *FTX* sponges miR-142-5p to regulate *GABPB1* expression. The overexpression of FTX attenuates ferroptosis of MGF-induced neurons via the *GABPB1*/miR-142-5p axis (Zhang et al. 2023). LncRNA MEG3 could be used as a therapeutic target for epilepsy treatment since it decreased the expression of pro-inflammatory cytokines, oxidative stress, neuronal apoptosis, and improved cell viability by activating PI3K/AKT/mTOR pathway in TLE rats. *MEG3* expression was downregulated in TLE rats (Zhang et al. 2020b). LncRNA *HOXA-AS2* has a positive correlation with mRNA STAT3. The expression levels of *HOXA-AS2* and *STAT3* are elevated during epilepsy while miR-372-3p is downregulated. By regulating the miR-372-3p/*STAT3* axis by *HOXA-AS2*, *HOXA-AS2* could exert a key role in the anti-epilepsy therapeutic method (Lixiang et al. 2022). Another LncRNA that regulates neuroinflammation in epilepsy is LncRNA *ILF3-AS1*. The inflammatory cytokines expression like IL-1β and TNF-α may lead to the expression of *ILF3-AS1 in* astrocytes which sponges miR-212 causing lower expression of miR-212 in TLE patients. *ILF3-AS1* has a critical role in the progression of TLE (Cai et al. 2020b) (Table 3).

LncRNAs Orchestrating Neuroinflammation in Traumatic Diseases

Spinal Cord Injury

Spinal Cord Injury (SCI) is manifested by high mortality and high rates of disability. In SCI, the mechanical insult leads to the blood-spinal cord barrier destruction and the rupture of topical capillaries. Neuronal disconnection and signaling transduction failure can be the consequences caused by the SCI (Li et al. 2023a). Oxidative stress, inflammation, and neuronal apoptosis have been recognized to be the secondary injury mechanism in SCI (Kimura et al. 2021). Neuroinflammation is embarked with the activation of TLR4, and pyroptosis is regulated by TLR4 via LncRNA. LncRNA *F630028O10Rik* has been identified to promote post-SCI microglial pyroptosis through PI3K/AKT pathway activation and functions as a ceRNA for miR-1231-5p/col1a1 axis. Moreover, *STAT1* was upregulated by the damage-responsive TLR4/MyD88 signaling (Xu et al. 2020). LncRNA *GBP9* could regulate neuroinflammation after SCI by regulating M1 macrophages. *GBP9* sponges miR-34a which induces the expression of *SOCS3* mRNA. *GBP9* regulates macrophage polarization via *STAT1*/*STAT6* signaling (Zhou et al. 2020b). *NEAT1* plays a key role in mediating neuronal apoptosis by inhibiting miR-29b. Downregulation of *NEAT1* decreased the expression of *GFAP* and elevated the *GAP43*, *SG10*, and *NCAM* expression (Bai et al. 2021). LncRNA *MIAT* has a therapeutic potential after SCI. Motor function recovery is induced by *MIAT* overexpression; It improves the morphology of injured tissues and regenerates neuron loss. *MIAT* regulates RBFOX2 protein expression by targeting it which causes the upregulation of anti-apoptotic *MCL-1L* and downregulation of pro-apoptotic *MCL-1S*. *MIAT* suppresses H2O2 which decreases cell viability and increases cell apoptosis (He et al. 2022). LncRNA *TSIX* is upregulated in SCI. Silencing *TSIX* would have a therapeutic effect by minimizing the lesion size, inhibiting inflammatory response, and decreasing cell apoptosis. Furthermore, *TSIX* binds to miR-3a via the ceRNA mechanism competing with *SOCS3* which is downregulated in SCI (Pan et al. 2023). LncRNA *NEAT1* could have some therapeutic potential. In fact, it enhanced the pro-inflammatory cytokines, including the expression of IL-6, IL-1β, and TNF-α. Moreover, it regulates the AQP4 signaling pathway to mitigate SCI by elevating miR-128-3p expression (Xian et al. 2021). Lithium exerts a therapeutic role in SCI by reducing the inflammatory responses through nuclear factor-kappa B (NF-κB) pathway inactivation; in

Table 3 A synopsis of LncRNA mechanisms regulating neuroinflammation in epilepsy

LncRNA	Mechanism of action	Function	Model	Effect on inflammation	References
TUG1	Sponging miR-199a-3p	Apoptosis and neuron cell activity and cell viability	TLE children	+	Li et al. (2021b)
ZFAST	Mediating the NF-κB activation pathway	Regulating apoptosis and inflammatory response	TLE patients	+	He et al. (2021a)
UCA1	*UCA1* sponges miR-132-3p and forms a complex formation with *EZH2*	Promoting autophagy gene expression	Cell model	+	Wen et al. (2022)
MALAT1	Regulating c-Met through binding to miR-101, also regulates the PI3K/Akt signaling pathway	Autophagy and apoptosis of hippocampal neurons	Mice model	+	Wu and Yi (2018)
ZNF883	*ZNF883* increases the epilepsy through sponging miR-138-5p to upregulate *USP47*. It also inhibits NLRP3 ubiquitination	Neuroinflammation and apoptosis	Mice model and cellular model	+	Gong et al. (2022)
CASC2	*CASC2* binds to *PTEN* which promotes the protective effect of *CASC2*	Apoptosis and astrocyte activation	Mice model	−	Zhu et al. (2020)
ZFAS1	There is a positive association between *ZFAS1* and *OXSR1* via sponging miR-15a-5p and activating the NF-κB pathway	Regulates neuroinflammation, and cell apoptosis	Cellular model	+	Wang et al. (2022a)
PVT1	*PVT1* inhibits the expression of miR-488-3p and regulates the *FOXD3*/*SCN2A* pathway	Mediating neuronal cell injury and inflammatory responses	Cellular and animal model	+	Wen et al. (2023)
GAS5	*GAS5* binds to *EZH2* which inhibits miR-219 expression and regulates CaMKIIγ/NMDAR pathway	Regulating inflammatory response and cell apoptosis	Cell model	+	Zhao et al. (2022b)
NEAT1	Sponging miR-129-5p and mediating pro-inflammatory cytokines release	Regulating neuroinflammation, and Notch signaling pathway	Cell model	+	Wan and Yang (2020)
H19	LncRNA *H19* targets let-7b via ceRNA to promote the activation of hippocampal glial cell by binding Stat3	Inflammatory response, and epileptic seizure	Mice model	+	Han et al. (2020)
SNHG1	Regulating the expression of miR-154-5p which binds to TLR5	Promoting neuronal cell injury	Mice model	+	Zhao et al. 2020a)
OIP5-AS1	*OIP5-AS1* interacts with miR-128-3p	Cell apoptosis	Mice model	+	Ye et al. (2023)
KCNQ1OT1	miR-138-5p/NF κB/*ABCB1* axis	Mediating the inflammatory response	Mice and cell model	+	Xie et al. (2019)
Peg13	LncRNA *Peg13* sponges miR-490-3p to upregulate *Psmd11*	Mediating inflammatory response and astrocytes and microglia activation	Mice model	−	Feng et al. (2020)
XIST	By sponging miR-29c-3p and regulating *NFAT5* expression	Inflammatory cytokines secretion	Mice model	+	Zhang et al. (2021a)
H19	*H19* mediates P-gp expression and neuronal damage through the NF-κB signaling pathway	Regulating the P-glycoprotein expression	Mice model	NA	Xie et al. (2023)
FTX	Mediating the miR-142-5p/*GABPB1* axis	MGF-induced neurons undergo ferroptosis and apoptosis	Mice model	−	Zhang et al. (2023)
MEG3	Activating PI3K/AKT/mTOR pathway	Reduction of the expression of IL-1β, IL-6, TNF-α, and apoptosis rate	Mice model	−	Zhang et al. (2020b)

Table 3 (continued)

LncRNA	Mechanism of action	Function	Model	Effect on inflammation	References
HOXA-AS2	Targeting miR-372-3p/*STAT3* axis	Regulating the expression of inflammatory cytokines and cell apoptosis	Mice Model	+	Lixiang et al. (2022)
ILF3-AS1	Targeting miR-212 which promotes the expression of inflammatory cytokines and MMPs	Mediating the expression of inflammatory cytokines and matrix-metalloproteinases (MMPs)	Patient Model	+	Cai et al. (2020b)

fact, Lithium mediates inflammatory responses and apoptosis by inducing LncRNA *BDNF-AS* expression and downregulation of miR-9-5p (Wang et al. 2021c). LncRNA *MEG* can regulate neuronal apoptosis by promoting the expression of *PDCD4* via miR-21-5p inhibition (Wang et al. 2021d). LncRNA *TUG1* plays a pivotal role in SCI biogenesis. It also mediates the NF-κB signaling pathway and the release of inflammatory cytokines via targeting miR-1192. In addition, *TUG1* and *TLR3* compete with each other for binding to miR-1192 which protects *TLR3* against degradation causing overexpression of *TLR3* and subsequently activating the downstream NF-κB signaling pathway. The LncRNA *TUG1*/miR-1192/*TLR3* axis is a key pathway for BPM to induce the inhibition of M1 macrophage polarization (Ju et al. 2023). LncRNA *FTX* could affect the microglial inflammatory response, to be more specific, MiR-382-5p could target both *FTX* and *NRG1*. The competition between *FTX* and *NRG1* for binding to miR-382-5p could lead to the inhibition of NRG1. Throughout the LncRNA *FTX*/miR-382-5p/*NRG1* axis, inflammatory responses of microglia could be improved, which could have a therapeutic effect on SCI (Xiang et al. 2021). LncRNA *Airsci* was the most significantly expressed LncRNA involved in the NF-κB pathway. Indeed, it reduces the inflammatory responses by NF-κB pathway inhibition, and likewise, *Airsci* attenuates the SCI and improves motor function recovery in SCI rats (Zhang et al. 2021b). LncRNA *CASC9* attenuates inflammation, oxidative stress, and cell apoptosis in SCI. It regulates apoptosis and expression of protein LDHA. Moreover, CASC9 sponges miR-383-5p, which targets LDHA; thus, it could be a promising prognostic factor or a therapeutic target (Guan and Wang 2021). LncRNA *SNHG5* enhances SCI by making astrocytes and microglia more viable. *SNHG5* is upregulated in SCI, and targets *KLF4* to repress apoptosis (Jiang and Zhang 2018). LncRNA *ZFAS1* which is upregulated in SCI targets miR-1953; besides, PTEN has been identified to be the downstream target of miR-1953. *ZFAS1* suppresses the PI3K/AKT pathway via upregulating *PTEN* (Chen et al. 2021c). LncRNA *XIST* which is upregulated in SCI can promote inflammation by inducing M1 macrophage polarization and cytokines concentration. Also, it sponges miR-124-3p and mediates *IRF1* expression to promote the level of inflammatory cytokines (Yang et al. 2023). LncRNA *H19* is upregulated in SCI and sponges miR-370-3p, which could block the NF-κB pathway by upregulating miR-370-3p. Restrained expression of LncRNA *H19* could attenuate SCI and inhibit ROS genesis (Li et al. 2021c). LncRNA *JHDM1-AS* could exert a protective function against neuronal apoptosis and microglial inflammation via reactivating *DUSP1* mRNA. Through the ceRNA mechanism, *JHDM1D-AS* binds to miR-101-3p, which bounds on the 3′UTR of DUSP1 (Liu et al. 2020b). The expression of *PTENP1* is upregulated in SCI. *PTENP1* restrained the miR-21 and miR-19b

expression, but it upregulated the *PTEN* expression, thereby *PTENP1* induces neuronal apoptosis (Wang et al. 2020b). LncRNA *HOTAIR* is upregulated in SCI. The knockdown of *HOTAIR* restrains oxidative stress, inflammatory injury, and neuronal apoptosis by inhibiting the ROS/NF-κB signaling pathway which induces the downregulation of *HMGB1* (Wang et al. 2022b). LncRNA *MALAT1* orchestrates inflammatory responses and neuronal apoptosis by regulating miR-199a-5p which binds to *PRDM5* (Guo et al. 2021) (Table 4).

Brain Injury

Traumatic Brain Injury (TBI) is considered to be one of the two main traumas of CNS which is caused by a mechanical and physical insult. TBI has severe consequences on the patient's life, such as disability and impairment of cognitive functions. The expression level of different LncRNAs altered in the injured and insulted CNS (Wu et al. 2022). LncRNA *PRR34-AS1* could exert a therapeutic target for TBI. In fact, *PRR34-AS* which is upregulated in injured model cells targets microRNA-498 in primary cortical neurons; moreover, via inhibiting the expression of *PRR34-AS1*, synthesis of inflammatory mediators and apoptosis are suppressed (Jin et al. 2023). LncRNA *KCNQ1OT1*, which exerts a pivotal role in TBI development, sponges miR-873-5p through the competitive endogenous RNA (ceRNA) mechanism. To be more specific, miR-873-5p targets 3′UTR of *TRAF6*. *KCNQ1OT1* mediates neuroinflammation by activating *TRAF6*-mediated p38 and NF-κB pathways (Liu et al. 2021c). LncRNA-*AK046375* could have a therapeutic role in TBI. *AK046375* sequesters miR-491-5p which improves the metallothinoein-2 (MT2) and induces mitigation in oxidative-induced cell injury. Indeed, it enhances the recovery of motor, learning, and memory functions after TBI (Tang et al. 2022). The expression level of *MEG3* is altered in TBI. *MEG3* and inflammatory cytokines have a negative association with each other; therefore, *MEG3* and inflammatory cytokines could be applied as means for the prognosis and diagnosis of TBI (Shao et al. 2019). The increase in the expression of LncRNA *MALAT1* inhibits brain edema in TBI and decreases the expression level of IL-6, NF-κB, and AQP4. It also mediates neuroinflammation by activating the downstream IKKβ/NF-κB signaling pathway via sponging miR-199b (Wang et al. 2022c). By silencing the expression of *ZFAS1* which is upregulated in TBI, the production of inflammatory factors is reduced and the apoptotic gene expression level is decreased, (Feng et al. 2021). LncRNA *HOXA11-AS*, which can promote neuroinflammation after TBI, increases brain edema, apoptosis, and also enhances the pro-inflammatory cytokines secretion, such as IL-1β, IL-6, and TNF-α. Furthermore, *HOXA11-AS* knockdowns the expression of miR-124-3p and upregulates the expression of *MDK* and TLR4-NF-κB pathway. LncRNA *MALAT1* is downregulated in TBI which plays a key role in astrocytes swelling and brain edema. Upregulation of *MALAT1*, which can be applied as a therapy for TBI, can reduce inflammatory responses, such as IL-6, NF-κB, and AQP4 expression after TBI (Zhang et al. 2019). LncRNA *GM4419* regulates neuroinflammation in TBI by increasing the expression level of TNF-α which leads to apoptosis in astrocytes (Lim et al. 2020). LncRNA *NKILA*, which has therapeutic potential for TBI, mediates inflammation and apoptosis in TBI; moreover, it competitively binds to miR-195 which directly targets *NLRX1* (He et al. 2021b) (Table 5).

Ischemic and Hemorrhagic Stroke

Stroke is a global health issue that has a high rate of incidence in both developing and developed countries. Stroke is also identified as the main cause of disability (Zhao et al. 2022a). There are two main types of strokes making the majority of stroke patients: ischemic and hemorrhagic stroke (Ewida et al. 2021). LncRNA *ZFAS1* is identified to have a therapeutic potential in cerebral ischemia–reperfusion injury (CI-RI). In fact, the expression level of *ZFAS1* is significantly decreased in patients with ischemic stroke. Furthermore, *ZFAS1*, which regulates the miR-582-3p expression via sponging it, could attenuate neuronal injury, inflammation, oxidative stress, and neuronal apoptosis (Zhang and Zhang 2020). The expression level of LncRNA *MALAT1* is elevated during CI-RI. It is also reported to promote CI-RI via binding to miR-145 with the ceRNA mechanism, which affects the expression of AQP4 (Wang et al. 2020c). LncRNA *MALAT1* is also identified to regulate miR-30a expression in cerebral ischemic stroke. Moreover, downregulation of *MALAT1* mitigated neuronal injury and cell death via suppressing Beclin1-dependent autophagy. Indeed, *MALAT1* targets miR-30a and has a negative correlation with it (Fig. 3) (Guo et al. 2017). LncRNA *MALAT1* is also closely associated with the occurrence and development of CI-RI, in fact, the expression level of *MALAT1* is significantly elevated and miR-211-5p is decreased in the peripheral blood of stroke-affected patients. LncRNA *MALAT1* acts on miR-211-5p to mediate *COX2* expression (Tan et al. 2021b). The elevated expression of *MALAT1* promotes cell proliferation and inhibit OGD/R-induced cell necrosis and apoptosis. Furthermore, LncRNA *MALAT1* can regulate neuroinflammation by reducing the level of TNF-α, IL-6, IL-1β, and ROS significantly ($P < 0.001$). It is negatively associated with miR-142-3p; in fact, *MALAT1* regulates the expression of *SIRT* by sponging miR-142-3p to improve CI-RI. LncRNA *MALAT1* is considered to function as a key player in inflammatory injury after brain ischemia (Cao et al. 2020c). LncRNA *H19* is identified to play a key role in the inflammation regulation after the subarachnoid hemorrhage

Table 4 A brief summary of LncRNA mediating neuroinflammation in Spinal Cord Injury (SCI)

LncRNA	Function	Mechanism	Model	Effect on inflammation	References
MIAT	Attenuating SCI, increasing cell viability, and decreasing cell apoptosis	Enhancing *RBFOX2*-mediated alternative splicing of *MCL-1*	Mice model	−	He et al. (2022)
MIAT	Inhibiting neuronal cell apoptosis and increasing cell viability	Overexpression of LncRNA *MIAT* activates *VEGFA* via *RAD21*	Mice model	−	Li et al. (2021d)
NEAT1	Attenuating SCI and regulating inflammatory cytokines	Elevating miR-128-3p expression	Mice model	−	Xian et al. (2021)
TSIX	Knockdown of *TSIX* promotes the recovery and mitigates SCI by inhibiting inflammatory responses and cell apoptosis	Following the miR-3a/*DOCS3* axis	Mice model	+	Pan et al. (2023)
BDNF-AS	Regulating inflammatory responses, and apoptosis	Reducing the expression of miR-9-5p	Mice model	−	Wang et al. (2021c)
TSIX	Apoptosis and inflammation	Exacerbating SCI by mediating PI3K/AKT pathway via miR-532-3p/DDOST axis	Mice model	+	Dong et al. (2023)
MEG	Regulating neuronal cell apoptosis	*MEG* regulates *PDCD4 expression* in SCI by miR-21-5p	Mice model	+	Wang et al. (2021d)
RMRP	Regulating proliferation and apoptosis	*RMRP* targets miR-766-5p which targets *FAM83A*	Mice model	−	Hong et al. (2022)
GAS5	Apoptosis and inflammation	Inhibiting *MMP-7*, cleaved caspase −3, and IL-1β	Mice model	+	Zhang et al. (2021c)
Vof-16	Regulating inflammation and apoptosis	NA	Mice model	+	Zhang et al. (2022b)
Kcnq1ot1	Apoptosis of neuronal cells	Transcription factor *STAT3* induces Kcnq1ot1 and regulates apoptosis by silencing p27 via recruiting *EZH2*	Mice model	+	Jiang et al. (2022)
Kcnq1ot1	Inflammatory response and apoptosis	Regulating the miR-589-5p/*NPTN* axis	Mice model	+	Chu et al. (2022)
MEG3	Regulating neuroinflammation, and mediating M1 polarization of microglia	HuR/A20/NF-κB axis	Mice model	−	Zhou et al. (2022a)
TCTN2	Mitigating neuronal apoptosis, inflammation, and oxidative stress	Targeting miR-329-3p to regulate the expression of *IGF1R*	Mice model	−	Liu et al. (2022b)
TCTN2	Apoptosis and autophagy	Targeting the miR-216b-Beclin-7 pathway	Mice model	−	Ren et al. (2019)
ZNF667-AS	Regulating inflammatory response and SCI recovery	JAK-STAT pathway suppression	Mice model	+	Li et al. (2018a)
XIST	Orchestrating inflammation, and apoptosis	miR-270/Smurf axis	Mice model	+	Zhao et al. (2020b)
F630028O10Rik	Enhancing microglial pyroptosis	Activating PI3K/AKT	Mice model	+	Xu et al. (2020)
GBP9	Macrophage polarization	Sponging miR-34a to upregulate the *SOCS3* expression	Mice model	+	Zhou et al. (2020b)
NEAT1	Neuronal apoptosis	Regulating the expression of *GFAP* by sponging miR-29b	Mice model	+	Bai et al. (2021)
NEAT1	Neuronal differentiation, apoptosis, and migration of *SC-NPCs*	Regulating miR-124-Neat1-Wnt/β-catenin signaling axis	Mice model	+	Cui et al. (2019)
GAS5	Orchestrating inflammation and apoptosis in SCI	*GAS5* sponges miR-93 which targets *PTEN*	Mice model	+	Cao et al. (2021b)
LEF1-AS1	Apoptosis and inflammation	MiR-222-5p/*RAMP3* axis	Mice model	+	Cui et al. (2021)

Table 4 (continued)

LncRNA	Function	Mechanism	Model	Effect on inflammation	References
MALAT1	Modulating autophagy and nerve cell apoptosis	The over- expressed *MALAT1* decreases OGD/R -induced apoptosis rate and improves Nrf2 nuclear translocation	Mice model	–	Hu et al. (2023)
LINC00158	Mediating apoptosis and inflammation	NA	Mice model	–	Qin et al. (2022)
H19	Pyroptosis and inflammation in SCI	Regulating pyroptosis via miR-181a-5p/*HMGB1* pathway	Mice model	+	Guo et al. (2022)
GM37494	Suppressing inflammatory cytokines expression, and inducing the M1-to- M2 shift of microglia	Targeting miR-130b-3p and enhancing PPARγ expression	Mice model	–	Shao et al. (2020)

Table 5 LncRNA playing a regulatory role in Brain Injury pathogenesis

LncRNA	Function	Mechanism of action	Model	Effect on inflammation	References
PRR34-AS1	Production of inflammatory cytokines, regulating apoptosis	Sponging miR-498	Mice model	+	Jin et al. (2023)
GAS5	Regulating inflammatory responses, and injury severity	NA	Patient model	+	Lei et al. (2022)
HOTAIR	Orchestrating neuroinflammation and microglia activation	Promoting Nrdp1-mediated ubiquitination of MYD88 protein	Mice model	+	Cheng et al. (2021b)
KCNQ1OT1	Neuroinflammation and microglial activation	Regulating the miR-873-5p- TRAF6-p38/NF-κB axis	Mice model	+	Liu et al. (2021c)
AK046375	Alleviating apoptosis, inhibiting oxidative stress, and promoting motor and memory function	Sequestring miR-491-5p which promotes *MT2* expression	Mice model	–	Tang et al. (2022)
ZFAS1	Regulating apoptosis and inflammatory response	NA	Mice Model	+	Feng et al. (2021)
HOXA11-AS	Promoting neuroinflammation and microglial activation	Regulating the miR-124-3p-*MDK* axis	Mice model	+	Li et al. (2022b)
SNHG3	Mediating neuroinflammation and pyroptosis	Regulating *NEK7*/NLRP3 axis	Mice model	+	Liang et al. (2023)
NKILA	Regulating neuroinflammation and apoptosis	*NKILA* binds to miR-195 which increases the expression level of *NLRX1*	Mice model	–	He et al. (2021b)
NEAT1	Inflammatory response, and apoptosis	*NEAT1*/miR-31-5p/Myd88 axis	Mice model	+	Wang et al. (2022d)

(SAH). LncRNA *H19* is reported to mediate *NLRP3* expression. In fact, there is a positive association between LncRNA *H19* and *NLRP3* inflammasome. Both *NLRP3* and *H19* peaked at 24h after SAH. Cessation of H19 decreased the expression of NLRP3 remarkably, and attenuated neuronal injury, and cerebral edema; moreover, LncRNA *H19* regulates the *NLRP3* inflammasome expression through sponging miR-138-5p via ceRNA mechanism which could open new windows in the therapeutic methods (Fig. 3) (Liu et al. 2022c). LncRNA *H19* which is decreased in hypoxic-ischemic brain-damaged rat models can be crucial in regulating inflammation and apoptosis in brain injury caused by hypoxia and ischemia (Fang et al. 2021). The elevated expression of LncRNA *H19* and *C1QTNF6* was reported in patients with ischemic stroke. Furthermore, LncRNA *H19* sponges miR-29b which targets C1QTNF6 mRNA to sustain the expression of *C1QTNF6*. The overexpression of *C1QTNF6* increases the release of inflammatory cytokines, such as TNF-α, and IL-1β which promotes BBB disruption and exacerbates cerebral ischemic injury (Li et al. 2022c). LncRNA *MEG3* is suggested to play a critical role in the development of Ischemic Stroke. It regulates neuronal

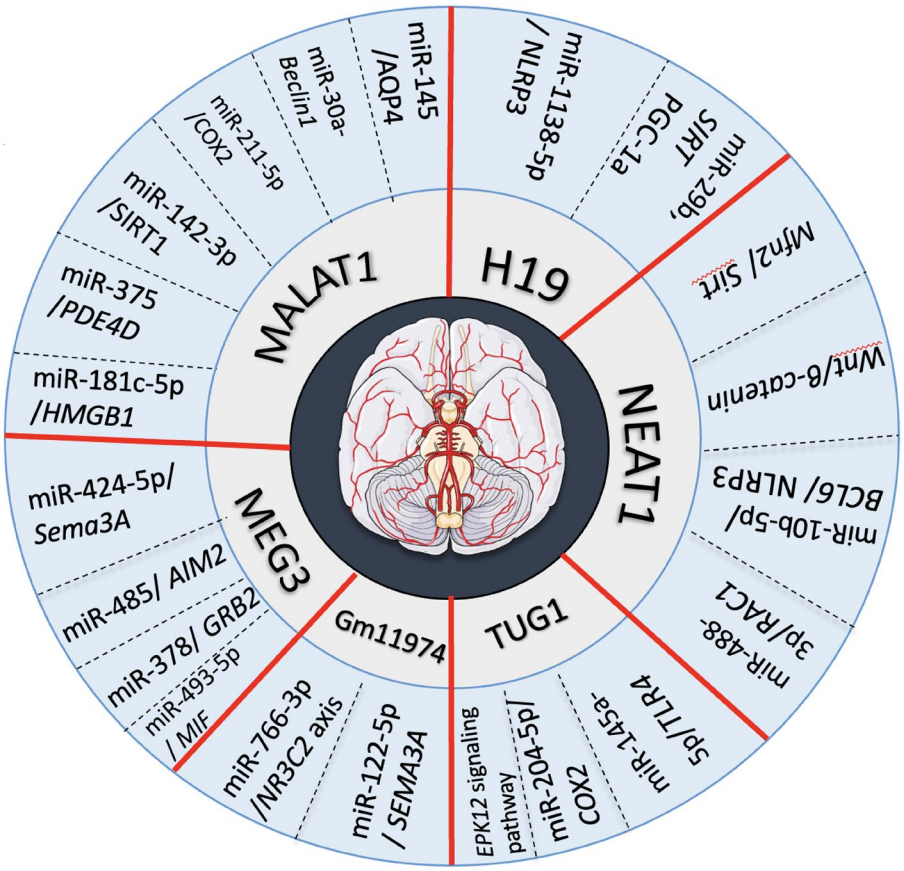

Fig. 3 A summary of the LncRNA mechanisms in regulating neuroinflammation in Ischemic and Hemorrhage Stroke

apoptosis in ischemic stroke by activating differential signaling pathways. One pathway in which *MEG3* takes part is targeting miR-424-5p which binds to *Sema3A*. Indeed, MEG3 knockdown decreased Sema3A expression which resulted in increased cell viability and decreased cell apoptosis (Xiang et al. 2020). In addition, the other pathway that *MEG3* regulates is the miR-122-5p/*NDRG3* axis, in fact, *MEG3* elevated the expression of *NDRG3* via targeting miR-122-5p. The upregulation of miR-122-5p significantly ($P < 0.001$) reverses the inhibitory effect of *MEG3* overexpression on the proliferation, migration, and angiogenesis of hCMEC/D3 cells (Luo et al. 2022). Moreover, *MEG3* is identified to have a regulatory role in neuroinflammation in cerebral ischemic injury. MEG3 knockdown decreased the synthesis of pro-inflammatory cytokines. It can bind to p65/p50 subunits of NF-κB which enhances the production of inflammatory cytokines, such as IL-1β, TNF-α, and IL-6 (Zhang et al. 2022c). LncRNA *KCNQ1OT1* plays a pivotal role in ischemic stroke progression by promoting autophagy. *KCNQ1OT1* expression is remarkably elevated in ischemic stroke, in fact, cessation of *KCNQ1OT1* brings about the alleviation of neurological impairment and reduction of infarct volume. Furthermore, LncRNA *KCNQ1OT1* sponges miR-200a via the ceRNA mechanism to mediate *FOXO3* expression which is reported to be the transcriptional regulator of *ATG7* (Yu et al. 2019). LncRNA *HOTAIR* is another LncRNA that mediates apoptosis and the progression of ischemic stroke. It is upregulated in ischemic stroke and increases neuronal apoptosis in stroke. Moreover, *HOTAIR* regulates apoptosis by mediating the expression of *EZH2* (Wang et al. 2022e). In a study conducted by Huang et al., *HOTAIR* was identified to exacerbate neurological injury and elevate apoptosis and inflammation. Knockdown of LncRNA *HOTAIR* mitigated apoptosis and inflammation. It targets miR-148a-3p by competing endogenous RNA mechanisms to maintain the expression of *KLF6*. Also, through the miR-148a-3p/*KLF6* axis pathway *STAT3* activation is suppressed (Huang et al. 2021b). Some substances have been discovered to have therapeutic potential or play a critical role in the development of stroke. Paeonol is reported to exert an important role in the development of Intracerebral Hemorrhage (ICH) Stroke. Paeonol is recognized to mediate ferroptosis and neuronal injury via regulating LncRNA *HOTAIR* expression. LncRNA *HOTAIR* regulates ferroptosis by targeting *UPF1* which subsequently degrades *ACSL4* through binding to it (Jin et al. 2021). LncRNA *Gm11974* exerts a critical role in the progression of ischemic stroke. It regulates apoptosis and neuronal cell death via *Gm11974*/miR-760-3p/*NR3C2* axis. Silencing LncRNA *Gm11974* decreased cell death rates and mitigated apoptosis

caused by OGD (Cai et al. 2019). Moreover, miR-122-5p, which is the target of LncRNA *Gm11974*, could have therapeutic potential by mitigating cell injury and apoptosis via targeting *SEMA3A*. In fact, there is a negative correlation between *Gm11974* and miR-122-5p expression. knockdown of *Gm11974* elevates miR-122-5p which subsequently decreases *SEMA3A* expression leading to decreased infarct volume and neuronal injury mitigation in ischemic stroke. LncRNA *TUG1* mediates inflammation and pyroptosis after stroke. Silencing miR-145a-5p, which is the target of *TUG1*, promoted *TLR4*, *P65*, and pyroptosis-associated protein. LncRNA *TUG1* regulates NLRP3 inflammasome-dependent pyroptosis via miR-145a-5p/*TLR4* axis (Yao et al. 2022). Furthermore, miR-204-5p is known to have a role in the progression of CI-RI. To be more specific, miR-204-5p overexpression decreases the infarct volume, and neurological impairment, and attenuates the inflammatory responses. LncRNA *TUG1* mediates the expression of miR-204-5p which regulates *COX2* expression (Xiang et al. 2022). *TUG1* regulates NF-κB signaling pathway activation which leads to the production of inflammatory cytokines. For instance, LncRNA *TUG1* regulates microglial polarization through binding to miR-145-5p, in fact, it has a negative association with miR-145a-5p, thereby the knockdown of *TUG1* suppressed NF-κB pathway activation and induced the microglial transformation from M1 to M2 phenotype which leads to the reduced production of inflammatory cytokines, such as TNF-α, IL-6 (Fig. 3) (Wang et al. 2019b). LncRNA *NEAT1* is another LncRNA identified to play a key regulatory role in the development of ischemic stroke. It regulates apoptosis and oxidative stress by mediating the *Mfn2*/*Sirt3* pathway via recruiting Nova (Zhou et al. 2022b). In addition, LncRNA *NEAT1* could have therapeutic potential as the expression level of *NEAT1* is decreased during ischemic stroke. Indeed, it regulates apoptosis and inflammatory responses by the Wnt/β-catenin pathway activation via upregulating Wnt3a in a *U2AF2*-dependent manner. LncRNA *NEAT1* can take another pathway to regulate immune activation and inflammatory responses. It ameliorates cell injury by sponging to miR-10b-5p with a ceRNA mechanism to maintain the *BCL6* level expression which is proven to play a pivotal role in inhibiting *NLRP3* expression as a repressive transcriptional factor (Zhou et al. 2022c). LncRNA *NEAT1* plays a robust role in microglial activation, as well. Indeed, it sponges miR-488-3p that regulates the expression of *RAC1* which mediates the activation of astrocytes (Zheng et al. 2023). LncRNA *ROR*, which has a pivotal role in the progression of ischemic stroke, promotes apoptosis and decreases the viability of PC12 cells. It binds to miR-135a-5p to regulate the *ROCK1/2* expression (Chen and Li 2019). Knockdown of *LncRNA TUG1*, which has a pivotal role in apoptosis, significantly decreased apoptosis rate and mitigated neuronal damage. In fact, the results demonstrated that *TUG1* mediates apoptosis and neuronal damage by regulating the *EPK12* signaling pathway (Chen et al. 2022b). LncRNA *MIAT* plays a pivotal role in stabilizing *EGLN2* after I/R injury. It stabilizes *EGLN2* via decreasing *MDM2* which binds to the N-terminal of *EGLN2* and mediates its K48-linked poly-ubiquitination. Moreover, it exacerbates ischemic reperfusion injury by promoting infarct volume and increasing neuronal apoptosis rate (Li et al. 2021e). LncRNA *SNHG12* is also reported to play a critical role in angiogenesis, inflammation, and microvascular endothelial death. As a matter of fact, it binds to miR-199a to regulate inflammatory responses and angiogenesis (Long et al. 2018). LncRNA *SNHG12* is reported to ameliorate cerebral I/R injury and develop a therapeutic strategy for ischemic stroke. It sponges microRNA-199a and then activates *SIRT1* expression inducing the *AMPK* signaling pathway activation (Yin et al. 2019) (Table 6).

Neuropathic Pain

Neuropathic Pain (NP) is a chronic complication of an injury or illness to the nervous system with a prevalence of 8% of the population. NP is closely associated with neuroinflammation, microglial, and astrocyte activation which can develop NP. Besides, LncRNAs are reported to play a robust role in regulating NP. For example, LncRNA *MEG3* is reported to be a key regulator in Neuropathic Pain (NP). The upregulation of *MEG3* exacerbates NP via promoting inflammatory cytokines secretion, such as IL-1β, TNF-α, and IL-6. In fact, it sponges miR-130a-5p by ceRNA mechanism to orchestrate the *CXCL12*/*CXCR4* axis (Dong et al. 2021c). LncRNA *P21* is considered to play a key role in regulating NP progression. The result depicted that the elevated expression of miR-181b reduced apoptosis and inflammatory responses which can be related to the activation of *AKT*/*cAMP* (Liu et al. 2021d). The elevated expression of LncRNA *KCNQ1OT1*, which has been identified to have therapeutic potential and relieve NP, has suppressed IL-1β, TNF-α, and IL-6 expression. Furthermore, the increased expression of *KCNQ1OT1* reduces the protein level of *Myd88* which results in the reduction of pro-inflammatory cytokines, and Iba-1 level (Li et al. 2023b). LncRNA *H19* is recognized to be a biomarker for NP, in fact, it exacerbates NP. Knockdown of *H19* suppressed the expression of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6 via binding to miR-141 which targets *GL12* (Meng et al. 2022). LncRNA *LNCENC1* is reported to orchestrate the activation of microglia and the production of pro-inflammatory cytokines, such as IL-1β, TNF-α, and MCP-1. It binds to *EZH2* to regulate the expression of *BA11*. Indeed, elevated expression of *LNCENC1* ameliorated neuropathic pain by decreasing inflammatory cytokines production via interacting with *EZH2* (Zhang et al. 2021e).

Table 6 LncRNA mediating neuroinflammation in Ischemic Hemorrhagic Stroke

LncRNA	Function	Mechanism	Model	Effect on inflammation	References
ZFAS1	Attenuating inhibiting inflammation, neuronal injury, oxidative stress, and apoptosis	Sponging miR-582-3p	Mice model	–	Zhang and Zhang (2020)
MALAT1	Regulating apoptosis and cell viability	Sponging miR-145 and orchestrating the expression of *AQP4*	Mice model	+	Wang et al. (2020c)
	Regulating apoptosis and cell death	*MALAT1*-miR-30a-*Beclin1* axis	Mice model	+	Guo et al. (2017)
	Promoting cerebral ischemia–reperfusion injury	Acting on miR-211-5p to orchestrate *COX2 expression*	Patient model	+	Tan et al. (2021b)
	Mediating inflammation, apoptosis, and necrosis	Sponging miR-142-3p which is the target gene of *SIRT1*	Mice model	–	Meng et al. (2023)
	Mediating cell apoptosis and inflammatory response	Knockdown of *MALAT1* mitigates CI/RI by orchestrating the miR-375/*PDE4D* axis	Mice model	+	Zhang et al. (2020c)
	Regulating inflammatory responses and cytokines production	*MALAT1*/miR-181c-5p/*HMGB1* axis	Mice model	+	Cao et al. (2020c)
H19	Regulating inflammation, and NLRP3-mediated pyroptosis	Sponging competitively to miR-138-5p	Mice model	+	Liu et al. (2022c)
	Neuronal apoptosis and cognitive dysfunction	*H19* sponges miR-107 and decreases its expression	Mice model	–	Fang et al. (2021)
	Regulating apoptosis and inflammatory response	Mediating miR-29b, *SIRT*, and PGC-1a expression level	Mice model	+	Xu et al. ((2021)
MEG3	Regulating apoptosis	*MEG3*/miR-424-5p/*Sema3A* axis	Mice model	–	Xiang et al. (2020)
	Pyroptosis and inflammation	Mediating miR-485/*AIM2* to activate caspase1 signaling pathway	Mice model	+	Liang et al. (2020)
	Neuronal death, and neurological function	*MEG3*/miR-378/*GRB2* regulatory axis	Mice model	+	Luo et al. (2020)
	Regulating neuronal stem cell proliferation after ischemic stroke	*MEG3*/miR-493-5p/*MIF* axis	Mice model	+	Zhao et al. (2021)
	Mediating ferroptosis	Regulating the expression of *GPX4* through orchestrating the *MEG3*-p53 signaling pathway	Mice model	+	Chen et al. ((2021a)
	Pyroptosis and inflammation	Mediating miR-485/*AIM2* to activate caspase 1 signaling pathway	Mice model	+	Liang et al. (2020)
	Neuronal death, and neurological function	*MEG3*/miR-378/*GRB2* regulatory axis	Mice model	+	Luo et al. (2022)
KCNQ1OT	Regulating cell viability and autophagy	*KCNQ1OT1*/miR-200a/*FOXO3*/*ATG7* pathway	Patient model	+	Yu et al. (2019)
HOTAIR	Apoptosis	*HOTAIR*/*EZH2* axis	Patient model	+	Wang et al. (2022e)
	Apoptosis and inflammation	Cessation of *STAT3* pathway by *HOTAIR*/miR-148-3p/*KLF6* axis	In vivo and in vitro models	+	Huang et al. (2021b)

Table 6 (continued)

LncRNA	Function	Mechanism	Model	Effect on inflammation	References
Gm11974	Mediating apoptosis	*Gm11974*/miR-766-3p/*NR3C2* axis	Mice model	+	Cai et al. (2019)
	Regulating cell injury and apoptosis	*Gm11974*/miR-122-5p/*SEMA3A* signaling pathway	Mice model	+	Yang et al. (2021)
TUG1	Regulating pyroptosis and cell death	*TUG1*/miR-145a-5p/*TLR4* axis	Mice model	+	Yao et al. (2022)
	Apoptosis	*EPK12* signaling pathway	Mice model	+	Chen et al. ((2022b)
	Regulating inflammatory responses, apoptosis, and infarct volume	*TUG1*/miR-204-5p/*COX2* axis	Mice Model	+	Xiang et al. (2022)
	Regulating the production of inflammatory cytokines and NF-κB signaling activation	*TUG1* sponges miR-145-5p	Mice model	+	Wang et al. (2019b)
NEAT1	Regulating apoptosis	*NEAT1*/*Mfn2*/*Sirt* pathway	Mice model	–	Zhou et al. (2022b)
	Regulating apoptosis and inflammatory response	Upregulating *Wnt3a* to activate *Wnt/β-catenin* pathway	Mice model	–	Zhou et al. (2022d)
	Regulating inflammatory response and microglial activation	*NEAT1*/miR-10b-5p/*BCL6*/NLRP3 regulatory axis	CIS patient model and cell model	–	Zhou et al. (2022c)
	Microglial activation	miR-488-3p/*RAC1* pathway	Mice model	+	Zheng et al. (2023)
ROR	Apoptosis	Sponging miR-135a-5p to mediate the ROCK1/2 expression	Mice model	+	Chen and Li (2019)
MIAT	Promoting infarct volume and increasing apoptosis	*MIAT* stabilizes *EGLN2* by decreasing *MDM2* mediated K48 poly-ubiquitination	Mice model	+	Li et al. (2021e)
	Apoptosis, and inflammation	Regulating the expression of miR-874-3p which targets *1L1B*	Mice model	+	Zhang et al. (2021d)
SNHG12	Regulating inflammatory response, and angiogenesis	Sponging miR-199a	Mice model	–	Long et al. (2018)
	Regulating miR-150/*VEGF* pathway	Regulating angiogenesis and recovery of neurological function	Mice model	–	Zhao et al. (2018)
	Apoptosis, and mediating the mitigation of cerebral I/R injury	*SNHG12*/miR-199a/*SIRT1*/AMPK axis	Mice model	–	Yin et al. (2019)
	Regulating apoptosis and cell proliferation	*SNHG12*/miR-136-5p/*Bcl-2* axis that activates *PI3K*/*AKT* signaling pathway	Mice model	–	Zhang et al. (2022d)

LncRNA *PCAT1* plays regulatory roles in the state of NP. It is proven to mediate neuroinflammation, thermal hyperalgesia, and mechanical ectopic pain. Furthermore, cessation of *PCAT1* reduced the expression of neuroinflammatory cytokines via sponging miR-182-5p. It mediates *JMJDA* gene expression via binding to miR-182-5p (Huo et al. 2022). Knockdown of *PVT1* attenuated NP, and astrocyte activation, and downregulated the expression of inflammatory cytokines. It binds to miR-186-5p which enhances the expression of *CXCL13*/*CXCR5* by the ceRNA mechanism (Zhang et al. 2021f). LncRNA *MALAT1* is identified to exert a major role in the progression and development of NP. It promotes NP development and increases the occurrence of NP via targeting miR-154-5p. To be more specific, elevated

expression of miR-154-5p which binds to *AQP9* alleviated NP and reduced its occurrence (Wu et al. 2020). In a study conducted on CCI rats, miR-330-3p is significantly upregulated in the CCI rat model. It is proved that there is a negative correlation between the expression of LncRNA *DGCR5* and miR-330-3p. Overexpression of *DGCR5* attenuated NP development and repressed the expression of inflammatory cytokines, such as IL-6, TNF-α, and IL-1β. It modulates the expression of miR-330-3p by targeting it via the ceRNA mechanism (Peng et al. 2019). LncRNA *UCA1* is another LncRNA regulating the inflammatory condition in NP. The elevated expression of *UCA1* mitigated NP via reducing inflammatory expression; in addition, it targets miR-135a-5p which mediates the progression of NP (Wu and Zhou 2023). LncRNA *SNHG5* is identified to play a critical role in the development of NP and regulation of inflammation. Knockdown of *SNHG5* attenuated the neuropathic pain by reducing the release and mRNA expression of IL-1β, IL-6, IL-10, and TNF-α. It sponges miRNA-142-5p by ceRNA mechanism which increases the expression of *CAMK2A* (Jin et al. 2022). LncRNA *XIST* is reported to have key roles in the development of NP. The upregulation of *XIST* leads to the development of NP in rats. Moreover, there is a negative association between *XIST* and miR-154-5p expression, indeed, it binds to miR-154-5p which targets toll-like receptor 5 (TLR5) (Wei et al. 2019). LncRNA *HAGLR* exacerbates NP and enhances inflammatory response. It sponges miR-182-5p to sustain the expression of *ATAT1* which activates NLRP3 that promotes the inflammatory response (Zhang et al. 2021g) (Fig. 4, Table 7).

Discussion

Most of the human genome is actively transcribed, and many of these transcriptions are proven to be functional. LncRNAs are a class of functional non-coding RNAs with a length greater than 200 nucleotides, in fact, LncRNAs regulate the cellular programs via various mechanisms (Policarpo et al. 2021; Srinivas et al. 2023). With the advent of technology in RNA sequencing, LncRNAs expression in different cells has been extensively studied. In addition, studies have shown the altered expression of LncRNAs in CNS diseases, e.g., neurodegenerative diseases, stroke, trauma, and infection (Tripathi et al. 2021). Other non-coding RNAs have been identified which play a key role in regulating immune responses, indeed, the RNA community recognizes miRNA, LncRNA, and circRNA as main ncRNAs which control the expression of other ncRNAs and function as key genetic regulators (Chen et al. 2024). ncRNAs (i.e., miRNAs, LncRNAs, and

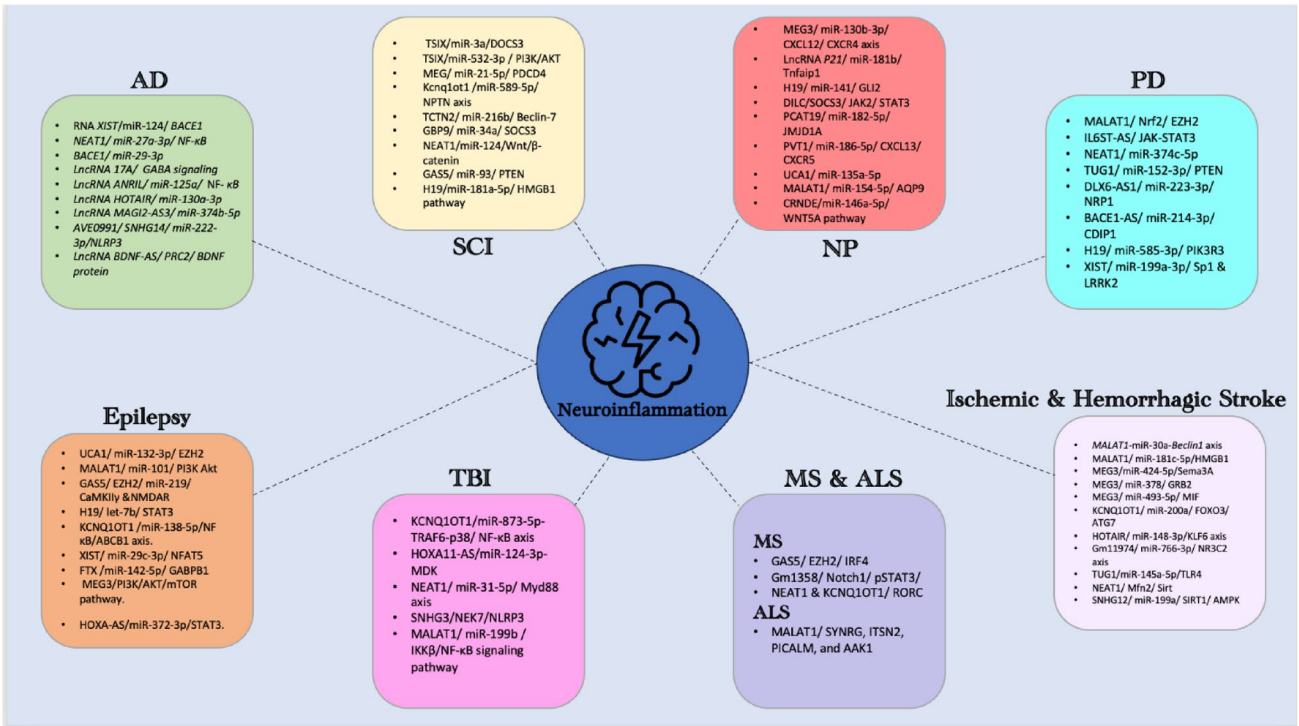

Fig. 4 The mechanism of actions of LncRNAs in a nutshell. LncRNAs mediate numerous pathways in neuroinflammation. Aberrant expression of LncRNAs leads to various neurological diseases, such as neurodegenerative diseases, neuropathic pain, and epilepsy. MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis; TBI: Traumatic Brain Injury; AD: Alzheimer's Disease; PD: Parkinson's Disease; SCI: Spinal Cord Injury; NP: Neuropathic Pain

Table 7 A concise summary of LncRNA regulating neuroinflammation in neuropathic pain (NP)

LncRNA	Function	Mechanism	Model	Effect on inflammation	References
MEG3	Mediating inflammatory cytokines expression, and astrocyte activation	*MEG3* regulates miR-130a-5p/*CXCL12*/*CXCR4* axis	Mice model	+	Dong et al. (2021c)
P21	Apoptosis and inflammatory response	LncRNA *P21*/miR-181b/Tnfaip1 axis	Mice model	+	Liu et al. (2021d)
MIAT	Enhancing the occurrence and development of NP	*MIAT* sponges miR-362-3p to maintain the expression of *BAMB1*	Mice model	+	Zhang et al. (2022e)
KCNQ1OT1	Mediating microglia activation, and pro-inflammatory cytokines	*KCNQ1OT1* sponges Myd88 to inhibit its regulation	Mice model	–	Li et al. (2023b)
H19	Regulating the expression of pro-inflammatory cytokines	*H19*/miR-141/*GLI2* axis	Mice model	+	Meng et al. (2022)
Lncenc1	Regulating microglial activation and production of inflammatory cytokines	Targeting *EZH2* to regulate *BAI1* expression	Mice model	+	Zhang et al. (2021e)
DILC	Mediating apoptosis and pro-inflammatory cytokines production	Mediating *SOCS3*/*JAK2*/STAT3 pathway	Mice model	+	Liu et al. (2020a)
PCAT19	Regulating NP behaviors, such as neuroinflammation	*PCAT19*/miR-182-5p/JMJD1A	Mice model	+	Huo et al. (2022)
PVT1	Neuroinflammation and astrocyte activation	*PVT1*/miR-186-5p/*CXCL13*/*CXCR5* axis	Mice model	+	Zhang et al. (2021f)
MALAT1	NP development and progression	*MALAT1*/miR-154-5p/*AQP9* axis	Mice model	+	Wu et al. (2020)
CRNDE	Regulating inflammatory response and pain-related behavior	miR-146a-5p/WNT5A pathway	Mice model	+	Zhang et al. (2021h)
UCA1	Regulating neuroinflammatory cytokines expression	*UCA1*/miR-135a-5p axis	Mice model	–	Wu and Zhou (2023)
LINC01119	Progression and development of NP via regulating the expression of inflammatory cytokines	*LINC0119*/*ELAVL1*/*BDNF* axis	Mice model	+	Zhang et al. (2021i)

circRNAs) form a complex regulatory network which requires in-depth bioinformatics analysis (Cipriano et al. 2024). LncRNAs' power comes from their diverse biological function. They fulfill their roles in all levels of genome organization, cell structure, and gene expression via interacting with protein, RNAs, e.g., miRNA, circRNA, mRNA, and DNA (Mattick et al. 2023). In this review, the pivotal role each LncRNA plays in regulating neuroinflammation is thoroughly discussed; moreover, the interplays between LncRNAs and miRNAs are also studied in the LncRNA-miRNA-mRNA axis.

LncRNAs and Main Pathways

LncRNAs mediate various pathways regulating myriads of cellular signaling and pathways; nevertheless, some pathways are more pervasive in mediating neuroinflammation, which are highlighted below. JAK-STAT mediates various cellular functions, e.g., hematopoiesis and immune development. Moreover, Gain-of-function mutations in the signaling pathway of JAK/STAT can result in human diseases, especially in the immune system. The pathway is followed in a linear manner comprising three sequential steps: 1. Cytokines and growth receptors 2. Janus Kinase (JAK), and 3. Signal Transducer and activator of transcripts (STAT). LncRNAs can regulate the JAK/STAT pathway; moreover, the JAK/STAT pathway is proven to mediate the expression of hundreds of long non-coding RNAs (Witte and Muljo 2014). LncRNA Gm13568 mediates neuroinflammation in MS via regulating the expression of NOTCH1 through phosphorylation of STAT3 (Liu et al. 2021a). Another popular target of LncRNAs in the pathogenesis of immune system diseases is nuclear factor-kappa B (NF-κB). NF-κB is an indispensable element of the inflammatory response required for the proper functioning of the innate immune system. In AD, NF-κB targets genes associated with AD pathogenesis, like *BIN1*, *APP*, and *COX2* (Kaltschmidt et al. 2022). LncRNA ANRIL sponges miR-125, thereby mediating NF-KB and the downstream pathways (Zhou et al. 2020a). PI3K is a key signaling cellular function that regulates a vast field of cellular mechanisms; moreover, another pathway identified to be connected to PI3K via serine/threonine kinase Akt is the mammalian target of rapamycin (mTOR) forming the PI3K/Akt/mTOR signaling pathway (Iranpanah et al. 2023). LncRNA MALAT1 and MEG3 are identified to regulate neuroinflammation in Epilepsy via the PI3K/Akt/

mTOR signaling pathway (Wu and Yi 2018; Zhang et al. 2020b). In addition, LncRNA TSIX plays a key role in mediating the PI3K/Akt pathway, thereby mediating apoptosis and neuroinflammation in SCI (Dong et al. 2023).

Therapeutic Potentials

LncRNAs are modulators of the plethora of biological processes with diverse mechanisms of action. It is proven that LncRNAs exert their role via binding to different molecules, such as DNA, RNA, and/or proteins; therefore, LncRNAs finetune the signaling pathways leading to pathogenesis. Given the fact that sundry LncRNAs are upregulated in the affected tissues, inhibiting the upregulated LncRNAs might contribute to the recovery of the tissues (Ilieva and Uchida 2022). However, limitations may arise from the therapeutic usage of LncRNAs; for example, LncRNAs may provoke an immune response from the body (Black et al. 2024). RNA-based therapy is a vast and pioneering field in medical treatment; indeed, RNA-based therapy relies mostly on Antisense oligonucleotides (ASO) and small interfering RNAs (siRNAs) (Winkle et al. 2021; Liu et al. 2022d). In Alzheimer's disease (AD) the progress has been more considerable, in fact, siRNA is utilized to inhibit BACE1-AS which has reduced the effect of BACE1, and consequently, memory and learning behavior have been improved in animal models (Anilkumar et al. 2024). Another LncRNA that is over-expressed in AD is BC200. Blocking of BC200 by siRNA has demonstrated promising results (Li et al. 2018b). One of the major obstacles impeding the growth of RNA-based therapies is the immunogenicity. Our immune system recognizes single- and double-stranded RNAs via various extra- and intracellular PAMP receptors. Besides, the main pathway through which the immune system recognizes RNA-based therapeutics is via TLR signaling which has to be extensively studied in future studies (Winkle et al. 2021). Another therapeutic method which can target LncRNA genes is the CRISPR/Cas systems. CRISPR/Cas system is a state-of-the-art technology recently used by scientists in recent years. CRISPR/Cas system can reshape human understanding of LncRNA mechanisms mainly via applications, namely LncRNA knockout, and knockdown, thereby opening new windows to target LncRNAs and finetune the downstream pathways (Zibitt et al. 2021). Exosomes are a major type of Extracellular Vesicles (EV) that play a key role in cell-to-cell communication. In addition, non-coding RNAs have been identified to be one of the main cargos in exosomes. Intriguingly, exosomes are found with untapped potential in therapy and diagnosis of CNS diseases; however, future studies should elaborate on this topic in greater depth (Mattingly et al. 2021). One of the limitations of Exosome therapy is that the content, function, and activity of exosomes rely on the generating cell; therefore, exosome generating cell should match the age, gender, and other associated factors (Chen and Chopp 2018).

Conclusion

LncRNAs are a subset of non-coding RNAs with more than 200 nucleotides playing a pivotal role in orchestrating neuroinflammation in CNS diseases. The functions of LncRNAs are determined by whether they bind to protein or non-coding RNAs; moreover, the structure of primary or secondary LncRNAs can also be a determining factor. LncRNAs regulate inflammation through different mechanisms, such as miRNA sponge, transcriptional activation/inhibition, post-transcriptional modification, chromatin remodeling, and regulation of protein activity. Different pathways were studied in neuroinflammation, namely, NF-κB, JAK/STAT, PI3K/AKT, and TLR. It should be noted that the two resident cells, microglia, and astrocytes, mediate how far and long the immune response will be by interacting with the peripheral immune system accompanied by LncRNAs interference. In this review, the existing evidence regarding the regulatory role of LncRNAs in neuroinflammation in different CNS diseases are summarized. Further investigations can delve into the role and mechanism of other LncRNAs in neuroinflammation regulation which remains elusive. Furthermore, a single drug cannot affect different pathologic processes in the disease process, thus exosomes having different components with advancements in drug technology can be a proper therapeutic option. In addition, other non-coding RNAs, e.g., circRNAs and miRNAs can regulate a broad range of mechanisms mainly via the cooperation of LncRNAs. Future studies can dive deeper into understanding the interplay among these RNAs. RNA-based therapies have also garnered attention in recent years; hence, future studies can focus on therapeutic techniques, especially the CRISPR/Cas9 system. LncRNAs can obtain complex secondary and tertiary structures, and their function mostly relies on the structure. Further studies can unpack the complexities of the structure, leading to a better understanding of LncRNAs structure and their mechanisms.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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