Involvement of non-coding RNAs in the pathogenesis of myocardial ischemia/reperfusion injury (Review)

QI LI[1,2], ZHUQING LI[1,2], ZHIXING FAN[3], YING YANG[4] and CHENGZHI LU[1,2]

[1]School of Medicine, Nankai University, Tianjin 300071; [2]Department of Cardiology, Tianjin First Center Hospital, Tianjin 300192; [3]Department of Cardiology, The First College of Clinical Medical Science, China Three Gorges University, Yichang, Hubei 443000; [4]Department of Cardiology, Beijing Tsinghua Changgeng Hospital, School of Clinical Medicine, Tsinghua University, Beijing 100084, P.R. China

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Abstract. Myocardial ischemia/reperfusion injury (MIRI) may cause myocardial stunning, reperfusion arrhythmia, no-reflow phenomenon and lethal reperfusion injury, which has a significant effect on the prognosis of patients undergoing thrombolytic agent therapy and percutaneous coronary intervention. Increasing evidence suggests that apoptosis, innate inflammation, oxidative stress, calcium overload and autophagy are involved in the pathogenesis of MIRI. Recent advancements in RNA sequencing technologies and genome-wide analyses led to the finding of small non-coding RNAs (ncRNAs). ncRNAs modulate cellular processes such as signal transduction, transcription, chromatin remodeling and post-transcriptional modification. The effects of ncRNAs on cellular biology is more considerable than initially expected, and thus ncRNAs have gained increasing attention and focus in modern medical research. There are several types of ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), which have been shown to regulate gene expression at the transcription, post-transcription and epigenetic levels. Dysregulation of ncRNAs, including miRNAs, lncRNAs and circRNAs, may participate in the molecular mechanisms of MIRI. The present review summarizes the characteristics and biological roles of miRNAs, lncRNAs and circRNAs, with particular emphasis on their role in MIRI, which show the novel complexity of ischemic hearts and may offer valuable insights into the pathogenesis of MIRI.

Correspondence to: Dr Chengzhi Lu, Department of Cardiology, Tianjin First Center Hospital, 24 Fukang Road, Nankai, Tianjin 300192, P.R. China
E-mail: 5020200072@nankai.edu.cn

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1. Introduction

Myocardial infarction (MI) is one of the main causes of morbidity and mortality in the United States, where approximately every 40 sec, an individual will suffer from MI (1). Recovering reperfusion using thrombolytic agents and percutaneous coronary intervention may rapidly reverse myocardial ischemia and preserve cardiac systolic function (2). However, the recanalization of blood flow can also result in irreversible detrimental effects known as myocardial ischemia/reperfusion injury (MIRI), which may cause myocardial stunning, reperfusion arrhythmia, or the no-reflow phenomenon and lethal reperfusion injury. Over the past two decades, a growing number of studies have demonstrated that apoptosis, innate inflammation, oxidative stress, calcium overload and autophagy are involved in the pathogenesis of MIRI (3-5). However, there is still no effective strategy for limiting or preventing MIRI. Thus, developing novel therapies for MIRI is crucial and remains an opportunity that will provide significant clinical benefits.

The human genome contains approximately 20,000 protein-coding genes. Only 2% of the human genome is transcribed into RNA transcripts, which are translated into protein, with the vast majority of transcripts comprising non-coding RNAs (ncRNAs) (6,7). There are numerous types of ncRNAs, which are generally divided into two categories according to their nucleotide length: Long ncRNAs (lncRNAs), which are ≥200 nucleotides in length, and small ncRNAs, which are ≤200 nucleotides in length, such as

microRNAs (miRNAs/miRs) (8,9). The newly defined classes of lncRNAs and miRNAs have been shown to regulate gene expression at the transcription, post-transcription and epigenetic levels. In addition, circRNAs have been identified as part of the lncRNA family, which also play important roles in the regulation of gene expression (10,11). These RNAs are covalently closed, endogenous biomolecules with no 5' end caps or 3' poly(A) tails, are not easily degraded by ribonuclease R and are more stable than other lncRNAs (10). The biogenesis of ncRNAs is complex, and the specific process of each ncRNA is shown in Fig. 1. Recent findings have shown that several novel ncRNAs can participate in a variety of important biological control processes and the development of multiple cardiovascular diseases, including MIRI (9,12-14). Such leads, not only enhance the understanding of disease pathogenesis, but also identify non-coding transcripts that potentially serve as MIRI diagnosis biomarkers or therapeutic targets.

The present review summarizes the characteristics and biological roles of miRNAs, lncRNAs and circRNAs, with particular emphasis on their role in MIRI. A more comprehensive understanding of these ncRNAs may bridge a major gap in the knowledge of the molecular mechanisms in the pathogenesis of MIRI.

2. Biological functions of miRNA

miRNAs, which are typically 20-22 nucleotides in length, are highly conserved and single-stranded ncRNAs that are encoded by the genome of several DNA viruses and all eukaryotic organisms (15). Their primary function is to negatively modulate gene expression by binding to the target mRNA and subsequently inhibiting its translation or promoting degradation in a sequence-dependent manner (16). Only mature miRNAs are incorporated into the RNA-induced silencing complex to direct mRNA target silencing. Canonically, this complex binds a target gene via partial sequence complementarity between the miRNA and a conserved site within the 3'-untranslated region of their target mRNAs. There are differences in the complementary degree between miRNAs: A single gene can be modulated by several miRNAs, whereas mRNA duplexes enable a single miRNA to target multiple mRNAs (17). miRNAs can regulate the translation of >60% of protein-coding genes. Furthermore, miRNAs can be sequestered by pseudogenes or other lncRNAs, introducing a new layer of regulatory complexity (18).

miRNAs that are present in cardiac tissue have important functional implications in cardiovascular biology, such as proliferation, smooth muscle maturation, cardiogenesis and endothelial function (19-22). All metabolic activities of an organism in the cardiovascular system are considered to be influenced by miRNA regulatory processes. Increasing evidence has shown that miRNAs are involved in the pathogenesis of MIRI, including inflammation, oxidative stress and apoptosis. Table I shows a summary of some important miRNAs (23-25).

3. Role of miRNAs in MIRI

miRNAs as mediators of cardiomyocyte apoptosis in MIRI. Cardiomyocyte apoptosis has been proven to be the main cause responsible for the secondary injury of the myocardium during MIRI. In addition, several miRNAs have been identified to be involved in the pathogenesis of MIRI through regulating cardiomyocyte apoptosis. It has been documented that the increased expression of miR-30e, miR-193b, miR-135a, miR-138, miR-140, miR-145, miR-15b-5p, miR-483 and miR-590-3p could suppress cardiomyocyte apoptosis induced by MIRI. Similar findings were observed following the decreased expression of miR-1, miR-327, miR-128-1-5p, miR-129-5p, miR-489 and miR-421 (4,13,23,25-35). Zhang *et al* (23) indicated that miR-193b overexpression may reduce apoptosis after MIRI and alleviate IR-induced myocardial injury by targeting mastermind-like 1, which is a transcriptional coactivator in the Notch signaling pathway. Wang *et al* (26) revealed that miR-135a targeted and negatively regulated protein tyrosine phosphatase 1B (*PTP1B*), and the expression of proapoptotic-related genes was reduced in association with *PTP1B* downregulation. In addition, miR-135a improved MIRI by reducing cardiomyocyte apoptosis both *in vitro* and *in vivo*. Liu *et al* (27) found that miR-138 upregulation inhibited the expression of proteins related to mitochondrial morphology and apoptosis by targeting hypoxia inducible factor-α (*HIF1-α*), thus exerting protective functions against MIRI.

Additionally, miR-128-1-5p was found to play a cardioprotective role in both H9c2 cardiomyocytes after hypoxia/reoxygenation (H/R) and H_2O_2-treated neonatal rat cardiomyocytes. This may have occurred by the regulation of miR-128-1-5p on growth arrest DNA damage-inducible gene 45 γ-mediated cardiomyocyte apoptosis in MIRI (28). Moreover, miR-129-5p overexpression could also attenuate cardiomyocyte apoptosis both in H9c2 cardiomyocytes after H/R and rats after I/R injury by targeting high mobility group box-1 (*HMGB1*) (29). Yang *et al* (30) demonstrated that miR-140 overexpression attenuated myocardial infarct size and myocardial enzymes via inhibition of mitochondrial-mediated apoptosis by targeting Yes-associated protein 1 (*YES-1*) in the progression of MIRI. Liu *et al* (31) reported that miR-145 exerted protective effects against MIRI by reducing cardiomyocyte apoptosis and the protective effects of miR-145 were possibly attributed to the inhibition of the CaMKII-mediated apoptosis signal-regulating kinase 1 anti-apoptotic signaling pathway.

Furthermore, Hao *et al* (13) found that inhibition of miR-1 alleviated MIRI by inhibiting MAPK3 via negatively regulating the PI3K/Akt signaling pathway, which is associated with reduced apoptosis. Niu *et al* (32) reported that miR-15b-5p was upregulated in MIRI rat models and could promote myocardial apoptosis via suppressing potassium voltage-gated channel subfamily J member 2 expression. Similarly, inhibition of miR-489 was found to promote activation of the PI3K/Akt signaling pathway by negatively targeting spindlin-1 and inhibiting apoptosis in H/R H9c2 cells (33). Our latest study reported that miR-327 downregulation improved I/R-induced myocardial injury and suppressed both extrinsic and intrinsic apoptotic cascades via targeting apoptosis repressor with caspase recruitment domain both *in vitro* and *in vivo* (34). Recently, inhibition of miR-483-3p was also demonstrated to ameliorate H/R injury and inhibit apoptosis in H9c2 cells via targeting murine double minute 4 via the p53 signaling pathway (35).

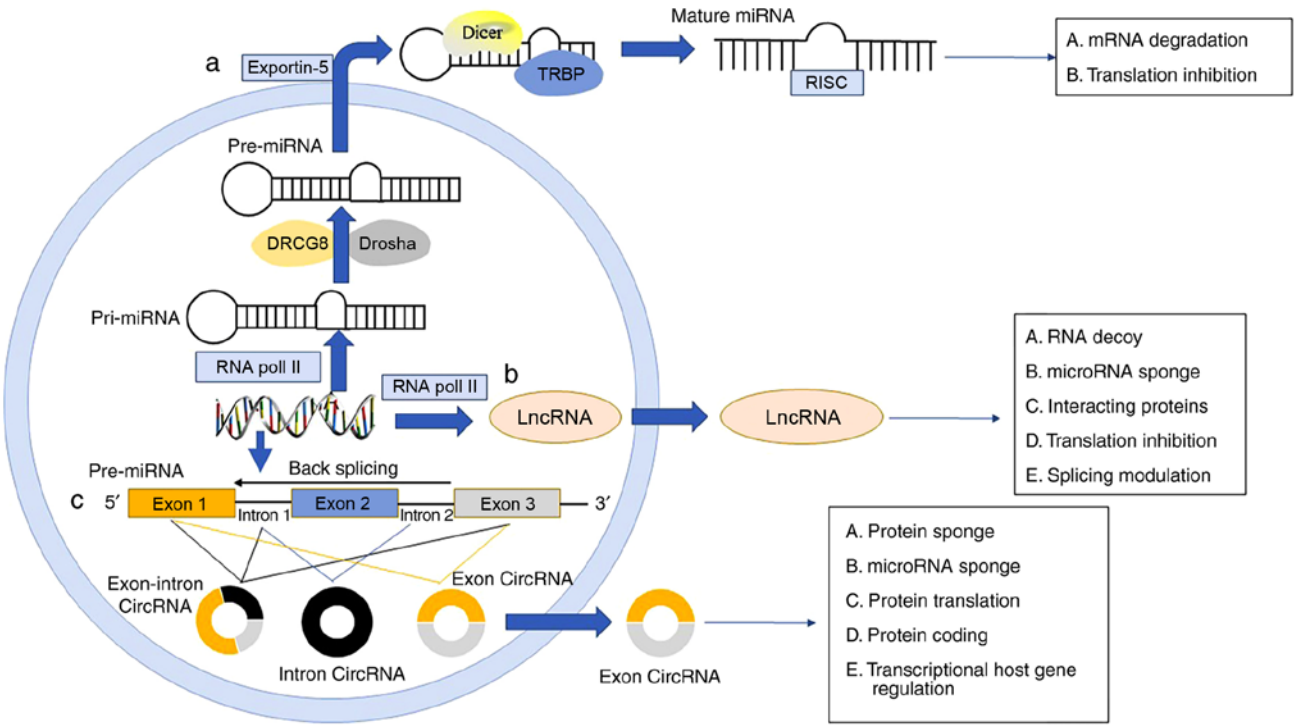

Figure 1. The biogenesis of miRNA, lncRNA and ciRNA. (a) miRNA genes are transcribed as pri-miRNA by RNA Pol II after which they are mediated by DRCG8 and RNAse III endonuclease Drosha, and pre-miRNA translocates from the nucleus to the cytoplasm mediated by exportin 5. Then, the RNase III endonuclease Dicer interacting with TRBP cleaves the pre-miRNA and mature miRNAs are incorporated into the RISC. (b) LncRNA genes are transcribed mostly by Pol II, and its biogenesis process is similar to miRNA. (c) circRNAs are generated by back-splicing events on maturing pre-mRNA that join together an exon at the upstream 3' splice site to an exon at the downstream 5' splice site resulting in a circular product, including exon, intron and exon-intron circRNA. circRNAs that are generated from exons only are mostly found in the cytoplasm, which suggests a role in post-transcriptional gene regulation. pri-miRNA, primary miRNA; Pol II, polymerase II; DRCG8, DiGeorge syndrome criticial region 8; pre-miRNA, precursor miRNA; TRBP, TAR RNA-binding protein; RISC, RNA-induced silencing complex.

miRNAs as mediators of inflammation in MIRI. Innate inflammation is an important pathological characteristic of MIRI, which can lead to the activation of diverse inflammatory factors. This effect can be regulated by miR-145, miR-181a, miR-202-3p, miR-22, miR-327 and miR-590-3p (24,29,32,34-36). Wei *et al* (24) found that miR-181a could efficiently attenuate MIRI in rats by inhibiting the inflammatory response and increasing the regulatory T-cell ratio. The mechanism of action may involve the inhibition of c-Fos protein, which is considered a key immunoactivator that contributes to dendritic cell-related immune functions from all links and processions. Liu *et al* (31) also demonstrated that upregulated miR-145 alleviated I/R-induced myocardial electrophysiological instability and inflammatory response, which may predominantly be due to inhibition of the NF-κB p65 anti-inflammatory signaling pathway. At the same time, Wu *et al* (36) indicated that miR-202-3p upregulation alleviated inflammatory response and oxidative stress by activating the TGF-β1/Smads signaling pathway by targeting transient receptor potential cation channel, subfamily M, member 6 (*TRPM6*) expression. The *TRPM6* gene is a member of the transient receptor potential channel gene family and has been found to play an important role in the regulation of extracellular divalent cations in cardiomyocytes (37). Previous findings showed that miR-22 had a protective effect on MIRI and this protective mechanism, at least in part, was due to its anti-inflammatory function via the suppression of the p38 MAPK/CBP/c-Jun-activator protein-1 (*AP-1*) signaling pathway (38). In addition to this, our latest findings suggested that inhibition of miR-327 improved MIRI by negatively targeting radioprotective 105 kDa protein by suppressing inflammation in rat models (39).

miRNAs regulate other pathological characteristics of MIRI. In addition to cardiomyocyte apoptosis and innate inflammation, miRNAs can also actively participate in the modulation of oxidative stress and other pathological characteristics of MIRI such as autophagy, pyroptosis and ventricular remodeling. Liu *et al* (25) reported that miR-421 promotes JNK/AP-1 pathway activation by directly targeting sirtuin-3 and further promotes H/R-induced oxidative stress and caspase-9/3-dependent cardiomyocyte apoptosis. Zheng *et al* (4) suggested that miR-30e serves a significant role in suppressing MIRI-induced oxidative stress and apoptosis via the Notch1/Hes1/Akt signaling pathway. In H/R H9c2 cells, overexpression of miR-590-3p inhibited activation of the NF-κB signaling pathway by targeting the inhibition of the receptor-interacting protein kinase 1 (*RIPK1*) gene, thereby alleviating oxidative stress, apoptosis and inflammatory response (40). In another H/R model and MIRI rat models, downregulated miR-29a could improve myocardial injury by negatively targeting sirtuin-1 by suppressing oxidative stress and NOD-like receptor pyrin domain-containing-3 (*NLRP3*)-mediated pyroptosis (41). Additionally, our unpublished data show that miR-327 knockdown can improve cardiac function after MIRI, partly through the suppression of oxidative stress. Recently,

Table I Summary of miRNAs in the pathogenesis of MIRI.

miRNA	Expression with MIRI	Targeted genes	Pathological mechanism	(Refs.)
miR-1	Increase	MAPK3	Pro-apoptotic	(13)
miR-15b-5p	Increase	KCNJ2	Pro-apoptotic	(31)
miR-22	Decrease	CBP	Anti-inflammatory	(38)
miR-29a	Increase	SIRT1	pro-oxidative stress	(41)
miR-30e	Decrease	Notch1	Anti-apoptotic	
			Anti-oxidative stress	(4)
miR-128-1-5p	Decrease	Gadd45g	Anti-apoptotic	(28)
miR-129-5p	Decrease	HMGB1	Anti-apoptotic	(29)
miR-135a	Decrease	PTP1B	Anti-apoptotic	(26)
miR-138	Decrease	HIF1-α	Anti-apoptotic	(27)
miR-140	Decrease	YES1	Anti-apoptotic	(30)
miR-145	Decrease	CaMKII	Anti-apoptotic	
		NF-κB	Anti-inflammatory	(31)
miR-181a	Decrease	c-Fos	Anti-inflammatory	(24)
miR-193b	Decrease	MAML1	Anti-apoptotic	(23)
miR-202-3p	Decrease	TRPM6	Anti-inflammatory	
			Anti-oxidative stress	(36)
miR-327	Increase	ARC	Pro-apoptotic	(34)
		RP105	Pro-inflammatory	(39)
miR-330	Increase	SRY	Ventricular r;emodeling	(42)
miR-421	Increase	Sirt3	Pro-apoptotic	
			Pro-oxidative stress	(25)
miR-483-3p	Increase	MDM4	Anti-apoptotic	(35)
miR-489	Increase	SPIN1	Pro-apoptotic	(33)
miR-590-3p	Decrease	RIPK1	Anti-apoptotic	
			Anti-inflammatory	
			Anti-oxidative stress	(40)

miRNA, microRNA; MIRI, myocardial ischemia/reperfusion injury.

Liu *et al* (42) demonstrated that inhibition of miR-330 inhibited TGF-β1/Smad3 signaling pathway activation by negatively targeting *SRY* and thus prevented left ventricular remodeling after MIRI.

Moreover, recent findings indicated that vitamin C attenuated the inflammation, apoptosis and oxidative damage of H_2O_2-induced human umbilical vein endothelial cells via miRNA signaling networks, including miR-3928-5p and miR-323a-5p (43). Given the important role of inflammation, apoptosis and oxidative stress in MIRI, miR-3928-5p and miR-323a-5p constitute potential therapeutic targets for treating MIRI. Future studies are needed to determine whether these miRNAs that are modified by anti-inflammation, anti-apoptotic and antioxidant effects affect MIRI. Generally, the critical contribution of miRNAs in apoptosis, inflammation, oxidative stress as well as other pathological characteristics via different signaling pathways has opened up new avenues to exploit their role in the pathogenesis of MIRI. Future research should pay attention to the interaction between miRNAs with the regulatory network in view of the contribution to the potential molecular mechanisms of MIRI.

4. Biological functions of lncRNAs

lncRNAs, a class of transcripts without protein-coding capacity, are expressed at low levels with 10-fold lower median expression abundance than their protein-coding counterparts (44). Although most lncRNAs are localized in the nucleus, several lncRNAs also exert functions in the cytoplasm (45). lncRNAs manifest specific and diverse subcellular localizations in various cell types depending on their molecular function. In the nucleus, lncRNAs can interact with DNA to form RNA-DNA complexes to regulate gene expression and act as molecular scaffolds to suppress or activate transcription. In addition, other lncRNAs are enriched in the cytoplasm, where they can also interact with proteins and modulate mRNA translation (46,47). In fact, it was shown that lncRNAs may participate in a wide range of pathophysiological processes and biological events. They regulate target gene expression mainly through *cis*- or *trans*-regulation (48).

Increasing evidence has suggested that lncRNAs act as regulators of almost every cellular process, and the expression of these molecules seems to be strictly regulated in physiological conditions and several cardiovascular diseases, including

Table II. Summary of lncRNAs in the pathogenesis of MIRI.

lncRNA	Expression with MIRI	Targeted genes	Pathological mechanism	(Refs.)
FOXD3-AS1	Increase	NFκB/iNOS/COX2	Pro-apoptotic	(48)
			Pro-autophagy	
LINC00652	Increase	GLP-1R	Pro-apoptotic	(49)
AK139128	Increase	miR-499	Pro-apoptotic	(56)
			Pro-autophagy	
H19	Decrease	miR-877-3p	Anti-apoptotic	(57)
		Bcl-2	Anti-apoptotic	
		miR-103	Anti-apoptotic	
		miR-107	Anti-necrosis	(71)
Oprm1	Decrease	miR-30b-5p	Anti-apoptotic	(54)
TUG1	Increase	miR-142-3p	Pro-apoptotic	(58)
			Pro-autophagy	
Neat1	Increase	miR-193a	Pro-apoptotic	(59)
AK088388	Increase	miR-30a	Pro-apoptotic	(60)
			Pro-autophagy	
MEG3	Increase	miR-7-5p	Pro-apoptotic	(61)
KCNQ1OT1	Increase	miR-204-5p	Pro-apoptotic	(62)
HIF1A-AS1	Increase	miR-204	Pro-apoptotic	(63)
			ventricular remodeling	
NRF	Increase	miR-873	Pro-necrosis	(67)
ROR	Increase	p38/MAPK	Pro-oxidative stress	(73)
Gpr19	Increase	miR-324-5p	Pro-apoptotic	(74)
			Pro-oxidative stress	
GAS5	Increase	miR-532-5p	Pro-apoptotic	(64)
HULC	Decrease	miR-377-5p	Anti-apoptotic	
			Anti-inflammatory	(70)
Gm4419	Increase	miR-682	Pro-inflammatory	
			Pro-apoptotic	(71)
MALAT1	Increase	miR-144-3p	Pro-apoptotic	(77)
		miR-26b		(78)

MIRI, myocardial ischemia/reperfusion injury; lncRNA, long non-coding RNAs.

MIRI (14,49). Since the discovery of lncRNAs, their functional characterization makes these molecules a potential biomarker and therapeutic target for MIRI as shown in Table II, which provides a summary of the major lncRNAs.

5. Role of lncRNAs in MIRI

LncRNAs as mediators of cardiomyocyte autophagy and apoptosis in MIRI. To date, a variety of lncRNAs have been revealed to participate in the regulation of cardiomyocyte autophagy and apoptosis during the process of MIRI. Ma *et al* (14) showed that lncRNA nuclear enriched abundant transcript 1 (Neat1) expression was increased after MIRI in diabetic rats, and increased Neat1 expression aggravated autophagy and apoptosis response via regulating forkhead box protein O1 expression during MIRI. LncRNA FOXD3 antisense RNA 1 (FOXD3-AS1) was also found to be upregulated during MIRI. Furthermore, FOXD3-AS1 overexpression promoted cardiomyocyte autophagy and apoptosis via activating the NF-κB/inducible nitric oxide synthase/cyclooxygenase 2 signaling pathway, which led to aggravated MIRI (49). During sevoflurane-induced cardioprotection against MIRI, lncRNA LINC00652 overexpression was identified to reduce this protective effect and increase infarct size and cell apoptosis via inactivating the cAMP/protein kinase A pathway by negatively targeting glucagon-like peptide-1 receptor (*GLP-1R*) (50). *GLP-1R* is a gut incretin hormone that exerts an anti-oxidative protective effect on various tissues. It has been identified as a vital physiological regulator of insulin secretion and a major therapeutic target for the treatment of ischemic stroke and diabetes (51,52). As a signaling molecule, hydrogen sulfide (H_2S) has been recognized as an endogenous critical gas that participates in the physiological and pathological progression of the cardiovascular system (53). Endogenous H_2S is produced by cystathionine-γ-lyase (*CSE*), which can be inhibited by the miR-30 family (54). Hu *et al* (55) suggested that lncRNA Mu-type opioid receptor (Oprm1) was competitively combined with miR-30b-5p, which inhibited *CSE* expression.

In-depth investigation showed that Oprm1 overexpression increased endogenous H_2S and reduced I/R-induced myocardial injury and apoptosis via activating the PI3K/Akt pathway by targeting the miR-30b-5p/CSE axis (55).

Competing endogenous RNA (ceRNA) is a novel pattern of lncRNA expression, which can indirectly modulate the expression of target genes by competing for binding with miRNAs (56). Zhu and Zhao (57) revealed that lncRNA AK139128 could be used as a ceRNA to adsorb miR-499 to suppress miR-499 expression, thereby promoting cardiomyocyte apoptosis and autophagy in H/R injury. H19, a well-known conserved lncRNA, is also abundantly expressed in murine hearts and can function as a ceRNA to regulate the availability of miR-877-3p. Upregulated H19 attenuated mitochondrial apoptosis and cardiomyocyte injury induced by MIRI via suppressing the miR-877-3p/Bcl-2 pathway (58). Su *et al* (59) reported that lncRNA taurine-upregulated gene 1 increased the expression of *HMGB1* and *Rac1* by sponging miR-142-3p, which critically contributed to autophagy and apoptosis under H/R conditions. A recent study by Ren *et al* (60) also suggested that lncRNA Neat1 played a promotive role in MIRI, and inhibition of lncRNA Neat1 enhanced cell proliferation and inhibited cell apoptosis, which may be the mechanisms through which lncRNA Neat1 negatively targets miR-193a in H/R injury H9c2 cells. Similarly, Wang *et al* (61) demonstrated that lncRNA AK088388 could increase the expression of LC3-II and Beclin-1 and eventually promote cardiomyocyte apoptosis and autophagy. The mechanism of action was attributed to competitive binding of miR-30a, which derepresses the miR-30a to regulate cardiomyocyte injury in an H/R model. Subsequently, Zou *et al* (62) reported that lncRNA maternally expressed gene 3 (*MEG3*) inhibition protected cardiomyocytes against I/R-induced apoptosis both *in vitro* and *in vivo*. The potential mechanisms were investigated, and it was found that lncRNA MEG3 negatively targeted miR-7-5p and its downstream target gene poly (ADP-ribose) polymerase (*PARP*)1 as well as the caspase-3 signaling pathway. In the same year, another study by Rong *et al* (63) revealed that lncRNA KCNQ1OT1 could regulate galectin-3 (LGALS3) expression by binding to miR-204-5p, which promoted cardiomyocyte apoptosis both in H/R and MIRI mouse models. Thus, the KCNQ1OT1/miR-204-5p/LGALS3 axis may provide a new therapeutic target for MIRI treatment.

It was also shown that lncRNA HIF1A-AS1 could function as a ceRNA of miR-204 to regulate the expression of suppressors of cytokine signaling 2, thus playing a key role in promoting ventricular remodeling and aggravating cardiac function after MIRI in mice (64). Han *et al* (65) revealed that lncRNA growth arrest specific 5 (GAS5) served a function in MIRI via the PI3K/Akt pathway by sponging miR-532-5p, and silencing lncRNA GAS5 could improve cell survival, decrease the occurrence of apoptosis and ultimately attenuate MIRI. Interestingly, lncRNA GAS5 was also found to function as a ceRNA of miR-137 to suppress miR-137 expression (66). Furthermore, previous findings have shown that miR-137 negatively regulated H_2O_2-induced cardiomyocyte apoptosis by targeting *CDC42* (67). This indicated that the lncRNA GAS5/miR-137/CDC42 axis may also be involved in the regulation of I/R-induced myocardial injury and apoptosis. However, this speculation requires further verification by experimental studies.

LncRNAs as mediators of cell necrosis and inflammation in MIRI. In addition to apoptosis, several lncRNAs can also modulate cell necrosis and inflammation, which is one of the pathological mechanisms of MIRI. Wang *et al* (68) showed that lncRNA necrosis-related factor contributed to H_2O_2-induced cardiomyocyte necrosis and I/R-induced myocardial injury by targeting miR-873 and regulating RIPK1/RIPK3. It is well known that RIPK1 is necessary in TRAIL, TNF-α and CD95 ligand-induced necrotic cell death and RIPK3 phosphorylates the mixed lineage kinase domain-like protein, which is also a key determinant in mediating the RIPK1 necrotic signaling pathway (69,70). Liang *et al* (71) reported that lncRNA HULC was downregulated and miR-377-5p was upregulated during MIRI, and HULC overexpression inhibited the inflammation and apoptosis of H/R-induced H9c2 cells. Mechanistic experiments revealed that lncRNA HULC sponged miR-377-5p to inactivate the NLRP3/caspase-1/IL-1β pathway to exert a protective effect. Furthermore, lncRNA Gm4419 was demonstrated to regulate MIRI by targeting the miR-682/TNF receptor-associated factor 3 axis, and Gm4419 knockdown reduced the myocardial infarction area, inflammatory cytokine levels and apoptosis (72). Another study by Wang *et al* (73) also revealed a novel function of H19 in modulating H9c2 cell necrosis induced by H_2O_2 and demonstrated that H19 acts as a ceRNA to repress miR-103/107, thereby regulating the expression of FADD, which acted as a negative regulator of necrosis by preventing the formation of the RIPK1/RIPK3 complex.

lncRNAs regulate other pathological characteristics of MIRI. Blood reflow during MIRI can result in reactive oxygen species (ROS) production, which causes cytotoxic and oxidative stress damage. LncRNA regulator of reprogramming was found to promote ROS production, NADPH oxidase (NOX) activity and NOX2 protein levels by regulating the p38/MAPK signaling pathway, thereby increasing oxidative damage and cardiomyocyte apoptosis as well as aggravating MIRI (74). Huang *et al* (75) showed that lncRNA Gpr19 was upregulated in an oxygen glucose deprivation/recovery system of neonatal rat ventricular cardiomyocytes or MIRI in mice, and inhibition of Gpr19 attenuated oxidative stress and apoptosis by regulation of the miR-324-5p/mitochondrial fission regulator 1 axis. Additionally, another lncRNA, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), which also acts as a ceRNA for numerous miRNAs, was upregulated in cardiac tissue, and its inhibition reduced cardiomyocyte apoptosis and improved left ventricular function in diabetic rats (76). Wang *et al* (77) inferred that MALAT1 may modulate cardiomyocyte inflammation and myocardial injury induced by I/R via negatively targeting miR-203 expression. Interestingly, Gong *et al* (78) recently demonstrated that MALAT1 promoted cardiomyocyte apoptosis following MIRI via targeting miR-144-3p, but not miR-203. However, the effects of MALAT1 in regulating MIRI-induced inflammatory response have not been completely elucidated. It is known that MALAT1 can also function as a ceRNA to suppress miR-26b expression (79). In addition, Ge *et al* (80) showed that miR-26b reduced the inflammatory response and improved myocardial remodeling during myocardial infarction via binding to prostaglandin-endoperoxide synthase 2 (*PTGS2*) and inactivating the MAPK pathway. Based on these data, we speculated that

Table III. Summary of circRNAs in the pathogenesis of MIRI.

circRNA	Expression with MIRI	Targeted genes	Pathological mechanism	(Refs.)
circNCX1	Increase	miR-133a-3p	Pro-apoptotic	(87)
ACR	Decrease	Dnmt3B	Anti-autophagy	(93)
CircDLGAP4	Decrease	miR-143	Anti-ER stress	(96)
			Anti-apoptotic	(98)
CircANXA2	Increase	miRNA-133	Pro-apoptotic	(88)
circTLK1	Increase	miR-214	Pro-apoptotic	(89)
circRNA-0068566	Decrease	miR-6322	Anti-apoptotic	
			Anti-oxidative stress	(99)
Circ-100338	Decrease	miRNA-200a-3p	Pro-angiogenic	(100)

MIRI, myocardial ischemia/reperfusion injury; circRNA, circular RNAs.

the MALAT1-miR-26b-PTGs2 axis may participate in MIRI and aggravate the inflammatory response induced by MIRI.

The exact molecular mechanism of lncRNAs in the pathogenesis of inflammatory response remains to be determined. Overall, the lncRNA-miRNA modulatory network is a potential axis that affects the progression of MIRI by modulating apoptosis, autophagy and oxidative stress. Although our understanding of lncRNAs is still developing, these examples provided valuable insights on how lncRNAs may ultimately be used in the clinic as new therapeutic targets for MIRI in the future.

6. Biological functions of circRNAs

circRNAs, a novel type of large endogenous transcripts, are typically produced by back-splicing events on maturing pre-mRNAs that join a donor site with an upstream acceptor site (81). These circRNAs differ from linear RNAs in that they are circularized RNA molecules with covalently closed loop structures without 5'-3' polarity or a polyadenylated tail. Most of them are stable, abundant, endogenous and exhibit cell type-, tissue- and developmental stage-specific expression patterns in eukaryotic cells (82). Compared to miRNAs and lncRNAs, the understanding of circRNA functions are still limited. At present, four main roles have been described and are shared by a subset of circRNAs. CircRNAs can function as miRNA sponges to inhibit the translation of mRNAs and interact with RNA-binding proteins to regulate protein levels. In addition, they can also act as regulators of splicing and transcription to alter gene expression and dynamic protein scaffolds to facilitate contact and assembly of proteins (11,83,84).

While the main function of circRNAs is exerted through their activity as miRNA sponges, their second most important function is exerted via circRNA-protein interactions, including as protein sponges, scaffolds, decoys and recruiters (84). In addition, several circRNAs were also reported to encode proteins through the translational machinery in a cap-independent manner (85). Thus, circRNA-protein interactions can also influence protein expression, biogenesis and pathophysiological processes, which requires further in-depth studies. Deep sequencing of cardiac tissues revealed the abundance, conservation, evolution and developmental stage-specific differentiation of circRNAs expressed in the heart (86). Since this has been identified in a number of other investigation areas, circRNA regulation and function in the cardiovascular system have also attracted widespread attention. Increasing evidence has demonstrated that circRNAs are involved in a wide variety of biological processes, such as cell proliferation, differentiation and apoptosis, and may play significant roles in MIRI, as shown in Table III which includes a summary of the major circRNAs (12).

7. Role of circRNAs in MIRI

CircRNAs as mediators of MIRI. More recently, deep sequencing studies revealed that >15,318 and 3,017 cardiac circRNAs were identified in human and mouse heart, respectively, some of which are correlated with apoptosis, autophagy and endoplasmic reticulum (ER) stress during MIRI (12,87). CircNCX1, a circRNA transcribed from the 2nd exon of the sodium/calcium exchanger 1 (*ncx1*) gene, is widely expressed in cardiac tissue and showed differential expression levels during cardiomyopathy. Li *et al* (88) revealed that circNCX1 was upregulated in response to MIRI. Furthermore, suppression of circNCX1 reduced apoptosis and attenuated I/R-induced myocardial injury by binding to miR-133a-3p and inhibiting miR-133a-3p regulation on pro-apoptotic gene cell death-inducing protein (*CDIP1*) activity. Thus, the circNCX1/miR-133a-3p/CDIP1 axis plays a critical regulatory role in regulating cardiomyocyte apoptosis, thus contributing to MIRI. Similarly, Zong and Wang (89) showed that circANXA2 promoted myocardial apoptosis during MIRI via suppressing miRNA-133 expression and aggravated myocardial injury.

Moreover, circTLK1 is an upregulated circRNA found in MIRI mouse models and could exacerbate myocardial injury and cardiomyocyte apoptosis during MIRI by targeting the miR-214/RIPK1-mediated TNF signaling pathway (90). As a conserved mitochondrial serine/threonine protein kinase, PTEN-induced putative kinase 1 (*PINK1*) can be imported into the mitochondrial matrix and targets the outer membrane of the mitochondria, which ensures quality control of the mitochondria (91,92). Previous findings suggested that *PINK1* is downregulated during human end-stage heart failure,

which showed that *PINK1* is essential for normal heart function (93). Recently, Zhou *et al* (94) reported that a circRNA known as autophagy-related circular RNA (ACR) attenuated cardiomyocyte autophagy and protected the heart from I/R injury by positively targeting Pink1. Moreover, they identified ACR-activated PINK1 expression by directly binding to Dnmt3B and blocking Dnmt3B-mediated DNA methylation of Pink1 promoter and regulated its downstream gene *FAM65B*, which inhibits autophagy and cell death in the heart.

Vascular endothelial cell dysfunction plays a significant role in the progression of MIRI, which is involved in angiogenesis via various mechanisms, such as ER stress, oxidative stress, autophagy and ubiquitination (95,96). CircDLGAP4 was found to be decreased in endothelial cells after MIRI. Moreover, miR-143 was the main sponge target of circDLGAP4, which was involved in endothelial cell dysfunction caused by I/R exposure via regulating miR-143 expression (97). One of the potential targets of miR-143 is E3 ubiquitin-protein ligase HECTD1 (*HECTD1*), a novel protein that participates in cell migration and apoptosis in endothelial cells (98). It was suggested that circDLGAP4 can regulate *HECTD1* expression by sponging miR-143 and mediate I/R-induced myocardial injury in endothelial cells through ER stress (97). Another interesting phenomenon was that miR-143 could also act as a sponge for Bcl-2, thereby inhibiting the apoptotic response (99). Consequently, the circDLGAP4/miR-143/Bcl-2 pathway may also play a critical regulatory role in cardiomyocyte apoptosis, thereby attenuating MIRI. Zhou *et al* (100) reported that circRNA-0068566 had a protective effect on MIRI and may significantly suppress I/R-induced cardiac dysfunction, apoptosis and oxidative stress by activating the miR-6322/PARP2 signaling pathway. In addition, Chang *et al* (101) revealed that Circ-100338 induced angiogenesis and regulated MIRI metastasis by combining with miRNA-200a-3p.

Other circRNAs identified in MIRI. At present, the understanding of circRNAs in the molecular mechanisms of MIRI remains limited. It is important to further investigate the pathological roles of circRNAs in the development of MIRI or other cardiovascular diseases. Numerous other circRNAs have been implicated in I/R injury. Ge *et al* (102) recently showed that 119 circRNAs were downregulated and 66 circRNAs were upregulated during MIRI, and 42 of them were newly identified circRNAs. Furthermore, they constructed a circRNA-miRNA network with five circRNAs, including mmu_circ_001007, mmu_circ_008351, mmu_circ_0001336, mmu_circ_008228 and mmu-circ007845, which could modulate miRNA expression. Moreover, circRNA-miRNA network analysis revealed that one miRNA could combine with multiple circRNAs and one circRNA can also function on different miRNAs. The identified circRNAs may participate in the pathology of MIRI. Compared with lncRNAs and miRNAs, the understanding of circRNAs in the molecular mechanisms of diabetic cardiomyopathy is still limited. Future studies are required to verify the exact mechanisms through which circRNAs interact with proteins and other ncRNAs to mediate the pathogenesis of MIRI.

8. Conclusion

ncRNAs, first discovered in 1993 by Lee and colleagues, modulate cellular processes such as signal transduction, transcription, chromatin remodeling and post-transcriptional modification (103). The effects of ncRNAs on cellular biology are more considerable than initially expected and thus makes ncRNAs the focus of modern medical research. Dysregulation of ncRNAs, including miRNAs, lncRNAs and circRNAs, can have a significant impact on myocardial function, thereby aggravating, maintaining and promoting MIRI processes. Another class of ncRNAs known as PIWI-interacting RNAs (piRNAs) was identified, and their regulatory roles in gene expression is increasingly studied (104). Evidence has demonstrated that piRNAs influence the Akt signaling pathway, a crucial network in cardiac physiopathology (105). Moreover, it was recently highlighted that anti-inflammatory treatment with vitamin C to attenuate H_2O_2-mediated endothelial cell senescence may be associated with changes in the expression of piRNAs that are linked to the cell cycle (106). Thus, piRNAs could play a functional role in inflammation and endothelial dysfunction-related cardiovascular regulatory pathways. Future mechanistic studies are required to determine whether the expression of piRNAs is crucial to MIRI.

The present review summarized the recent progress in the involvement of ncRNAs in the pathogenesis of MIRI, such as apoptosis, autophagy, inflammation and oxidative stress. In fact, a number of miRNAs, more recently circRNAs and lncRNAs, have been shown to be potential therapeutic targets in the treatment of MIRI. The main function of ncRNAs is to regulate the expression of target genes by binding to the target mRNA or sponging miRNAs. The therapeutic targeting of ncRNAs in MIRI has only been recently identified and more information remains to be studied, particularly on lncRNAs and circRNAs. In order to keep up the pace and identify more novel ncRNAs, a highly organized network of ncRNA research institutes is essential. Finally, further studies are required to clarify the molecular mechanisms of ncRNAs in the development of MIRI and determine whether there are other novel molecules that regulate lncRNAs and circRNAs, thus forming novel therapeutic targets for MIRI and other cardiovascular diseases.

In conclusion, the pathological roles of ncRNAs in the progression of MIRI shows the complexity of the ischemic heart and may provide valuable insights into the pathogenesis of ischemic heart disease.

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Authors' contributions

QL, ZL, ZF, YY and CL conceived and designed the article. QL and YY prepared the figures. QL and ZL drafted the manuscript.

CL and ZF critically revised the article for important intellectual content. All authors read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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