An update on the functional roles of long non-coding RNAs in ischemic injury (Review)

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Abstract. Ischemic injuries result from ischemia and hypoxia in cells. Tissues and organs receive an insufficient supply of nutrients and accumulate metabolic waste, which leads to the development of inflammation, fibrosis and a series of other issues. Ischemic injuries in the brain, heart, kidneys, lungs and other organs can cause severe adverse effects. Acute renal ischemia induces acute renal failure, heart ischemia induces myocardial infarction and cerebral ischemia induces cerebro-vascular accidents, leading to loss of movement, consciousness and possibly, life-threatening disabilities. Existing evidence suggests that long non-coding RNAs (lncRNAs) are regula-tory sequences involved in transcription, post-transcription, epigenetic regulation and multiple physiological processes. lncRNAs have been shown to be differentially expressed following ischemic injury, with the severity of the ischemic injury being affected by the upregulation or downregulation of certain types of lncRNA. The present review article provides an extensive summary of the functional roles of lncRNAs in ischemic injury, with a focus on the brain, heart, kidneys and lungs. The present review mainly summarizes the func-tional roles of lncRNA MALAT1, lncRNA MEG3, lncRNA H19, lncRNA TUG1, lncRNA NEAT1, lncRNA AK139328 and lncRNA CAREL, among which lncRNA MALAT1,

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in particular, plays a crucial role in ischemic injury and is currently a hot research topic.

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1. Introduction

Ischemic injury is caused by insufficient blood perfusion in cells, tissues and organs due to a limited blood supply. Given that blood is the carrier of oxygen, the main cause of ischemia is hypoxia. However, ischemia also involves an insufficient supply of nutrients and clearance of metabolic wastes, which leads to inflammation, acidosis and an electrolyte imbalance. Ischemic injuries to the brain, heart, kidneys, lungs and other organs can cause severe damage (1). For instance, stroke is an acute brain injury that involves brain damage and neurological dysfunction, and is associated with a high mortality or disability rate glob-ally. Acute renal ischemia can cause acute renal failure, while heart ischemia can cause myocardial infarction (2-4).

Long non-coding RNAs (lncRNAs) refer to the transcripts of non-coding RNAs that are >200 nucleotides in length (5). Previous research defined lncRNAs as by-products of transcrip-tion; however, recent research has found that they regulate various physiological and pathophysiological processes (6). lncRNAs regulate gene expression at the epigenetic, transcrip-tional, post-transcriptional and chromatin remodeling levels (6). They also activate or inhibit the expression of target genes by directly binding them or recruiting transcription factors (5).

Recently, research on lncRNAs has become a hot topic, with several studies suggesting that lncRNAs are involved in ischemic injuries (7,8). For instance, experimental models (9) have found that lncRNA expression differs between stroke patients and healthy individuals, and that genetic variations of lncRNA loci are associated with an increased risk of suffering from a stroke (2). lncRNAs are highly specific in the central nervous system and stroke is known to induce changes in several lncRNAs in the brain. Therefore, lncRNAs play a crucial role in the complex pathological processes associated with stroke, and may regulate the development of the central nervous system and disease progression (10). During the tra/rensplantation of lungs, kidneys and other organs, ischemia/reperfusion (I/R) is a critical factor affecting the success rate of organ transplantation (11,12). The present review article discusses the functional roles of lncRNAs in ischemic injuries in different organs.

2. Synthesis of lncRNAs

RNA-producing genes can be divided into two main types: Protein-coding genes and non-protein-coding genes. Of the 180,000 transcripts in human cells, ~20,000 are protein-coding and the remaining 160,000 are non-coding transcripts (6). Non-coding RNAs are divided into two groups based on their size: Short non-coding RNAs (<200 nt), e.g., microRNAs (miRNAs/miRs) and long non-coding RNAs (≥200 bp), such as lncRNAS (13). Recent estimates suggest there are >100,000 lncRNAs (14,15). In most cases, mRNA and lncRNA are similar in several aspects of their biogenesis, although there are differences between them (5,16). Similar to mRNAs, the synthesis of lncRNAs requires one of the two strands of DNA as a template. The majority of lncRNAs are transcribed by RNA polymerase II (pol II), m^7G capped at 5'-end and polyadenylated at 3'-end (17). In contrast to mRNAs, lncRNAs are not well conserved in evolution, consist of fewer exons and are expressed at relatively low levels; large proportions of lncRNAS are also retained in the nucleus (18).

Increasing evidence has indicated that lncRNAs play a crucial role in regulating gene expression, such as gene silencing or gene activation. Furthermore, the regulation of lncRNAs can affect the transcription, splicing, translation, output, import and stability of mRNAs (19). The role of lncRNAs in the process of ischemic injury will be discussed in detail in the following sections.

3. Role of lncRNAs in cerebral ischemic injury

Cerebral ischemic injuries, including ischemic stroke and cerebral ischemia-reperfusion injuries, can lead to severe brain dysfunction, disability and a high mortality. lncRNAs are highly expressed in the brain, indicating that they may be involved in the physiological and pathological processes of the brain, such as cerebral ischemic injury, neurodegeneration, neurodevelopment and plasticity (20,21). A number of studies have demonstrated that lncRNAs play a central role in ischemic brain injuries (Table I).

Metastatic-associated lung adenocarcinoma transcript 1 (MALAT1). Cerebral ischemic stroke is a main cause of mortality and long-term disability globally (5) and is one of the most common cerebral diseases, particularly among the elderly. MALAT1 is closely associated with abnormal cellular signaling, as well as with the occurrence, development and response to the treatment of human diseases. It has been shown that MALAT1 plays a role in the pathophysiology of a number of diseases and may be a therapeutic or prognostic biological target (22,23). A previous study demonstrated that MALAT1 was strongly induced in anoxic mouse organs, particularly in the spleen, kidneys, testicles, lungs and brain (24).

In 2017, Zhang *et al* (25) explored the relevant mechanisms of MALAT1 in regulating cerebral vascular lesions in ischemic stroke. These authors established a mouse model of transient focal cerebral ischemia through intracavitary middle cerebral artery occlusion (MCAO) and then evaluated the infarct volume, neurological deficits and sensorimotor function. Additionally, they simulated ischemic injury *in vitro* by exposing rat brain microvascular endothelial cells (BMECs) to oxygen-glucose deprivation (OGD) for 16 h. RNA sequencing revealed that the levels of MALAT1 in the OGD-exposed BMEC cells and in ischemic cerebral microvessels were significantly increased, suggesting that the upregulation of MALAT1 may play a crucial role in cerebrovascular pathologies induced by ischemic stroke (25). Furthermore, fluorescein-labeled MALAT1-Gapmer was introduced into mouse BMECs in *in vitro* culture to achieve targeted MALAT1 degradation, resulting in a significant reduction in the changes of OGD-induced MALAT1 levels, accompanied by increased cerebrovascular endothelial cell death and programmed death-activating factor caspase-3 activity. In addition, MALAT1 knockout mice and litter control mice were briefly treated with MCAO for 1 h and perfused for 24 h. The results revealed that MALAT1 knockout mice displayed a larger infarct volume and significantly more severe neurological deficits. These results suggest that the loss of MALAT1 exacerbates ischemic brain injury. In subsequent experiments, the researchers found that MALAT1 bound directly to Bim (a pro-apoptotic regulator) and e-selectin. The silencing of MALAT1 increased the expression of Bim and pro-inflammatory cytokines. Cerebrovascular endothelial inflammation and subsequent endothelial function damage are associated with ischemic brain injuries (21).

Similarly, in 2018, Zhang *et al* (26) also explored the mechanisms of MALAT1 in ischemic stroke. The mouse dual-2-min homolog (MDM2) gene encodes the E3 ubiquitin ligase of p53 in mitotic cells, which is an oncoprotein that blocks the transcriptional activation mediated by p53 tumor suppressors. MALAT1 was found to be highly expressed in ischemic stroke samples, including human brain microvascular endothelial cells (HBMECs). MALAT1 significantly promoted the occurrence of an ischemic stroke by regulating MDM2 expression and activating the p53 signaling pathway. Subsequently, Zhang *et al* (26) found that MALAT1 and MDM2 were highly expressed in HBMECs and that both MALAT1 and MDM2 were localized in the nucleus following OGD/reoxygenation (OGD/R). The expression of the p53 signaling pathway-related proteins was highly increased in HBMECs exposed to OGD/R. Furthermore, the knockdown of MALAT1 effectively reduced the expression of MDM2, while the knockdown of MDM2 had no effect on the expression of MALAT1. These results revealed that MALAT1 regulated and

Table I. Role of lncRNAs in cerebral ischemic injuries.

lncRNA	Effect on miRNAs and signaling pathways (Refs.)	Effect on inflammation	Effect on apoptosis	Effect on autophagy	Effect on other aspects	Effect on cerebral ischemic injury
KCNQ1OT1	miR-200a/FOXO3/ATG7 (51)			↑		↑
MALAT1	miR-30a/Beclin1/autophagy (27)			↑		↑
	miR-145/AQP42 (28)					↓
	miR-211-5p (52)	↑				↑
	miR-142-3p/SIRT1 (53)				Acts as ceRNA for miR-142-3p	↑
	miR-375/PDE4D (54)	↑				↑
	miR-181c-5p/HMGB1 (29)	↑			Acts as ceRNA for miR-181c-5p	↑
	miR-195a-5p/HMGA1 (55)				Sponging miR-195a-5p to upregulate HMGA1	↑
	miR-182-5p/TLR4 (56)					↑
	miR-375/PDE4D (54)					↑
	Bim and E-selectin (25)	↓	↓			↑
	ERK/MAPK (57)					↑
	MyD88/IRAK1/TRAF6 (58)	↑				↑
	AQP4 (59)					↑
Gm11974	miR-766-3p/NR3C2 (46)					↑
	miR-122-5P/SEMA3A (60)					↓
MEG3	miR-485/AIM2 (35)					↓
	miR-378/GRB2 (61)					↑
	miR-181c-5p/ATG7 (62)			↑	Protect neurons	↑
	NF-κB (63)	↑				↑
	p53/GPX4 (64)				Mediate ferroptosis of brain microvascular endothelial cells	
H19	miR-29b/Akt3/mTOR (40)			↓	Acts as a miR-29b sponge	↓
	miR-138-5p/p65 (65)	↑				↑
	miRNA-29b/SIRT1/PGC-1α (66)	↑				↑
	miR-107 (41)		↓			↓
	miR-1306-5p/BCL2L13 (67)		↑		Acts as a miR-1306-5p sponge	↑
	miR-19a-3p/PTEN (68)					↑
	DUSP5-ERK1/2 (69)				Inhibits axon sprouting and functional recovery	
	IGF1/mTOR (42)			↓		
ROR	miR-135a-5p/ROCK1/2 (70)					↑
Nespas	Modulates TNFα-induced apoptosis (71)					↓
SNHG12	miR-199a/SIRT1/AMPK (72)	↓				↓
	Inhibits TRIM8-related K63-linked polyubiquitination of TAK1 (73)		↓			↓

Table I. Continued.

lncRNA	Effect on miRNAs and signaling pathways (Refs.)	Effect on inflammation	Effect on apoptosis	Effect on autophagy	Effect on other aspects	Effect on cerebral ischemic injury
	Acts as an autophagy inducer (74)					↓
	SIRT1/FOXO3a (75)					↓
SNHG14	miR-136-5p/ROCK1 (76)	↑				↑
	miR-182-5p/BINP3 (77)					↑
	miR-181c-5p/BMF (78)					↑
	miR-199b/AQP4 (79)					↑
MIAT	miR-204-5p/HMGB1 (80)					↑
	miR-211/GDNF (48)		↓			
	REDD1 (81)		↑	↑		
TUG1	miR-145a-5p (82)	↑				↑
	miR-204-5p/COX2 (83)	↑			Sponging miR-204-5p	↑
	miR-145/AQP4 (84)		↑		Sponging miR-145	
	miR-200a-3p/NLRP3 (45)	↑				
	miR-142-3p (85)					↑
	miR-493-3p or miR-410-3p (44)				Sponging miR-493-3p/miR-410-3p	↑
RMST	miR-150 (86)	↑			Inhibits cell proliferation	
	Protects against MCAO-induced ischemic stroke (87)					
N1LR	p53 (86)					↓
CHRF	miR-126/SOX6 (47)					↑
	Inhibits p53 phosphorylation (88)					↓
Oprm1	miR-155/GATA3 (49)		↓			

lncRNA, long non-coding RNA; MALAT1, metastatic-associated lung adenocarcinoma transcript 1; TUG1, taurine up-regulated gene 1; I/R, ischemia/reperfusion; MEG3, maternal expression of gene 3; MCAO, middle cerebral artery occlusion; KCNQ1OT1, potassium voltage-gated channel subfamily Q member 1 opposite strand 1; SNHG12, small nuclear RNA host gene 12; SNHG14, small nuclear RNA host gene 14; MIAT, myocardial infarction associated transcript; RMST, rhabdomyosarcoma 2-associated transcript; N1LR, novel I/R-induced lncRNA; CHRF, cardiac hypertrophy-related factor; Oprm1, opioid receptor Mu 1. The '↓' symbol implies the downregulation of inflammation, apoptosis, etc.; and the '↑' symbol implies thje upregulation of inflammation, apoptosis, etc.

promoted the expression of MDM2 following OGD/R. OGD/R also promoted apoptosis through the p53 signaling pathway, while the silencing of MALAT1 and MDM2 inhibited this effect. MCAO/reperfusion (MCAO/R) in mouse brains also caused a similar effect on expression of related proteins and lncRNAs (26).

Additionally, several studies have indicated that MALAT1 plays a crucial role in the progression of ischemic brain injury. In 2017, Guo et al (27) found that MALAT1, the autophagy-related microtubule-related proteins light chain 3-I (LC3-I)/LC3-II and Beclin1 were upregulated in the cortical neurons of mice following MCAO/R. Furthermore, neuronal cell death was significantly increased following OGD compared with the sham group; the downregulation of MALAT1 significantly reversed this effect. Additionally, the downregulation of MALAT1 significantly inhibited the increase in LC3-I/LC3-II and Beclin1 levels induced by OGD (27). This indicates that the downregulation of MALAT1 can inhibit the occurrence of autophagy and ischemic injury. It was also demonstrated that the downregulation of MALAT1 alleviated neuronal cell death by regulating the Beclin1-dependent autophagy of miR-30a during an ischemic stroke (27).

In 2020, Wang et al (28) established the OGD/R an in vitro astrocyte model and an MCAO/R in vivo mouse model. In both models, the level of MALAT1 was significantly upregulated and the expression of aquaporin 4 (AQP4) was significantly increased. Following intervention with MALAT1 siRNA, the cell survival rate was increased and apoptosis was reduced. Further experiments revealed that MALAT1 siRNA could not reduce the aggravation of the injury induced by a miR-145 inhibitor. This indicates that MALAT1 silencing protects the cerebral ischemia-reperfusion injury through miR-145. These results suggest that MALAT1 positively regulates AQP4 expression through miR-145 and promotes cerebral ischemia-reperfusion injury (28). Cao et al (29) also found that the depletion of MALAT1 suppressed inflammatory injury in the ischemic brain and that the overexpression of MALAT1 had an adverse effect; in fact, MALAT1 positively regulates the high-mobility Group Box 1 (HMGB1) to promote inflammation by acting as a competing endogenous RNA (ceRNA) to inhibit the function of miR-181C-5p (29). Another study demonstrated that MALAT1 also inhibited PI3K/AKT signaling by sponging miR-126 to promote the OGD-induced apoptosis of cerebral microvascular endothelial cells (30). Thus, MALAT1 may be a novel target for the treatment of cerebral ischemic stroke.

Nevertheless, a few studies have reported inconsistent results concerning the effects of MALAT1 in ischemic brain injuries. For example, polydatin (a natural product) upregulated MALAT1 expression and activated the C/EBP/MALAT1/CREB/PGC-1/PPAR pathway to protect the brain microvascular integrity and decrease the damage caused by cerebral stroke (31). MALAT1 can protect cerebral microvascular endothelial cells from OGD injuries by sponging miR-26b and upregulating the expression of ULK2 (12,32).

Maternal expression of gene 3 (MEG3). MEG3 plays an antitumor role in various types of cancer by regulating the major tumor suppressor genes, p53 and Rb, inhibiting angiogenesis-related factors and controlling miRNAs (33). Recent experiments have also explored the mechanisms of MEG3 involved in cerebral ischemic injuries.

In 2019, You and You (34) found that MEG3 was upregulated in rat models of MCAO. The rats with MACO exhibited evident nervous system injuries, infarction areas, an increase in the blood-brain barrier (BBB) permeability, water content, neuronal apoptosis and necrosis. An increase was also observed in the levels of the Wnt/β-catenin signaling pathway key proteins, including brain-derived neurotrophic factor (BDNF), the nerve growth factor (NGF) and basic fibroblast growth factor (bFGF). The depletion of MEG3 by siRNA (si-MEG3) resulted in alleviated neurological damage, reduced infarct area, water content, BBB permeability, neuronal apoptosis and necrosis, and significantly increased neurogenesis, whereas the overexpression of MEG3 exerted opposite effects. Following treatment with the classic Wnt pathway inhibitor, DKK1, the effect of si-MEG3 was reversed. The effect of MEG3 was also reversed following treatment with LiCl, a classical Wnt pathway activator. These experimental results suggest that the downregulation of the lncRNA MEG3 activates the Wnt/β-catenin signaling pathway, which further promotes nerve cell growth in rats following cerebral I/R injury, and alleviates nervous tissue injuries (34).

In 2020, Liang et al (35) reported that MEG3 was significantly upregulated and miR-485 was significantly downregulated in brain tissues following cerebral I/R, suggesting that MEG3 and miR-485 may be involved in the regulation of brain I/R. The pyroptosis in the brains of rats wit h MCAO was significantly higher than that in the sham-operated group, while the expression of absent in melanoma 2 (AIM2), an inflammatory factor closely related to pyroptosis, was also significantly increased in the I/R group. The protein levels of several key components of the AIM2 inflammatory signal pathway, including AIM2, lysed caspase-1 (c-caspase-1), IL-1β and IL-18 were significantly increased in the brains of rats in the I/R group, suggesting that I/R in the brain activates AIM2 inflammasome signaling, and subsequently induces pyroptosis and the secretion of inflammatory cytokines (35). Further data indicated that MEG3 negatively regulated the expression of miR-485, which can directly bind the 3'-UTR of AIM2 to inhibit its expression. Furthermore, the knockdown of MEG3 inhibited OGD/R-induced pyroptosis by directly increasing the level of miR-485 (35). Other studies have reported similar observations. For example, several researchers have found that MEG3 exacerbrates oxygen-deficient damage in PC12 cells by targeting miR-147 (36). MEG3 silencing also protects PC12 cells from hypoxic damage by sponging miR-21 and regulating both the PI3K/AKT and NF-κB pathways (37). MEG3 silencing can also enhance the cerebral protective effect of dexmedetomidine against hypoxic-ischemic brain injuries in newborn mice via the upregulation of miR-129-5p, leading to decreased neuronal cell death and cerebral atrophy (38).

These studies also demonstrate that the regulation of brain neurogenesis by targeting miRNAs is a common action form of MEG3. The data suggest that MEG3 inhibits AIM2 expression by sponging miR-485 during the I/R process in the brain, leading to pyroptosis and inflammation (31), thus providing a novel direction for the targeted therapy of ischemic stroke.

lncRNA H19. lncRNA H19 was previously misidentified as 'transcriptional noise' (39). Existing studies have found that H19 plays a critical role in the pathogenesis of various central nervous system diseases, such as Parkinson's disease, Alzheimer's disease, cerebral ischemia, cerebral hemorrhage and neuroblastoma (39). A number of studies have been conducted to investigate the mechanisms of the role of H19 in the process of ischemic brain injury.

In a study in 2020, the researchers established a neonatal rat model of hypoxic-ischemic encephalopathy (HIE), which exhibited an increased area of cerebral infarction, apoptosis and impaired neurological function in neonatal rats with HIE (40). That study confirmed that the overexpression of H19 functioned as a sponge for miR-29b and attenuated neural damage and reduced autophagy in brain tissue in neonatal rats with HIE by upregulating the Akt3/mTOR pathway. The effect produced by the overexpression of H19 could also be partially reversed by autophagy activators, which suggests that H19 affects autophagy (40). Furthermore, research on hypoxic-ischemic brain injury has confirmed that H19 overexpression is able to decrease miR-107 expression and increase VEGF expression, which results in the inhibition of neuronal apoptosis and the alleviation of cognitive dysfunction (41).

The two aforementioned studies demonstrate the positive role of H19 overexpression in cerebral I/R; other studies have demonstrated that H19 knockdown is capable of ischemic brain injury-induced inflammation and neurological damage. For example, the knockdown of lncRNA H19 has been shown to promotes axon sprouting and functional recovery following cerebral ischemic stroke (42). Another study established an *in vivo* model of I/R using rats with MCAO and an *in vitro* model of cells exposed to OGD/R and revealed that the knockdown of H19 promoted cell proliferation, decreased the rate of apoptosis, and alleviated the inflammatory status following OGD/R (39). That study also revealed that H19 was involved in this process by regulating the miR-138-5p/p65 axis (39). Similarly, another study established *in vitro* and *in vivo* models of cerebral I/R (40). The results of that study confirmed that lncRNA H19 knockdown attenuated the OGD-mediated down-regulation of miR-29b, SIRT1 and PGC-1α expression levels, which in turn ameliorated the OGD-induced increase in apoptosis and the concentration of inflammatory cytokines (40). Another study also demonstrated that H19 functioned as a sponge for miR-1306-5p and triggered cerebral I/R-induced injury, and that the knockdown of H19 alleviated injury (41). Blocking the lncRNA H19-miR-19a-Id2 axis has also been found to attenuate hypoxia/ischemia-induced neuronal injuries (43). Other pathways in which H19 is involved are listed in Table I, which also fully illustrates the close association of H19 with cerebral I/R.

The existing studies suggest that H19 plays a crucial role in cerebral I/R and is involved in various mechanisms, such as autophagy, apoptosis and inflammation.

lncRNA taurine upregulated gene 1 (TUG1). lncRNA TUG1 is one of the first lncRNAs identified to be associated with human diseases, and is known to be involved in and to regulate the biological processes of a number of human diseases. Several studies have been conducted to investigate its mechanisms of action in cerebral ischemic injury.

Several studies have described that TUG1 functions by sponging miRNAs. For example, a study published in 2022 demonstrated that TUG1 sponged miR-204-5p and induced the downregulation of miR-204-5p in the blood of patients with ischemic stroke and in the brains of rats with MCAO/R (43). By contrast, the intracerebral injection of miR-204-5p in rats significantly decreased COX2, IL-1β, TNFα and PGE2 expression, increased IL-10 expression and ameliorated brain injury, inhibited apoptosis, and significantly decreased brain infarcts in rats with MCAO/R. That study confirmed that the TUG1/miR-204-5p/COX2 axis is one of the pathways involved in cerebral ischemic injury associated with TUG1 (43).

A study published in 2020 also reported that TUG1 promoted inflammation and apoptosis by sponging miR-145 and thereby upregulating AQP4 expression in an *in vitro* cellular model of OGD/R and a rat model of MCAO (44). TUG1 has also been shown to activate the JNK and p38 MAPK signaling pathways by sponging miR-493-3p or miR-410-3p (44). In addition, TUG1 can also promote inflammation in brain ischemic injury through other miRNA (miR-145a-5p or miR-200a-3p)-mediated signaling pathways (45).

All the aforementioned studies have demonstrated that TUG1 negatively affects ischemic injury, increases the expression of inflammatory factors and the occurrence of apoptosis, and that these pathways are dependent on many targeted miRNAs.

Other lncRNAs. Additionally, a large number of studies have examined the involvement of other lncRNAs in cerebral ischemic injuries. Similarly, the majority of these lncRNAs aggravate or protect ischemic brain injuries by directly or indirectly acting on miRNAs and associated signaling pathways. For example, the knockdown of lncRNA Gm11974 has been shown to provide protection against cerebral I/R through the miR-766-3p/NR3C2 axis (46). The lncRNA SNHG12 is a potent autophagy inducer that exerts neuroprotective effects against cerebral I/R injuries (46). The lncRNA CHRF modulates the progression of cerebral I/R injuries via the miR-126/SOX6 signaling pathway (47).

Both the upregulation and downregulation of several lncRNAs can influence ischemic brain injuries. For example, the overexpression of lncRNA MIAT has been found to reduce neuronal apoptosis in a neonatal rat model of hypoxic-ischemic injury through the miR-211/GDNF pathway (48). The overexpression of the lncRNA Oprm1 and Rian attenuate cell apoptosis induced by cerebral ischemia-reperfusion injuries through the Oprm1/miR-155/GATA3 and Rian/miR-144-3p/GATA3 axes, respectively (49,50).

On the whole, a number of lncRNAs are involved in cerebral ischemic injuries and some of these are listed in Table I (25,27-29,35,40-42,44-49,51-88).

4. Role of lncRNAs in heart ischemic injury

Ischemic heart disease mainly refers to myocardial ischemia induced by coronary artery obstruction or stenosis. It often leads to myocardial infarction, left ventricular aneurysm, ventricular septal defect and mitral insufficiency, which is common among middle-aged and older individuals. Myocardial infarction is caused by vascular stenosis, blocked circulation blood flow and

insufficient myocardial blood supply due to atherosclerosis in the coronary artery wall. The high incidence of myocardial infarction is a major human health concern. Therefore, it is of utmost clinical significance to comprehensively understand the relevant mechanisms underlying ischemic heart diseases.

lncRNA AK139328 and lncRNA CAREL. In recent years, lncRNAs have been reported to be associated with ischemic heart diseases. Similar to ischemic brain injuries, lncRNAs can promote or prevent the occurrence of ischemic heart injuries via acting on various miRNAs. It has been shown that patients with diabetes display a higher risk of ischemic heart disease and myocardial I/R injury (89). Yu *et al* (90) investigated the effect of the lncRNA AK139328 on myocardial I/R injury in diabetic mice. First, the researchers established I/R models in normal mice and diabetic mice. Compared to other RNAs, AK139328 was the most notably upregulated in DM and the expression levels of phosphocreatine kinase (CK), creatine kinase myocardial band (CK-MB) and lactate dehydrogenase (LDH) (enzymes associated with myocardial injury) were higher following I/R in the diabetic mice compared with the normal mice. The downregulation of AK139328 significantly inhibited the expression of CK, CK-MB and LDH. While I/R induced the apoptosis of myocardial cells of both normal and diabetic mice, the rate of apoptosis was significantly higher in the myocardial cells of diabetic mice. The downregulation of AK139328 significantly inhibited the activity of caspase-3 in DM and inhibited the apoptosis of cardiomyocytes. Myocardial I/R injuries promoted the expression of the autophagy-related proteins, Atg7, Atg5 and LC3-II/LC3-I, and decreased p62 expression; downregulation of AK139328 reversed the changes in the expression of these proteins and inhibited autophagy. In fact, the knockdown of AK139328 significantly alleviated I/R injury in diabetic mice by regulating miR-204-3p expression (86).

Another study explored the influence of the lncRNA CAREL on heart regeneration, demonstrating that the overexpression of CAREL in cardiomyocytes decreased the division and proliferation of cardiomyocytes, and attenuated heart regeneration after injury. By contrast, the silencing of CAREL significantly promoted cardiac regeneration and improved cardiac function following myocardial infarction in both neonatal and adult mice. In fact, CAREL functioned as the ceRNA for miR-296 which suppressed the expression of its target genes, Trp53inp1 and Itm2a. Furthermore, the overexpression of miR-296 significantly increased the replication of myocardial cells and heart regeneration following injury (91).

lncRNA nuclear enriched transcript 1 (NEAT1). In recent studies, the function of lncRNA NEAT1 in myocardial I/R injuries has been described. For example, a study in published 2020 demonstrated that NEAT1 was highly expressed in the blood of patients with myocardial infarction and in mouse cardiomyocytes (92). lncRNA NEAT1 inhibited the expression of miR-378a-3p, which in turn inhibited the expression of Atg12 and affected autophagy in cardiomyocytes. It was also found that lncRNA NEAT1 significantly promoted the proliferation and migration of cardiomyocytes and had a protective effect against myocardial injury (92).

In addition to its functions in autophagy, NEAT1 affects cardiac functions, infarct size and myocardial apoptosis. The knockdown of NEAT1 has been shown to attenuate myocardial I/R injury through the miR-140/RhoA axis (93). This demonstrates a negative effect of NEAT1 on myocardial injury, an observation that was confirmed by another study, wherein the inhibition of NEAT1 reduced apoptosis and also attenuated the hypoxia-induced inhibition of proliferation (94). In another study, it was demonstrated that in lipopolysaccharide-induced myocardial injury, the knockdown of NEAT1 significantly ameliorated I/R-induced cardiac insufficiency, oxidative stress and inflammatory response, and also alleviated lipopolysaccharide-induced myocardial injury by inhibiting the TLR2/NF-κB signaling pathway (91).

The existing studies indicate that NEAT1 is involved in various pathways, such as apoptosis, autophagy, inflammatory response and oxidative stress. NEAT1 plays a double-sided role in ischemic injury of the heart, and may thus provide novel strategies for the clinical targeting of myocardial injury.

Other lncRNAs. There are other lncRNAs that have also been implicated in ischemic heart injuries (Table II) (92-121). Several studies found that lncRNAs play a key role in alleviating myocardial infarction injuries and myocardial ischemia-reperfusion injuries. These findings provide new insight into the pathophysiology of acute myocardial I/R injuries, and may lead to the identification of novel biomarkers and therapeutic targets for the detection and treatment of acute myocardial infarction. The pharmacological and genetic manipulation of lncRNAs has the therapeutic potential to improve the clinical outcomes of patients with acute myocardial infarction (122).

5. Role of lncRNAs in renal ischemic injury

An ischemic renal injury refers to damage caused by severe renal ischemia resulting from severe stenosis or obstruction of the main renal artery or its branches. Acute renal ischemia and renal I/R injuries are the main causes of acute renal failure. Chronic ischemia often leads to chronic ischemic nephropathy in middle-aged and elderly patients (123). Several studies have demonstrated that various lncRNAs play a potential role in renal I/R injuries (124,125).

lncRNA MALAT1. The findings of recent studies analyzing the role of MALAT1 in renal ischemic injuries have been inconsistent. For example, one study demonstrated that expression of MALAT1 was significantly increased in mouse kidneys following I/R injury and in human proximal renal tubular epithelial cells (HK2) under hypoxic conditions (111). The knockdown of MALAT1 significantly increased both the expression of NF-κB and HIF-1α, and the secretion of IL-6 and TNFα in hypoxic HK2 cells. This suggests that the knockdown of MALAT1 expression can promote hypoxia-induced inflammation in HK2 cells (111).

Nevertheless, other studies have suggested that MALAT1 may have no effect on renal I/R injury. For instance, Kölling *et al* (126) found that the level of MALAT1 was increased in kidney biopsies and plasma from patients with acute kidney injury; MALAT1 expression was also increased in hypoxic mouse kidney tissues, endothelial cells and tubular

Table II. Role of lncRNAs in ischemic heart injury.

lncRNA	Effect on miRNAs and signaling pathways (Refs.)	Effect on inflammation	Effect on apoptosis	Effect on autophagy	Effect on ischemic heart injury	Effect on other aspects
NEAT1	miR-27b/PINK1 (95)				↑	
	miR-129-5p (94)		↑			Suppresses proliferation
	miR-378a-3p/Atg12 (92)				↑	
	miR-140/RhoA (93)		↑		↑	
	TLR2/NF-κB signaling pathway (96)				↑	
	Decreases pri-miRNA processing (97)				↑	
H19	miR-22-3P (98)				↓	
	miR-22-3p/KDM3A (99)	↓	↓		↓	
	miR-675/PPARα (100)	↑	↑		↑	
	miR-29b-3p (101)		↓		↓	
	YB-1 protein (102)				↑	Results in cardiac dilatation, and cardiac fibrosis
	Increases the stability of nucleolin protein (103)				↓	Is involved in myocardial ischemic preconditioning (IP)
TUG1	miR-132-3p/HDAC3 (104)				↑	
	miR-142-3p (105)				↓	
	miR-9a-5p/KLF5 (106)		↑			
	miR-29a-3p (107)				↑	
	miR-532-5p/Sox8 (108)				↑	
MALAT1	miR-20b (109)				↑	
	miR-133 (110)		↑			
	miR-320/Pten (111)				↑	
	β-catenin (112)				↑	
ANRIL	miR-7-5p/SIRT1 (113)				↓	
HOTAIR	miR-125/mmp2 (114)				↓	
GAS5	miR-142-5p (115)				↑	
CAIF	p53 (116)			↓	↓	
XIST	miR-133a/SOCS2 (117)				↓	
HIF1A-AS1	miRNA-204/SOCS2 (118)				↓	Promotes ventricular remodeling
LET	miR-138 (118)				↓	
Gm2691	PI3K/AKT (119)	↓	↓			
MIAT	NF-κB (120)		↓			
RMRP	miR-206/ATG3 (121)				↑	

lncRNA, long non-coding RNA; MALAT1, metastatic-associated lung adenocarcinoma transcript 1; TUG1, taurine up-regulated gene 1. NEAT1, nuclear enriched abundant transcript 1; ANRIL, antisense non-coding RNA in the INK4 locus; HOTAIR, HOX transcript antisense RNA; GAS5, growth arrest-specific transcript 5; CAIF, cardiac autophagy inhibitory factor; XIST, X-inactive specific transcript; LET, low expression in tumor; MIAT, myocardial infarction associated transcript; RMRP, RNA component of mitochondria RNA processing endoribonuclease. The '↓' symbol implies the downregulation of inflammation, apoptosis, etc.; and the '↑' symbol implies thje upregulation of inflammation, apoptosis, etc.

epithelial cells. However, MALAT1 knockout mice exhibited the same degree of extramedullary injury, capillary thinning, fibrosis, inflammatory cell infiltration, inflammatory gene expression and proliferation as that in wild-type mice under unilateral renal I/R injuries. MALAT1 knockout mice and wild-type mice also exhibited similar renal dysfunction in bilateral kidney I/R injuries (126). However, a review of the role of MALAT1 in vascular and psychosomatic diseases stated that most experimental studies have shown that the downregulation of MALAT1 leads to more pronounced

atherosclerotic lesions and aggravates renal and other organ damage after ischemia (127).

I/R injury is not only a main cause of acute kidney injury, but also a critical risk factor for delayed or non-functional graft function in renal transplantation. In 2019, Su *et al* (11), using microarray data, found that MALAT1 was upregulated in I/R injury; MALAT1 expression was increased 3.79-fold in the kidneys of mice with I/R injury when compared with sham-operated mice. The researchers also detected a 40.4% decrease in the expression of miR-139-5p in the kidneys of the mice with I/R injury compared with the sham-operated mice, which is closely related to cell proliferation (11). The afore-mentioned data indicate that both MALAT1 and miR-139-5p are involved in renal I/R injury, although the specific associa-tion between them has not yet been fully elucidated.

Other lncRNAs. A number of studies have demonstrated that other lncRNAs play a crucial role in renal ischemic injuries. Several studies have analyzed the miRNA axis under renal ischemic injuries. For example, lncRNA NEAT1 has been shown to promote hypoxia-induced renal tubular epithelial apoptosis through the downregulation of miR-27a-3p (128). The lncRNA GAS5 has also been found to promote apoptosis by competing with endogenous RNA for miR-21 via thrombo-spondin 1 in acute ischemic kidney injury (129). Furthermore, another study demonstrated that the downregulation of lncRNA TUG1 attenuated inflammation and apoptosis in renal tubular epithelial cells induced by ischemia-reperfusion by sponging miR-449b-5p via HMGB1 and MMP2 (130).

Other studies have confirmed that lncRNAs can regulate renal ischemic injuries by activating other signal pathways. For example, LINC00520, which targets miR-27b-3p, regu-lates the expression of oncostatin M receptor to promote the development of acute kidney injuries through the PI3K/AKT signaling pathway (131). The lncRNA np_5318 promotes renal I/R injuries through the TGF-β/Smad signaling pathway (132). The lncRNA XLOC_032768 protects renal tubular epithelial cells against apoptosis in renal I/R injuries by regulating FNDC3B/TGF-β1 signaling pathway (133). Additionally, a previous clinical study demonstrated that changes in the concentration of circulating lncRNAs in the plasma of patients with acute kidney injury were predictive of cohort mortality (134). This also reveals the practical application of lncRNAs in clinical ischemic injuries.

6. Role of lncRNAs in lung ischemic injury

Lung I/R is a common type of ischemic injury, as well as a common post-operative complication of lung transplantation with high morbidity and mortality rates. The elucidation of the mechanisms of pulmonary ischemic injury is of utmost signifi-cance for the clinical diagnosis and treatment of the condition. However, only a few studies to date have analyzed the role of lncRNAs in pulmonary ischemic injury, at least to the best of our knowledge.

In line with its effects on the brain, heart and kidneys, it is also assumed that MALAT1 plays a crucial role in isch-emic lung injuries. In 2019, Wei *et al* (12) explored the role of MALAT1 in inflammatory injuries following lung transplanta-tion I/R (LTIR). The expression of MALAT1 was significantly

increased in the lung tissues of rats with LTIR. The expression of IL-8 was the highest among all examined inflammatory factors and was significantly higher in the serum and in bron-choalveolar lavage fluid of rats with LTIR compared with the control animals. The knockdown of MALAT1 significantly reduced the expression of IL-8 (mRNA and protein) and suppressed the apoptosis of pulmonary epithelial cells. In fact, MALAT1 was directly bound to p300 and activated Il-8 tran-scription. The silencing of MALAT1 alleviated inflammatory injury in rats with LTIR by suppressing IL-8 expression, and inhibiting neutrophil activation and infiltration (8).

Primary graft dysfunction (PGD) is an acute lung injury caused by I/R injury, which is the main cause of early morbidity and mortality following transplantation (135). A previous study found that lncRNA X-inactive-specific tran-script (XIST) upregulated IL-12A expression by binding to miR-21, thus inducing the formation of neutrophil extracellular traps (NETs) and accelerated PGD following lung transplanta-tion (136). In that study, miR-21 expression was significantly reduced in patients with PGD following lung transplantation compared with non-PGD patients, while its expression level was inversely associated with the PGD grade. Moreover, the level of the pro-inflammatory cytokines, IL-6, CXCL10, CCL2, and the chemokine, IL-8, in patients with PGD was higher than that in patients without PGD. An elevated expression of XIST was also detected in the alveolar lavage fluid from patients with PGD (136). During acute immune responses, neutrophils migrate to the site of inflammation and decompose their nuclear inclusions to form NETs, which are a possible risk factor for PGD. XIST was found to negatively correlate with miR-21, but to positively correlate with IL-12A. Silencing XIST also downregulated the expression of IL-12A by upregulating miR-21, inhibiting the formation of NETs, and ultimately reducing PGD following lung transplantation (136).

7. Overview of lncRNAs in ischemic injuries

A large number of *in vitro* and *in vivo* experiments have demonstrated that multiple lncRNAs are involved in the isch-emic injury to different organs, among which MALAT1, H19, MEG3 and TUG1 are the most commonly described lncRNAs. Some lncRNAs exhibit similar expression patterns in ischemic cell and animal models and in the plasma of ischemic patients (Table SI), while the knockdown/overexpression of lncRNAs in animal models recapitulates the pathology of ischemic patients, suggesting that lncRNAs may contribute to the forma-tion and progression of ischemic injury in patients. However, the mechanisms and associated signaling pathways of the majority of lncRNAs in ischemic injuries remain unclear and the effect of some lncRNAs remains controversial (126,127).

Based on review of the entire literature, it can be concluded that MALAT1 plays a critical role not only in cerebral ischemic injury, but also in the ischemic injury of the heart, kidneys and lungs. Why is the lncRNA MALAT1 of such vital importance to ischemic injury? MALAT1 is a highly conserved nuclear retained lncRNA and plays a role in the transcriptional and post-transcriptional regulation of gene expression in an envi-ronment-dependent manner (137,138). Furthermore, MALAT1 is involved in a variety of physiological processes, including alternative splicing, epigenetic modification of gene expression,
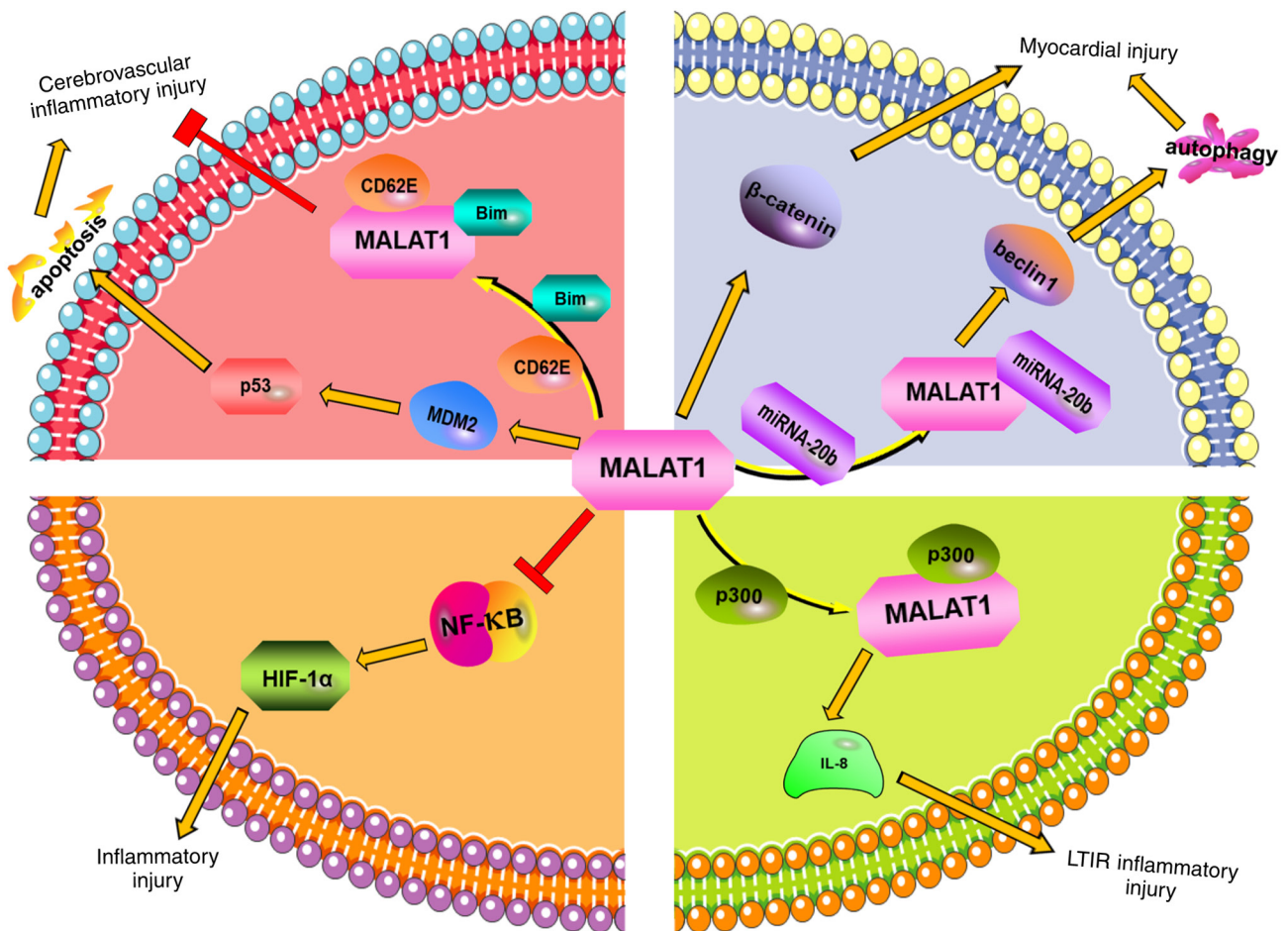
Figure 1. In cerebral ischemic injury, MALAT1 directly binds to Bim and CD62E, thereby reducing the expression of Bim and the level of pro-inflammatory cytokines following ischemic injury and reducing inflammatory injury. MALAT1 can promote apoptosis through the MDM2/p53 pathway, and then aggravate the inflammatory injury of cerebrovascular endothelium. In ischemic heart injury, MALAT1 can directly promote β-catenin expression. It can also promote the expression of Beclin1 by binding with miRNA-20, enhance autophagy, and finally further aggravating myocardial injury. In renal ischemic injury, the knockdown of MALAT1 can activate NF-κB, increase the expression of HIF-1α, and thereby reduce the inflammatory injury caused by renal ischemia/reperfusion injuries. In ischemic lung injury, MALAT1 can directly bind to p300, then upregulate IL-8, and finally promote the inflammatory damage caused by lung transplantation ischemia-reperfusion. MALAT1, metastatic-associated lung adenocarcinoma transcript 1; MDM2, murine double minute 2.

synapse formation and myogenesis (138). In recent years, it has been found that an abnormal MALAT1 expression is closely related to cancer. MALAT1 regulates cancer progression by interacting with molecules, such as proteins, RNA and DNA to alter different signaling pathways (23). In addition to lung cancer, recent studies have shown that MALAT1 is involved in other types of cancer, such as breast, pancreatic, prostate cancer, glioma and leukemia (139). MALAT1 is therefore considered as a potential biomarker for the diagnosis and prediction of cancer, as well as a therapeutic target for specific tumors.

The present review article demonstrates that MALAT1 plays a key role in ischemic injury, and is involved in the heart, brain, lungs and kidneys (Fig. 1). Similarly, studies have shown that in most cases, MALAT1 expression or overexpression can aggravate ischemic injury in these organs. Moreover, MALAT1 is involved in the regulation of ischemic injury mainly through the miRNA-mediated regulation of inflammatory factors, apoptosis, autophagy and other pathways. MALAT1 promotes the development of stroke by regulating MDM2 and subsequently activating the p53 signaling pathway. Further study of the MALAT1/MDM2/p53 signaling pathway may provide

a more effective clinical treatment strategy for patients with ischemic stroke (Fig. 1). Accordingly, MALAT1 may be a novel target for the treatment of cerebral ischemic stroke. In heart ischemic injury, MALAT1 can function as a ceRNA for miR-20b-5p to upregulate expression of Beclin1 and enhance autophagy-mediated cardiomyocyte injury (109). MALAT1 can also sponge miR-133 and miRNA-320 to enhance inflammation in ischemia-reperfusion injury and apoptosis in acute myocardial infarction (110,111). The Wnt/β-catenin signal pathway has been shown to exert a protective effect in cerebral, hepatic and myocardial I/R injury (140-142). The knockdown of MALAT1 attenuates I-R induced myocardial infarction and downregulates β-catenin expression (112). The mechanisms underlying the regulation of β-catenin expression by MALAT1 require further investigation. MALTA1 also exacerbates I/R injury following lung transplantation by upregulating IL-8 expression (12). However, MALAT1 has no effect or, in fact, the opposite effect on renal I/R injury (111,127). The underlying mechanisms of the functional difference of MALAT1 between organs warrant further investigation.

The function of lncRNAs in ischemic injury appears to be complex. An single lncRNA may have multiple
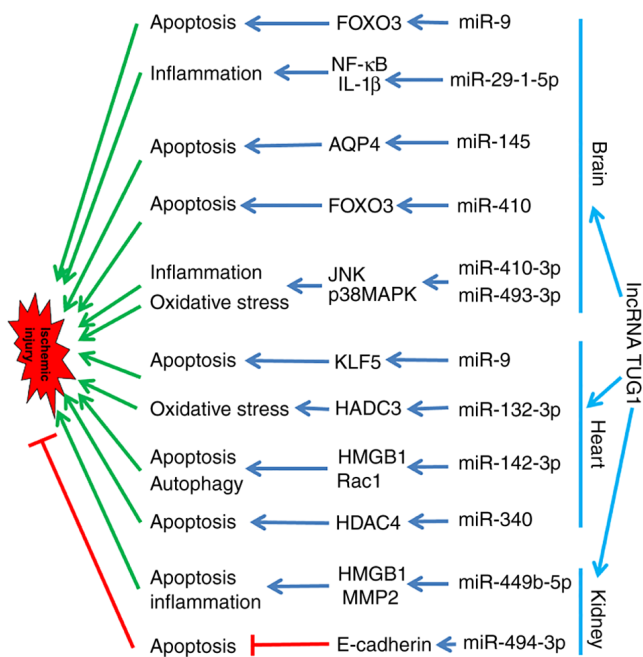
Figure 2. Individual lncRNAs have multiple miRNA targets and involve different signaling pathways. In brain ischemic injury, for example, lncRNA TUG1 can bind miR-9, upregulate FOXO3 expression and increase neuronal apoptosis in mice with middle cerebral artery occlusion (143); lncRNA TUG1 binds miR-29b-1-5p, activates the NF-κB/IL-β signaling pathway, and induces inflammatory damage in rats with spinal cord I/R injury (144); lncRNA TUG1 can directly interact with miR-145 and function as a competing endogenous RNA of miR-145, regulate AQP4 expression and induce cell damage in cerebral I/R injury (84); lncRNA TUG1 binds miR-410, regulates FOXO3 expression and induces apoptosis and inflammation in cerebral I/R injury (145); lncRNA TUG1 binds miR-410-3p and miR-493-3p, activates the JNK and p38 MAPK signaling pathways, and induces inflammation and oxidative damage in cerebral I/R injury (44). In heart ischemic injury, lncRNA TUG1 binds miR-9, regulates KLF5 expression and induces apoptosis in myocardial I/R injury (106); lncRNA TUG1 activates HDAC3 by sponging miR-132-3p, stimulates intracellular ROS accumulation and aggravates myocardial ischemic injury (104); lncRNA TUG1 binds miR-142-3p, regulates expression of HMGB1 and Rac1, and induces the apoptosis and autophagy of ischemic/hypoxia cardiomyocytes (104); lncRNA TUG1 binds miR-340, regulates HDAC4 expression, mediates β-catenin/GLUT1 and induces apoptosis in myocardial I/R injury (146). In kidney ischemic injury, lncRNA TUG1 interacts with miR-449b-5p, and then regulates expression of HMGB1 and MMP2, inducing apoptosis and inflammation in I/R injury (130). However, lncRNA TUG1 binds miR-494-3p, regulates E-cadherin expression and inhibits apoptosis, alleviating I/R induced acute kidney injury (147). lncRNA, long non-coding RNA; TUG1, taurine up-regulated gene 1; I/R, ischemia/reperfusion; KLF5, Kruppel like factor 5; HMGB1, high mobility group box 1; HDAC3, histone deacetylase 3.

miRNA targets and is associated with different signaling pathways. For example, in brain ischemic injury, lncRNA TUG1 can sponge miR-9, miR-29b-1-5p, miR-145, miR-410, miR-410-3p and miR-493-3p, can regulate expression of downstream targeting genes, markedly induce apoptosis and inflammation, and aggravate brain ischemic injury (Fig. 2) (44,84,143-145); in heart ischemic injury, lncRNA TUG1 can bind to miR-9, miR-132-3p, miR-142-3p and miR-340, subsequently regulating the expression of targeting genes, enhancing oxidative damage, autophagy and apoptosis, and promoting heart ischemic injury (Fig. 2) (104-106,146); in kidney ischemic injury, the reported effects of lncRNA TUG1 on ischemic injury are not consistent. A previous study demonstrated that lncRNA TUG1 sponged miR-494-3p and

disinhibited E-cadherin, reducing I/R induced acute kidney injury (147). However, another study reported that lncRNA TUG1 interacted with miR-449b-5p and induced apoptosis and inflammation, aggravating I/R induced kidney injury (Fig. 2) (130). It is interesting that lncRNA TUG1 sponges the same miRNA (miR-9), but that the downstream target is different (FOXO3 in the brain and RLF5 in the heart) (Fig. 2). The complex multiple targets and associated signaling pathways of lncRNA renders the development of treatments more challenging.

8. Conclusion and future perspectives

Ischemic injuries cause severe trauma to the body and are associated with high morbidity and mortality rates. Ischemic stroke, myocardial infarction and renal transplantation failures have attracted extensive clinical attention. Numerous studies (cited in the present review) have demonstrated that lncRNAs play an essential role in ischemic injuries and that their interaction with miRNA is the main mode of action. The downregulation of the majority of lncRNAs reduces inflammation, apoptosis, autophagy, or other cell damage, thus alleviating ischemic injuries. Since the plethora of data are derived from *in vitro* and pre-clinical studies, further investigations are urgently required to develop novel therapeutic strategies for patients with ischemic injury.

Availability of data and materials

Not applicable.

Authors' contributions

LS and BY contributed to the conception of the study. YC, JL, QL, KH and NJ analyzed the data from the literature for inclusion in the review and prepared the manuscript. JR and XS revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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