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REVIEW

Emerging Role of LncRNAs in Ischemic Stroke—Novel Insights into the Regulation of Inflammation

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Abstract: As a crucial kind of pervasive gene, long noncoding RNAs (lncRNAs) are abundant and key players in brain function as well as numerous neurological disorders, especially ischemic stroke. The mechanisms underlying ischemic stroke include angiogenesis, autophagy, apoptosis, cell death, and neuroinflammation. Inflammation plays a vital role in the pathological process of ischemic stroke, and systemic inflammation affects the patient's prognosis. Although a great deal of research has illustrated that various lncRNAs are closely relevant to regulate neuroinflammation and microglial activation in ischemic stroke, the specific interactional relationships and mechanisms between lncRNAs and neuroinflammation have not been described clearly. This review aimed to summarize the therapeutic effects and action mechanisms of lncRNAs on ischemia by regulating inflammation and microglial activation. In addition, we emphasize that lncRNAs have the potential to modulate inflammation by inhibiting and activating various signaling pathways, such as microRNAs, NF-κB and ERK.

Keywords: ischemic stroke, long noncoding RNA, microglia, neuroinflammation

Introduction

Approximately 16.67% of people worldwide may experience an ischemic stroke in their lifetime,[1] and such strokes are responsible for almost 6 million deaths and more than 10% of all mortalities each year; moreover, two-thirds of ischemic survivors remain disabled.[2] Despite the thrombectomy and recombinant tissue plasminogen activator (rtPA) being the main accepted treatments,[3] whether neuroinflammation affects the prognosis of ischemic stroke after such treatment remains controversial since stroke-induced inflammation is one of the most vital factors that limits treatment efficiency. Neuroinflammation plays a vital role in the pathological process of stroke, and systemic inflammation affects patient prognosis.[4–6] Focal cerebral ischemia in animals leads to an inflammatory cascade that includes oxidative stress, excitotoxicity, inflammatory cell activation, and toxic inflammatory mediators, which in turn impair nerve tissue and cells. On the other hand, inflammation contributes greatly to the recovery of damaged tissue and cells by promoting microglia to immediately migrate to the infarction site.[7,8] In the past one decade, researchers have performed many studies to explore the therapeutic potential of long noncoding RNAs (lncRNAs), which are endogenous ncRNAs >200 nucleotides in length that lack an open reading frame.[9] LncRNAs are considered a key factor in regulating the expression and function of protein-coding genes, and they are involved in different signaling pathways of cellular processes,

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such as cell apoptosis, inflammation angiogenesis and autophagy, thereby regulating stroke prognosis.[10] Previous research indicates that modulating lncRNA expression can inhibit microglial activation and improve neurological functions.[11] To date, the literature investigating the interactional relationship between neuroinflammation and lncRNAs in ischemia is still limited, and the mechanisms have also not been estimated accurately. The purpose of this review is to summarize the potential therapeutic effects and pathways of lncRNAs in stroke based on their ability to regulate inflammation.

Neuroinflammatory Response and Related Mechanisms in Stroke

Neuroinflammation is integral to the poststroke pathophysiological process and causes the disruption of tissue homeostasis,[12,13] including acidosis, excitotoxicity mediated by reactive oxygen species (ROS), increased cytoplasmic Ca^{2+} concentrations, loss of glucose and oxygen, complement activation, destruction of the blood–brain barrier (BBB), mitochondrial damage and secondary messengers by resident central nervous system (CNS) glia and endothelial cells.[14–16] On the other hand, inflammation combines innate and peripheral immune responses involved in physiological brain development and different pathologic conditions, such as neurodegenerative diseases or stroke.[17,18] In summary, inflammatory cells are classically involved in innate responses and activated within hours and perfectly situated to sense imbalances in the CNS,[19–21] including natural killer cells, neutrophils, dendritic cells, macrophages, microglia and astrocytes that participate in the secretion of inflammatory chemokines and the selective recognition and clearance of pathogens and toxic cell debris during infection or tissue injury.[22–24]

During the early phase of stroke, the peripheral immune responses of inflammation initiate immediately at a second massive cascade of inflammation, and different damage-associated molecular patterns (DAMPs), such as high mobility group box 1, heat shock proteins, interleukin-33, purines (ATP and UTP), mitochondrial-derived N-formyl peptides and peroxiredoxins, can gain access to the systemic circulation.[25–27] These molecules activate pattern recognition receptors on microglia and astrocytes and on brain resident immune cells,[27,28] and subsequently, the activation of endothelial cells aggravates BBB breakdown, thus allowing peripheral leukocytes to arrive in the injured area.[29–31] Due to the disruption of the BBB, DAMPs and cytokines induce a response of the immune system in primary and secondary lymphoid organs, which leads to systemic inflammatory response syndrome and activates some inflammatory pathways, such as mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).[32–34] All these factors can greatly affect the prognosis of patients.[35,36] Thus, exposing the role and mechanism of inflammation and identifying a treatment for the recovery of stroke have been driving forces for extensive studies in recent decades.

Significant Role of Long Noncoding RNAs in Cerebral Ischemia

Essential Characteristics and Associated Functions of LncRNAs

LncRNAs are a type of RNA defined as transcripts with a length of >200 nucleotides that are not directly translated into proteins.[37] These transcripts regulate the expression of genes through affecting epigenetics, transcription, and translation, playing important physiological and pathological roles, and participating in various signaling pathways underlying multiple diseases.[38] LncRNAs are located in the nucleus or cytoplasm and regulate the expression of genes at the transcriptional or posttranscriptional level. LncRNAs in the nucleus regulate gene expression in various modes, such as isolating transcription factor/protein complexes from chromatin and gathering different proteins to form ribonucleoprotein complexes in response to stimuli.[39] However, cytoplasmic lncRNAs stabilize ribonucleoprotein complexes, regulate the stability of mRNA or bind miRNAs as competitive endogenous RNAs (ceRNAs). Transcription or recruitment of chromatin-modifying enzymes to target genes induces chromosomal circulation to increase the association between enhancer and promoter regions.[40] Various lncRNAs also regulate gene expression by modifying chromosome and mRNA expression, and lncRNAs even act as ceRNAs and cause RNA degradation.[41]

LncRNAs and Cerebral Ischemia

Increasing evidence shows that hundreds of abnormally expressed lncRNAs have been found in ischemic models and play a crucial role in the pathogenesis of stroke.[42–44] LncRNA profiles have been reported to greatly influence ischemic injury progression in microvascular endothelial cells during ischemia after oxygen-glucose deprivation and reperfusion (OGD/R),[45–47] rodent focal stroke,[48–50] and

some blood samples.[51,52] Recently, several specific lncRNAs, such as H19, taurine upregulated gene 1 (TUG1), growth arrest-specific 5 (GAS5), CaMK2D-related transcript 1 (C2dat1), small nucleolar RNA host gene 14 (SNHG14), HOXA distal transcript antisense RNA (HOTTIP), and N1LR, have been shown to be increased in ischemia.[46,47,52–62] LncRNAs have been reported to stimulate apoptosis, angiogenesis, inflammation, and neuronal death after ischemic stroke.[47,52–55,63] These findings demonstrate that the brain responds to stroke-associated stimuli by altering lncRNA transcriptomic profiles. These robust stroke-induced lncRNA aberrations suggest the potential functional roles and predictive value of lncRNAs as new biomarkers for stroke. An overview of how lncRNAs act on neurological recovery is given in Figure 1.

LncRNAs Regulate Cell Death and Apoptosis in Cerebral Ischemia

Numerous studies have demonstrated that changes in lncRNA levels are related to cell death after ischemic stroke. A previous study indicated that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) promotes neuronal death via targeting miR-30a in ischemic stroke.[49] It protects the cerebral microvasculature and parenchyma from cerebral ischemic insults by inhibiting endothelial cell death and

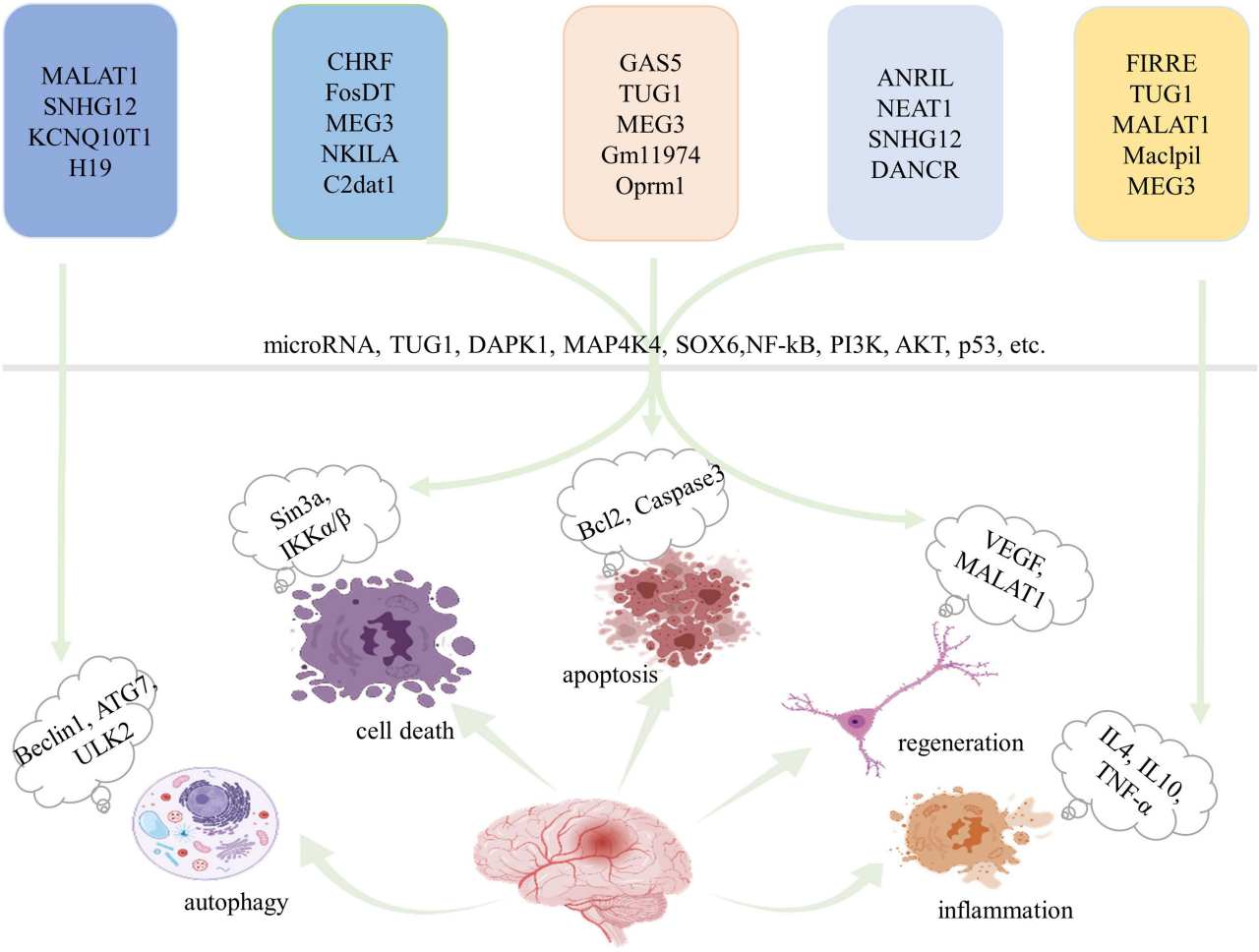

Figure 1 Overview of the effects of lncRNAs on neurological recovery. LncRNAs predominantly modulate autophagy, cell death, apoptosis, regeneration and inflammation through various pathways, and microRNAs are key players. Created with Biorender.com.

Abbreviations: MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SNHG12, small nucleolar RNA host gene 12; KCNQ1OT1, potassium voltage-gated channel subfamily Q member 1 opposite strand 1; CHRF, cardiac hypertrophy-related factor; FosDT, Fos downstream transcript; MEG3, maternally expressed gene 3; NKILA, NF-κB interacting lncRNA; C2dat1, CAMK2D-associated transcript 1; GAS5, growth arrest-specific 5; TUG1, taurine-upregulated gene 1; Oprm1, opioid receptor μ1 gene; ANRIL, antisense noncoding RNA in the INK4 locus; NEAT1, nuclear paraspeckle assembly transcript 1; DANCR, differentiation antagonizing nonprotein-coding RNA; FIRRE, functional intergenic repeating RNA element; Maclpil, macrophage containing lymphocyte cytosolic protein 1 factor (LCP1)-related proinflammatory; DAPK1, death-associated protein kinase 1; MAP4K4, mitogen-activated protein kinase 4; SOX6, sex-determining region Y-box 6; NF-κB, nuclear factor kappa B; VEGF, vascular endothelial growth factor.

inflammation and plays roles in the progression of cerebrovascular permeability and BBB integrity after stroke.[46] In addition, MALAT1 interacted with miR-26b and upregulated ULK2 expression, which in turn suppressed neuronal death.[47] In addition, N1LR and maternally expressed 3 (MEG3) also interact with neuronal death after ischemic stroke by inactivating p53.[58] Knockdown of MEG3 inhibits neuronal death by targeting the miR-21/PDCD4 signaling pathway.[54] Consistent with these findings, growth arrest-specific 5 (GAS5) inhibits cell death and increases neuronal survival by targeting the miR-137/Notch1 signaling pathway,[57] small nucleolar RNA host gene 14 (SNHG) mediated by hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) signaling acts as a ceRNA for miR-18a, thereby affecting cerebral infarction.[60] To date, a series of preclinical studies have assessed the effects of lncRNAs on regulating cell death in ischemia models.

Among the various programmed cell death pathways,[64] apoptosis accounts for a large proportion of neuronal death through brain ischemia,[65] which efficiently removes damaged cells from DNA damage or during development.[66] Apoptosis plays a pivotal role in the homeostasis of normal tissues, and researchers have recently found that lncRNAs have essential effects on regulating cell apoptosis following stroke.[67] LncRNA growth arrest-specific 5 (GAS5), a ceRNA for miR137, was upregulated and negatively correlated with miR137 expression in stroke mice and OGD/R-treated primary neurons.[68] Chen et al[69] illustrated that lncRNA TUG1 was significantly upregulated in ischemia in an MCAO model. TUG1 has been proven to interact with miR-9 and decrease Bcl2 protein, which activates bax and ultimately leads to neuronal apoptosis.[70] Overexpression of lncRNA opioid receptor μ1 gene (Oprm1) attenuated apoptosis-induced cerebral injury via the Oprm1/miR-155/GATA3 axis by reducing cleaved caspase-3 levels.[71] One study illustrated that lncRNA rhabdomyosarcoma 2-associated transcript (RMST) promoted OGD-induced injury in brain microvascular endothelial cells by regulating the miR204–5p/VCAM1 pathway.[72] To date, a great number of studies have assessed the effect of lncRNAs on regulating apoptosis in ischemia. The characteristics of some of these studies are summarized in Table 1.

LncRNAs Regulate Angiogenesis in Cerebral Ischemia

During angiogenesis, the blood supply recovers in damaged regions after ischemia, thus alleviating ischemic necrosis by assisting the brain in restoring collateral circulation.[73] Current studies have indicated that several lncRNAs play a vital role in regulating endothelial cell survival, vascular integrity, and angiogenesis in ischemia. Numerous lncRNAs are associated with angiogenesis after stroke by affecting transcription and translation.[74] A recent study found that the overexpression of MEG3 suppresses functional recovery after ischemia, the silencing of MEG3 ameliorates brain lesions, and the expression of MEG3 increases angiogenesis after ischemia by promoting endothelial cell migration, proliferation, sprouting, and tube formation by regulating the Notch pathway.[75] Furthermore, another study demonstrated that lncRNA Aerrie and SNHG12 contribute to DNA signaling and repair mechanisms and relieve endothelial cell injury after ischemic stroke.[76–78] In addition, another clinical study demonstrated that lncRNA MACC1-AS1 also exerts a protective role after stroke.[74] To date, a range of preclinical studies have assessed the effect of lncRNAs on regulating neurogenesis and angiogenesis in cerebral ischemia. The characteristics of some of these studies are summarized in Table 2.

LncRNAs Regulate Autophagy in Cerebral Ischemia

Autophagy is an evolutionarily conserved cellular mechanism that can maintain cellular nerve homeostasis, and it is associated with degraded misfolded or nonfunctional proteins and damaged organelles.[67,79] Numerous studies confirm that autophagy provides a neuroprotective effect on stroke by promoting the clearance of damaged proteins and organelles, which facilitates energy recycling and cellular defense.[67] It is widely accepted that various lncRNAs affect cell survival in stroke by regulating autophagy.[66] MALAT1 is one of the most significantly upregulated lncRNAs in both in vivo and in vitro models of stroke and serves as a competing endogenous RNA by sponging miR-126 to upregulate its target ULK2 under hypoxic injury based on the protective effect of autophagy.[47] Similarly, lncRNA antisense noncoding RNA in the INK4 locus (ANRIL) and lncRNA FosDT were all elevated by negatively regulating miR-127 expression[80] and interacting with REST-associated chromatin-modifying proteins separately to protect against ischemic stroke.[81] In contrast, exogenous overexpression of H19 results in autophagic cell death in cerebral ischemia.[82] Acting as a competing endogenous RNA of miR-200a, lncRNA

Table 1 Preclinical and Clinical Stroke Studies Assessing the Effect of Different LncRNAs on the Regulation of Apoptosis and Cell Death

Author, Year	LncRNA	Models	Species	Regulation	Targets	Functions
LncRNAs regulate apoptosis in stroke						
Xiao et al 2019	H19	MCAO, OGD/R	Human, Rats, Cells	Up	miR-19a	Modulate hypoxia induced neuronal apoptosis
Wang et al 2020	MEG3	MCAO, OGD/R	Human, Mice, Cells	Up	Bax, cleaved Caspase-3	Promote cell apoptosis and aggravates hypoxia
Xiang et al.	MEG3	MCAO, OGD/R	Mice, Cells	Up	miR-424-5p, MAPK	Mediate neuronal apoptosis
Luo et al 2020	GAS5	OGD/R	Human, Cells	Up	Bax, Bcl-2, cleaved caspase-3	Regulate neuronal apoptosis and infarction size
Wu et al 2017	N1LR	MCAO, OGD/R	Mice, Cells	Up	P53	Promote neuroprotection
Zhou et al 2020	SNHG7	MCAO, OGD/R	Mice, Cells	Down	miR-9, SIRT1	Alleviate neuronal injury
Jing et al 2019	Oprm1	MCAO, OGD/R	Mice, Cells	Up	miR-155, GATA3, Caspase-3	Overexpression alleviates apoptosis
Cheng et al 2020	RMST	OGD/R	Cells	Up	miR-107, Bcl2, Bax, p53	Promote OGD-induced neuronal apoptosis
Yao et al 2019	Rian	MCAO, OGD/R	Mice, Cells	Down	miR-144-3p, caspase-3, Bax, Bcl-2	Attenuated cell apoptosis from cerebral I/R injury
Gao et al	HCP5	OGD/R	Cells	Up	miR-652-3p, LC3, p62	Protect against cerebral I/R injury
Cao et al 2021	TALNEC2	MCAO, OGD/R	Mice, Cells	Up	miR-650, APAF1	Aggravate apoptosis cerebral I/R injury
LncRNAs regulate cell death in stroke						
Yan et al 2016	MEG3	MCAO, OGD/R	Rats, Cells	Up	P53	As a cell death promoter
Yan et al 2017	MEG3	MCAO, OGD/R	Mice, Cells	Up	miR-21	Target miR-21/PDCD4 signaling pathway
Deng et al 2019	Nespas	MCAO, OGD/R	Mice, Cells	Up	Bcl-2, Bax	Silence aggravates I/R-induced ischemic damage
Xu et al 2020	D63785	OGD/R	Cells	Down	miR-422a	Overexpression reverses neuronal cell death
Guo et al 2017	MALAT1	MCAO, OGD/R	Mice, Cells	Up	miR-30a	Downregulation attenuates neuronal cell death
Wang et al 2018	NKILA	OGD/R	Cells	Up	miR-103, miR-107	Upregulation mediates neuronal cell death

Abbreviations: LncRNA, long non-coding RNA; MCAO, middle cerebral artery occlusion; OGD/R, oxygen glucose deprivation/re-oxygenation; I/R, ischemia and reperfusion; MAPK, Mitogen-activated protein kinases; APAF1, apoptotic peptidase activating factor 1; MEG3, maternally expressed gene 3; PDCD4, programmed cell death 4; MALAT1, metastasis associated lung adenocarcinoma transcript 1; NKILA, NF-kB interacting long non-coding RNA.

Table 2 Preclinical and Clinical Stroke Studies Assessing the Effect of Different LncRNAs on the Regulation of Neurogenesis and Angiogenesis

Author, Year	LncRNA	Species	Models	Regulation	Targets	Main Functions
Wang et al 2019	H19	Mice	MCAO	Up	Notch1, p53	Prevent the process of neurogenesis
Zhang et al 2020	EPS	Mice	MCAO	Up	NA	Accelerate neuron regeneration
You et al 2019	MEG3	Rats	MCAO	Up	Wnt/β-catenin, BDNF	Down-regulation enhance nerve growth and alleviated neurological impairment
Sui et al 2020	MEG8	Mice, Cells	MCAO, OGD/R	Up	miR-130a, VEGFA	Promote angiogenesis and attenuates cerebral ischemia
Zhao et al 2018	SNHG12	Mice, Cells	MCAO, OGD/R	Up	miR-150, VEGF	Promote the angiogenesis
Yan et al 2020	MACC1-AS1	Cells	OGD/R	Down	miR-68675p, VEGFA	Attenuates microvascular endothelial cell injury and promotes angiogenesis
Zhang et al 2019	DANCR	Cells	OGD/R	Up	miR-33a-5p, XBP1s	Enhanced survival and angiogenesis
Wang et al 2018	SNHG1	Cells	OGD/R	Up	miR-199, VEGFA	Upregulation promotes the angiogenesis of brain microvascular endothelial cells
Li et al 2017	HIF-1A-AS2	Mice, Cells	pMCAO, OGD/R	Up	miR-155, VEGFA	Influence angiogenesis in hypoxia

Abbreviations: LncRNA, long non-coding RNA; NA, not available; MCAO, middle cerebral artery occlusion; OGD/R, oxygen glucose deprivation/re-oxygenation; MEG3, maternally expressed gene 3; BDBF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; XBP1, X-box-binding protein 1; pMCAO, permanent middle cerebral artery occlusion.

KCNQ1OT1 is significantly upregulated in ischemic stroke and increased the infarct volume and neurological impairments in mice induce transient middle cerebral artery occlusion (MCAO).[83] To date, a vast number of studies have assessed the effect of lncRNAs on regulating autophagy in ischemia. The characteristics of some of these studies are summarized in Table 3.

LncRNAs Regulate Neuroinflammation in Cerebral Ischemia

Data from four electronic databases, PubMed, Cochrane Library, EMBASE, and Web of Science, were retrieved to identify all literature (clinical and preclinical) evaluated the effect of lncRNAs on the regulation of neuroinflammation in stroke conditions. Two independent authors (YLP and WQX) searched for related publications using the following keywords in combination with Boolean logic: ("noncoding RNA" or "lncRNA") and ("inflammation" or "microglia") and ("ischemia" or "ischemic" or "stroke" or "hypoxia"). In addition, reference lists were manually checked to identify other potential literature associated with the effect of lncRNAs on neuroinflammation. Finally, a total of 39 studies that included 27 kinds of lncRNAs were identified.[11,84–121] Of these 39 articles, ten studies focused on clinical research, twenty-nine studies focused on preclinical stroke, and nearly half of them focused on microglial functions. More details are shown in Table 4.

LncRNAs Modulate Inflammation and Regulate Microglia Activation in Preclinical Stroke Studies

The inflammatory response is a double-edged sword after ischemia because it not only intensifies secondary injury to the brain but also promotes the recovery of neurological function, thus revealing that inflammation is associated with the pathogenesis and prognosis of ischemia. A large number of studies have illustrated that various lncRNAs are closely associated with the regulation of inflammation and microglial activation in ischemia.[66] Several studies have revealed that knocking down lncRNA MALAT1 reduces inflammatory damage after ischemia by Myd88

Table 3 Preclinical and Clinical Stroke Studies Assessing the Effect of Different LncRNAs on the Regulation of Autophagy

Author, Year	LncRNA	Models	Species	Regulation	Targets	Main Functions
Yu et al 2019	KCNQ1OT1	tMCAO, OGD/R	Human, Mice, Cells	Up	miR-200a, FOXO3, ATG7	Knockdown inhibits autophagy and increase cell viability
Luo et al 2020	MEG3	MCAO, OGD/R	Mice, Cells	Up	miR-378, Beclin1, LC3	MEG3/miR-378/GRB2 protected against neuronal autophagy
Yao et al 2019	SNHG12	MCAO, OGD/R	Mice, Cells	Up	Beclin1, LC3, p62	Up-regulation of SNHG12 induce autophagy activation
Wu et al 2020	SNHG12	OGD/R	Cells	Up	SIRT1, FOXO3a	Knockdown inhibits SIRT1/FOXO3a signaling-mediated autophagy
Gao et al 2020	LNHG3	tMCAO, OGD/R	Mice, Cells	Up	miR-485, LC3, Beclin1	Knockdown improve brain I/R injury to restrain autophagy
Li et al 2017	MALAT1	OGD/R	Mice, Cells	Up	miR-26b, LC-3, p62	MALAT1 promote BMEC autophagy and survival under OGD/R condition
Wang et al 2019	MALAT1	OGD/R	Cells	Up	miR-300c-3p, p62, LC3	MALAT1 activate autophagy and promoted cell survival under hypoxic condition
Guo et al 2021	MIAT	MCAO, OGD/R	Rats, Cells	Up	LC3, p62	MIAT promote autophagy of neural cells and aggravate ischemic stroke
Xu et al 2021	C2dat2	MCAO, OGD/R	Mice, Cells	Up	miR-30d-5p, LC3, Beclin1, p62	C2dat2/miR-30d-5p/DDIT4/mTOR facilitate autophagy

Abbreviations: LncRNA, long non-coding RNA; MCAO, middle cerebral artery occlusion; tMCAO, transient middle cerebral artery occlusion; OGD/R, oxygen glucose deprivation/re-oxygenation; I/R, ischemia and reperfusion; FOXO3, forkhead box O3; MEG3, maternally expressed gene 3; BMEC, Brain microvascular endothelial cell; CIRI, cerebral ischemia-reperfusion injury.

signaling while overexpressing lncRNA MALAT1 is positively associated with higher levels of interleukin (IL-1β), tumor necrosis factor α (TNF-α) and IL-6.[122] H19 is one of the most representative lncRNA genes that can be activated after hypoxia, and it can potentially increase inflammation.[123] Knockdown of lncRNA H19 in the MCAO model promoted cerebral recovery, increased plasma IL-10 levels, and reduced TNF-α and IL-1β levels.[121] Higher lncRNA H19 levels in stroke participants inhibited the recovery of neurological function and were associated with the levels of TNF-α.[123]

Normally, microglia are the main resident immune cells and contain a ramified structure to maintain homeostasis in the area surrounding microglial cells. Microglia in the central nervous system are activated immediately when ischemic stroke occurs.[124] Microglial activation is the first step of the inflammatory response, and then other immune cells, such as neutrophils, T cells, and natural killer cells, are activated in the brain.[125,126] There are dual subtypes of microglia in the pathological process of stroke, including M1 and M2 microglia.[127,128] M1 microglia exacerbate brain damage by producing IL-6, IL-1β, nitric oxide (NO), TNF-α, etc., while M2 microglia repair the brain by secreting IL-4, IL-10, and transforming growth factor (TGF-β).[129,130] A series of studies provided the initial evidence that lncRNA SNHG14 and SNHG4 are highly expressed under ischemic conditions and upregulate the expression of inflammation-related cell pathways, such as signal transducer and activator of transcription (STAT) 6 and AQP4, by regulating miR-145–5p and miR-199b, thus leading to the microglial activation in cerebral infarction.[110,131,132] By regulating Kruppel-like factor 4 and protein kinase B (AKT)/STAT3 cell pathway, lncRNA MEG3 and nuclear paraspeckle assembly transcript 1 (NEAT1) affect microglial polarization and the levels of proinflammatory and anti-inflammatory factors.[133,134] Finally, the inhibition of H19 also can reduce activation of microglia and promote microglial M2 polarization.

LncRNA Regulation Correlates with the Level of Inflammatory Cytokines in Stroke Patients

In the pathogenesis of ischemic conditions, the inflammatory response is regarded as one of the most

Table 4 Preclinical and Clinical Stroke Studies Assessing the Effect of LncRNA on the Regulation of Inflammation

Author, Year	LncRNA	Provenance	Cell	Expression	Signaling Pathways	Microglia	Inflammatory Factors	Model
Cao et al 2020	MALAT1	Mice, Cells	BV2	Decrease	miR-181c-5p/ HMGB1	Activation	IL-1β, IL-6, TNF-α, IL-10	MCAO
Zhang et al 2017	MALAT1	Mice, Cells	Mouse BMECs	Increase	NA	NA	MCP-1, IL-6, and E-selectin	MACO, OGD/R
Ren et al 2020	MALAT1	Human	Blood	Decrease	NA	NA	CRP, TNF-a, IL-6, 8, 10, 17, 22	AIS
Ruan et al 2018	MALAT1	Rats, Cells	rBMVECs	Increase	CREB/PGC-1α/ PPARγ	NA	TNF-a, IL-6, IL-1β	tMCAO, OGD/R
Wang et al 2017	MALAT1	Rats, Cells	Microglia	Increase	MyD88/IRAK1/ TRAF6	Activation	IL-1β, IL-6, TNF-α	MCAO
Zhong et al 2019	SNHG14	Rats, Cells	PC12	Increase	miR-136-5p/ ROCK1	NA	IL-1β, IL-6, TNF-α	MCAO, OGD/R
Qi et al 2020	SNHG14	Mice, Cells	BV2	Increase	miR-145-5p/ PLA2G4A	Activation	TNF-α	MCAO, OGD/R
Zhang et al 2021	SNHG14	Mice, Cells	BV2	Increase	miR-199b/AQP4	Activation	IL-1β, TNF-α	MCAO, OGD/R
Lv et al 2020	SNHG1	Cells	HCMIEC/ D3	Decrease	miR-376a/CBS/ H2S	NA	IL-6, IL-1β, TNF-α	OGD/R
Zhang et al 2020	SNHG4	Human, Rats	Blood, HEK293	Increase	miR-449c-5p/ STAT6	Activation	IL-1β, TNF-α, IL-4, 6, 10	AIS, MCAO, OGD/R
Guo et al 2020	SNHG15	Mice, /Cells	N2a	Increase	miR-18a/ CXXL13/ERK/ MEK	NA	TNF-a, IL-1β	MCAO, OGD/R
Hu et al 2021	SNHG15	Mice, Cells	HT22, BV2	Increase	miR-302a-3p/ STAT1/NF-κB	Activation	IL-1β, IL-6, TNF-α	MCAO, OGD/R
Xu et al 2021	H19	Mice, Cells	HT22	Increase	miR-29b/SIRT1/ PGC-1α	NA	IL-6, 1β, 10, TNF-α, TGF-β1	MCAO, OGD/R
Li et al 2020	H19	Rats, Cells	PC12	Increase	miR-138-5p/p65	NA	IL-6, IL-1β, TNF-α	tMCAO OGD/R
Wang et al 2017	H19	Human, Mice, Cells	Blood, BV2	Increase	HDAC1	Polarization	IL-1β, TNF-α, IL-10	MCAO, OGD/R
Zhang et al 2021	NEAT1	Rats	Neuron	Increase	miR-22-3p	NA	IL-1β, IL-18	MCAO, OGD/R
Li et al 2019	NEAT1	Human	Blood	Increase	miR124, miR125a	NA	IL-6, 8, 10, 17, 22, 1β, TNF-α,	AIS
Ni et al 2020	NEAT1	Human	Blood, BV2, N2a	Increase	NA	Activation	CD16, 32, 86, BDNF, PDGF, Arg-1	AIS, OGD/R

(*Continued*)

Table 4 (Continued).

Author, Year	LncRNA	Provenance	Cell	Expression	Signaling Pathways	Microglia	Inflammatory Factors	Model
Li et al 2020	MEG3	Mice, Cells	BV2	Increase	KLF4	Polarization	IL-4, IL-1β, TNF-α, IL-10	MCAO, OGD/R
Liang et al 2019	MEG3	Rats, Cells	Cells	Increase	miR-485/AIM2	NA	IL-1β, IL-18	MCAO, OGD/R
Wen et al 2017	Gm4419	Cells	Microglia	Increase	NF-κB	Activation	TNF-α, IL-1β, and IL-6	OGD/R
Kuai et al 2021	THRIL	Rats, Cells	SH-SY5Y	Increase	miR-24-3p/ NRP1/NF-κB	NA	IL-6, IL-1β, TNF-α	MCAO, OGD/R
Chen et al 2021	OIP5-AS1	Human, Rats	Blood, BV2	Decrease	miR-186-5p/ CTRP3	Activation	TNF-α, IL-1β, IL-6	AIS, OGD/R
Zhang et al 2019	1810034E14Rik	Mice, Cells	Microglia	Decrease	NA	activation	TNF-α, IL-1β, 4, 6, and 10	MCAO, OGD/R
Tian et al 2020	Snhg8	Mice, Cells	Microglial	Decrease	miR-425-5p/ SIRT1/NF-κB	Activation	TNF-α, IL-1β, IL-6	MCAO, OGD/R
Wang et al 2019	TUG1	Cells	BV2, SH-SY5Y	Increase	miR-145a-5p/ NF-κB	Polarization	TNF-α, IL-6, IL-10	OGD/R
Wang et al 2020	EPS	Mice	NSC, microglia	Increase	NA	Migration	TNF-α, IL-1β, and IL-6	tMCAO
Gao et al 2019	FAL1	Cells	HBMVECs	Decrease	PAK1/AKT	NA	IL-6, MCP-1	OGD/R
Hao et al 2021	TTTY15	Cells	PC12	Increase	miR-766-5p	NA	TNF-α, IL-1β, IL-18, IL-10	OGD/R
Yi et al 2020	KCNQ1OT1	Human	Blood, PC12	Increase	miR-140-3p	NA	IL-1β, TNF-α, IL-6	AIS, OGD/R
Zhang ert al. 2019	ITSN1-2	Human	Blood	Increase	miR-107, miR-125a, miR-146a	NA	TNF-α, IL-1β, 6, 8, 17, 22	AIS
Chen et al 2021	U90926	Mice, Cells	Microglia, BV2	Increase	MDH2/ CXCL2	NA	CD45, 11b, 19, 8, Ly6G,	tMCAO, OGD/R
Wang et al 2021	Fender	Mice, Cells	BV2	Increase	HERC2/NLRC4	NA	IL-1β, IL-18	MCAO, OGD/R
Wang et al 2021	SOX2OT	Rats, Cells	PC12	Increase	miR-135a-5p/ NR3C2	NA	IL-1β, IL-6	MCAO, OGD/R
Wang et al 2021	XIST	Mice, Cells	PC12	Increase	miR-362/ ROCK2	NA	IL-1β, IL-6, TNF-α	MCAO, OGD/R
Zhang et al 2020	ZFAS1	Rats, Cells	PC12	Decrease	miR-582-3p	NA	IL-1β, MCP-1, TNF-α	MCAO, OGD/R
Wang et al 2020	Maclpil	Mice, Cells	Cells	Increase	LCPI	NA	IL-1β, IL-4	MCAO

(*Continued*)

Table 4 (Continued).

Author, Year	LncRNA	Provenance	Cell	Expression	Signaling Pathways	Microglia	Inflammatory Factors	Model
Feng et al 2018	ANRIL	Human	Blood	Decrease	NA	NA	IL-6, 8, 10, 17, IL-1β, TNF-α	AIS
Ren et al 2020	UCA1	Human	Blood	Increase	NA	NA	IL-6, IL-17	AIS

Abbreviations: NA, not available; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HMGB1, high-mobility group box 1; IL, interleukin; TNF, tumor necrosis factor; MCAO, middle cerebral artery occlusion; BMECs, brain microvascular endothelial cells; MCP1, monocyte chemoattractant protein 1; CRP, C-reactive protein; AIS, acute ischemic stroke; rBMVECs, rat brain microvascular endothelial cells; CREB, cAMP response element binding; PGC-1α, peroxisome proliferator-activated receptor gamma co-activator 1α; PPARγ, peroxisome proliferative activated receptor γ; tMCAO, transient middle cerebral artery occlusion; FAL1, focally amplified lncRNA on chromosome 1; HBMVECs, human primary brain microvascular endothelial cells; MCP-1, monocyte chemotactic protein-1; OGD, oxygen-glucose deprivation; SNHG, small nucleolar RNA host gene; CXCL13, CXC chemokine ligand 13; ERK, extracellular signal-regulated kinase; MEK, mitogen- activated protein kinase; NF-κB, nuclear factor-κB; HCMIEC/D3, human cerebral microvascular endothelial cell line; TTTY15, testis-specific transcript Y-linked 15; THRIL, HNRNPL related immunoregulatory long non-coding RNA; NRP1, neuropilin-1; SIRT1, silent mating-type information regulation 2 homolog 1; TGF, transforming growth factor; HDACs, histones catalyzed by histone deacetylases; MEG3, maternally expressed gene 3; KLF4, Krüppel-like factor 4; YY1, Yin Yang 1; FGF21, fibroblast growth factor 21; LCP1, lymphocyte cytosolic protein 1; NR3C2, nuclear receptor subfamily 3 group C member 2; ROCK2, Rho-related coiled-coil containing protein kinase 2; ITSN1-2, intersectin 1-2; OIP5-AS1, Opa-interacting protein 5 antisense RNA 1; CTRP3, C1q/TNF-related protein 3; Snhg8, Small nucleolar RNA host gene 8; TUG1, taurine up-regulated gene 1; NSC, neural stem cell.

essential pathogenetic processes and an indicator for the development of cerebral arterial emboli.[135] To date, however, the association between varied lncRNAs and stroke risk and severity, as well as the expression of cytokines related to inflammation in stroke patients, remains unknown. A rigorous search of publications on the expression of various lncRNAs in clinical studies published in three electronic databases, namely, PubMed, the Web of Science and EMBASE, until May 31, 2021, identified 6 studies that included 966 participants.[100–105] Several lncRNAs have been revealed as novel biomarkers that predict higher or lower stroke risk and contribute to the evaluation of disease severity, inflammation level, and prognosis in stroke participants.[136] Ren et al illustrated that lncRNA MALAT1 decreased and revealed a strong relationship with ischemic conditions, and a higher level was positively associated with a changed National Institutes of Health Stroke Scale (NIHSS) score and induced IL-10 in 200 ischemic stroke cases.[102] A dominant upregulation of KCNQ1OT1 in ischemic participant plasma and an OGD/R model in PC12 cells contributes to the higher expression of eNOS through the miR-40–3p/hypoxia-inducible factor-1α axis and is reversed by lncRNA KCNQ1OT1 knockdown and miR-140–3p overexpression.[104] The short duration of follow-up, the small sample size of patients, the utilization of only plasma, and lack of detail on the molecular mechanisms are still the primary limitations of current trials.

LncRNA–microRNA–mRNA Axis is the Key Player in Regulating Inflammation Upon Ischemic Stroke

MiRNAs belong to a subtype of noncoding RNAs of approximately 22 nucleotides that have a stabilizing effect on mRNA, interact with target genes via degradation or suppression of mRNAs, and then inhibit gene translation.[137] MiRNAs can act as mediators in regulating multiple target genes, and one target gene is always modulated by multiple miRNAs.[138] LncRNAs are the widest subtype of noncoding RNAs, and they have direct 'sponging-like effects' on miRNAs,[139] which in turn regulates the transcriptional and epigenetic levels of target genes through imperfect complementarity targeting the 3-UTR of mRNA. Some lncRNAs bind to mRNAs, thereby competing directly with miRNAs.[137] The lncRNA–microRNA–mRNA axis, therefore, contributes to the regulation of disease. Current evidence has shown that the anti- or proinflammatory effects of specific miRNAs are highly regulated by lncRNAs after ischemic stroke. LncRNA SNHG14 modulates microglial activation and achieves its proinflammatory ability by sponging miR-136–5p, miR-145–5p, and miR-199b.[110,117,140] Knockdown of lncRNA H19 increased functional recovery after cerebral ischemia by targeting miR-29b and miR-138–5p[90,141] and promoted microglial M2 polarization due to its stimulative effect on HDAC1.[121] Several studies have shown that miR-145 functions as an inflammatory mediator, while miR-145 overexpression has the potential to suppress inflammatory injury after ischemic stroke.[112] LncRNA TUG1 is able to bind to miR-145a-5p directly,

while the protective effects of lncRNA TUG1 knockdown are reversed by miR-145a-5p siRNA, demonstrating a negative association between TUG1 and miR-145a-5p.[112] Different signaling pathways describing the process of regulation of inflammation by the lncRNA–miRNA–mRNA axis is shown in Figure 2.

LncRNAs Regulate Inflammation Through the TRAF, STAT, and NF-κB Pathways Upon Ischemic Stroke

NF-κB is present in almost all kinds of cells and mainly acts as a transcription factor. It plays a key role in various biological processes, including inflammation, stress response, B cell development and lymphoid organ formation.[142] NF-κB is reported to promote various proinflammatory mediators, and inhibition of NF-κB signaling has beneficial effects in cerebral stroke.[143] LncRNA Snhg8 serves as a competitive endogenous RNA by sponging miR-425–5p, and a bioinformatics analysis showed that this process promotes inflammation by the NF-κB pathway, which was confirmed in microglia.[11] Similarly, Kuai et al illustrated that lncRNA THRIL was negatively correlated with recovery of rat neurological functioning and affected ischemia-reperfusion injury-induced neuronal apoptosis and inflammatory response by regulating NF-κB through miR-24–3p.[89] However, the following question remains: how can these lncRNAs achieve this pro-inflammatory effect through the NF-κB signaling pathway? The STAT pathway is well known to participate in the cell proliferation, apoptosis and immune modulation and plays a crucial role in the signal transduction of a great number of cytokines.[144] M1 microglia are characterized by the induction of STAT1 and NF-κB transcription factors, while the M2 type is related to the transcription factor STAT6.[116] LncRNA SNHG15 increases neuronal damage and microglial inflammation by sponging miR-302a-3p as a competitive endogenous RNA, while this miRNA targets STAT1 and negatively regulates the NF-κB pathway.[88] In addition, Kuai et al[89] and Tian et al[11] revealed that lncRNAs Snhg8 and THRIL regulate inflammation and microglia activation via SIRT1 and neuropilin-1 (NRP1), respectively, by regulating the NF-κB pathway. Thus, lncRNAs might contribute to regulating neuroinflammation and microglia activation by THRIL, NRP1, and STAT1, which further regulate the NF-κB pathway. Information regarding this aspect, however, is scarce.

LncRNAs Regulate Inflammation Through the AKT and ERK Pathways Upon Stroke

Akt includes three subtypes: Akt1, Akt2 and Akt3.[145] Numerous scientists have recently focused on the protective effects of Akt by increasing phosphorylated Akt in

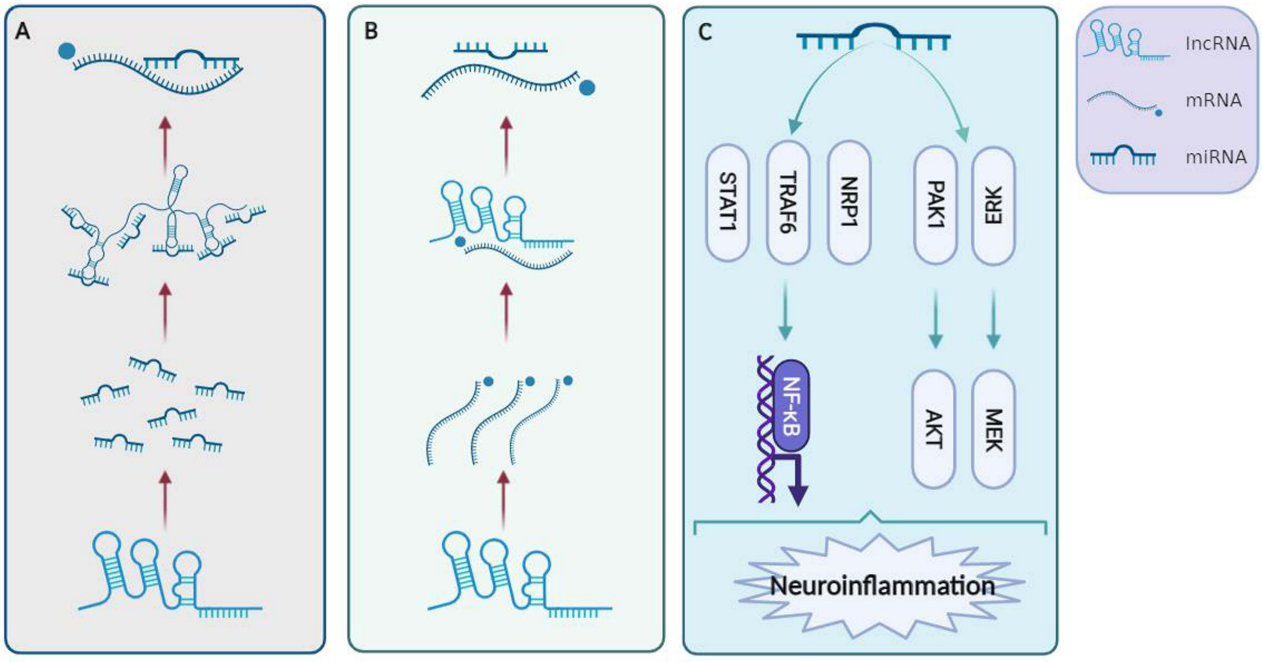

Figure 2 Signaling pathways that describe the process of inflammation regulation by the lncRNA–miRNA–mRNA axis. (**A**) LncRNAs have 'sponging-like effects' on miRNAs directly and target mRNAs. (**B**) Some lncRNAs can bind to mRNAs that compete with miRNAs directly. (**C**) LncRNAs can regulate inflammation through the NF-κB, AKT, and MEK pathways. Created with Biorender.com.

Abbreviations: ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NRP1, neuropilin-1; STAT1, signal transducer and activator of transcription 1; PDK1, phosphoinositide dependent kinase-1; AKT, protein kinases B.

stroke conditions.[146] The Akt pathway has been shown to participate in neuronal survival and inflammation regulation after ischemic stroke,[147] thus illustrating that pharmacological upregulation of Akt signaling might be a potential target for protecting the injured brain. Gao et al pointed out that lncRNA FAL1 has the potential to protect primary brain microvascular endothelial cells against OGD/R-induced endothelial inflammation by regulating the PAK1/AKT signaling pathway.[85] Phosphorylated PI3K can convert Akt into phosphorylated Akt and activate the key subunit of NF-κB to phosphorylated p65, which leads to the nuclear entry of NF-κB and subsequently causes the genetic transcription of inflammatory factors.[147] Silencing of lncRNA SNHG15 can decrease the levels of proinflammatory cytokines (TNF-α and IL-1β) and apoptosis of N2a cells via sequestering the miR-18a and subsequently activating the extracellular signal-regulated kinase (ERK) signaling pathway.[86] Similarly, lncRNA ANRIL knockdown can suppress mouse mesangial cell proliferation, inflammation and fibrosis via ERK pathways in a diabetic nephropathy model.[148] Akt also participates in inhibiting cell apoptosis and reducing eNOS expression via the ERK pathway in a bilateral common carotid occlusion model.[149]

Conclusion

Neuroinflammation usually results in aberrant expression of numerous lncRNAs that exert important functions in epigenetic and transcriptional regulation of the expression of genes. LncRNAs can modulate inflammation by interacting with different signaling pathways, which offers an exceptional opportunity for adjuvant stroke treatment. A great amount of evidence illustrates that numerous lncRNAs can regulate microglial activation and polarization and modulate the inflammatory response in clinical and preclinical stroke studies. The lncRNA–microRNA–mRNA axis is a key player in regulating inflammation upon ischemic stroke, and the NF-κB and AKT pathways are also essential. Although we have witnessed remarkable progress in our understanding of the vital role of lncRNAs in regulating neuroinflammation, many lncRNAs have not yet been functionally characterized and their molecular mechanisms are poorly known. Further efforts should be made to identify more inflammatory lncRNAs species that function under hypoxia. With a better understanding of the gene regulation modalities of lncRNAs, greater progress in this area can be made.

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Disclosure

Yongli Pan, Qingzheng Jiao, Wei Wei and Tianyang Zheng should be considered co-first authors. The authors declare that they have no competing interests.

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