Long Non-Coding RNA-Mediated Competing Endogenous RNA Networks in Ischemic Stroke: Molecular Mechanisms, Therapeutic Implications, and Challenges

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Ischemic stroke (IS) is a disease that is characterized by high mortality and disability. Recent studies have shown that LncRNA-mediated competing endogenous RNA (ceRNA) networks play roles in the occurrence and development of cerebral I/R injury by regulating different signaling pathways. However, no systematic analysis of ceRNA mechanisms in IS has been reported. In this review, we discuss molecular mechanisms of LncRNA-mediated ceRNA networks under I/R injury. The expression levels of LncRNAs, microRNAs (miRNAs), and messenger RNAs (mRNAs) and their effects in four major cell types of the neurovascular unit (NVU) are also involved. We further summarize studies of LncRNAs as biomarkers and therapeutic targets. Finally, we analyze the advantages and limitations of using LncRNAs as therapeutics for IS.

Keywords: long non-coding RNA, competing endogenous RNA network, ischemic stroke, ischemia-reperfusion injury, therapeutic target

INTRODUCTION

Ischemic stroke (IS) is a neurological disorder that is characterized by blockage of blood vessels and accounts for approximately 87% of strokes (Fann et al., 2013; Lin et al., 2016; Kuriakose and Xiao 2020). Currently, the accepted therapeutic strategy for IS is vascular recanalization therapy which including thrombolysis (with agents such as tissue plasminogen activators), mechanical thrombectomy, and the combination of them. However, reperfusion therapy must be applied within a very short period, which drastically limits the population that is eligible for treatment. Moreover, ischemia-reperfusion (I/R) injury occurs when blood is resupplied to cerebral ischemic tissues, as it is harmful to blood vessels and brain cells such as brain microvascular endothelial cells (BMECs), neurons, and microglial cells. The extent of the ensuing lesion is dependent on the active
and complicated interaction between vascular cells, neurons, and glial cells (Trendelenburg and Dirnagl 2005). The precise mechanisms underlying I/R injury remain unknown. However, oxidative stress, inflammation, autophagy, apoptosis, and blood-brain barrier disruption are potential mechanisms (Zhu et al., 2020).

Long non-coding RNAs (LncRNAs), a class of non-coding RNAs that are more than 200 nucleotides in length (Kapranov et al., 2007), have been widely studied. It has been reported that LncRNAs affect the occurrence and outcome of several diseases by regulating chromatin modification, post-transcription, and transcription (Ma et al., 2013; McDonel and Guttman 2019; Nair et al., 2020). LncRNAs are also involved in the pathological progression of tumors, nervous system disorders, cardiovascular diseases, and other diseases (Schmitz et al., 2016; Peng et al., 2017; Huang 2018; Wolska et al., 2020). Recent studies have shown that LncRNAs, such as LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), play important roles in IS (Zhang et al., 2017a). Another class of non-coding RNAs is microRNAs (miRNAs), which are single-stranded endogenous RNAs with a length of 19–25 nt (Lu and Rothenberg 2018). It has been shown that miRNAs function by targeting the 3′-untranslated (3′-UTR) region of messenger RNAs (mRNAs), thus inhibiting protein synthesis or promoting mRNA degradation (Kabekkodu et al., 2018). Since miRNAs are involved in disease development, they have been a potential target for therapeutic approaches, especially in cancer management (Rupaimoole and Slack 2017; Fan et al., 2019).

The competing endogenous RNA (ceRNA) hypothesis was first proposed by Salmena et al. in 2011 (Salmena et al., 2011). The concept suggests that there are ceRNAs such as LncRNAs, circular RNAs, pseudogenes, and mRNAs in cells. Additionally, ceRNAs can competitively bind to the same mRNA by interacting with miRNA response elements (MREs) to build communication networks between messenger RNAs and non-coding RNAs (Salmena et al., 2011; Sanchez-Mejias and Tay 2015). Thus, LncRNAs can compete with an mRNA, bind to the same miRNA, and regulate the expression of the mRNA if they have the same MRE (Figure 1).

In this review, we focus on LncRNAs that mediate ceRNA networks and regulate key processes involved in I/R injury to explore the potential roles of LncRNAs in regulating IS. We have also summarized the molecular mechanisms of the LncRNA-miRNA-mRNA axis in autophagy, apoptosis, angiogenesis, microglial activation, and polarization in different cell lines (Table 1). Furthermore, we have discussed the therapeutic implications and challenges of LncRNAs in IS.

**ARTICLE SEARCH PROCESS**

Studies included in the review were obtained by searching the PubMed database. The following search syntaxes were used (long non-coding RNA) AND (ischemic stroke) AND (competing endogenous RNA) AND (ischemic stroke). Review articles and meta-analyses were included for possible support (Figure 2).

**REGULATORY ROLES OF LNCRNAs IN NEURONS**

The focal areas of IS are the ischemic core area and the penumbra. In the ischemic core area, failure of the ion pump of the neuronal cell membrane and energy metabolism leads to irreversible damage to the brain tissue. However, there are collateral circulations and surviving neurons in the ischemic penumbra. Thus, restoring blood supply to the ischemic penumbra as soon as possible and using effective neuroprotective drugs are important research aspects in IS. Furthermore, prevention and inhibition of neuronal cell injury are potential treatment strategies. In this section, we summarize the effects and ceRNA networks of LncRNAs in neurons and provide evidence for the development of RNA drugs (Figure 3).

**poptosis**

LncRNA Maternally Expressed Gene 3

In a previous study, LncRNA MEG3 expression was upregulated in middle cerebral artery occlusion/reperfusion (MCAO/R) models, which mainly protected ischemic neurons. Additionally, MEG3 served as a ceRNA for microRNA-21 (miR-21), which was downregulated in vivo and in vitro in contrast to MEG3. Furthermore, programmed cell death 4 (PDCD4), a gene that mediates neuronal cell death, binds to miR-21. Overexpression of miR-21 resulted in protection against oxygen-glucose deprivation and reoxygenation (OGD/R)-induced apoptosis, whereas knockdown of MEG3 resulted in protection against I/R injury and improved neurological function in IS patients (Yan et al., 2017). Similarly, Liang et al. observed that inhibition of MEG3 expression contributed to pyroptosis via activation of the miR-485/absent in melanoma 2 (AIM2)/caspase-1 pathway (Liang et al., 2020). Moreover, MEG3 targets miR-424-5p via neuronal apoptosis mediated via the mitogen-activated protein kinase (MAPK) pathway (Xiang et al., 2020).
TABLE 1 | Studies evaluating LncRNA-mediated ceRNA networks in IS.

| Reference            | LncRNA       | Model                                         | Pathophysiological mechanism | Axis                              | Effects                                                                 |
|----------------------|--------------|-----------------------------------------------|------------------------------|-----------------------------------|--------------------------------------------------------------------------|
| Yan et al. (2017)    | LncRNA ME3  | C57BL/6 J mice, N2a cells                     | Apoptosis                    | LncRNA MEG3/miR-21/PDCD4          | MEG3 aggravated apoptosis of neurons and ischemic damage                 |
| Liang et al. (2020)  | LncRNA ME3  | Sprague Dawley (SD) rat, SK-N-SH, SH-SY5Y cells | Pyroptosis, inflammation     | LncRNA MEG3/miR-485/AIM2/caspase-1 | MEG3 contributed to pyroptosis and inflammation via miR-485/IMD in cerebral I/R injury |
| Luo et al. (2020)    | LncRNA ME3  | C57BL/6J mice, primary mouse cortical neurons | Autophagy                    | LncRNA MEG3/miR-378/GRB2/Akt/mechanistic target of rapamycin (mTOR) | Knockdown of LncRNA MEG3 resulted in reduced autophagy via targeting of the miR-378/GRB2/Akt/mTOR axis |
| Xiang et al. (2020)  | LncRNA ME3  | C57BL/6J mice, SD rats, N2a cells              | Apoptosis                    | LncRNA MEG3/miR-424-5p/Sema3A/MAPK pathway | Downregulation of LncRNA MEG3 expression resulted in reduced apoptosis and suppressed MAPK pathway via targeting of miR-424-5p and then modulation of Sema3A expression |
| Xu et al. (2021)     | LncRNA H19  | C57BL/6J mice, HT22 cells                     | Apoptosis, inflammation      | LncRNA H19/miR-29b/SIRT1/PGC-1α   | Knockdown of LncRNA H19 resulted in ameliorated OGD-induced inflammation and apoptosis via regulation of the miR-29b/SIRT1/PGC-1α axis |
| Xiao et al. (2019)   | LncRNA H19  | Patients with anterior circulation ischemia, SH-SY5Y cells, human embryonic kidney (HEK) 293T cells, SD rats | Apoptosis                    | LncRNA H19/miR-19a/id2           | Suppression of LncRNA H19 expression resulted in protection against neuronal injury induced by hypoxia/ischemia via regulation of the miR-19a/id2 axis |
| Chen et al. (2018)   | LncRNA GAS5 | C57BL/6J mice, mouse primary brain neurons     | Apoptosis                    | LncRNA GAS5/miR-137/Notch1 signaling pathway | GAS5 functioned as a ceRNA for miR-137 to regulate Notch1 and promote neuronal injury by inhibiting the Notch1 signaling pathway |
| Wu et al. (2021)     | LncRNA GAS5 | SD rats, PC12 cells                            | Apoptosis, mitochondrial damage | LncRNA GAS5/miR-455-5p/PTEN       | Upregulation of GAS5 expression resulted in downregulated miR-455-5p expression, which promoted PTEN expression, aggravated mitochondrial damage, worsened neurobehavior, and promoted apoptosis and oxidative injury |
| Zhou et al. (2020)   | LncRNA SNHG7| C57BL/6J mice, PC12 cells                     | Apoptosis                    | LncRNA SNHG7/miR-9/SIRT1          | LncRNA SNHG7 served as a ceRNA for miR-9 to regulate SIRT1 expression, thus alleviating neuronal injury |
| Yan et al. (2020b)   | LncRNA SNHG12| SH-SY5Y cells                                 | Apoptosis                    | SNHG12/miR-181a-5p/NEGR1          | SNHG12 inhibited OGD-induced apoptosis of SH-SY5Y cells via the miR-181a-5p/NEGR1 axis |
| Guo et al. (2020)    | LncRNA SNHG15| C57BL/6J mice, N2a cells                      | Apoptosis                    | LncRNA SNHG15/miR-18a/CXCL13/ERK/MEK | Silencing of SNHG15 resulted in enhanced viability and reduced apoptosis of N2a cells via the miR-18a/CXCL13/ERK/MEK axis |
| Fan et al. (2021)    | LncRNA SNHG15| PC12 cells                                    | Apoptosis, inflammation      | LncRNA SNHG15/miR-455-3p/TP53INP1 | Knockdown of SNHG15 resulted in protection against OGD/R-induced neuronal injury via regulation of the miR-455-3p/TP53INP1 axis |
| Zhao et al. (2021)   | LncRNA RMST  | IS patients, N2a cells                         | Apoptosis                    | RMST/miR-377/SEMA3A               | Upregulating RMST expression promoted apoptosis and oxidative stress via regulation of the miR-377/SEMA3A axis in IS patients |
| Cheng et al. (2020)  | LncRNA RMST  | HT-22 cells                                    | Apoptosis                    | RMST/hnRNPK/p53/miR-107/8c22     | The RMST/hnRNPK/p53/miR-107 axis inhibited Bcl222 expression and promoted apoptosis |
| Guo et al. (2017)    | LncRNA MALAT1| C57BL/6J mice, cerebral cortex neurons         | Autophagy                    | LncRNA MALAT1/MIR-30a/Bcl-1       | Suppressing MALAT1 expression attenuated neuronal death via splicing of miR-30a to regulate Bcl-1 expression in cerebral IS |

(Continued on following page)
| Reference | LncRNA | Model | Pathophysiological mechanism | Axis | Effects |
|-----------|--------|-------|------------------------------|------|---------|
| Jia et al. (2021) | LncRNA MALAT1 | HT-22 cells | Apoptosis | LncRNA MALAT1/miR-195a-5p/HMGA1 | MALAT1 promoted neuronal injury through binding to miR-195a-5p and then by upregulating HMGA1 expression |
| Zhang et al. (2020a) | LncRNA MALAT1 | SD rats, PC12 cells | Inflammation, apoptosis | LncRNA MALAT1/miR-375/PDE4D | Suppressing MALAT1 expression alleviated inflammation and apoptosis in a rat model of MCAO/R through modulation of the miR-375/PDE4D axis |
| Liu et al. (2019) | LncRNA ANRIL | PC12 cells | Apoptosis | LncRNA ANRIL/miR-127/Mcl-1 | LncRNA ANRIL/MTL-127/3-MCL1 axis |
| Zhong et al. (2020) | LncRNA ANRIL | C57BL/6J mice, N2a cells | Apoptosis | LncRNA ANRIL/miR-199a-5p/CAV-1/phosphorylation of MEK/ERK | ANRIL protected N2a cells by sponging miR-199a-5p, thus downregulating CAV-1 expression and activating the MEK/ERK pathway |
| Chen et al. (2017) | LncRNA TUG1 | SD rats, Primary cortical neurons, SH-SY5Y cells | Apoptosis | LncRNA TUG1/miRNA-9/BC211 | TUG1 sponges miR-9 to aggregate neuronal apoptosis by upregulating BC211 expression |
| Wang et al. (2018a) | LncRNA HOTTIP | C57BL/6J mice, Primary cortical neurons from mouse embryos | Apoptosis, glycolytic metabolism | LncRNA HOTTIP/miR-143/hexokinase 2 | HOTTIP reduced OGD/R-induced neuronal injury by regulating the miR-143/hexokinase 2 axis |
| Cai et al. (2019) | LncRNA Gm11974 | HEK293T cells, N2a cells | Apoptosis | LncRNA Gm11974/miR-766-3p/NR3C2 | Knockdown of Gm11974 resulted in protection against neuronal apoptosis via the miR-766-3p/NR3C2 axis |
| Gai et al. (2019) | LncRNA CHRF | C57BL/6J mice, N2a cells | Apoptosis | CHRF/miR-126/SOX6 | Knockdown of CHRF resulted in reduced ischemic neuronal death via upregulation of miR-126 expression and reduction in SOX6 expression |
| Jing et al. (2019) | LncRNA Oprm1 | C57BL/6J mice, N2a cells | Apoptosis | Oprm1/miR-155/GATA3 axis | Oprm1 played a protective role in cerebral stroke by acting as a ceRNA for miR-155 to target GATA3 |
| Wei et al. (2019) | LncRNA AK038897 | C57BL/6J mice, N2a cells | Apoptosis | AK038897/miR-26a-5p/DAPK1 | LncRNA AK038897 aggravated cerebral I/R injury by regulating the expression of miR-26a-5p and DAPK1 |
| Zhang et al. (2019b) | LncRNA FGDS-AS1 | Primary cortical neurons isolated from the brains of SD rats | Apoptosis | FGDS-AS1/miRNA-223/IGF1R | FGDS-AS1 acted as a protective factor in OGD/R-induced neuronal injury via competitive binding to miR-223 and regulation of IGF1R expression |
| Lu et al. (2020) | LncRNA FOXD3-AS1 | C57BL/6J mice, N2a cells | Apoptosis | FOXD3-AS1/miR-765/BCL2L13 | Knockdown of FOXD3-AS1 resulted in protection against cerebral I/R injury via binding to miR-765 to regulate BCL2L13 expression |
| Yao et al. (2020) | LncRNA Rian | C57BL/6J mice, N2a cells | Apoptosis | Rian/miR-144-3p/GATA3 | Overexpression of LncRNA Rian caused a reduction in apoptosis induced by cerebral I/R injury via the miR-144-3p/GATA3 axis |
| Zhang et al. (2019a) | LncRNA SHHG6 | C57BL/6J Mice, primary mouse cortical neurons | Apoptosis | LncRNA SHHG6/miR-181c-5p/BIM | SHHG6 functioned as a ceRNA to regulate neuronal apoptosis by regulating the miR-181c-5p/BIM axis in IS |
| Cao et al. (2020a) | LncRNA TALNEC2 | C57BL/6J mice, N2a cells | Apoptosis | TALNEC2/miR-650/APAF1 | TALNEC2 aggravated cerebral I/R injury by serving as a ceRNA for miR-650 to target APAF1 |
| Zhou et al. (2020) | LncRNA GAS5 | SD rats, HEK293 cells, primary rat cortical cells, B35 cell line | Apoptosis | GAS5/miR-221/p53 | GAS5 aggravated apoptosis induced by OGD/R injury by regulating the miR-221/p53 axis |
| Yu et al. (2019) | KCNQ1OT1 | Acute IS patients, C57BL/6J mice, N2a cells | Autophagy | KCNQ1OT1/miR-200a/FOXO3/ATG7 pathway | KCNQ1OT1 promoted autophagy by modulating the miR-200a/FOXO3/ATG7 axis in IS |

(Continued on following page)
| Reference        | LncRNA         | Model                          | Pathophysiological mechanism       | Axis                              | Effects                                                                 |
|------------------|----------------|--------------------------------|-----------------------------------|----------------------------------|------------------------------------------------------------------------|
| Yi et al. (2020) | KCNQ1OT1       | IS Patients, PC12 cells        | Apoptosis                         | KCNQ1OT1/miR-140-3p/HIF-1α       | KCNQ1OT11 exacerbates apoptosis and I/R injury by regulating the miR-140-3p/HIF-1α axis |
| Li et al. (2017b)| LncRNA MALAT1  | BMECs, C57BL/6J mice          | Autophagy                         | LncRNA MALAT1/miR-26b/ULK2       | MALAT1 promoted BMEC autophagy and survival by working as a ceRNA to sponge miR-26b and by upregulating ULK2 expression |
| Teng et al. (2020)| LncRNA SNHG16  | HBMECs                        | Apoptosis                         | LncRNA SNHG16/miR-15a-5p/Bcl2    | SNHG16 promoted against OGD/R-induced apoptosis of HBMECs by regulating the miR-15a-5p/Bcl2 axis |
| Yin et al. (2021)| LncRNA RMST    | HBMECs, bEnd.3 cells         | Apoptosis                         | RMST/miR-204-5p/VCAM1            | Knockdown of RMST resulted in reduced OGD-induced injury via regulation of the miR-204-5p/VCAM1 axis |
| Chen et al. (2020)| LncOGD-1006   | Primary BMECs                 | Apoptosis                         | LncOGD-1006/miR-184-5p/CAAP1     | LncOGD-1006 alleviates OGD-induced apoptosis via the miR-184-5p/CAAP1 axis |
| Li et al. (2017a)| LncRNA HIF1A-AS2| SD rats, HUVECs               | Angiogenesis                       | LncRNA HIF1A-AS2/miR-153-3p/HIF-1αVEGFA/Notch1 | HIF1A-AS2 promoted angiogenesis in HUVECs by binding to miR-153-3p to upregulate HIF-1α expression |
| Zhao et al. (2018)| LncRNA SNHG12  | C57BL/6J mice, bEnd.3 cells | Angiogenesis                       | LncRNA SNHG12/miR-150/VEGF      | SNHG12 played a protective role in angiogenesis reduction in IS by regulating the miR-150/VEGF axis |
| Wang et al. (2018b)| LncRNA SNHG1  | C57BL/6J mice, BMECs         | Angiogenesis                       | LncRNA SNHG1/miR-18a/HIF-1αVEGFA | SNHG1 played a protective role in angiogenesis as a ceRNA through HIF-1αVEGFA signaling in IS |
| Yang et al. (2018)| LncRNA SNHG1  | BMECs                         | Angiogenesis                       | LncRNA SNHG1/miR-338/HIF-1αVEGFA | SNHG1 protected BMECs against OGD-induced injury by regulating the miR-338/HIF-1αVEGFA-A axis |
| Yan et al. (2020a)| LncRNA MACC1-AS1| HBMECs                      | Angiogenesis                       | LncRNA MACC1-AS1/miR-6867-5p/TWIST1 | MACC1-AS1 protected hypoxic HBMECs by promoting angiogenesis via regulation of the miR-6867-5p/TWIST1 axis |
| Zhang et al. (2020)| LncRNA DANCR  | BMECs                         | Angiogenesis                       | LncRNA DANCR/miR-33a-5p/XBP1s    | DANCR promoted cell survival and angiogenesis by regulating the miR-33a-5p/XBP1s axis |
| Gao and Wang (2020)| LncRNA MALAT1  | bEnd.3 cells, HEK293T cells | Apoptosis                          | LncRNA MALAT1/miR-205-3p/PTEN    | MALAT1 suppressed apoptosis in IS and functioned as a ceRNA for miR-205-3p to modulate PTEN expression |
| Gao et al. (2020a)| LncRNA MALAT1  | HBMECs                        | Angiogenesis                       | LncRNA MALAT1/miR-205-5p/VEGFA   | MALAT1 promoted angiogenesis in HBMECs subjected to OGD/R by interacting with the miR-205-5p/VEGFA axis |
| Tian et al. (2021)| LncRNA Snhg8   | BMECs, primary microglial cells | Microglial inflammation, BBB disruption | LncRNA Snhg8/miR-425-5p/SIRT1/3HF-1αB pathway | Snhg8 inhibited microglial activation and alleviated BMEC injury by sponging miR-425-5p and regulating the SIRT1/3HF-1αB pathway |
| Zhang et al. (2020a)| LncRNA SNHG14  | C57BL/6J mice, BV2 cells     | Inflammation                       | LncRNA SNHG14/miR-199b/AQP4 Axis | SNHG14 knockdown resulted in reduced inflammation and oxidative stress via regulation of the miR-199b/AQP4 axis |
| Qi et al. (2017)| LncRNA SNHG14  | C57BL/6J mice, microglia, neurons | Microglial activation, apoptosis  | LncRNA SNHG14/miR-145-5p/PLA2G4A | SNHG14 promoted microglial activation and apoptosis by regulating the miR-145-5p/PLA2G4A pathway |
| Chen et al. (2021b)| LncRNA OIP5-AS1| SD rats, microglial cells     | Inflammation, neuronal apoptosis, oxidative stress | OIP5-AS1/miR-186-5p/CTRP3 axis   | Upregulation of OIP5-AS1 expression resulted in protection against neuronal injury in MCAO/R-induced inflammation and oxidative stress in microglia/macrophages via CTRP3 activation and interaction with miR-186-5p (Continued on following page) |
LncRNA H19

In a previous study, LncRNA H19 expression was found to be upregulated in SD rats, C57 mice, and an OGD cell culture model. Additionally, H19 siRNA improved apoptosis and inflammation and influenced the expression of miR-29b, sirtuin1 (SIRT1), and peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1a expression in OGD cell culture models (Xu et al., 2021). Another report indicated that H19 levels were elevated in patients with anterior circulation ischemia and that H19 knockdown resulted in reduced apoptosis in OGD neuronal cells. Furthermore, inhibition of H19 expression in a rat model of MCAO/R resulted in a marked decrease in brain infarct volume, neurological deficits, and neuronal apoptosis. It was also found that H19 plays a critical role in neuronal apoptosis as a ceRNA by interfering with the binding of inhibitor of DNA binding 2 (Id2) and PTEN to miR-19a and miR-19a-3p (Xiao et al., 2019; Gao N. et al., 2020).

LncRNA Growth Arrest-specific 5

LncRNA GAS5 expression is attributed to negative regulation of cell survival. Upregulation of GAS5 expression has been

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**TABLE 1 | (Continued) Studies evaluating LncRNA-mediated ceRNA networks in IS.**

| Reference          | LncRNA   | Model                                      | Pathophysiological mechanism | Axis                                      | Effects                                                                 |
|--------------------|----------|--------------------------------------------|------------------------------|-------------------------------------------|-------------------------------------------------------------------------|
| Wang et al.        | LncRNA MALAT1       | C57BL/6J mice, astrocytes            | Apoptosis                     | LncRNA MALAT1/miR-145/ AQP4               | LncRNA MALAT1 aggravated apoptosis by improving AQP4 expression via miR-145 sponging axis |
| Song et al.        | KCNQ1OT1 | HMC3 cells                                 | Inflammation, apoptosis       | KCNQ1OT1/miR-30e-3p/ NLRP3                | Inhibition of KCNQ1OT1 reduced the inflammation and apoptosis via miR-30e-3p/NLRP3 pathway |
| Ren et al.         | KCNQ1OT1 | Primary mouse cerebral cortical neurons    | Apoptosis                     | KCNQ1OT1/miR-9/MMP8 axis                  | Inhibition of KCNQ1OT1 possibly ameliorated neuronal injury by regulating miR-9/MMP8 axis |
| Wang et al.        | KCNQ1OT1 | Primary mouse cerebral cortical neurons    | Apoptosis                     | KCNQ1OT1/miR-153-3p/ FOXO3 Axis           | KCNQ1OT1 promoted neuronal injury through regulating Foxo3 expressions via miR-153-3p |
| Zhong et al.       | LncRNA SNHG14      | C57BL/6J mice, SD rats, PC-12 cells       | Inflammation                  | LncRNA SNHG14/miR-136-5p/ROCK1            | LncRNA SNHG14 promoted neurological impairment and inflammatory response via miR-136-5p/ROCK1 axis |
| Deng et al.        | LncRNA SNHG14      | HT22 cells                                 | Mitophagy                     | LncRNA SNHG14/miR-182-5p/BINP3            | LncRNA SNHG14 promoted neuron injury by regulating mitophagy via miR-182-5p/BINP3 axis |
| Li et al.          | LncRNA H19         | SD rats, PC-12 cells                      | Inflammation                  | LncRNA H19/miR-138-5p/p65                | LncRNA H19 promoted inflammation by regulating miR-138-5p/p65 axis |
| Gao et al.         | LncRNA H19         | C57BL/6J mice, SH-SYSY cells              | Oxidative stress, apoptosis   | LncRNA H19/miR-19a-3p/PTEN axis          | LncRNA H19 promoted Oxidative stress and apoptosis induced by 1R or OGD/R through miR-19a-3p/PTEN axis |
| Shan et al.        | LncRNA TUG1        | C57BL/6J mice, MA-C cells                 | Apoptosis                     | LncRNA TUG1/miR-145/ AQP4                | LncRNA TUG1 aggraviated apoptosis by improving AQP4 expression via miR-145 sponging axis |
| Cao et al.         | LncRNA Malat 1     | C57BL/6J mice, BV-2 cells                 | Inflammation                  | LncRNA Malat1/miR-181c-5p/HMGB1         | LncRNA Malat1/miR-181c-5p/HMGB1 axis may play a vital role in poststroke inflammation |
| Cao et al.         | LncRNA Malat 1     | C57BL/6J mice, BV-2 cells                 | Inflammation                  | LncRNA Malat1/miR-181c-5p/HMGB1         | LncRNA Malat1/miR-181c-5p/HMGB1 axis may play a vital role in poststroke inflammation |

In the axis column, upregulated actors are in red font, downregulated factors are in blue font, whereas unknown factors are in black font.

**FIGURE 2 | Article selection process.**
demonstrated both in vivo and in vitro. It has also been reported that GAS5 knockdown results in a significant increase in cell viability, suppression of caspase-3 activation, and the induction of neuronal apoptosis after OGD. Moreover, GAS5 serves as a molecular sponge for miR-137 to regulate Notch1 expression and reduce neuron survival (Chen et al., 2018). Wu et al. revealed the functions of the GAS5/miR-455-5p/phosphatase and tension homolog deleted on chromosome ten (PTEN) axis in cerebral IS. It was found that GAS5 and PTEN levels were upregulated whereas miR-445-5p level was downregulated in brain and PC12 cell models of MCAO/R injury that were subjected to OGD/R. Additionally, suppression of GAS5 expression or miR-455-5p overexpression improved neurobehavior and decreased apoptosis and oxidative injury (Wu et al., 2021).

**LncRNA Small Nucleolar RNA Host Genes**

SNHG5s are a group of LncRNAs that are overexpressed in various cancers. They include SNHG1, SNHG3, SNHG5, SNHG6, SNHG7, SNHG12, SNHG15, SNHG16, and SNHG20 (Zimta et al., 2020). It has been reported that SNHG6 functions as a ceRNA for miR-181c-5p to regulate Bcl2 interacting mediator of cell death (BIM) expression and promote apoptosis (Zhang X. et al., 2019). In a previous study, SNHG7 expression was downregulated in C57 mice and PC12 cells. Additionally, SNHG7 overexpression or suppression of miR-9 expression resulted in decreased reactive oxygen species and malondialdehyde levels and increased cell viability. It has been reported that SNHG7 reduces OGD/R-induced neuronal apoptosis and functions as a ceRNA for miR-9 and SIRT1 targeted by miR-9. In summary, LncRNA SNHG7 serves as a ceRNA for miR-9 to regulate SIRT1 activity, thus alleviating neuronal injury (Zhou et al., 2020).

In another study, SNHG12 was highly expressed in SH-SY5Y cells subjected to OGD/R. Furthermore, SNHG12 targeted miR-181a-5p and negatively regulated its expression. Moreover, miR-181a-5p is a target of nerve growth factor receptor 1 (NEGR1) and negatively regulates the expression of NEGR1 in OGD-induced neuronal apoptosis (Yan Y. et al., 2020). SNHG15 expression was also upregulated in C57 mice, neuro-2a (N2a) cells, and PC12 cells in previous studies (Guo et al., 2020; Fan et al., 2021). Guo et al. found that silencing SNHG15 resulted in upregulation of the expression of C-X-C motif chemokine ligand 13 (CXCL13) through suppression of the activation of miR-18a and extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase kinase (MEK). These resulted in reduced apoptosis and enhanced cell viability (Guo et al., 2020). Furthermore, Fan et al. revealed that downregulation of LncRNA SHNG15 expression plays a protective role in OGD/R-induced neuronal injury through downregulation of the expression of tumor protein p53 inducible nuclear protein 1 (TP53INP1) via miR-445-3p targeting (Fan et al., 2021).

**LncRNA Rhabdomyosarcoma 2-Associated Transcript**

The expression of LncRNA RMST was upregulated whereas that of miR-377 was downregulated in serum samples collected from patients with IS. Furthermore, suppression of RMST expression resulted in reduced oxidative stress and apoptosis in an N2a cell culture model of OGD. Semaphorin 3A (SEMA3A) is a target gene of miR-377, and RMST regulates SEMA3A expression as a sponge for miR-377 (Zhao et al., 2021). A previous study revealed that RMST interacts with heterogeneous nuclear ribonucleoprotein K (hnRNPK) and then regulates the p53/
miR-107 axis, thus promoting apoptosis of HT-22 cells (Cheng et al., 2020).

**LncRNA Antisense Non-Coding RNA in the INK4 Locus**

It has been reported that LncRNA ANRIL is involved in neuronal apoptosis, and its expression was decreased in patients with acute IS, rat, and mouse models of MCAO/R, (Feng et al., 2019; Liu et al., 2019; Zhong et al., 2020). Interestingly, one study demonstrated that the level of LncRNA ANRIL in N2a cells significantly decreased within 12 h after OGD but increased at 18 h and peaked at 24 h after OGD (Zhong et al., 2020). Another study also revealed that LncRNA ANRIL expression is downregulated within 8 h after OGD in PC12 cells (Liu et al., 2019). Furthermore, silencing ANRIL aggravated OGD-induced PC12 cell injury via the reduction in cell viability and increase in apoptosis, while overexpression of ANRIL contributed to opposite effects. Overexpression of miR-127 and myeloid cell leukemia-1 (Mcl-1) results in significantly enhanced cell injury. Additionally, miR-127 negatively regulates Mcl-1 expression, whereas ANRIL upregulates Mcl-1 expression by downregulating miR-127 expression (Liu et al., 2019). It has been revealed that ANRIL competitively interacts with miR-199a-5p in N2a cells. Additionally, overexpression of ANRIL or suppression of miR-199a-5p expression results in the protection of cells against I/R injury and improved cell viability through the cavelon-1 (CAV-1)-mediated MEK/ERK pathway (Zhong et al., 2020).

**LncRNA MALAT1**

LncRNA MALAT1 has been reported to be highly expressed in both in vivo and in vitro models of ischemia (Guo et al., 2017; Zhang G. et al., 2020; Jia et al., 2021). In addition, It has also been claimed that downregulation of MALAT1 expression alleviates neuronal apoptosis. Furthermore, suppression of MALAT1 expression or overexpression of miR-375 leads to a decrease in the levels of inflammatory factors and lactate dehydrogenase as well as a reduction in apoptosis. Furthermore, miR-375 targets both MALAT1 and phosphodiesterase 4D (PDE4D) (Zhang G. et al., 2020). It has also been reported that MALAT1 knockdown causes a reversal in OGD/R-induced apoptosis and endoplasmic reticulum stress through the targeting of miR-195a-5p and regulating the expression of high mobility group AT-hook1 (HMGA1) (Jia et al., 2021).

**LncRNA Potassium Voltage-Gated Channel Subfamily Q Member one Opposite Strand 1 (KCQN1OT1)**

KCQN1OT1 was highly expressed in patients with acute IS, MCAO/R models, and OGD cell culture models in a previous study. Further, downregulation of KCQN1OT1 expression significantly ameliorated apoptosis in OGD/R treated PC12 cells. It has also been reported that KCQN1OT1 serves as a ceRNA for miR-140-3p and regulates the expression of hypoxia-inducible factor (HIF)-1α, which is a target of miR-140-3p (Yi et al., 2020). KCQN1OT1 and MMP8 expressions were significantly increased in neurons but miR-9 was downregulated. Inhibiting KCQN1OT1 or overexpressing miR-9 protected OGD/R-induced neuronal injury (Wang HJ. et al., 2020; Ren et al., 2020). Another study revealed KCQN1OT1 promoted neuronal apoptosis via miR-153-3p/forkhead box O3 (FOXO3) axis (Wang HJ. et al., 2020).

**Other LncRNAs**

Other LncRNA-mediated ceRNA networks have been studied in neuronal cell cultures. For instance, LncRNA taurine-upregulated gene 1 (TUG1) has been shown to play an important role in apoptosis in IS. TUG1 expression was found to be upregulated in cultured neurons under OGD insult. Additionally, knockdown of TUG1 reportedly results in decreased apoptosis and increased cell survival in vitro. It has been found that TUG1 directly binds to miR-9 and that downregulating miR-9 expression reverses the suppressive effect of TUG1 on B-cell lymphoma-2 like-11 (Bcl2l11) expression (Chen et al., 2017). In a study conducted by Wang et al., LncRNA HOXA transcript at the distal tip (HOTTIP) was found to induce neuronal injury by modulating the miR-143/hexokinase 2 pathway (Wang Y. et al., 2018). In other studies, the LncRNA Gm11974/miR-766-3p/nuclear receptor subfamily 3 group C member 2 (NR3C2) and LncRNA cardiac hypertrophy-related factor (CHRF)/miR-126/sex-determining region Y box 6 (SOX6) axes protected against cerebral I/R injury and reduce neuronal apoptosis (Cai et al., 2019; Gai et al., 2019). Jing et al. also found that overexpression of LncRNA mu-1-opioid peptide receptor (Oprm1) results in the alleviation of apoptosis from cerebral I/R injury through the Oprm1/miR-155/GATA binding protein 3 (GATA3) axis (Jing et al., 2019). Furthermore, the LncRNA AK038897/miR-26a-5p/death-associated protein kinase 1 (DAPK1), FG5d antiseis RNA 1 (FG5d-AS1)/miRNA-223/insulin-like growth factor (IGF)-1 receptor (IGF1R), tumor-associated LncRNA expressed on chromosome 2 (TALNEC2)/insulin-like growth factor (IGF)-1 receptor bound protein 2 (GRB2) axis plays a role in neuronal autophagy and impairment of neurological function in IS (Luo et al., 2020). Knockdown of KCQN1OT1 resulted in reduced infarct volume in mice subjected to MCAO as well as neuronal autophagy via the miR-200a/forkhead box O3 (FOXO3)/autophagy-related protein 7 (ATG7) axis (Yu et al., 2019). Downregulation of MALAT1 expression was shown to result in ischemic injury and autophagy suppression. MALAT1 served as a molecular sponge for miR-30a and interfered with the inhibitory effect of miR-30a on ischemic injury and autophagy by suppressing the expression of Beclin-1, which is a direct target of miR-30a. Altogether, suppression of MALAT1 expression attenuates neuronal cell death via the miR-30a/Beclin-1 axis (Guo et al., 2017). LncRNA SNHG14 and BIPN3, a pro-

**Autophagy**

Several ceRNA networks were related to the autophagy of neurons. Luo et al. suggested that the MEG3/miR-378/growth factor receptor-bound protein 2 (GRB2) axis plays a role in neuronal autophagy and impairment of neurological function in IS (Luo et al., 2020). Knockdown of KCQN1OT1 resulted in reduced infarct volume in mice subjected to MCAO as well as neuronal autophagy via the miR-200a/forkhead box O3 (FOXO3)/autophagy-related protein 7 (ATG7) axis (Yu et al., 2019). Downregulation of MALAT1 expression was shown to result in ischemic injury and autophagy suppression. MALAT1 served as a molecular sponge for miR-30a and interfered with the inhibitory effect of miR-30a on ischemic injury and autophagy by suppressing the expression of Beclin-1, which is a direct target of miR-30a. Altogether, suppression of MALAT1 expression attenuates neuronal cell death via the miR-30a/Beclin-1 axis (Guo et al., 2017). LncRNA SNHG14 and BIPN3, a pro-
apoptotic mitochondrial protein, were upregulated in OGD/R-induced HT22 cells, but miR-182-5p was downregulated. What’s more, SNHG14 could regulate the expression of BNIP3 via targeting to miR-182-5p. Overall, SNHG14 promoted mitophagy via miR-182-5p/BINP3 (Deng et al., 2020).

Inflammation
In a previous study, LncRNA SNHG14 was found upregulated in MCAO/R rats and OGD/R-induced PC-12 cells. SNHG14 acted as a sponge of miR-136-5p and positively regulated the expression of Rho-associated coiled-coil-containing protein kinase 1 (ROCK1), thus promoting neurological impairment and inflammation (Zhong et al., 2019). P65 is a subunit of nuclear factor NF-κB, which is related to an inflammatory response. Li et al. underlined that LncRNA H19 targeted p65 by sponging of miR-138-5p, thus promoting inflammatory response and improving neurological functions (Li et al., 2020).

REGULATORY ROLES OF LncRNAs IN BMECS
BMECs are important components of the cerebral microvascular system and form a part of the blood-brain barrier (BBB). I/R injury leads to autophagy and apoptosis of BMECs, which accounts for BBB disruption and enhances vascular permeability, thus resulting in an unfavorable prognosis among patients suffering from IS (Li et al., 2014). Furthermore, vascular remodeling plays an important role in ischemic cardiovascular diseases. Angiogenesis in ischemic areas promotes blood supply to ischemic areas (Xu et al., 2018; Zhao et al., 2020). Thus, protecting BMECs from I/R injury or promoting angiogenesis can improve the prognosis of stroke (Zhu et al., 2021). In this section, we have discussed the roles of LncRNAs in BMECs after cerebral I/R injury (Figure 4).
**Autophagy and Apoptosis**

LncRNA MALAT1 is one of the most highly upregulated I/R- or OGD/R-responsive endothelial LncRNAs that plays roles in apoptosis and inflammation (Zhang et al., 2017b; Yang et al., 2018; Zhang et al., 2018). One study revealed that MALAT1 promoted BMEC autophagy and survival by binding to miR-26b and downregulating its expression. Furthermore, miR-26b inhibited autophagy and cell survival, whereas overexpression of MALAT1 resulted in a reversal of this effect by promoting the expression of Unc-51 like autophagy activating kinase 2 (ULK2), a target of miR-26b (Li Z. et al., 2017). However, it was found that MALAT1 expression was downregulated in an OGD BMEC model. It was also claimed that MALAT1 can suppress apoptosis and function as a molecular sponge of miR-205-3p to modulate PTEN expression (Gao and Wang 2020). Altogether, MALAT1 can be a protective factor against BMEC injury. Furthermore, it has been reported that overexpression of miR-15a-5p results in decreased cell proliferation and increased apoptosis via downregulation of Bcl2 expression. It has been indicated that SNHG16 expression gradually decreases following OGD/R and that its overexpression results in the downregulation of miR-15a-5p expression, which promotes cell proliferation and decreases apoptosis. Overall, SNHG16 protects HBMECs from OGD/R-induced apoptosis via the miR-15a-5p/Bcl2 axis (Teng et al., 2020). In another study, LncRMST expression was upregulated in HBMECs and bEnd.3 cells subjected to OGD. Silencing LncOGD-1006 also aggravated OGD-induced injury in bEnd.3 cells via increased apoptosis, whereas overexpression of LncOGD-1006 led to opposite effects. Furthermore, LncOGD-1006 functions as a ceRNA for miR-184-5p to facilitate the expression of conserved anti-apoptotic protein 1 (CAAP1) (Chen JY. et al., 2020).

**Angiogenesis**

Vascular endothelial growth factor (VEGF) is an angiogenesis inducer that promotes the growth of vascular endothelial cells. It has been reported that HIF-1 plays a key role in hypoxic responses and regulates VEGF expression (Ferrara 2004).

The LncRNA HIF1A-AS2 regulates the expression of HIF-1α by sponging miR-153-3p. In permanent MCAO and human umbilical vein endothelial cell (HUVEC) models, LncRNA HIF1A-AS2 expression is upregulated, whereas miR-153-3p expression is reduced as a result of higher protein levels of HIF-1α, VEGFA, and Notch1. Moreover, HUVEC viability, migration ability, and tube formation are promoted. Therefore, activating the LncRNA HIF1A-AS2/miR-153-3p/HIF-1α/VEGFA/Notch1 axis promotes angiogenesis in HUVECs (Li L. et al., 2017). Furthermore, SNHG12 upregulation or knockdown contributes to the regulation of VEGFA and fibroblast growth factor-beta mRNA and protein levels under OGD/R conditions. Additionally, capillary-like tube formation changes with SNHG12 expression, which indicates that SNHG12 promotes BMEC angiogenesis by targeting miR-199a (Long et al., 2018). It was shown in another study that SNHG12 improves angiogenesis following IS by regulating the miR-150/VEGF axis (Zhao et al., 2018). LncRNA Snhg1 promoted BMEC migration and tube formation after OGD insult in a previous study. Moreover, mechanistic studies have suggested that Snhg1 targets miR-338a and regulates HIF-1α and VEGF expression (Wang Z. et al., 2018). It has been reported that LncRNA MALAT1 protected against angiogenesis in HBMECs under OGD conditions via the miR-205-5p/VEGFA axis (Gao C. et al., 2020). Additionally, LncRNA metastasis-associated colon cancer 1 (MACCI)-AS1, which sponges miR-6867-5p/TWIST1, regulates the proliferation, survival, and migration of hypoxic HBMECs (Yan G. et al., 2020). Differentiation antagonizing non-protein coding RNA (DANCR) overexpression results in the promotion of spliced X-box binding protein 1 (XBP1s) expression in BMECs subjected to OGD. It has been shown that miR-33a-5p binds to DANCR and the 3'-UTR of XBP1. Moreover, miR-33a-5p overexpression causes inhibition of cell proliferation, migration, and angiogenesis. In summary, DANCR promotes cell survival and angiogenesis by regulating the miR-33a-5p/XBP1s axis (Zhang M. et al., 2020).

**Inflammation**

Vascular cell adhesion molecule 1 (VCAM1), an endothelial-specific marker, is related to inflammation in cerebrovascular disease (Maglinger et al., 2021; Wang et al., 2021). It has been shown that miR-204-5p is a target of VCAM1 and that RMST serves as a ceRNA that regulates VCAM1 expression by sponging miR-204-5p. Consequently, knockdown of RMST results in reduced OGD-induced injury through regulation of the miR-204-5p/VCAM1 axis (Yin et al., 2021).

**REGULATORY ROLES OF LncRNAs IN MICROGLIA ACTIVATION AND POLARIZATION**

Resting microglia can be activated and polarized into two phenotypes in IS. M1 microglia produce pro-inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin (IL)-6, interferon-γ, IL-1β, inducible nitric oxide synthase, and proteolytic enzymes (matrix metalloproteinase [MMP] 9 and MMP3), which are harmful to brain tissues. Conversely, M2 microglia, which are also called tissue restorative microglia, produce pro-angiogenic and anti-inflammatory factors such as IL-10, transforming growth factor β, IGF, and VEGF, which promote ischemia (Qin et al., 2019). Here we have discussed the roles of several LncRNAs in microglial cells (Figure 5).

The expression of LncRNA Snhg8 was downregulated in ischemic regions in mice subjected to MCAO/R and in primary microglial cells subjected to OGD. Additionally, LncRNA Snhg8 serves as a ceRNA for miR-425-5p, which promotes microglial inflammation and BMEC injury by targeting the SIRT1/nuclear factor-κB (NF-κB) axis (Tian et al., 2021). The expression of the LncRNA SNHG14 was found to be strongly upregulated in mice with ischemic cerebral infarction and BV2 cells following OGD treatment.
Gain and loss of function experiments revealed that SNHG14 regulates BV2 cell activation, TNF-\(\alpha\) and nitric oxide production, and miR-145-5p and PLA2 group IVA (PLA2G4A) expression levels. Furthermore, overexpression of miR-145-5p caused a reversal of BV2 cell activation. Further studies have supported that SNHG14 directly binds to miR-145-5p and that the binding site of miR-145-5p exists on the 3'-UTR of PLA2G4A. Overall, LncRNA SNHG14 promotes microglial activation by regulating the miR-145-5p/PLA2G4A axis (Qi et al., 2017). It has also been reported that the expression of LncRNA Opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) and C1q/TNF-related protein 3 (CTRP3) is downregulated, while that of miR-186-5p is upregulated in BV2 cells subjected to OGD/R. Furthermore, it has been indicated that miR-186-5p promotes inflammation and oxidative stress in microglia and shares targets with CTRP3 and OIP5-AS1. Moreover, overexpression of LncRNA OIP5-AS1 promotes protection against I/R injury via miR-186-5p (Shan et al., 2020).

**REGULATORY ROLES OF LncRNAs IN ASTROCYTES**

There are fewer studies on LncRNAs in astrocytes than in other cell lines. Aquaporin 4 (AQP4) is highly expressed in astrocytes and involved in the development of brain edema following intracerebral hemorrhage (Fu et al., 2007). It has been revealed that LncRNA MALAT1 exacerbates cerebral I/R injury, which regulates the expression of AQP4 by competitively binding to miR-375 (Wang H. et al., 2020). Moreover, LncRNA TUG1 aggravated apoptosis by upregulating AQP4 via miR-145 (Shan et al., 2020).

**LncRNAs in the Neurovascular Unit**

Neuroprotective treatment strategies for IS face significant challenges in clinical settings. Numerous preclinical studies have demonstrated the potential benefits of neuroprotective therapy in animal models of IS. However, the clinical application of neuroprotective therapies tested in preclinical studies has mostly failed. Thus, it is critical to identify multi-target drugs to treat IS. The NVU is a multicellular complex composed of neurons, endothelial cells, astrocytes, myocytes, pericytes, microglia, and extracellular matrix. It is an intricate network that maintains a balanced neuronal microenvironment in the body (Muoio et al., 2014). LncRNAs that are widely expressed in cells of the NVU exert specific biological functions, which include multi-target and multi-link comprehensive regulation and precise regulation of the downstream network. However, to date, no study has investigated the relationship between LncRNAs and the NVU. In this section, we have summarized the roles of several LncRNAs expressed in different cells and identified their functions in IS.
LncRNA MALAT1
The functions of LncRNA MALAT1 have been examined in different brain cells in previous studies. MALAT1 expression is upregulated after OGD/R treatment in neurons, BV-2 cells, and astrocytes, which results in MALAT1 acting as a harmful factor in I/R injury by promoting cell death via apoptosis and inflammation (Guo et al., 2017; Wang H. et al., 2020; Zhang G. et al., 2020; Cao et al., 2020; Jia et al., 2021). However, MALAT1 plays a protective role in BMECs subjected to OGD/R because it reduces apoptosis and promotes angiogenesis (Li Z. et al., 2017; Gao C. et al., 2020; Gao and Wang 2020). In summary, the roles of LncRNA MALAT1 in IS include a protective effect on endothelial cells; however, it may induce cell death in neurons and astrocytes.

LncRNA RMST
It has been reported that the expression of LncRNA RMST is upregulated in HT22, bEnd.3, N2a, and BV2 cells, as well as in HBMECs and IS patients (Hou and Cheng 2018; Sun et al., 2019; Cheng et al., 2020; Yin et al., 2021; Zhao et al., 2021). Additionally, suppressing RMST expression results in reduced apoptosis of bEnd.3, HBMECs, and N2a cells, whereas overexpression of RMST promotes apoptosis of HT22 and BV2 cells. Collectively, these data indicate that LncRNA RMST may serve as an apoptosis promoter to regulate cerebral I/R injury.

LncRNAs as potential diagnostic and prognostic biomarkers
Some studies related to lncRNAs have been conducted in patients, in order to explore the clinical values (Figure 6). One study showed that Inc-ITSN1-2 expression was positively correlated with the National Institutes of Health Stroke Scale (NIHSS) score and reflected the severity of stroke. (Zhang and Niu 2020). Another case study was conducted to investigate the relationship between LncRNA MEG3 and prognostic value. MEG3 was upregulated in IS patients, positively associated with the NIHSS score, and negatively related to the prognosis of IS patients (Wang M. et al., 2020). Thus, MEG3 is a potential marker for diagnosis and prognosis. For prognosis, high Inc-ITSN1-2 expression was correlated with worse Relapse-Free Survival (RFS) in AIS patients (Zhang and Niu 2020). Higher Myocardial infarction associated transcript (MIAT) expression had a relatively poor prognosis. Meanwhile, the multivariate analysis revealed that MIAT was an independent prognostic marker of functional outcome and death in patients with IS. Data suggested that MIAT might be a potential diagnostic and prognostic indicator in IS (Zhu et al., 2018). LncRNA HULC is correlated with higher AIS risk, increased disease severity, and worse prognosis in AIS patients (Ren et al., 2021). Meanwhile, it associates with higher IL-6, elevated intercellular adhesion molecule 1 (ICAM1), and lower miR-9 AIS patients (Chen X. et al., 2020). The H19 gene plays a functional role in increasing the prevalence of IS risk factors. The upregulation of H19 may be considered as a diagnostic biomarker in IS among the Iranian population. But ROC curve analysis revealed that the peripheral blood expression level of H19 could not be considered as a promising marker for the functional outcome and mortality prediction of IS patients, thus it cannot serve as a useful prognostic marker (Rezaei et al., 2021).

Advantages and limitations of using LncRNAs as therapeutics for IS
Nucleic acid-based RNA targeting approaches have been concerned by researchers. CeRNA networks provide a variety of therapies, such as ncRNA replacement therapy and ncRNA inhibition therapy (Dragomir et al., 2020). NcRNA replacement therapy is devoted to improving conditions of IS patients by supplementing ncRNAs. NcRNA inhibition therapy focuses on inhibiting the expression of harmful ncRNAs to slow the progress of IS. Furthermore, LncRNAs can be detected in the serum, which is more efficient in supporting the diagnosis and classification of IS patients.

However, the clinical application of LncRNAs has several limitations. Firstly, besides ceRNA network mechanisms, LncRNAs regulate gene expressions at multiple levels, including regulating chromatin modification, post-transcription, and transcription. Secondly, the levels of LncRNA, miRNA, and mRNA can be influenced by other molecular counterparts, which makes it difficult to fully explore the intrinsic regulation mechanism of ceRNA and therefore require further investigations. Thirdly, since LncRNAs are not highly conserved among species, studies are mostly conducted in animal and cell models. Thus, there is a lack of reports on clinical studies on LncRNAs. Forthly, The development of ncRNA drugs is facing great difficulties, such as the degradation and delivery of ncRNA drugs. Finally, there is no sufficient information about exosomal LncRNAs in stroke pathogenesis, thus the functions of LncRNAs in NUV remain unclear and considerable research is needed in this field.

Conclusion
The pathological process of cerebral I/R injury is complex. The lack of oxygen and energy causes ion pump failure, apoptosis,
inflammation, glutamate excitatory toxicity, and oxidative stress, which are harmful to the cell components of NVU, such as neurons, glial cells, BMECs, and astrocytes. Previous studies have identified LncRNAs that are related to the occurrence and progression of IS. In this review, we first summarized how the LncRNA-mediated ceRNA networks take part in the process of ischemic stroke in different brain cell lines. Available data indicate that LncRNA MALAT1, MEG3, and RMST serving as ceRNAs, play an important role in neuroprotection, which mainly involves regulation of neuronal cell death by targeting miRNAs and mRNAs, such as PDC4D, caspases, SIRT1, and Beclin-1. Furthermore, some studies have identified the anti-apoptotic, anti-inflammatory, and angiogenic roles of LncRNAs in BMECs. Several LncRNAs function as ceRNAs to bind to miRNAs and regulate the expression of VEGF, which is an important angiogenic factor. Some ceRNA networks are also involved in the activation and polarization of microglia, whereas others can regulate the expression of inflammatory factors. Secondly, we analyzed the functions of LncRNAs that are expressed in different types of brain cells to better understand the relationship between LncRNAs and the NVU. Thirdly, some researchers have shown that the expression level of LncRNAs is related to neurological deficits and prognosis among IS patients. These results indicate that LncRNAs may be potential therapeutic targets and biomarkers. What’s more, LncRNA mediated ceRNA networks are involved in different pathological mechanisms in aggravating I/R damage; however, the underlying mechanisms are not fully understood. Although studies related to LncRNAs have been conducted based on clinical samples, the differences between different races and nationalities blocked LncRNAs from being effective IS markers in diagnosing and prognosing. More studies should be conducted to explore the clinical and medical value of LncRNAs or ceRNAs in IS.

**AUTHOR CONTRIBUTIONS**

SZ initiated this review, collected the references, mapped figures, and drafted the manuscript. TZ revised our first draft and provided valuable comments. QL revised our manuscript. GS and XS supported the funding and revised the manuscript. All authors approved the submitted version.

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GLOSSARY

3'‐UTR 3’‐untranslated region
AIM2 absent in melanoma 2
ANRIL antisense non‐coding RNA in the INK4 locus
APAF1 apoptotic peptidase activating factor 1
AQP4 aquaporin 4
ATG7 autophagy related protein 7
BBB blood‐brain‐barrier
Bcl2 B‐cell lymphoma‐2
BMEC brain microvascular endothelial cell
BIM Bcl2 interacting mediator of cell death
CAAP1 conserved anti‐apoptotic protein 1
CAV‐1 caveolin‐1
ceRNA competing endogenous RNA
CHRF cardiac hypertrophy‐related factor
CTRP3 C1q/TNF‐related protein 3
CXCL13 C‐X‐C motif chemokine ligand 13
DANCR differentiation antagonizing non‐protein coding RNA
DAPK1 death‐associated protein kinase 1
ERK extracellular signal‐regulated kinase
FGD5‐AS1 FGD5 antisense RNA 1
FOXD3‐AS1 FOXD3 antisense RNA 1
FOXO3 forkhead box O3
GAS5 growth arrest‐specific 5
GATA3 GATA binding protein 3
GRB2 growth factor receptor‐bound protein 2
HIF‐1 hypoxia‐inducible factor 1
HMGA1 high mobility group AT‐hook1
hnRNPK heterogeneous nuclear ribonucleoprotein K
HOTTIP HOXA transcript at the distal tip
HUVEC human umbilical vein endothelial cell
I/R ischemia‐reperfusion
Id2 inhibitor of DNA binding 2
IGF insulin‐like growth factor
IGF1R IGF‐1 receptor
IL interleukin
IS ischemic stroke
KCNQ1OT1 potassium voltage‐gated channel subfamily Q member 1 opposite strand 1
LncRNA long non‐coding RNA
MACC1 metastasis‐associated colon cancer 1
MALAT1 metastasis associated lung adenocarcinoma transcript 1
MAPK mitogen‐activated protein kinase
MCAO/R middle cerebral artery occlusion/reperfusion
Mcl‐1 myeloid cell leukemia‐1
MEG3 maternally expressed gene 3
MEK mitogen‐activated protein kinase
miRNA microRNA
MMP matrix metalloproteinase
MRE microRNA response element
mTOR mechanistic target of rapamycin
N2a neuro‐2a
NEGRI neuronal growth regulator 1
NO nitric oxide
NF‐κB nuclear factor‐κB
NR3C2 nuclear receptor subfamily 3 group C member 2
NVU neurovascular unit
OGD/R oxygen‐glucose deprivation and reoxygenation
OIP5‐AS1 Opa‐interacting protein 5 antisense transcript 1
Oprm1 opioid receptor mu 1
PDCD4 programmed cell death 4
PDE4D phosphodiesterase 4D
PGC‐1α peroxisome proliferator‐activated receptor‐gamma coactivator 1 alpha
PLA2G4A phospholipase A2 group IVA
PTEN phosphatase and tensin homolog deleted on chromosome ten
PUMA p53 upregulated modulator of apoptosis
Rian RNA imprinted and accumulated in nucleus
RMST rhabdomyosarcoma 2‐associated transcript
SD Sprague Dawley
SEMA3A semaphorin 3A
SIRT1 sirtuin1
SNHG5 small nucleolar RNA host genes
SOX6 sex‐determining region Y box six
TALNEC2 tumor‐associated lncRNA expressed on chromosome two
TNF‐α tumor necrosis factor α
TP53INP1 tumor protein p53 inducible nuclear protein one
TUG1 taurine upregulated gene one
ULK2 Unc‐51 like autophagy activating kinase two
VCAM1 vascular cell adhesion molecule one
VEGF vascular endothelial growth factor
XBP1s X‐box binding protein 1