Review Article

Long Noncoding RNA/Circular RNA-miRNA-mRNA Axes in Ischemia-Reperfusion Injury

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Ischemia-reperfusion injury (IRI) elicits tissue injury involved in a wide range of pathologies. Multiple studies have demonstrated that noncoding RNAs (ncRNAs), including long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs), participate in the pathological development of IRI, and they may act as biomarkers, therapeutic targets, or prognostic indicators. Nonetheless, the specific molecular mechanisms of ncRNAs in IRI have not been completely elucidated. Regulatory networks among lncRNAs/circRNAs, miRNAs, and mRNAs have been the focus of attention in recent years. Studies on the underlying molecular mechanisms have contributed to the discovery of therapeutic targets or strategies in IRI. In this review, we comprehensively summarize the current research on the lncRNA/circRNA-miRNA-mRNA axes and highlight the important role of these axes in IRI.

1. Introduction

Ischemia-reperfusion injury (IRI) occurs after an initial restriction of blood supply to an organ followed by restoration of perfusion [1]. The mechanisms contributing to the pathogenesis of IRI include oxidative/nitrosative stress, mitochondrial dysfunction, calcium overload, inflammation, and activation of apoptotic and autophagic pathways, among other mechanisms [2]. Studies have reported single-target interventions for these pathogeneses of IRI. Nitric oxide (NO) reduces mitochondrial damage and reactive oxygen species (ROS) derived from reperfusion by mimicking the protective effect of kinase pathways that decrease apoptosis and tissue damage. However, it has been difficult to determine the optimal NO dose, and excess NO levels have been determined to be harmful [3]. To reduce the calcium overload, the inhibition of proteins, of which sustained activation causes excessive cation influx, is believed to have a protective effect in ischemia models [4]. When preventative strategies against IRI cannot be used, suppression of the inflammatory response is beneficial for IRI. However, the inflammatory pathways are so complex that blocking any medium in the system may not provide definitive and effective treatment [5]. Compared with single-target interventions, multitarget interventions may have better efficacy in the treatment of IRI.

For decades, research has focused on the 2% of the human genome that codes for proteins [6]. In recent years, researchers have found that the remaining 98% of the genome that was once considered as nonfunctional “junk” includes noncoding RNAs (ncRNAs) that play important roles in a wide range of biological processes such as growth, development, and organ function. Furthermore, ncRNAs have been found to function in all kinds of human diseases and conditions, including IRI [7–9]. MicroRNAs (miRNAs) are a family of ncRNAs comprising 21–25 nucleotides and are the most commonly researched class of ncRNAs. miRNAs play essential regulatory roles in the expression of proteins by binding specific target mRNAs for cleavage or translational repression [10]. Long noncoding RNAs (lncRNAs), the class of ncRNA making up the largest portion of the mammalian ncRNAs, are a heterogeneous group of ncRNAs more than 200 nucleotides long that regulate gene expression through a diverse range of mechanisms [11]. Circular RNAs (circRNAs), characterized by their covalently
closed-loop structures without 5’ caps and 3’ poly tails, comprise a large class of ncRNAs that are produced by a noncanonical splicing event called back-splicing [12]. Recent studies have also revealed a role of IncRNAs/circRNAs as competing endogenous RNAs (ceRNA) that sponge specific miRNAs to indirectly regulate the expression of many genes. Increasing evidence has identified the abnormal expression of ncRNAs in IRI of multiple organs, especially the heart, brain, liver, and kidney [13–16]. Furthermore, several studies have identified IncRNAs/circRNAs that function as ceRNAs in regulating the expression of many genes as vital to the development and progression of IRI, which may provide multitarget interventions for the treatment of IRI.

In this review, we provide an overview of the roles of the IncRNA/circRNA-miRNA-mRNA axis as potential biomarkers and therapeutic targets for the detection and treatment of IRI in different organs, including the heart, brain, liver, and kidney (Figures 1 and 2) and as mediators and effectors of organ protection. In addition, we discuss prospective tactics for targeting ncRNAs as potential novel therapies for IRI to reduce tissue injury of important organs.

2. IncRNA/circRNA-miRNA-mRNA Axis in IRI

Tissue injury elicited by ischemia and reperfusion (I/R) occurs in a wide range of pathologies, especially in myocardial infarction (MI), ischemic stroke of the brain, retinal vascular occlusion, and organ transplantation [1]. Previous studies have shown that ncRNAs play an important role in I/R. Multiple pathological processes that contribute to I/R are associated with cell dysfunction, including apoptosis and necrosis, or autophagy dysfunction, cell proliferation, and sterile inflammation [1, 2, 17].

2.1. Heart. Cell death is a cardinal contributor to most cardiovascular diseases such as MI, IRI, and heart failure [18]. The high morbidity and mortality of cardiac diseases is mainly caused by myocardial cell death due to I/R [19]. See Table 1 for a summary of the studies of the IncRNA-miRNA-mRNA axes in myocardial IRI.

2.1.1. IncRNA/circRNA-miRNA-mRNA Axis Regulates Apoptosis of Cardiomyocytes in IRI. Apoptosis is the major form of programmed cell death. Accumulating evidence has demonstrated that the IncRNA/circRNA-miRNA-mRNA axis plays an important role in IRI by mediating cell apoptosis. IncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was reported to promote cardiomyocyte apoptosis in an IRI-induced MI mouse model via PDCD4 (Programmed cell death 4) upregulation by sponging miR-200a-3p [20]. Another study suggested that MALAT1 may function as a ceRNA to upregulate NLRC5 (nucleotide-binding and oligomerization domain-like receptor C5) by binding to miR-125b-5p in an IRI-induced acute myocardial infarction (AMI) mouse model, leading to the apoptosis of myocardial cells [21]. Another report showed that the cardiac protective effect of fentanyl was abrogated by MALAT1 through its negative regulation of the miR-145/Bnip3 (Bcl2 19kDa Protein-Interacting Protein 3) pathway [22].

The IncRNA H19 is transcribed from the imprinted H19-insulin growth factor 2 locus [23]. The exact functions of H19 in cancer have been controversial because it has been identified not only as an oncogene but also a tumor suppressor. Similarly, H19 seems to have a contradictory effect in IRI. Some studies showed that the overexpression of H19 reduced cell apoptosis and alleviated myocardial IRI of mice and cardiomyocyte injury induced by H2O2 or hypoxia-reoxygenation (H/R) through interacting with different miRNAs and mRNAs [24–26]. Conversely, Luo et al. [27] showed that knockdown of H19 promoted cell viability, inhibited cell apoptosis, reduced inflammatory cytokines, suppressed oxidative stress, and decreased infarct size in a myocardial I/R mouse model through the miR-675/PPARα ( Peroxisome proliferator-activated receptor α) pathway. Further research is needed to clarify the definitive mechanism and function of H19 in IRI of the heart.

The IncRNA nuclear-enriched abundant transcript 1 (NEAT1), transcribed from a common promoter by RNA polymerase II, is commonly expressed in mammalian cells and acts as a scaffold for the nucleus [28–30]. Multiple studies that investigated the effects of NEAT1 in myocardial IRI demonstrated that NEAT1 was abnormally upregulated in vitro and in vivo [31–34]. NEAT1 was also significantly upregulated in peripheral blood of patients with unstable angina and patients with ischemic cardiomyopathy/MI in comparison with healthy controls [34]. Furthermore, the overexpression of NEAT1 promoted the apoptosis of cardiomyocytes and enhanced myocardial IRI via different axes, such as the NEAT-miR-495-3p-MAPK6 and NEAT-miR-27b-PINK1 axes [31, 35]. However, Yan et al. reported the opposite results and found that NEAT1 was downregulated in cardiomyocytes following IRI in vivo and hydrogen peroxide treatment in vitro and acted as a miRNA sponge to target miR-125a-5p, leading to the upregulation of Bcl12112 (B-cell lymphoma-12-like 12) and the inhibition of cardiomyocyte apoptosis [36].

Previous studies showed that suppression of the IncRNA HOX transcript antisense RNA (HOTAIR) exasperated cell viability and migration potential and increased apoptosis induced by oxidative stress in H9C2 cells, which may be partly attributed to the HOTAIR/miR-125/MMP-2 (Matrix metalloproteinase-2) axis [37]. Correspondingly, HOTAIR prevented oxidative stress and cardiac myocyte apoptosis in myocardial IRI, which involves AMPKα activation via the EZH2/miR-451/Cab39 pathway [38]. Yu and Chen [39] speculated that circulating HOTAIR/miR-126 may be a potential biomarker and risk factor predictor for myocardial IRI.

Multiple studies have investigated the effects of other IncRNA-miRNA-mRNA axes in myocardial IRI on myocardial cell apoptosis. Enhanced expression of the IncRNA five prime to XIST (FTX) curbed cardiomyocyte apoptosis via targeting the miR-29b-1-5p/Bcl2l2 and miR-410-3p/Fmr1 axes [40, 41]. The mitochondrial dynamic-related IncRNA (MDRL) reduces mitochondrial fission and apoptosis upon I/R by downregulating miR-361, which inhibits the progression of miR-484 by binding directly to the primary transcript.
Figure 1: lncRNA-miRNA-mRNA axes in ischaemia/reperfusion injury. lncRNA-miRNA-mRNA axes regulating the pathogenesis of ischemia/reperfusion injury are shown, which are associated with cell apoptosis, autophagy, and proliferation, as well as inflammation and others. Colors in the boxes represent different organs. Colors in lines mean that different lncRNAs target their corresponding miRNAs and mRNAs. Abbreviations: lncRNA: long noncoding RNA; miRNAs: microRNAs; Rian: RNA imprinted and accumulated in nucleus; HIF1A-AS1: hypoxia inducible factor 1a-antisense RNA 1; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; TUG1: taurine-upregulated gene 1; Mbd2: methyl-CpG-binding domain protein 2; APF: autophagy-promoting factor; GASS: growth arrest specific 5; MEG3: maternally expressed gene 3; CHRF: cardiac hypertrophy-related factor; HOTAIR: HOX transcript antisense RNA; NLRC5: nucleotide-binding and oligomerization domain-like receptor C5; AKT: protein kinase B; PDCD4: programmed cell death 4; TSP-1: thrombospondin 1; PI3K: phosphatidylinositol 3 kinase; FADD: Fas-associated protein with death domain; cIAP1: cellular protein 3; ULK2: Unc-51-like kinase 2; AQP4: aquaporin 4; TRPV4: transient receptor potential vanilloid 4; SPRR2F: small proline-rich protein oligomerization domain-like receptor C5; AKT: protein kinase B; PDCD4: programmed cell death 4; PTGS2: prostaglandin-endoperoxide gene 1; Mbd2: methyl-CpG-binding domain protein 2; APF: autophagy-promoting factor; GAS5: growth arrest specific 5; UCA1: urothelial carcinoma-inhibitor of apoptosis protein 1; PARP1: poly(ADP-ribose) polymerase 1; PPARα: peroxisome proliferator-activated receptor α; Cab39: calcium-binding protein 39; ZO-1: zonula occludens 1; Rock2: rho-associated protein kinase 2; Id2: inhibitor of DNA binding/differentiation 2; AIM2: absent in melanoma 2; SOX6: sex-determining region Y box 6; Nrfl2: nuclear factor erythroid 2-related factor; UCA1: urothelial carcinoma-associated 1; NEAT1: nuclear paraspeckle assembly transcript 1; HULC: highly upregulated in liver cancer; XIST: X chromosome inactivation; FTX: five prime to Xist; SNHG1/12/14/16: small nucleolar RNA host gene 1/12/14/16; RMRP: mitochondrial RNA-processing endoribonuclease; PINT: p53-induced transcript; NRF: necrosis-related factor; OIP5-AS1: Opa-interacting protein 5-antisense transcript 1; CARL: cardiac apoptosis-related lncRNA; MDRL: mitochondrial dynamics-related lncRNA; KCNQ1OT1: KCNQ1 opposite strand/antisense transcript 1; CasC7: cancer susceptibility candidate 7; HSP70: heat shock protein 70; MAPK6: mitogen-activated protein kinase 6; ATG3/7/12: autophagy-related gene 3/7/12; PINK1: PTEN-induced putative kinase 1; Beclin2/12: B-cell lymphoma-2-like 2/12; IL-1β: interleukin-1β; HIF-1α: hypoxia inducible factor-1α; VEGF: vascular endothelial growth factor; Fmr1: fragile X mental retardation 1; OSMR: oncostatin M receptor; SIRT1: sirtuin 1; LIMK1: the LIM motif-containing protein kinase family-contained LIM kinase 1; ROCK1: rho-associated coiled-coil-containing protein kinase 1; FOXO3/4: forkhead box O3/4; CK: creatine kinase; CM-MB: creatine kinase MB form; LDH: lactate dehydrogenase; TRAF6: TNF receptor-associated factor 6; CSE: cystathionine-γ-lyase; RIPK 1/3: receptor-interacting serine/threonine-protein kinase 1/3; AMPK: adenosine monophosphate-activated protein kinase; PGC1α: peroxisome proliferator-activated receptor-γ coactivator-1α; PHB2: prohibitin 2; LGALS3: galectin-3; DAPK1: death-associated protein kinase 1; NR3C2: nuclear receptor subfamily 3 group C member 2; CHOP: C/EBP homologous protein.
of miR-484 and precludes Drosha from processing it into pre-miR-484 [42]. The cardiac apoptosis-related IncRNA (CARL) functions as a ceRNA to sponge miR-539 and regulates apoptosis-related circRNA; ANRIL: antisense noncoding RNA in the INK4A locus; YAP1: yes-associated protein 1; TLK1: serine/threonine-protein kinase tousled-like 1; Bcl2: B-cell lymphoma protein 2; HECTD1: HECT domain E3 ubiquitin protein ligase 1; CDIP1: cell death-inducing protein; MTP18: mitochondrial protein 18 kDa; RIPK1: receptor-interacting serine/threonine-protein kinase 1; EphA2: ephrin type-A receptor 2; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; Sertad1: SERTA domain-containing protein 1; Nudcd1: NudC domain-containing protein 1; Jam2: junctional adhesion molecule B; PKC: protein kinase C; ERK: mitogen-activated protein kinase; TIPARP: TCDD inducible poly(ADP-ribose) polymerase; GSK3B: glycogen synthase kinase 3 beta.

Figure 2: circRNA-miRNA-mRNA axes in ischaemia/reperfusion injury. circRNA-miRNA-mRNA axes regulating the pathogenesis of ischemia/reperfusion injury are shown, which is associated with cell apoptosis, autophagy, and proliferation, as well as inflammation and others. Colors in the boxes represent different organs. Colors in lines mean that different circRNAs target their corresponding miRNAs and mRNAs. Abbreviations: circRNA: circular RNA; miRNAs: microRNAs; NCX1: sodium/calcium exchanger 1; MFACR: mitochondrial fission and apoptosis-related circRNA; ANRIL: antisense noncoding RNA in the INK4A locus; YAP1: yes-associated protein 1; TLK1: serine/threonine-protein kinase tousled-like 1; Bcl2: B-cell lymphoma protein 2; HECTD1: HECT domain E3 ubiquitin protein ligase 1; CDIP1: cell death-inducing protein; MTP18: mitochondrial protein 18 kDa; RIPK1: receptor-interacting serine/threonine-protein kinase 1; EphA2: ephrin type-A receptor 2; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; Sertad1: SERTA domain-containing protein 1; Nudcd1: NudC domain-containing protein 1; Jam2: junctional adhesion molecule B; PKC: protein kinase C; ERK: mitogen-activated protein kinase; TIPARP: TCDD inducible poly(ADP-ribose) polymerase; GSK3B: glycogen synthase kinase 3 beta.
| Models                                      | Species        | Cell dysfunction       | Expression | lncRNA     | miRNA     | mRNA    | Function                                                                 | Mechanism                                                                 | Relationship                  | Prediction tool               | Ref     |
|--------------------------------------------|----------------|------------------------|------------|------------|-----------|---------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------|-----------------------------|---------|
| HL-1 cells and MCM under H/R treatment    | Mouse          | Autophagy              | ↑          | AK088388   | miR-30a   | Beclin1/LC3 | Interfering AK088388 can promote the viability of H/R cardiomyocytes, reduce lactate dehydrogenase release, and reduce apoptosis | miR-30a had binding sites on AK088388                                    | NR                          | n/a                          | [75]    |
| I/R in rats and newborn rats' primary cardiomyocytes under H/R treatment | Rat            | Autophagy; apoptosis   | ↑          | AK139128   | miR-499   | FOXO4   | Knockdown of AK139128 impressively alleviates cardiomyocyte autophagy and apoptosis | There are several complementary binding sites within miR-499 and AK139128 | NR                          | starBase v3.0; TargetScan    | [73]    |
| I/R in mice and mice primary cardiomyocytes under H/R treatment | Mouse          | Autophagy; apoptosis   | ↑          | AK139328   | miR-204-3p | CK; CK-MB; LDH | Modulated miR-204-3p directly                                             |                                                                            | NR                          | n/a                          | [74]    |
| I/R in mice and mice primary cardiomyocytes under A/R | Mouse          | Autophagy              | ↑          | APF        | miR-188-3p | ATG7    |                                                                            |                                                                            | NR                          | n/a                          | [76]    |
| I/R in mice and mice primary cardiomyocytes under anoxia | Mouse          | Apoptosis              | ↓          | CARL       | miR-539   | PHB2    |                                                                            |                                                                            | NR                          | n/a                          | [43]    |
| H9C2 cells under H/R treatment            | Human; rat     | Proliferation; apoptosis| ↓          | FTX        | miR-410-3p | Fmr1    |                                                                            |                                                                            | NR                          | LncBase predicted v.2        | [41]    |
| I/R in mice and mouse primary cardiomyocytes under H$_2$O$_2$ treatment | Mouse          | Apoptosis              | ↓          | FTX        | miR-29b-1-5p | Bcl2L2 | Enhanced expression of FTX inhibits cardiomyocyte apoptosis               | Functions as endogenous sponge for miR-29b-1-5p                          | NR                          | RNA hybrid                    | [40]    |
| Models                              | Species | Cell dysfunction | Expression | IncRNA | miRNA    | mRNA     | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool | Ref  |
|------------------------------------|---------|-----------------|------------|--------|----------|----------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|-----------------|------|
| IRI in rats and H9C2 cells under H/R treatment | Rat     | Apoptosis       | ↑          | GAS5   | miR-532-5p | PI3K/AKT | Silencing of IncRNA GAS5 was able to attenuate myocardial damage, as cell viability increased and the apoptosis rate decreased | Functioned as a molecular sponge of miR-532-5p | NR           | RNA hybrid      | [44] |
| IRI                                | n/a     | n/a             | n/a        | GAS5   | miR-137  | Serpina3 | IncRNA GAS5 may exacerbate myocardial I/R injury through regulating serpina3 via targeting miR-137 | Serve as a ceRNA for miR-137 | n/a          | n/a            | [45] |
| Neonatal rats' primary cardiomyocytes under H/R treatment | Rat     | Apoptosis       | ↓          | H19    | miR-29b-3p | cIAP1    | H19 mediated the antiapoptotic effect of H/post against H/R-induced injury to aged cardiomyocytes | Participated in the regulation of miR-29b-3p | NR           | Bioinformatics analysis | [24] |
| IR                                 | n/a     | Apoptosis       | n/a        | H19    | miR-22-3p | n/a      | H19 mediates necrotic cell death in cardiomyocytes | Acts as a ceRNA to suppress the activity of miR-22-3p | PR           | n/a            | [25] |
| I/R in mice and H9C2 cells under H2O2 treatment | Mouse   | Necrosis        | ↓          | H19    | miR-103/107 | FADD     | Overexpression of H19 alleviated myocardial I/R of mice and cardiomyocyte injury induced by H2O2 | Functions as a ceRNA | NR           | RegRNA2.0; starBase; TargetScan | [26] |
| I/R in mice and NMVCs under H2O2 treatment | Mouse   | Apoptosis       | ↓          | H19    | miR-877-3p | Bcl2     | Knockdown of H19 significantly reduced infarct size, increased left ventricular systolic pressure, and decreased left ventricular end-diastolic pressure in a mouse model of myocardial I/R | Is a precursor of miR-675 | PR           | n/a            | [27] |
| Mouse primary cardiomyocytes under OGD/R condition | Mouse   | Viability; apoptosis; inflammation; oxidative stress | ↑          | H19    | miR-675  | PPARα    | Knockdown of H19 significantly reduced infarct size, increased left ventricular systolic pressure, and decreased left ventricular end-diastolic pressure in a mouse model of myocardial I/R | Is a precursor of miR-675 | PR           | n/a            | [27] |
| Models                                      | Species          | Cell dysfunction          | Expression | lncRNA     | miRNA   | mRNA   | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool               | Ref |
|---------------------------------------------|------------------|---------------------------|------------|------------|---------|--------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|-------------------------------|-----|
| I/R in mice                                 | Mouse            | Fibrosis; apoptosis       | ↑          | HIF1A-AS1  | miR-204 | SOCS2  | Downregulation of HIF1A-AS1 alleviates ventricular remodeling and improve cardiac function in mice after myocardial I/R injury | Adsorbs miR-204 as a ceRNA                                                | NR           | RNA22 [46]                    |     |
| IRI in mice and H9C2 cells under H/R treatment | Mouse            | Apoptosis                 | ↑          | HOTAIR     | miR-451 | Cab39  | Hotair overexpression prevented I/R-induced oxidative stress, cardiac myocyte apoptosis, and cardiac dysfunction | Contributed to Hotair-mediated miR-451 inhibition                         | NR           | n/a [38]                      |     |
| IR                                          | n/a              | n/a                       | ↓          | HOTAIR     | miR-126 | n/a    | Circulating HOTAIR/miR-126 axis maybe a potential biomarker and risk factor predictor for MI/R injury | Act as a ceRNA                                                           | n/a          | n/a [39]                      |     |
| H9C2 cells under H2O2 treatment             | Rat              | Apoptosis; proliferation  | ↓          | HOTAIR     | miR-125 | MMP-2  | Repression of HOTAIR accelerates H9c2 cells injury in response to oxidative stress | miR-125 is a target of HOTAIR                                             | NR           | Bioinformatic analysis [37]  |     |
| IRI in rats and H9C2 cells under H/R treatment | Rats             | Inflammation; apoptosis   | ↓          | HULC       | miR-377-5p | NLRP3/Caspase-1/IL-1β | HULC modulated myocardial I/R injury in rat models and cardiomyocyte apoptosis in H/R cell models via targeting miR-377-5p through NLRP3/Caspase-1/IL-1β pathway | Acted as a ceRNA by sponging miR-377-5p                                   | NR           | Bioinformatic analysis [57]  |     |
| IRI in mice and mice primary cardiomyocytes under H/R treatment | Mouse            | Apoptosis                 | ↑          | KCNQ1OT1   | miR-204-5p | LGALS3 | The downregulation of LGALS3 resulted in the alleviation of myocardial IR injury in mouse models | Bind to miR-204-5p                                                       | NR           | LncBase v.2; miRDB; DIANA TOOLS | [47]|
| AMI in rats and HL-1 cells under H/R treatment | Rat              | Apoptosis                 | n/a        | MALAT1     | miR-125b-5p | NLRC5  | Downregulation of MALAT1 attenuated heart damage in an AMI model rat      | MALAT1 negatively regulates miR-125b-5p expression                       | NR           | TargetScan [21]               |     |
| Models                                      | Species | Cell dysfunction          | Expression | lncRNA | miRNA   | mRNA    | Function                                                                                      | Mechanism                                                                 | Relationship | Prediction tool | Ref   |
|---------------------------------------------|---------|---------------------------|------------|--------|---------|---------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------|-----------------|-------|
| MI in mice and AC16 cells under hypoxia condition | Mouse   | Apoptosis; proliferation  | ↑          | MALAT1 | miR-200a-3p | PDCD4 | Knockdown of MALAT1 enhanced cell viability, promoted cell cycle progress, and suppressed cell apoptosis | Acted as a ceRNA to sponge miR-200a-3p | NR           | starBase v.2.0 | [20]  |
| IRI                                         | n/a     | Inflammation              | ↑          | MALAT1 | miR-26b  | PTGS2  | Aggravate inflammation response through regulating PTGS2 by targeting miR-26b in MI/R injury | Can act as ceRNA by binding to consensus MREs of miR-26b    | n/a          | n/a             | [88]  |
| IR                                          | n/a     | Autophagy                 | ↑          | MALAT1 | miR-204  | LC3-II | MALAT1/miR-204/LC3-II axis is a potential regulated axis of autophagy in myocardial I/R injury IncRNA MALAT1 may increase cardiomyocyte inflammation and myocardial injury during I/R | Can sponge miR-204                                             | n/a          | n/a             | [72]  |
| IR                                          | n/a     | Inflammation              | ↑          | MALAT1 | miR-203  | n/a    | n/a                                                                                         |                                                                 | n/a          | n/a             | [89]  |
| IR                                          | n/a     | Inflammation              | ↑          | MALAT1 | miR-133  | NLRP3  | IncRNA MALAT1 may sponge miR-133 to promote NLRP3 inflammasome expression in ischemia-reperfusion-injured heart | Acted as a ceRNA to inhibit miR-133 action | NR           | n/a             | [87]  |
| I/R in mice and HL-1 under H/R treatment    | Mouse   | Apoptosis                 | ↑          | MALAT1 | miR-145  | Bnip3  | MALAT1 overexpression reverses cardioprotective effects of fentanyl as indicated by an increase in LDH release and cell apoptosis | Being regulated by miR-145 of MALAT1                         | NR           | n/a             | [22]  |
| Models                                      | Species | Cell dysfunction    | Expression | IncRNA | miRNA     | mRNA     | Function                                                                 | Mechanism                                                                 | Relationship                  | Prediction tool   | Ref  |
|--------------------------------------------|---------|---------------------|------------|--------|-----------|----------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------|------------------|------|
| H9C2 cells under OGD/R condition          | Mouse   | Autophagy           | ↑          | MALAT1 | miR-20b-5p| Beclin1   | MALAT1 antagonized the inhibitory effects of miR-20b-5p on Beclin1-related cardiomyocyte autophagy in OGD/R injury          | Functions as a ceRNA for miR-20b-5p                                    | NR                             | n/a              | [70] |
| IR                                        | n/a     | Autophagy           | ↑          | MALAT1 | miR-204   | n/a      | lncRNA MALAT1 may increase cardiomyocyte autophagy and myocardial injury during I/R by negatively regulating miR-204 expression | Might serve as a sponge to suppress miR-204 action                           | NR                             | n/a              | [69] |
| I/R in mice and mice primary cardiomyocytes under A/R | Mouse   | Apoptosis           | ↓          | MDRL   | miR-361   | miR-484  | Knockdown of MDRL induced mitochondrial fission and apoptosis           | Is a functional sponge for miR-361                                      | NR                             | n/a              | [42] |
| I/R in rats and H9C2 cells under H/R treatment | Rat     | Apoptosis; proliferation | ↑         | MEG3   | miR-7-5p  | PARP1; Caspase-3 | Overexpression of MEG3 increased the I/R-induced CK and LDH activities and cell apoptosis and decreased cell proliferation | By directly binding to miR-5-7p                                      | NR                             | n/a              | [48] |
| I/RI                                      | n/a     | n/a                 | ↑          | MEG3   | miR-223   | n/a      | Circulating MEG3/miR-223 axis maybe a potential biomarker and risk factor predictor for MI/R injury                          | Acted as an endogenous sponge for miR-223                                  | n/a                            | n/a              | [49] |
| MI/R in mice and H9C2 cells under H₂O₂ treatment | Mouse   | Proliferation       | ↑          | NEAT1  | miR-495-3p| MAPK6    | Loss of NEAT1 in H9C2 cells could repress the viability and proliferation of cells                                         | Sponges miR-495-3p                                                       | NR                             | n/a              | [31] |
| I/R in rats and H9C2 cells under H/R treatment | Rat     | Apoptosis           | ↑          | NEAT1  | miRNA-520a| n/a      | Knockdown of NEAT1 serves a protective role against H/R-induced cardiomyocyte apoptosis                                  | miR-520a was indicated to directly target NEAT1                            | NR                             | Bioinformatics analysis | [32] |
| Models                                                                 | Species          | Cell dysfunction                  | Expression | IncRNA | miRNA         | mRNA | Function                                                                 | Mechanism                                                                 | Relationship                      | Prediction tool       | Ref  |
|----------------------------------------------------------------------|------------------|-----------------------------------|------------|--------|----------------|------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------|----------------------|------|
| H9C2 cells under OGD/R condition                                     | Rat              | Proliferation; apoptosis          | ↑          | NEAT1  | miR-193a       | n/a  | Downregulation of Inc-NEAT1 promoted cell proliferation and inhibited cell apoptosis | miR-193a was targeted by Inc-NEAT1 in I/R injury H9c2 cells                 | NR                   | starBase; miRcode    | [33] |
| I/R in mice and rat primary cardiomyocytes under H2O2 treatment      | Mouse            | Apoptosis                        | ↓          | NEAT1  | miR-125a-5p    | Bcl2l12 | Ectopic overexpression of NEAT1 suppresses cardiomyocyte apoptosis induced by hydrogen peroxide | Functions as miR-125a-5p sponge | NR                   | starBase v2.0       | [36] |
| IR                                                                  | n/a              | n/a                               | ↑          | NEAT1  | miR-27b        | PINK1 | IncRNA NEAT1 may aggravate diabetic MI/R injury                            | Can sponge miR-27b               | n/a                  | n/a                | [35] |
| IR in mice and newborn rat primary cardiomyocytes under hypoxia condition | Mouse            | Proliferation; apoptosis          | ↑          | NEAT1  | miR-378a-3p    | ATG12 | IncRNA NEAT1 significantly promoted cell proliferation and migration of cardiomyocytes | Was capable of targeting miR-378a-3p | NR                   | RNA hybrid           | [34] |
| I/R in mice and mice primary cardiomyocytes under H2O2 treatment      | Mouse            | Necrosis                         | ↑          | NRF    | miR-873        | RIPK1/RIPK3 | Knockdown of NRF antagonizes necrosis in cardiomyocytes and reduces necrosis and myocardial infarction upon I/R injury | As an endogenous sponge RNA     | NR                   | n/a                | [82] |
| IRI in rats and H9C2 cells under H/R treatment                       | Rats             | Apoptosis                        | ↓          | Oprm1  | miR-30b-5p     | CSE  | Overexpression of IncRNA Oprm1 mitigated MIRI and preserved the cardiac function in vivo | Competitively combines with miR-30b-5p | NR                   | Bioinformatic analysis | [58] |
| IRI in rats and H9C2 cells under OGD/R condition                     | Rats             | Apoptosis                        | ↓          | OIP5-ASI | miR-29a        | SIRT1/AMPK/PGC1α | Acted as a ceRNA of miR-29a | Acted as a ceRNA of miR-29a | NR                   | DIANA-LncBase; starBase | [59] |
| Models                                      | Species | Cell dysfunction       | Expression | lncRNA | miRNA     | mRNA          | Function                                                                                       | Mechanism               | Relationship | Prediction tool | Ref |
|--------------------------------------------|---------|------------------------|------------|--------|-----------|---------------|------------------------------------------------------------------------------------------------|-------------------------|--------------|----------------|-----|
| AMI in rats                                | Rat     | Apoptosis ↑            | PINT       | miR-208a-3p | JUN       | Low expression of LINC-PINT could suppress myocardial infarction apoptotic cells               | Could sponge miR-208a-3p | NR           | n/a            | [50]|
| H9C2 cells under hypoxia condition         | Rat     | Apoptosis ↑            | RMRP       | miR-206 | ATG3      | Upregulation of RMRP may aggravate myocardial I/R injury                                      | Sponging miR-206        | NR           | n/a            | [51]|
| IRI in rats and HCMs under H/R treatment   | Rats    | Inflammation; apoptosis↑ | ROR        | miR-124-3p | TRAF6     | Overexpression of ROR further enhanced the H/R-induced inflammation and cell apoptosis       | Sponged and negatively regulated miR-124-3p | NR           | Bioinformatics analysis | [56]|
| MI/R in mice and HUVECs under H/R treatment| Human; mouse | Proliferation ↑     | SNHG1      | miR-140-3p | HIF-1α/VEGF | SNHG1 upregulation under H/R increased HUVEC proliferation, tube formation, and cell migration | Functioned as a ceRNA of miR-140-3p | NR           | TargetScan | [55]|
| IR in mice and neonatal mice primary cardiomyocytes under H₂O₂ treatment | Mouse   | Cell viability; apoptosis↑ | TUG1       | miR-132-3p | HDAC3     | Knocking down TUG1 significantly improved viability, inhibited apoptosis, and reduced ROS production in H₂O₂-stressed cardiomyocytes in vitro, and alleviated I/R-induced AMI in vivo | Sponging miR-132-3p | NR           | TargetScan | [52]|
| IRI in mice and mouse primary cardiomyocytes under H₂O₂ treatment | Mouse   | Autophagy; apoptosis↑  | TUG1       | miR-142-3p | HMGB1/Rac1 | Inhibition of TUG1 and overexpression of miR-142-3p inhibited cell apoptosis and autophagy in cardiomyocytes | Sponging miR-142-3p     | NR           | n/a            | [53]|
| IRI in rats and H9C2 cells under H/R treatment | Rat     | Autophagy ↓            | UCA1       | miR-128  | HSP70     | Inhibition of TUG1, UCA1/miR-128 mediated the mechanism of MPostC on autophagy and myocardial injury | Could bind with miR-128   | NR           | n/a            | [77]|
| Models | Species | Cell dysfunction | Expression | lncRNA | miRNA | mRNA | Function | Mechanism | Relationship | Prediction tool | Ref |
|--------|---------|------------------|------------|--------|-------|------|----------|-----------|--------------|----------------|-----|
| IRI    | n/a     | Apoptosis        | ↓          | UCA1   | miR-143 | n/a  | IncRNA UCA1 interferes with miR-143 expression to modulate cardiomyocyte apoptosis in myocardial I/R injury | IncRNA UCA1 directly interacts with miR-143 | NR  | n/a         | [54] |

[†]: the upward arrow indicates increased expression of lncRNAs; [↓]: the downward arrow indicates decreased expression of lncRNAs; NR: lncRNAs negatively regulate miRNAs; PR: lncRNAs positively regulate miRNAs; RC: reciprocal correlations between lncRNAs and miRNAs; IRI: ischemia-reperfusion injury; AMI: acute myocardial infarction; H/R: hypoxia-reoxygenation; HCMs: human cardiac myocytes; HUVECs: human umbilical vein endothelial cells; ceRNA: competing endogenous RNA; HIF1A-AS1: hypoxia inducible factor 1α-antisense RNA 1; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; TUG1: taurine-upregulated gene 1; APF: autophagy-promoting factor; GASS: growth arrest specific 5; MEG3: maternally expressed gene 3; HOTAIR: HOX transcript antisense RNA; HULC: highly upregulated in liver cancer; IL-1β: interleukin-1β; UCA1: urothelial carcinoma-associated 1; NEAT1: nuclear paraspeckle assembly transcript 1; FTX: five prime to Xist; SNHG1: small nucleolar RNA host gene 1; RMRP: mitochondrial RNA-processing endoribonuclease; PINT: p53-induced transcript; NLRP5: necrosis-related factor; OIP5-AS1: Opa-interacting protein 5-antisense transcript 1; CARL: cardiac apoptosis-related IncRNA; MDRL: mitochondrial dynamic-related IncRNA; KCNQ1OT1: Kcnq1 orthologous transcript 1; NLRCS: nucleotide-binding and oligomerization domain-like receptor C5; AKT: protein kinase B; PDCD4: programmed cell death 4; PTGS2: prostaglandin-endoperoxide synthase 2; NLRP3: nod-like receptor protein-3; BNIP3: Bcl2 19 kDa protein-interacting protein 3; SOCS2: suppressor of cytokine signaling 2; HDAC3: histone deacetylase 3; ATG7: autophagy-related gene 7; PI3K: phosphatidylinositol 3 kinase; FADD: Fas-associated protein with death domain; clAP1: cellular inhibitor of apoptosis protein 1; PARP1: poly(ADP-ribose) polymerase 1; PPARα: peroxisome proliferator-activated receptor α; Cab39: calcium-binding protein 39; MMP-2: matrix metalloproteinase-2; Bcl2: B-cell lymphoma-2; HSP70: heat shock protein 70; MAPK6: mitogen-activated protein kinase 6; ATG3/7/12: autophagy-related gene 3/7/12; Bax: B-cell lymphoma protein 2- (Bcl2-) associated X; PINK1: PTEN-induced putative kinase 1; Beclin-2/12: B-cell lymphoma-2-like 1/2; HIP-1: hypoxia inducible factor-1; VEGF: vascular endothelial growth factor; Fmr1: fragile X mental retardation 1; FOXO4: forkhead box O4; Ck: creatine kinase; CM-MB: creatine kinase MB form; LDH: lactate dehydrogenase; RIPK1/3: receptor-interacting serine/threonine-protein kinase 1/3; CSE: cystathionine-γ-lyase; SIRT1: sirtuin 1; AMPK: adenosine monophosphate-activated protein kinase; PGC1α: peroxisome proliferator-activated receptor-γ coactivator-1α; TRAF6: TNF receptor-associated factor 6; HMGB1: high-mobility group box 1; Rac1: Ras-related C3 botulinum toxin substrate 1; PHB2: prohibitin 2; LGALE3: galecin-3.
and increased the production of ROS in cardiomyocytes treated with H$_2$O$_2$ and aggravated I/R-induced AMI in a mouse model [52, 53]. Yu et al. [54] confirmed that the lncRNA urothelial carcinoma-associated 1 (UCAI) interferes with miR-143 expression to modulate cardiomyocyte apoptosis in myocardial IRI. The lncRNA small nucleolar RNA host gene 1 (SNHG1) was found to promote the proliferation and enhance the function of human umbilical vein endothelial cells by activating the HIF-1α/VEGF signaling pathway though miR-140-3p [55]. In addition, ORR and HULC both modulated myocardial IRI in rat models and H/R-induced inflammation and cell apoptosis through the miR-124-3p/TRA6 and miR-377-5p/NLRP3 (Nod-like receptor protein-3)/Caspase-1/IL-1β axes, respectively [56, 57]. Hu et al. [58] showed that the lncRNA Opmr1 alleviated myocardial IRI to preserve cardiac function, increased cystathionine-γ-lyase activity, and inhibited cell apoptosis through miR-30b-5p, in which activation of the PI3K/Akt pathway and inhibition of HIF-1α activity are involved. Furthermore, the lncRNA Opa-interacting protein 5-antisense transcript 1 (OIP5-AS1) alleviated oxygen-glucose deprivation and reperfusion-induced cell apoptosis, oxidative stress, and mitochondrial membrane depolarization in H9c2 cells; OIP5-AS1 prevented OGD/R injury via regulation of miR-29a and the SIRT1 (Sirtuin 1)/AMPK/PGC1α (peroxisome proliferator-activated receptor-γ coactivator-1α) pathway [59].

In addition to lncRNA-related axes, increasing evidence has suggested that circRNA-miRNA-mRNA axes regulate the apoptosis of cardiomyocytes in IRI of heart disease (see Table 2 for a summary of the studies of circRNAs-miRNAs-mRNAs in IRI). A letter published in 2019 speculated that the circDLGAP4/miR-143 pathway may be a potential regulator of cardiomyocyte apoptosis in myocardial IRI [60]. Intriguingly, a study by Chen et al. confirmed this speculation [61]. The authors found that the overexpression of circDLGAP4 effectively restored the decreased expression of the circRNA HECT domain E3 ubiquitin protein ligase 1 (HECTD1) resulting from miR-143 inhibition in human umbilical vein endothelial cells, which contributed to the attenuation of endothelial cell dysfunction induced by IRI by increasing cell viability and decreasing cell apoptosis and migration [61]. The circRNA sodium/calcium exchanger 1 (circNCX1) was upregulated in both H9c2 cells and neonatal rat myocardial cells after treatment of H$_2$O$_2$ or H/R and promoted the production of ROS and myocardial cell apoptosis induced by IRI by targeting miR-133a-3p and leading to overexpression of proapoptotic gene cell death-inducing protein (CDP1) in a myocardial I/R mouse model [62]. In addition, mitochondrial fission and apoptosis-related circRNA (MFACR) regulated mitochondrial fission and apoptosis in the heart by directly targeting and downregulating miR-652-3p, which blocked mitochondrial fission and reduced cardiomyocyte cell death by suppressing MTP18 translation. Consequently, the knockdown of MFACR attenuated the I/R-induced upregulation of mitochondrial fission, apoptosis, and MI size [63]. Furthermore, the circRNA serine/threonine-protein kinase toullos-like 1 (circTTLK1) was prominently upregulated in a myocardial IRI mouse model, leading to significantly increased cardiomyocyte apoptosis by its activity as a sponge of miR-214. miR-214 abolished the negative effects of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) in myocardial IRI, including an impaired cardiac function index, distensible infarct area, and cell apoptosis. These results indicate that the circTTLK1/miR-214/RIPK1 axis plays a crucial role in myocardial IRI, which may provide therapeutic targets for treatment [64]. Chang et al. [65] reported that circ_100338 regulates angiogenesis and metastasis of myocardial I/R through miRNA-200a-3p/FUS.

As described above, many lncRNA/circRNA-miRNA-mRNA axes mediate cell apoptosis of cardiomyocytes in IRI. Apoptosis is induced by the “extrinsic” and “intrinsic” pathways, and there are multiple biochemical and functional linkages between the two pathways. I/R, as cytotoxic stimuli, induces the translocation and integration of prodeath members of the Bcl2 protein family (e.g., Bax and Bak) into the outer mitochondrial membrane [18]. However, ischemia per se is not sufficient for activation of Bcl2 proteins because many are redox sensitive, requiring the oxidative stress that is evoked by reperfusion. I/R-induced cell death is reduced in animals treated with pan-caspase inhibitors, providing additional support for the notion that apoptosis contributes to the death of cardiac myocytes [66, 67]. While such observations might lead to the proposal that targeting caspsases may be an important therapeutic means to reduce I/R injury, caspase inhibition may not be ideal because other aspects of mitochondrial function will be adversely affected. Therefore, these lncRNA/circRNA-miRNA-mRNA axes may be a suitable alternative in the regulation of cardiomyocyte apoptosis and represent potential therapeutic targets of cell apoptosis during cardiac I/R injury.

2.1.2. IncRNA-miRNA-mRNA Axis Regulates Autophagy of Cardiomyocytes in IRI. Autophagy is a highly conserved catabolic process that provides organelle quality control and generates intracellular nutrients from lysosomal processing of cellular structures [68]. Yu et al. first speculated that MALAT1 may negatively regulate the expression of miR-204, which could increase the autophagy of cardiomyocytes and myocardial IRI [69]. Furthermore, MALAT1 promoted OGD/R-induced H9C2 cell injury by sponging miR-20b to enhance Beclin1-mediated autophagy [70]. miR-204 was found to regulate autophagy through LC3-II during myocardial I/R [71]. Based on the above conclusions, Wang et al. [72] ultimately speculated that the MALAT1/miR-204/LC3-II pathway may be an important regulatory axis of autophagy in myocardial IRI. Nonetheless, further experimental evidence is needed to confirm this possibility. The lncRNA AK139128 is involved in the regulation of autophagy and apoptosis in myocardial IRI by targeting the miR-499/FOXO4 axis [73]. In addition, silencing AK139328 by siRNA significantly enhanced miR-204-3p expression and suppressed cardiomyocyte autophagy, thereby attenuating myocardial IRI in diabetic mice [74]. The lncRNA AK088388 competitively binds to miR-30a, which promotes the expression of autophagy-related proteins, Beclin1 and LC3-II, and eventually leads to cell damage in myocardial
| Tissues          | Models                                      | Species         | Cell dysfunction | Expression | circRNA  | miRNA   | mRNA      | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool | Ref     |
|-----------------|---------------------------------------------|-----------------|------------------|------------|----------|---------|-----------|-------------------------------------------------|---------------------------------------------------------------------------|--------------|-----------------|---------|
| Myocardial      | MI/R in mice and HUVECs under I/R           | Human; mouse    | Apoptosis; migration | ↓          | DLGAP4   | miR-143 | HECTD1   | Had no effect on apoptosis in endothelial cells; attenuated the I/R-induced increase in endothelial cell migration | The negative regulation of mimic-miR-143 on HECTD1 protein was abolished by the overexpression of circDLGAP4 | NR           | Bioinformatics analysis [61] |
| IR              | n/a                                         | Human           | Apoptosis        | ↓          | DLGAP4   | miR-143 | Bcl2      | Functions as an endogenous miR-143 sponge        | n/a                                                      | n/a          | [60]             |
| I/R in mice and H9C2 cells under H2O2 or H/R treatment | Mouse                                      | Mouse           | Apoptosis       | ↑          | NCX1     | miR-133a-3p | CDIP1   | Knockdown of circNCX1 in murine cardiomyocytes and heart tissues reduced the levels of CDIP1 and attenuated the apoptosis and I/R injury | Acting as an endogenous miR-133a-3p sponge | NR           | RNA hybrid [62] |
| IR in mice and mouse primary cardiomyocytes under A/R treatment | Mouse                                      | Mouse           | Apoptosis       | ↑          | MFACR    | miR-652-3p | MTP18    | The knockdown of MFACR attenuated the I/R-induced upregulation of mitochondrial fission, apoptosis, and MI size | Acts as a miR-652-3p sponge | NR           | n/a             | [63]    |
| HUVECs under H/R treatment | Human                                      | Human           | Proliferation; migration; angiogenesis | ↓          | circ_100338 | miR-200a-3p | FUS      | Overexpression of circ_100338 promotes angiogenesis | circ_100338 can indeed regulate angiogenesis by binding to miRNA-200a-3p. | NR           | n/a             | [65]    |
| Tissues | Models | Species | Cell dysfunction | Expression | circRNA | miRNA | mRNA | Function | Mechanism | Relationship | Prediction tool | Ref |
|---------|--------|---------|------------------|------------|---------|-------|------|----------|-----------|--------------|----------------|-----|
| I/R in mice | Mouse | Apoptosis | ↑ | TLK1 | miR-214 | RIPK1 | Overexpression of RIPK1 led to impaired cardiac function indexes, increased infarct area, and cell apoptosis | Acted as a sponge of miR-214 | NR | starBase | [64] |
| Cerebral | NSCs under OGD/R condition | Mouse | Apoptosis | ↑ | cZNF292 | miR-22 | Wnt/b-catenin; PKC/ERK | Silencing cZNF292 alleviated OGD/R-stimulated damage in NSCs | miR-22 expression was negatively regulated by cZNF292 | NR | n/a | [116] |
| | tMCAO/R in mice and mouse primary cortex neurons under OGD/R condition | Human; mouse | Apoptosis; atrophy | ↑ | TLK1 | miR-335-3p | TIPARP | Knockdown of circTLK1 significantly decreased infarct volumes, attenuated neuronal injury, and improved neurological deficit | Functioned as an endogenous miR-335-3p sponge | NR | RNA hybrid; ArrayStar, TargetScan, miRanda | [117] |
| | MCAO/R in mice | Mouse | Apoptosis | ↑ | circRNA_008018 | miR-99a | PI3K/AKT/GSK3b | Knockdown of circ_008018 attenuated cerebral I/R-induced brain tissue damage and neurological deficits in mice | Inhibits the transcriptional activity of miR-99a | NR | starBase v.2.0; circBase | [118] |
| | tMCAO/R in mice and mouse primary astrocytes under OGD/R condition | Human; mouse | Autophagy | ↑ | Hectd1 | miR-142 | TIPARP | Knockdown of circHectd1 expression significantly decreased infarct areas, attenuated neuronal deficits, and ameliorated astrocyte activation in tMCAO mice | Functions as an endogenous miR-142 sponge | NR | RNA hybrid; TargetScan | [119] |
| Tissues                  | Models                      | Species | Cell dysfunction                      | Expression | circRNA          | miRNA            | mRNA            | Function                                                      | Mechanism                                      | Relationship | Prediction tool                                      | Ref  |
|-------------------------|-----------------------------|---------|---------------------------------------|------------|------------------|------------------|------------------|--------------------------------------------------------------|-----------------------------------------------|--------------|------------------------------------------------------|------|
|                           |                             |         |                                       |            |                  |                  |                  | Apoptosis-related pathways; metabolism-related pathways; immune-related pathways | May function as a sponge for its targeted miRNAs |             | TargetScan; miRanda                                  | [115]|
| HT22 cells under OGD/R condition |                             | Mouse   | n/a                                   | ↑          | circRNA_015947   | miR-188-3p, miR-329-5p, miR-3057-3p, miR-5098, miR-683 | 99 target genes |                           |                                               |                                               |             |                                                      |      |
| HBMECs under OGD/R condition |                             | Human   | Proliferation; apoptosis; inflammation | ↑          | ANRIL            | miR-622          | p65 and IκBα     |                           | Overexpression of circANRIL significantly inhibited the proliferation of OGD/R-induced HBMECs and aggravated OGD/R-induced cell apoptosis | Served as an miR-622 sponge                   | NR           | Bioinformatics analysis                              | [120]|
| Hepatic I/R in mice       |                             | Mouse   | Inflammation                          | ↑          | mmu_circRNA_005186 | miR-124-3p       | Epha2            |                           | Serving as a mRNA sponge for miR-124-3p                 |                                               | NR           | Cytoscape software                                  | [128]|
| Renal HK-2 cells under I/R treatment |                             | Human   | Apoptosis; inflammation               | ↓          | YAPI             | miR-21-5p        | PI3K/AKT/mTOR     |                           | Sponge to miR-21-5p                                     |                                               | RC           | Circular RNA Interactome                             | [140]|
| Intestinal I/R in mice    |                             | Mouse   | n/a                                   | ↓          | circRNA_012412   | miR-7649-3p      | Sertad1          |                           | May play pivotal roles in endogenous protective signaling in iPoc |                                               | n/a          | TargetScan; miRanda; miRDB                           | [149]|
| Tissues | Models | Species | Cell dysfunction | Expression | circRNA | miRNA | mRNA | Function | Mechanism | Relationship | Prediction tool | Ref |
|---------|--------|---------|------------------|------------|---------|-------|------|----------|-----------|--------------|----------------|-----|
|         |        |         |                  | ↓          | circRNA_012412 | miR-3473c | Sertad1 |          |           |             |                |     |
|         |        |         |                  | ↓          | circRNA_012412 | miR-6991-3p | Nudcd1 |          |           |             |                |     |
|         |        |         |                  | ↓          | circRNA_012412 | miR-6991-3p | Jam2   |          |           |             |                |     |

↑: the upward arrow indicates increased expression of circRNAs; ↓: the downward arrow indicates decreased expression of circRNAs; n/a: not applicable; NR: circRNAs negatively regulate miRNAs; PR: circRNAs positively regulate miRNAs; RC: reciprocal correlations between circRNAs and miRNAs; circRNA: circular RNA; miRNAs: microRNAs; IRI: ischemia-reperfusion injury; NSCs: neural stem cells; HUVECs: human umbilical vein endothelial cells; HBMECs: human brain microvascular endothelial cells; tMCAO/R: transient middle cerebral artery occlusion/reperfusion; OGD/R: oxygen-glucose deprivation and reperfusion; H/R: hypoxia-reoxygenation; A/R: anoxia/reoxygenation; NCX1: sodium/calcium exchanger 1; MFACR: mitochondrial fission and apoptosis-related circRNA; ANRIL: antisense noncoding RNA in the INK4A locus; YAP1: yes-associated protein 1; TLK1: serine/threonine-protein kinase toseddi-like 1; Bcl2: B-cell lymphoma protein 2; HECTD1: HECT domain E3 ubiquitin protein ligase 1; CDIP1: cell death-inducing protein; MTP18: mitochondrial protein 18 kDa; RIPK1: receptor-interacting serine/threonine-protein kinase 1; EphA2: ephrin type-A receptor 2; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; Sertad1: SERTA domain-containing protein 1; Nudcd1: NudC domain-containing protein 1; Jam2: junctional adhesion molecule B; PKC: protein kinase C; ERK: mitogen-activated protein kinase; TIPARP: TCDD inducible poly(ADP-ribose) polymerase; GSK3B: glycogen synthase kinase 3 beta.
IRI [75]. The IncRNA autophagy-promoting factor (APF) mediates the conduction of autophagic-related signals in cardiomyocytes and competitively binds to miR-188-3p, thus indirectly upregulating the expression of ATG7 (Autophagy-related gene 7) and affecting autophagic cell death and MI [76]. Furthermore, Chen et al. [77] found that I/R induced a significant increase in miR-128 associated with a decrease in UCA1 and HSP70, which was reversed by morphine postconditioning treatment that also ameliorated infarct size and cell autophagy. This result suggested that morphine postconditioning treatment preserved myocardium from injury by mediating the UCA1/miR-128/HSP70 pathway.

Autophagy is actually a cell survival mechanism rather than a cell death process and can be activated by I/R-related conditions (e.g., energy deprivation, oxidative stress, and ER stress) [78]. However, uncontrolled autophagy ultimately leads to cell death and may contribute to I/R injury. Autophagy is involved in myocardial IRI through a dual regulation: protection of myocardial cell death during the myocardial ischemia stage and prevention of myocardial cell death during the myocardial reperfusion stage. Inhibition of autophagy has been shown to amplify I/R-induced damage [78,79], while pharmacologic stimulation of autophagy confers protection against I/R [80,81].

2.1.3. lncRNA-miRNA-mRNA Axis Regulates Necrosis of Cardiomyocytes in IRI. Distinct from the programmed process of apoptosis and autophagy, necrosis is an uncontrolled process that occurs randomly under the condition of overwhelming stress and contributes to the “accidental” death of the cell [2]. The IncRNA necrosis-related factor (NRF) functions by directly binding to miR-873 and regulates RIPK1/RIPK3 expression and necrosis. Necrosis in cardiomyocytes and MI induced by IRI is attenuated when the expression of NRF is knocked down. Furthermore, p53 regulates cell necrosis in the heart by targeting NRF, miR-873, and the RIPK1/RIPK3 axis in the necrotic cascades [82]. The death program of cytokine-induced necrosis in myocardial IRI was further aggravated when H19 was downregulated by RNA interference. Further research found that H19 decreased the necrotic cell death of cardiomyocytes by interfering with the expression of miR-103/107 that promoted cell necrosis in a cardiac model treated with H2O2 and in a myocardial IR mouse model by inhibiting the expression of FADD (Fas-associated protein with death domain) [83]. Further studies should explore how the H19-miR-103/107-FADD pathway is involved in the intricate necrotic cascade.

Necrosis is one of the main forms of cell death that is most prominent in the I/R heart. Cells can be driven to necrosis by I/R via the activation of at least three separate signaling pathways: necroptosis, mitochondrial permeability transition-dependent regulated necrosis, and parthanatos [84, 85]. Although these IncRNA-miRNA-mRNA axes mediate necrosis of cardiomyocytes in IRI, how these axes integrate into the complex necrotic cascade and the relationships with other necrotic-related factors remain to be studied.

2.1.4. lncRNA-miRNA-mRNA Axis Regulates Inflammation of Cardiomyocytes in IRI. The I/R-induced inflammatory response in most organs has been termed sterile inflammation because of the absence of microorganisms. However, similar to the response to all kinds of microorganism pathogens, sterile inflammation derived from IRI is characterized by the recruitment of peripheral immune cells to the injured tissue sites, accompanied with the production and release of cytokines and chemokines [86]. As discussed above, MALAT1 plays vital roles in I/R pathogenesis by mediating cell death. Some studies speculated that MALAT1 regulates the inflammatory response in myocardial IRI via targeting different targets. One of the first studies showed that MALAT1 upregulates NLRP3 inflammasome expression potentially by sponging miR-133 in the I/R-injured heart [87]. Moreover, Ruan et al. [88] speculated that MALAT1 may aggravate the inflammation response through regulating PTGS2 (Prostaglandin-endoperoxide synthase 2) by targeting miR-26b in myocardial IRI. MALAT1/miR-203 was also considered important in I/R by increasing cardiomyocyte inflammation and myocardial injury [89].

Inflammation plays a prominent role in the reperfusion component of total tissue injury in I/R, which is characterized by leukocyte trafficking to ischemic sites that occur primarily during reperfusion, and I/R-induced leukocyte infiltration contributes to a large number of pathologic processes [86]. Furthermore, leukocyte endothelial cell adhesive interactions, which precipitate the microvascular complications and tissue injury induced by reperfusion, are one of the earliest signs of tissue dysfunction and injury elicited by I/R [90, 91]. Multiple factors are involved in the dynamic regulation of inflammation in myocardial IRI upon AMI, and thus inhibition of the inflammatory response may be a potential therapeutic strategy [92]. Therefore, it may be possible to reduce or prevent the production of IRI by interfering with the inflammatory response produced by these axes.

2.2. Brain. Acute ischemic stroke (AIS) is a pathological process that starts with local cerebral vascular occlusion and is accompanied by a series of changes in cellular behaviors, leading to sudden local brain dysfunction [93]. The effective treatment for AIS is to restore blood flow, which can lead to reperfusion injury. Cerebral IRI often occurs in stroke and cardiac arrest and induces neuronal damage. Increasing evidence demonstrates that ischemia is often associated with a series of neurological disorders, such as hypoxia, oxidative stress, and inflammatory responses, which eventually lead to acute necrosis, apoptosis, and autophagy of ischemic brain cells [94]. In recent years, ncRNAs were found to play important roles in physiopathological processes related to stroke (see Table 3 for a summary of the studies on IncRNAs-miRNAs-mRNAs in cerebral IRI).

2.2.1. lncRNA-miRNA-mRNA Axis Regulates Apoptosis of Nerve Cells in IRI. In cerebral IRI, the main mechanism of brain injury mainly involves apoptosis of nerve cells. MALAT1 and TUG1 may exhibit similar roles in cerebral IRI. MALAT1 and TUG1 were significantly upregulated in both a middle cerebral artery occlusion/reperfusion...
| Models                                                                 | Species                        | Cell dysfunction | Expression | IncRNA   | miRNA    | mRNA     | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool                        | Ref         |
|----------------------------------------------------------------------|-------------------------------|-----------------|------------|----------|----------|----------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|-----------------------------------------|-------------|
| MCAO/R in mice and mice primary astrocytes under OGD/R condition    | Mouse                         | Apoptosis       | ↑          | MALAT1   | miR-145  | AQP4     | Knockdown of MALAT1 increased cell viability and reduced cell apoptosis in MA-C cells | miR-145 was identified as a potential target of MALAT1                  | NR           | starBase; TargetScan                  | [95]        |
| Mouse primary BMECs under OGD/R condition                            | Mouse                         | Autophagy       | ↑          | MALAT1   | miR-26b  | ULK2     | MALAT1 promoted BMEC autophagy and survival under OGD/R condition        | MALAT1 served as a ceRNA by sponging miR-26b                           | NR           | IncRNA database v2.0; miRDB            | [107]       |
| MCAO/R in mice and mice primary cortical neurons under OGD/R condition| Mouse                         | Autophagy       | ↑          | MALAT1   | miR-30a  | Beclin1  | Downregulation of MALAT1 suppressed ischemic injury and autophagy in vitro and in vivo | May serve as a molecular sponge for miR-30a                             | NR           | RNA hybird; starBase v.2.0            | [108]       |
| MCAO/R in mice and primary mouse astrocytes under OGD/R condition    | Mouse                         | Apoptosis       | ↑          | TUG1     | miR-145  | AQP4     | Knockdown of TUG1 decreased lactate dehydrogenase levels and the ratio of apoptotic cells and promoted cell survival in vitro and reduced the infarction area and cell apoptosis in I/R mouse brains in vivo | May function as a ceRNA for miR-145                                   | NR           | Bioinformatic analysis                | [96]        |
| tMCAO/R in rats and PC-12 cells under OGD/R condition                | Rat                           | Proliferation; apoptosis; inflammation | ↑          | H19      | miR-138-5p | p65      | H19 promotes inflammatory response and improved neurological function in tMCAO rat model | Negatively regulated miR-138-5p expression                             | NR           | n/a                                    | [97]        |
| MCAO/R in mice and N2a cells under OGD/R condition                   | Mouse                         | Apoptosis       | ↑          | H19      | miR-148a-3p | Rock2    | IncRNA-H19 altered OGD/R-induced oxidative stress                         | May act as a molecular sponge of miR-148a-3p                           | NR           | starBase                               | [99]        |
| MCAO/R in rats and neuronal cells under OGD/R condition              | Human; rats                   | Apoptosis       | ↑          | H19      | miR-19a  | Id2      | Knockdown of H19 alleviated cell apoptosis, significantly decreased neurological deficit, brain infarct volume, and neuronal apoptosis | miR-19a directly binds to H19                                         | NR           | starBase 2.0                           | [98]        |
| Models                                      | Species   | Cell dysfunction | Expression | IncRNA     | miRNA      | mRNA          | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool | Ref     |
|---------------------------------------------|-----------|------------------|------------|------------|------------|----------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|---------------|---------|
| MCAO/R in mice and N2a cells under OGD/R condition | Mouse     | Apoptosis        | ↓          | Rian       | miR-144-3p | GATA3          | Overexpression of Rian could inhibit the cell apoptosis induced by OGD and distinctly reduce the infarct size | miR-144-3p directly interacts with Rian | NR           | DIANA online tools | [100]   |
| MCAO/R in rats and SK-N-SH and SH-SY5Y cells under OGD/R condition | Rat       | Pyroptosis       | ↑          | MEG3       | miR-485    | AIM2           | Knockdown of MEG3 inhibited OGD/R-induced pyroptosis and inflammation, and inhibited Caspase-1 signaling and decreased the expression of AIM2, ASC, cleaved-Caspase-1 and GSDMD-N | Acted as a molecular sponge to suppress miR-485 | NR           | n/a            | [114]   |
| MCAO/R in mice and N2a cells under OGD/R condition | Mouse     | Apoptosis        | ↑          | MEG3       | miR-21     | PDCD4          | Knockdown of MEG3 protects against ischemic damage and improves overall neurological functions in vivo | Functions as a ceRNA for directly binding to miR-21 | NR           | InCeDB         | [144]   |
| N2a cells under OGD/R condition            | Mouse     | Apoptosis        | ↑          | Gm11974    | miR-766-3p | NR3C2          | Knockdown of IncRNA Gm11974 alleviated the apoptosis induced by OGD and cell death rates were significantly reduced | Could negatively regulate the expression of miR-766-3p | NR           | Bioinformatics software | [101]   |
| MCAO/R in mice and N2a cells under OGD/R condition | Mouse     | Apoptosis        | ↑          | Oprm1      | miR-155    | GATA3          | Overexpression of IncRNA Oprm1 alleviated the apoptosis induced by OGD and distinctly decreased infarct size | miR-155 is a direct target of IncRNA Oprm1 | NR           | TargetScan     | [102]   |
| tMCAO/R in mice and N2a cells under OGD/R condition | Human; mouse | Autophagy       | ↑          | KCNQ1OT1   | miR-200a   | FOXO3/ATG7     | Knockdown of KCNQ1OT1 remarkably reduced the infarct volume and neurological impairments in tMCAO mice and might inhibit I/R-induced autophagy and increase cell viability | Acted as a ceRNA of miR-200a | NR           | Lncbase        | [109]   |
| Mice primary cortical neurons under OGD/R condition | Mouse     | Apoptosis        | ↑          | KCNQ1OT1   | miR-9      | MMP8           | KNCNQ1OT1 regulates OGD/R-induced injury in cultured primary cortical neurons via modulating miR-9/MMP8 axis as a ceRNA | Directly binds to miR-9 | NR           | Bioinformatic analysis | [106]   |
| MCAO/R in mice and N2a cells under         | Mouse     | Apoptosis        | ↑          | AK038897   | miR-26a-5p | DAPK1          | AK038897 knockdown protected against MCAO/R-induced brain injury and neurological deficits in vivo | Functions as a ceRNA for miR-26a-5p | NR           | starBase; TargetScan | [103]   |
| Models                        | Species     | Cell dysfunction       | Expression | lncRNA | miRNA  | mRNA | Function                                                                 | Mechanism                                                                 | Relationship                  | Prediction tool       | Ref         |
|------------------------------|-------------|------------------------|------------|--------|--------|------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|----------------------|-------------|
| OGD/R condition MCAO/R in    | Mouse       | Apoptosis ↑            | CHRF       | miR-126| SOX6   |      | CHRF knockdown in vivo markedly prevented ischemic damage and alleviated neurological dysfunctions | Played as a ceRNA to direct binding with miR-126                              | NR                  | TargetScan [104] |
| mice and N2a cells under     |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |
| OGD/R condition              |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |
| SH-SY5Y cells under OGD/R    | Human       | Apoptosis ↓            | SNHG16     | miR-106b-5p | LIMK1 |      | In lncRNA SNHG16 promoted OGD/R-induced SH-SY5Y cell survival and suppressed its apoptosis and Caspase-3 activity | Directly targeted miR-106b-5p                                             | NR                  | starBase; MiRTarBase [105] |
| condition                    |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |
| MCAO/R in rats and PC-12     | Rat         | Inflammation ↑         | SNHG14     | miR-136-5p | ROCK1 |      | Interference of SNHG14 by shRNA vector enhanced neuron survival and suppressed inflammation in response to OGD/R insult. SNHG14 promoted neurological impairment and inflammatory response | Acting as a sponge of miR-136-5p                                          | NR                  | starBase [113]      |
| cells under OGD/R condition  |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |
| N2a cells under OGD/R condition | Mouse     | Proliferation; apoptosis ↑ | SNHG12     | miR-199a | SIRT1 |      | Knockdown SNHG12 inhibited cell proliferation under OGD/R condition       | SNHG12 blocks the expression of miR-199a                                     | NR                  | http://microRNA.org [110] |
| Mouse primary BMECs under    | Mouse       | Cell death; inflammation ↑ | SNHG12     | miR-199a | n/a   |      | Overexpression of SNHG12 inhibited BMEC death and the inflammatory response but promoted angiogenesis after OGD/R | Directly targets miR-199a                                                   | NR                  | miRcode [111]       |
| OGD/R condition              |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |
| Mouse primary BMECs under     | Mouse       | Cell death; migration   ↑ | SNHG1       | miR-199a | HIF-1α; VEGF |      | Promoted BMEC survival under OGD/R condition, and angiogenesis after OGD/R treatment | Snhg1 targets miR-199a by binding to complementary miR-199a seed regions     | NR                  | miRDB [112]         |
| OGD/R condition              |             |                        |            |        |        |      |                                                                          |                                                                                |                               |                      |             |

↑: the upward arrow indicates increased expression of lncRNAs; ↓: the downward arrow indicates decreased expression of lncRNAs; n/a: not applicable; NR: lncRNAs negatively regulate miRNAs; PR: lncRNAs positively regulate miRNAs; RC: reciprocal correlations between lncRNAs and miRNAs; tMCAO/R: transient middle cerebral artery occlusion/reperfusion; BMECs: brain microvascular endothelial cells; ceRNA: competing endogenous RNA; Rian: RNA imprinted and accumulated in nucleus; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; TUG1: taurine-upregulated gene 1; MEG3: maternally expressed gene 3; CHRF: cardiac hypertrophy-related factor; HOTAIR: HOX transcript antisense RNA; SNHG1/12/14/16: small nucleolar RNA host gene 1/12/14/16; LIMK1: the LIM motif-containing protein kinase family-contained LIM kinase 1; KCNQ1 opposite strand/antisense transcript 1; MMP-8: matrix metalloproteinase-8; Id2: inhibitor of DNA binding/differentiation 2; GATA3: GATA-binding protein 3; ULK2: Unc-51-like kinase 2; AQP4: aquaporin 4; Rock2: Rho-associated protein kinase 2; AIM2: absent in melanoma 2; SOX6: sex-determining region Y box 6; HIF-1α: hypoxia inducible factor-1α; VEGF: vascular endothelial growth factor; SIRT1: sirtuin 1; GATA3: GATA-binding protein 3; ROCK1: Rho-associated coiled-coil-containing protein kinase 1; FOXO3: forkhead box O3; ATG7: autophagy-related gene 7; DAPK1: death-associated protein kinase 1; NR3C2: nuclear receptor subfamily 3 group C member 2. 

Table 3: Continued.
(MCAO/R) model and an OGD/R model, and knockdown of both lncRNAs increased cell viability and reduced apoptosis. Furthermore, MALAT1 and TUG1 promote cerebral IRI by targeting miR-145/AQP4, which may be a potential treatment strategy for ischemic stroke [95, 96]. A previous report showed that the H19/miR-138-5p/p65 axis critically regulates inflammation and neurological function in cerebral IRI. H19 inhibited cell proliferation, increased cell apoptosis, and aggravated inflammation after OGD/R stimulation in vitro. And H19 also deteriorated inflammation and neurological function in a transient middle cerebral artery occlusion (tMCAO) rat model in vivo [97]. The H19/miR-19a/Id2 axis regulates hypoxia-induced neuronal apoptosis, and inhibition of this axis may serve as a novel therapeutic strategy for ischemic brain injury [98]. Previous reports have established a role and mechanism of metformin in shock-related brain injury [99]. Zeng et al. [99] found that H19 modulated oxidative stress under OGD/R by binding to miR-148a-3p to upregulate Rock2 (Rho-associated protein kinase 2) expression, which was reversed by metformin. The study ultimately showed that metformin plays a neuroprotective role by regulating ischemic stroke-induced oxidative stress injury through H19/miR-148a-3p/Rock2. In addition, upregulation of Rian reduced the OGD-induced N2a cell apoptosis, reduced the miR-144-3p/GATA3-mediated infarct size, and ameliorated the neurological score [100]. Other signal axes mediate brain damage by affecting neuronal apoptosis, including the Rian/miR-144-3p/GATA3, Gm11974/miR-766-3p/NR3C2, Otmp1/miR-155/GATA3, AK038897/miR-26-5p/DAPK1, CHRF/miR-126/SOX6, SNHG16/miR-106b-5p/LIMK1, and KCNQ1OT1/miR-9/MMP-8 axes [100–106].

2.2.2. lncRNA-miRNA-mRNA Axis Regulates Autophagy of Nerve Cells in IRI. By regulating the miR-26b/ULK2 and miR-30a/Beclin1 pathways, MALAT1 promoted OGD/R-induced nerve cell autophagy and ischemic injury [107, 108]. Yu et al. [109] showed that the lncRNA KCNQ1OT1 promotes I/R-induced autophagy and reduces cell viability by regulating the miR-200a/FOXO3/ATG7 axis. Furthermore, KCNQ1OT1 was significantly increased in the plasma of patients with AIS, and its expression was positively correlated with the severity of stroke, which implied that KCNQ1OT1 may be a diagnostic biomarker or severity evaluation indicator.

2.2.3. lncRNA-miRNA-mRNA Axis Regulates Inflammation of Nerve Cells in IRI. SNHG12 (Small nucleolar RNA host gene 12)/miR-199a inhibits BMECs and N2a cell death and the inflammatory response and promotes angiogenesis after OGD/R by targeting different mRNAs [110, 111]. Interestingly, SNHG1/miR-199a promoted BMEC survival, migration, and tube formation under OGD/R by elevating the expression of HIF-1α and VEGF [112]. In addition, the SNHG14 (Small nucleolar RNA host gene 14)/miR-136-5p/Rock1 axis contributed to neurological impairment and inflammatory response in cerebral ischemia stroke [113]. Some small nucleolar RNA host genes (SNHG) and miR-199a are important mediators in cerebral IRI. Furthermore, MEG3 promoted pyroptosis and inflammation under OGD/R and facilitated Caspase-1 signaling by binding miR-485 to increase AIM2 expression [114].

2.2.4. circRNA-miRNA-mRNA Axis in Brain IRI. Lin et al. [115] explored the potential function of circRNAs in the etiopathogenesis of cerebral IRI. The authors investigated the expression profiles of circRNAs between HT22 cells with OGD/R and controls using a circRNA microarray. The results showed that 15 circRNAs were markedly altered in the OGD/R model group. The authors selected mmu-circRNA-015947 for further verification by qRT-PCR. Bioinformatics analysis showed that mmu-circRNA-015947 could bind with miRNAs (mmu-miR-188-3p, mmu-miR-329-5p, mmu-miR-3057-3p, mmu-miR-5098, and mmu-miR-683) and thereby elevate the expression of target genes. This research indicates that increasing the level of mmu-circRNA-015947 might contribute to the process of cerebral IRI and provides a potential strategy for clinical treatment. In addition, three circRNAs (cZNF292, TLK1, and circ_008018) were significantly increased in the MCAO/R mouse model and mouse neurons under OGD/R and knockdown of the circRNAs attenuated neuronal injury during cerebral I/R. These effects were related to cell apoptosis mediated by targeting miR-22/Wnt/b-catenin (under OGD/R), miR-335-3p/TIPARP (under OGD/R and cerebral I/R), and miR-99a/Pi3k/Akt/GSK3β (cerebral I/R) [116–118]. Furthermore, the expression levels of circTLK1 in patients with AIS were notably increased in comparison with healthy controls. Interestingly, the expression levels of circTLK1 in plasma from patients with stroke were associated with lesion localization and infarct volumes [117]. Han et al. [119] found that the levels of circHECTD1 were elevated in tMCAO mouse stroke models and in plasma of AIS patients. Knockdown of circHECTD1 contributed to reduction in infarct areas, attenuation of neuronal deficits, and amelioration of astrocyte activation via mediating autophagy in tMCAO mice through miR-142/TIPARP. Thus, circHECTD1 was considered a new biomarker and therapeutic target for stroke. Jiang et al. [120] found that an upregulated circRNA, antisense noncoding RNA in the INK4A locus (circANRIL), inhibited OGD/R-induced HBMEC proliferation and promoted cell apoptosis and phosphorylation of p65 and IκBα, which were abrogated by miR-622. These results demonstrated that circANRIL aggravated OGD/R-induced injury in HBMECs by mediating the NF-κB pathway through sponging miR-622.

2.3. Liver

2.3.1. lncRNA-miRNA-mRNA Axis Regulates Apoptosis of Hepatocytes in IRI. Liver IRI, which occurs in hemorrhagic shock, resection, and transplantation, starts with local ischemic insult, followed by inflammation-mediated reperfusion injury [121] (see Table 4 for a summary of the studies of lncRNAs-miRNAs-mRNAs in other diseases with IRI). A recent study investigated the role of the lncRNA Gm4419 in hepatic I/R [122]. The authors found that Gm4419 was upregulated in hepatic IRI rats, and knockdown of Gm4419 aggravated I/R-induced liver damage in hepatic IRI rats.
| Tissues       | Models                                                                 | Species | Cell dysfunction | Expression | IncRNA    | miRNA    | mRNA     | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool                  | Ref     |
|--------------|------------------------------------------------------------------------|---------|------------------|------------|-----------|-----------|----------|----------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|----------------------------------|---------|
| Hepatic      | I/R in rats and BRL-3-A cells under H/R treatment                      | Rats    | Apoptosis        | ↑          | Gm4419    | miR-455   | SOX6     | Knockdown of Gm4419 alleviated I/R-induced liver damage and alleviated H/R-induced apoptosis | Could sponge miR-455                                                   | NR           | miRDB; TargetScan                | [122]   |
|              | IRI in mice and mice primary hepatocytes under H2O2 treatment           | Mouse   | Autophagy        | ↑          | HOTAIR    | miR-20b-5p| ATG7     | Knockdown of the expression of HOTAIR attenuated autophagy induced by hydrogen peroxide | Function as ceRNA for miR-20b-5p                                         | NR           | TargetScan; starBase             | [127]   |
|              | H/R in mice and HL7702 under H/R treatment                             | Mouse   | Apoptosis        | ↓          | MEG3     | miR-34a   | Nrf2     | MEG3 overexpression could improve hepatic function of I/R mice, and markedly decreased the expression of serum ALT and AST | Functioned as a ceRNA for miR-34a                                       | NR           | DIANA tools                      | [123]   |
|              | IRI in mice and BNL-CL.2 cells under H/R treatment                     | Mouse   | Apoptosis        | ↑          | AK054386  | miR-199   | CHOP     | Increased expression of AK054386, which might be mediated by activated NF-kB, resulted in sustained ERS and increased cell apoptosis and death in hepatic I/R mouse and cellular models | Acted as a ceRNA of miR-199                                             | NR           | RNA22                            | [124]   |
| Renal        | I/R in mice and HK-2 cells under H/R treatment                         | Human; mouse | Apoptosis    | ↑          | GAS5     | miR-21    | TSP-1    | GAS5 facilitated apoptosis in renal I/R injury                               | Competitively sponging miR-21                                           | RC           | n/a                              | [134]   |
|              | IRI in rats and HK-2 cells under OGD/R treatment                       | Rats    | Inflammation; apoptosis | ↑          | TUG1     | miR-449b-5p| HMGB1; MMP2 | TUG1 silencing attenuates I/R-induced inflammation and apoptosis | miR-449b-5p was a direct target of TUG1                                  | NR           | starBase                         | [137]   |
|              | HK-2 cells under H/R treatment                                         | Human; rat | Apoptosis    | ↑          | NEAT1    | miR-27a-3p| n/a      | Repression the expression of NEAT1 decreased CoCl2-induced injury in HK-2 | NEAT1 was a direct target of miR-27a-3p and miR-27a-3p was a direct target of NEAT1 | RC           | TargetScan; starBase; http://microRNA.org | [136]   |
|              | IRI in mice                                                             | Mouse    | Proliferation   | ↑          | MALAT1   | miR-139-5p| SPRR2F, SPRR1A, MMP-10 | Noncoding RNAs MALAT1 and miR-139-5p were involved in IRI | n/a                                      | NR           | n/a                              | [133]   |
| Tissues                  | Models                                                                 | Species                  | Cell Dysfunction | Expression | IncRNA | miRNA     | mRNA  | Function                                                                 | Mechanism                                                                 | Relationship | Prediction tool                                                                 | Ref         |
|-------------------------|------------------------------------------------------------------------|--------------------------|------------------|------------|--------|-----------|-------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------|-------------|
| IRI in rats and HK-2 cells under H/R treatment | Human; rats                                                           | Apoptosis                | ↑                | LINC00520  | miR-27b-3p | OSMR   | Knockdown of LINC00520 reduced acute renal injury both in vitro and in vivo | LINC00520 binds to miR-27b                                              | NR           | Cytoscape software                                                            | [139]       |
| AKI in rats and HK-2 cells under CoCl2 treatment | Human; rats                                                           | Proliferation; apoptosis | ↑                | XIST       | miR-142-5p | PDCD4  | Knockdown of PDCD4 rescued the effects of CoCl2 on the proliferation and apoptosis of HK-2 cells | miR-142-5p was a target of XIST                                          | NR           | Bioinformatic analysis                                                           | [138]       |
| IRI in mice and GC-1 spermatogenic cells under OGD/R treatment | Mouse                                                                  | Apoptosis; proliferation | ↑                | MALAT1     | miR-214   | TRPV4  | MALAT1 promotes cell apoptosis and suppresses cell proliferation in vitro and in vivo | Directly binds to miR-214                                               | NR           | LncBase experimental v.2 database                                                |             |
| Intestinal IRI in mice | Mouse                                                                  | Proliferation            | n/a              | H19        | miR-675   | ZO-1/E-cadherin | H19 overexpression resulting in the dysfunction of the epithelial barrier | Serving as a precursor for miR-675                                      | PR           | n/a                                                                            | [148]       |
| Retinal I/R in mice and newborn mouse primary RGCs under ischemic treatment | Mouse                                                                  | Apoptosis                | ↑                | Mbd2-AL1   | miR-188-3p | Traf3  | Mbd2-AL1 mediates I/R-induced RGC apoptosis                                | Sponged miR-188-3p                                                     | NR           | RegRNA                                                                        | [142]       |
| I/R in mice and neonatal mouse primary retinal microglia and RGCs under OGD/R treatment | Mouse                                                                  | Pyroptosis; apoptosis; inflammation | ↑                | H19        | miR-21    | PDCD4  | Increased IncRNA-H19 expression significantly promotes NLRP3/6 inflammasome imbalance and results in microglial pyroptosis, cytokine overproduction, and neuronal death | Functioned via sponging miR-21                                         | NR           | n/a                                                                            | [143]       |
| Spinal cord I/R in rats and SH5Y-SY cells under OGD/R treatment | Rat                                                                    | Apoptosis                | ↓                | CasC7      | miR-30c   | Beclin1 | Knockdown of CasC7 could promote cell apoptosis and downregulate miR-30c target gene expression | Functioned as a miR-30c decoy                                          | NR           | n/a                                                                            | [146]       |
| IRI in rats and HN neuronal cells under | Rat                                                                    | Apoptosis                | ↓                | MALAT1     | miR-204   | Bcl2   | Knockdown of MALAT1 increased cell apoptosis                               | Overexpression of MALAT1 downregulated miR-204                          | NR           | n/a                                                                            | [147]       |
Table 4: Continued.

| Tissues | Models | Species | Cell Dysfunction | Expression | lncRNA | miRNA | mRNA | Function | Mechanism | Relationship | Prediction tool | Ref |
|---------|--------|---------|------------------|------------|--------|-------|------|----------|-----------|--------------|----------------|-----|
| OGD/R treatment | ↑: the upward arrow indicates increased expression of lncRNAs; ↓: the downward arrow indicates decreased expression of lncRNAs; n/a: not applicable; NR: lncRNAs negatively regulate miRNAs; PR: lncRNAs positively regulate miRNAs; RC: reciprocal correlations between lncRNAs and miRNAs; IRE: ischemia-reperfusion injury; AKI: acute kidney injury; H/R: hypoxia-reoxygenation; ceRNA: competing endogenous RNA; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; TUG1: taurine-upregulated gene 1; Mbd2-AL: methyl-CpG-binding domain protein 2-associated long noncoding RNA 1; GAS5: growth arrest specific 5; MEG3: maternally expressed gene 3; HOTAIR: HOX transcript antisense RNA; NEAT1: nuclear paraspeckle assembly transcript 1; CasC7: cancer susceptibility candidate 7; TRPV4: transient receptor potential vanilloid 4; SPRR2F: small proline-rich protein 2F; SPRR1A: small proline-rich protein 1A; MMP-2/10: matrix metalloproteinase-2/10; CHOP: C/EBP homologous protein; HMGB1: high-mobility group box 1; Bcl2: B-cell lymphoma-2; TRAIL: tumor necrosis factor (TNF) receptor-associated factor 3; XIST: X chromosome inactivation; PDCD4: programmed cell death 4; TSP-1: thrombospondin 1; ZO-1: zonula occludens 1; Nrf2: nuclear factor erythroid 2-related factor; ATG7: autophagy-related gene 7; Bax: B-cell lymphoma protein 2- (Bcl2-) associated X; Bcl2: B-cell lymphoma protein 2; SOX6: sex-determining region Y box 6; OSMR: oncostatin M receptor β. |
Gm4419 promoted H/R-induced apoptosis by sponging miR-455 and regulating SOX6 in BRL-3A cells. Therefore, Gm4419 accelerated hepatic IRI by interacting with the miR-455/SOX6 axis. Huang et al. [123] reported that the expression levels of MEG3 and Nrf2 were decreased in hepatic I/R mice and in HL7702 cells with H/R treatment, while miR-34a was increased. Overexpression of MEG3 inhibited apoptosis and affected the production of ROS in vitro, which was abrogated by miR-34a inhibitor treatment. MEG3 overexpression ameliorated the hepatic function of hepatic I/R mice and significantly reduced the level of serum ALT and AST. These results indicated that MEG3 protected hepatocytes from hepatic IRI through miR-34a/Nrf2. Furthermore, Dai et al. [124] found that the levels of AK054386, miR-199, and CHOP (C/EBP homologous protein) were elevated, decreased, and elevated in hepatic IRI models, respectively. Overexpression of AK054386 promoted cell apoptosis in the BNL-CL2 IRI cell model and CHOP expression, which were rescued by miR-199 overexpression. These results suggest that AK054386 plays a crucial role in hepatic IRI via miR-199 by mediating the ERS pathway.

2.3.2. lncRNA-miRNA-mRNA Axis Regulates Autophagy of Hepatocytes in IRI. Autophagy has been proven to be involved in hepatic IRI [125, 126]. Liver IRI induces elevated levels of HOTAIR and ATG7 and increases autophagy, which is attenuated by the knockdown of HOTAIR. In addition, HOTAIR acts as a ceRNA for miR-20b-5p and increases the expression of ATG7. These results indicated that the HOTAIR/miR-20b-5p/ATG7 axis plays a crucial role in hepatic IRI via autophagy [127].

2.3.3. circRNA-miRNA-mRNA Axis in Liver IRI. Zhang et al. [128] first examined circRNA expression profiles during hepatic IRI by microarray hybridization analysis and found that circRNAs are closely associated with hepatic IRI and ischemic postconditioning (IPO). The analyses revealed that the expression of 1599 circRNAs was altered, including 213 upregulated and 493 downregulated circRNAs, between the I/R group and the control group. In a comparison of the IPO group with the I/R group, the results revealed that 641 circRNAs were upregulated and 252 circRNAs were downregulated. Moreover, the ceRNA network, including 6 circRNAs, 47 miRNAs, and 90 mRNAs, illustrated that the "housekeeping" function of circRNAs is abnormally regulated in hepatic IRI. The mmu_circRNA_005186/miR-124-3p/Epha2 axis was chosen for further study after qRT-PCR validation. Silencing of mmu_circRNA_005186 moderated lipopolysaccharide-induced inflammation by elevating miR-124-3p and reducing Epha2, which suggests that the mmu_circRNA_005186/miR-124-3p/Epha2 axis might play an important role in hepatic IRI.

2.4. Kidney

2.4.1. lncRNA-miRNA-mRNA Axis in Renal IRI. Renal IRI, which contributes greatly to AKI, is one of the most critical issues for many clinical situations, including renal transplantation, nephrectomy, sepsis, and repair of suprarenal aneu-
ultimately, four pathways, circRNA_012412/miR-7649-3p/Sertad1 (SERTA domain-containing protein 1), circRNA_012412/miR-3473c/Sertad1, circRNA_012412/miR-6991-3p/Nudcd1 (NudC domain-containing protein 1), and circRNA_012412/miR-6991-3p/Jam2 ( Junctional adhesion molecule B), were constructed based on the TargetScan, miRanda, and miRDB databases. These circRNA regulatory pathways may be closely associated with endogenous protective signaling in IPO during intestinal I/R and warrant further investigation. The study was the first to fully describe the circRNA expression profiles during intestinal I/R, and the results showed that IPO was associated with altered circRNAs, which provides a new perspective to clarify how IPO protects against intestinal IRI.

2.5.2. lncRNA-miRNA-mRNA Axis in Testicular IRI. Li et al. [145] examined the potential role of MALAT1 in testicular IRI. The authors demonstrated that the expression level of MALAT1 in animal testis samples and GC-1 cells was elevated. Overexpression of MALAT1 promoted apoptosis and inhibited proliferation as testicular IRI progressed. Furthermore, MALAT1 inhibited expression of miR-214 and positively regulated TRPV4 (Transient receptor potential vanilloid 4) expression. These results indicated that the MALAT1/miR-214/TRPV4 axis plays an important role in testicular IRI by mediating cell apoptosis and proliferation.

2.5.3. lncRNA-miRNA-mRNA Axis in Spinal Cord IRI. Liu et al. [146] found that inhibition of the lncRNA cancer susceptibility candidate 7 (CasC7) promoted cell apoptosis in SH55-Y-SY cells under OGD/R treatment and increased infarct size in spinal cord IRI rats through miR-30c/Bclin1, which was reversed by NaSH preprocessing. The study concluded that hydrogen sulfide saves the spinal cord from IRI by the CasC7/miR-30c/Bclin1 axis. The expression of MALAT1 and Bcl2 was suppressed while miR-204 was upregulated in a rat spinal cord IRI model and hypoxia-induced neurocyte lines [147]. Furthermore, knockdown of MALAT1 promoted cell apoptosis, which was associated with downregulation of Bcl2 and upregulation of miR-204. MALAT1-treated spinal cord IRI rats also showed lower motor deficit index scores. Therefore, these results indicated that MALAT1 plays a neuroprotective role in spinal cord IRI rats by binding miR-204/Bcl2.

2.5.4. lncRNA/circRNA-miRNA-mRNA Axis in Intestinal IRI. Zhou et al. [148] revealed that H19 overexpression increased the level of miR-675, which in turn inhibited the expression of ZO-1 (Zonula occludens 1) and E-cadherin, leading to dysfunction of the epithelial barrier. These effects were reversed by upregulation of the RNA-binding protein HuR in H19-overexpressing cells. These results revealed that H19 and HuR act upon each other, and H19 mediates the intestinal epithelial barrier function via the miR-675/ZO-1/E-cadherin axis. Feng et al. [149] explored the expression profiles of circRNAs after intestinal I/R with or without IPO and investigated the underlying mechanisms of IPO associated with the altered circRNAs. The authors identified 62 circRNAs and 521 mRNAs differentially expressed in the intestinal I/R group compared with the sham group, as well as 33 circRNAs and 303 mRNAs that were altered between the IPO group and I/R group. Two circRNAs, circRNA_012412 and circRNA_016863, were identified as closely related to the protective mechanisms of IPO. Ultimately, four pathways, circRNA_012412/miR-7649-3p/Sertad1 (SERTA domain-containing protein 1), circRNA_012412/miR-3473c/Sertad1, circRNA_012412/miR-6991-3p/Nudcd1 (NudC domain-containing protein 1), and circRNA_012412/miR-6991-3p/Jam2 ( Junctional adhesion molecule B), were constructed based on the TargetScan, miRanda, and miRDB databases. These circRNA regulatory pathways may be closely associated with endogenous protective signaling in IPO during intestinal I/R and warrant further investigation. The study was the first to fully describe the circRNA expression profiles during intestinal I/R, and the results showed that IPO was associated with altered circRNAs, which provides a new perspective to clarify how IPO protects against intestinal IRI.

3. Conclusions and Future Perspectives

Over the past few decades, ncRNAs have been found to play complex roles in the development and gene regulatory processes of many diseases. However, understanding of the mechanisms of lncRNAs and circRNAs in different organs and dysfunctional states and their potential as therapeutic targets or diagnostic markers of IRI is still in its infancy. Furthermore, the interactions of the lncRNAs/circRNAs-miRNAs-mRNAs are complex and dynamic. First, a specific lncRNA or circRNA plays a variety of roles in IRI of different organs by targeting different miRNAs/mRNAs. The expression levels of lncRNAs and circRNAs in animal and cell models seem to be similar as in patient serum and were associated with the severity of the disease, providing evidence for clinical diagnosis and prognosis. Second, the same lncRNA or circRNA can play a contradictory role in IRI of the same organ, potentially contributing to other molecules in response to stress conditions. For example, H19 showed opposite expression levels and effects in myocardial IRI, and future studies should investigate the various regulatory mechanisms. Third, some lncRNAs and circRNAs can target the same miRNAs/mRNAs in different organs. For instance, MEG3 and H19 both performed their functions in cerebral IRI and in retinal IRI, respectively, by sponging miR-21 and targeting PDCD4 to mediate cell apoptosis [143, 144]. Finally, some drugs and treatments play an important role in IRI through the functions of these axes. For example, metformin protects against oxidative stress injury in cerebral IRI by affecting the H19/miR-148a-3p/Rock2 axis [99], while the cardioprotective effects of fentanyl in cardiac IR appeared to be abrogated by the MALAT1/miR-145/Bnip3 axis [22]. Furthermore, IPO can attenuate liver IRI and exhibit significant intestinal protection through circRNAs-miRNAs-mRNAs [128, 149], and the renal protection of delayed IPC involves preconditioning-induced upregulation of miR-21 and downregulated expression of GASS and TSP-1 [134]. Although these studies have shown some benefit, they have not been able to identify a specific effective protocol of IPC/IPO for a clinical study, perhaps because it has been very difficult to systematically illuminate the underlying complex mechanisms of ncRNAs. Therefore, further investigations focusing on revealing the specific molecular mechanisms of ncRNAs in the development of IRI and abnormal conditions are needed.
Although cardiac magnetic resonance imaging remains the gold standard to assess the consequences of acute IRI in AMI patients in terms of MI size and adverse left ventricular remodeling, this technique is limited in terms of ease of access and availability of skilled personnel [150]. However, the presence of ncRNAs in the serum plasma has suggested that these molecules may serve as biomarkers in AMI patients or patients with myocardial IRI [34, 41, 117, 119, 151]. Although plasma contains RNases, circulating ncRNAs, especially IncRNAs, have been shown to be stable in this environment, which indicates that they are relatively resistant to nucleolytic degradation and making them potentially useful as circulating biomarkers for AMI. Furthermore, ncRNA or the antisense molecules may be delivered to the ischemic heart using several approaches including intravenous or intramyocardial injections or carriers such as viruses, nanoparticles, or exosomes. Zhang et al. [152] found that hypoxia modified the expression of several miRNAs in exosomes secreted by H9c2 cells, and these exosomal miRNAs protected H9c2 cells against simulated IRI and prevented apoptosis through HIF-1, TNF, MAPK, and mTOR signaling pathways. Some miRNAs or IncRNAs that are downregulated following AMI are known to be beneficial for cardioprotection, and one therapeutic strategy is to deliver ncRNA mimics targeting these miRNAs or IncRNAs to the ischemic heart. Furthermore, an alternative approach to upregulate cardioprotective miRNAs may involve a small-molecule therapeutic strategy. Therefore, further research on these ncRNAs involved in IRI of different organs is urgently needed, and these studies may lead to the identification of other unknown signaling pathways or reactions in IRI. This research will also help elucidate the contribution of ncRNAs to the pathophysiology of IRI and subsequent clinical outcomes and provide support for them as potential markers or therapeutic targets for IRI.

In summary, the IncRNA/circRNA-miRNA-mRNA axes have multiple roles in IRI, and factors in these axes may function as diagnostic markers and therapeutic targets. Several studies involving the IncRNA/circRNA-miRNA-mRNA axis are imperative and continuous efforts will be necessary for us to integrate these axes with clinical practice.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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