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Review article

Long noncoding RNA/circular noncoding RNA–miRNA–mRNA axes in cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Non-coding RNAs including long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) and microRNAs (miRNAs) have been reported to participate in pathological developments of CVDs through various mechanisms. Among them, the networks among lncRNAs/circRNAs, miRNAs, and mRNAs have recently attracted attention. Understanding the molecular mechanism could aid the discovery of therapeutic targets or strategies in CVDs including atherosclerosis, myocardial infarction (MI), hypertrophy, heart failure (HF) and cardiomyopathy. In this review, we summarize the latest research involving the lncRNA/circRNA–miRNA–mRNA axis in CVDs, with emphasis on the molecular mechanism.

Abbreviations: AKT, protein kinase B; ANF, atrial natriuretic factor; Ang II, angiotensin II; ANRIL, antisense non-coding RNA in the INK4 locus; APF, autophagy promoting factor; API5, apoptosis inhibitor 5; ATG7, autophagy-related gene 7; BCL2L12, BCL2 like 12; BCL2L2, BCL-2 like protein 2; BNIP3, Bcl2/adenovirus EIB 19kD-interacting protein 3; BNP, brain natriuretic peptide; Brg1, brahma-related gene 1; CaMKIIδ, Ca^{2+}/calmodulin-dependent protein kinase II delta; CARL, cardiac apoptosis-related lncRNA; CCL5, CC chemokine ligand 5; CDIP1, cell death-inducing protein; Cdr1as, cerebellar degeneration-related protein 1 transcript; ceRNA, competing endogenous RNA; CERS1, ceramide synthase 1; CFs, cardiac fibroblasts; CHRF, cardiac hypertrophy related factor; cIAP1, cellular inhibitor of apoptosis protein 1; circRNAs, circular RNAs; Col1a2, human type I collagen α2; CPC, cardiac progenitor cell; CTGF, connective tissue growth factor; CVDs, cardiovascular diseases; CXCR2, CXC chemokine receptor 2; DAPK2, death-associated protein kinase 2; DIGIT, Divergent to GSC induced by TGF-b family signaling; ECs, endothelial cells; FADD, Fas-associated protein with death domain; FGF10, fibroblast growth factor 10; FGF2, fibroblast growth factor 2; FoxO, Forkhead box O 4; FTX, five prime to Xist; GAS5, growth arrest-specific 5; H/R, hypoxia/reoxygenation; HA, human aorta; HAS2, hyaluronan synthase 2; HF, heart failure; Hic-5, hydrogen peroxide-inducible clone-5; HIF-1α, hypoxia-inducible factor 1α; HMGB1, high mobility group box 1; HO-1, heme oxygenase 1; HOTAIR, HOX antisense intergenic RNA; HOXA9, homeobox A9; HRCR, heart-related circRNA; HSP70, heat shock protein70; HULC, highly upregulated in liver cancer; HUVECs, human umbilical cord vein endothelial cells; I/R, ischemia-reperfusion; ISO, isoproterenol; JAK2, Janus kinase 2; JMJD6, jmjC domain-containing protein 6; KLF2, kruppel-like factor 2; LARP1, La ribonucleoprotein domain family, member 1; LC3-II, microtubule-associated protein 1 light chain 3; lncRNAs, long ncRNAs; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; Mcm7, minichromosomal maintenance 7; MEF2A, myocyte enhancer factor-2A; MEG3, maternally expressed gene 3; MFACR, mitochondrial fission and apoptosis-related circRNA; Mfn2, Mitofusin 2; MI, myocardial infarction; MIAT, myocardial infarction-associated transcript; miRNAs, microRNAs; MMP2, matrix metalloproteinase 2; MMPs, matrix metalloproteases; MTP18, mitochondrial protein 18; Myd88, myeloid differentiation primary response gene 88; NAMPT, nicotinamide phosphoribosyltransferase; NAT8L, *N*-acetyltransferase 8-like; ncRNAs, noncoding RNAs; ncx1, sodium/calcium exchanger 1; NFIA, nuclear factor IA; NF-κb, nuclear factor-kappa B; NLRP3, nod-like receptor protein-3; NOD2, Nucleotide-Binding Oligomerization Domain 2; NRF, nuclear respiratory factor; ox-LDL, oxidized low-density lipoprotein; PA2G4, proliferation-associated protein 2G4; PDCD4, Programmed cell death 4; PE, phenylephrine; PFL, pro-fibrotic lncRNA; PHB2, prohibitin 2; PPAR, poly ADP-ribose polymerase; PPARα, poly ADP-ribose polymerase α; Ptafr, platelet-activating factor receptor; PTEN, phosphatase and tensin homology; RhoB, GTPase ras homolog gene family, member B; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RIPK3, receptor-interacting serine/threonine-protein kinase 3; RNCR3, retinal non-coding RNA3; ROBO1, roundabout 1; ROR, regulator of reprogramming; SENCR, smooth muscle and endothelial cell-enriched migration/differentiation-associated long noncoding RNA; SIRT1, Sirtuin 1; SMILR, smooth muscle-induced lncRNA enhances replication; SNHG1, small nucleolar RNA host gene 1; SOX6, sex-determining region Y-box 6; STAT3, signal transducer and activator of transcription 3; STIM1, stromal interaction molecule 1; TAC, transverse aortic constriction; TGFB2-OT1, TGFB2 overlapping transcript 1; TGF-β1, transforming growth factor-β1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRPC, transient receptor potential canonical; TUG1, taurine up-regulated gene 1; UCA1, urothelial carcinoma-associated 1; ULK1, unc-51-like kinase 1; VDAC1, voltage-dependent anion channel 1

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1. Introduction

Despite advances in disease prevention, diagnosis, and treatment, cardiovascular diseases (CVDs) remain the leading cause of mortality and morbidity worldwide. It is estimated that by 2030, nearly 23.6 million will die from CVDs, primarily from heart disease and stroke [1,2]. Thus, there is urgent need to understand the pathogenesis of CVDs at the molecular level. When heart exposed to certain stresses, a variety of abnormalities can manifest, including the abnormal proliferation, migration, autophagy, apoptosis, and necrosis of cardiomyocyte, endothelial cells (ECs), fibroblasts and vascular smooth muscle cells (VSMCs).

Numerous studies have shown that noncoding RNAs (ncRNAs) play essential roles in regulating the network governing the physiology and pathology of CVDs and could be used for diagnosing and preventing CVDs [3]. Less than 2% of the human genome comprises coding transcripts, while the rest of the genome contains non-coding sequences, some of which are transcribed as ncRNAs [4]. Previously, ncRNAs were considered “evolutionary junk”, but current data suggest important roles for these sequences in pathological and physiological conditions. Based on their transcript size, ncRNAs have been broadly classified into two categories: small ncRNAs, which are up to 200 nucleotides long, and long ncRNAs, which are typically longer than 200 nucleotides [5]. MicroRNAs (miRNAs), the most widely studied small ncRNAs, are short, highly conserved, single stranded RNAs that regulate gene expression through binding to complementary sequences on 3′-untranslated regions (3′-UTR) of their target mRNA, thus inhibit mRNA translation or promote mRNA degradation [6,7]. Long non-coding RNAs (lncRNAs) have mRNA-like structure with a 5′-end methylated cap and a 3′-end poly-A tail and are transcribed by RNA polymerase II. Based on location in the gene or relation to nearby protein-coding genes, they are generally subclassified as sense, antisense, intronic, bidirectional, or intergenic. There is evidence that lncRNA localizes to both the nucleus and cytoplasm, indicating that this form of gene regulation can be performed independently at transcriptional and post-transcriptional levels. In addition, chromatin remodeling is also involved in the regulation of gene expression [8,9]. Circular RNAs (circRNAs) are evolutionarily conserved, stable, endogenous, type- and tissue-specific molecules that are produced by back-splicing events. They comprise covalently closed continuous loop structures lacking a 5′-terminal cap and 3′-terminal poly A. Based on their molecular mechanisms of biogenesis, circRNAs are commonly divided into four categories: exonic circRNAs, circular intronic RNAs, exon-intron circRNA, and intergenic circRNAs. Due to their versatility, circRNAs serve several biological functions, including miRNA sponge, protein sponge, parental gene transcription, and even little protein coding capacity [10,11].

Recent evidence indicates that ncRNAs play a dominant role in the development of CVDs through various mechanisms [12]. Among them, the novel regulatory mechanism incorporating crosstalk between lncRNA/circRNA, miRNA, and mRNA has attracted more attention [13,14]. The lncRNAs and circRNAs interact with miRNAs and then influence the relevant mRNAs expression. The lncRNA/circRNA-miRNA-mRNA axis that participates in pathophysiological processes of cardiomyocytes and endothelial cells such as apoptosis, autophagy, necrosis, contributes to the initiation and progression of CVD. In this review, we highlight innovations of lncRNA/circRNA -miRNA-mRNA axis in the development of CVDs including atherosclerosis, myocardial infarction (MI), cardiac hypertrophy and heart failure (HF) and cardiomyopathy.

2. LncRNA/circRNA-miRNA-mRNA axis in the pathophysiology of CVDs

In response to stress stimuli, apoptosis, autophagy, necrosis, fibrosis as well as proliferation and migration of cardiomyocytes and endothelial cells (ECs), cardiac fibroblasts (CFs), and vascular smooth muscle cells (VSMCs), contribute to the initiation and progression of CVDs. Meanwhile, the lncRNA/circRNA-miRNA-mRNA axis involved in the process (Fig. 1).

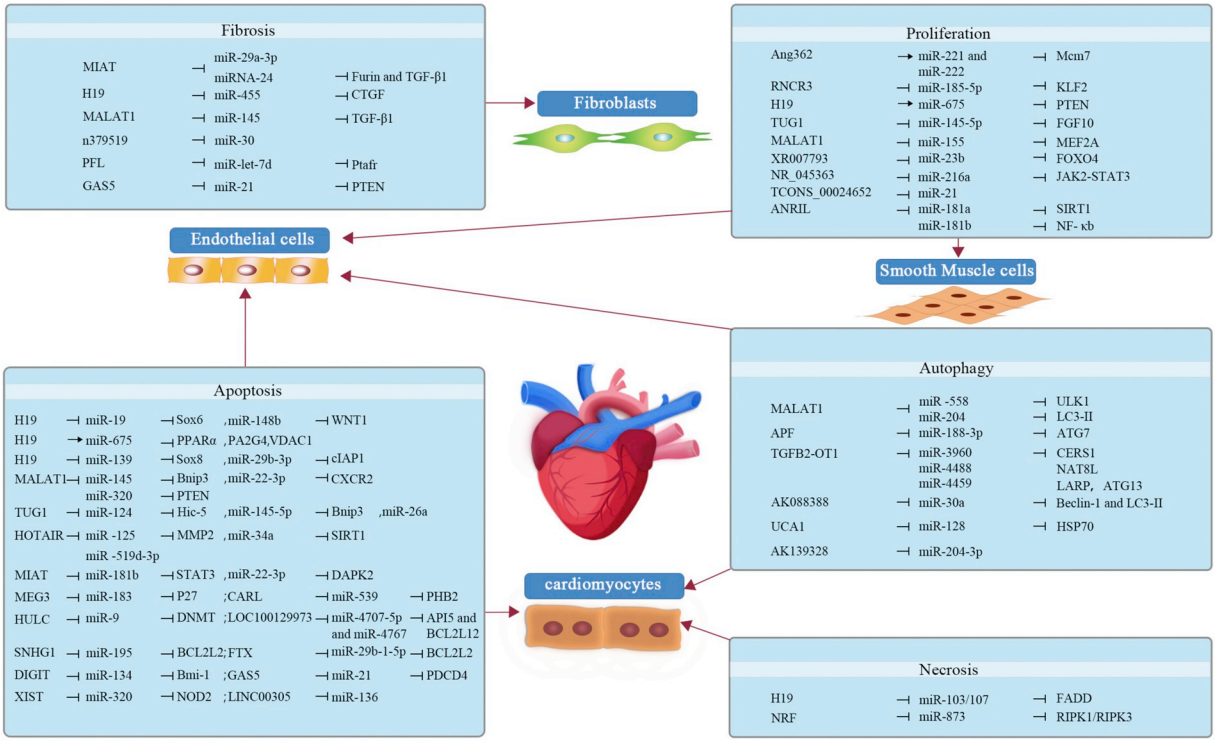

Fig. 1. LncRNA -miRNA-mRNA axis in the pathophysiology of CVDs including fibrosis, apoptosis, proliferation, autophagy and necrosis. →: Promotion, ⊣: Inhibition.

2.1. Apoptosis

Apoptosis, a highly regulated program of cell death, plays a pivotal role in the pathogenesis of a variety of cardiovascular diseases. A wide variety of apoptotic signals, including cytokines, hypoxia, increased oxidative stress and DNA damage, activate the intrinsic pathway [15], which was also associated with lncRNA/circRNA-miRNA-mRNA axis. Cardiac apoptosis-related lncRNA (CARL) inhibited the expression of miR-539 via a sponge effect causing upregulation of the downstream target prohibitin 2 (PHB2) to maintain the homeostasis of mitochondrial dynamics and reduce apoptosis [16]. LncRNA small nucleolar RNA host gene 1 (SNHG1) levels decreased in human cardiomyocytes in response to H_2O_2. Overexpressed SNHG1 plays a crucial role in regulating cell viability and apoptosis by inhibiting and increasing the expressions of miR-195 and BCL-2 like protein 2 (BCL2L2), respectively [17]. It was shown that overexpression of lncRNA five prime to Xist (FTX) inhibited apoptosis in H_2O_2 treated cardiomyocyte and ischemia-reperfusion (I/R) injury mice model by negatively regulating miR-29b-1-5p, targeting BCL2L2 [18]. LncRNA H19 upregulated the expression of sex-determining region Y-box 6 (Sox6) by sponging miR-19b and exert anti-apoptosis effect in cardiomyocyte cell line P19CL6 cells [19]. A circRNA transcribed from the sodium/calcium exchanger 1 (ncx1) gene (circNCX1) played a critical role in the regulation of cardiomyocyte apoptosis by modulating miR-133a-3p and its target cell death-inducing protein (CDIP1). Knockdown of ncx1 reduced apoptosis of H9c2 cells treated with H_2O_2, as well as in I/R injury heart by inhibiting miR-133a-3p expression and reducing the level of CDIP1 [20].

In tumor necrosis factor-α (TNF-α)-stimulated human umbilical cord vein endothelial cells (HUVECs), lncRNA highly upregulated in liver cancer (HULC) regulated the development of apoptosis by inhibiting miR-9 in a process related to DNA methyltransferases [21]. TUG1 expression decreased in ApoE(−/−) mice or ECV304 cells treated with tanshinol, inhibition of TUG1 could attenuate the apoptosis of ECs by upregulating the level of miR-26a [22]. LINC00305 was induced by hypoxia and acted as a molecular sponge for miR-136 to regulate proliferation and apoptosis of HUVECs [23]. LOC100129973 functions as an endogenous sponge of miR-4707-5p and miR-4767. It also directly targeted apoptosis inhibitor 5 (API5) and BCL2 like 12 (BCL2L12) to improve endothelial function by inhibiting apoptosis in vascular endothelial cells (VECs) [24]. LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) reduced the protective effects of fentanyl in hypoxia/reoxygenation (H/R)-HL-1 cells. Through sponging miR-145, MALAT1 upregulated the expression of apoptosis-related gene Bcl2/adenovirus EIB 19kD-interacting protein 3 (BNIP3), and thus alleviated the cardioprotective effects of fentanyl as detected by lactate dehydrogenase release and cell apoptosis [25]. Has_circ_0010729 was significantly upregulated in HUVECs under hypoxia and contained complementary binding sites with miR-186 to act as a miRNA sponge. Additionally, Has_circ_0010729/miR-186 regulated VECs proliferation and apoptosis by targeting hypoxia-inducible factor 1α (HIF-1α) [26]. CircRNA-ZNF609 was identified as a functional sponge of miR-615-5p. Silencing this circRNA increased ECs migration and tube formation and suppressed pathological angiogenesis and apoptosis by directly regulating the level of miR-615-5p, subsequently down-regulating the expression of its target myocyte enhancer factor-2A (MEF2A) [27].

2.2. Autophagy

Autophagy plays dual roles in cardiovascular diseases through adaptive or maladaptive regulation [28]. Impaired autophagy contributes to cardiovascular disease development, which also was regulated by lncRNA/circRNA-miRNA-mRNA axis. The lncRNA autophagy promoting factor (APF) targets miR-188-3p, which caused upregulation of autophagy-related gene 7 (ATG7) to promote cardiomyocyte autophagy in myocardial I/R injury [29]. The lncRNA TGFB2 overlapping transcript 1 (TGFB2-OT1, also known as FLJ11812) contained binding sites for three miRNAs (miR-3960, miR-4488, and miR-4459) and acted as a sponge. Up-regulated expression of TGFB2-OT1 promoted autophagy and inflammation in VECs by inhibiting miR-3960, miR-4488, miR-4459, and up-regulating their respective targets ceramide synthase 1 (CERS1), *N*-acetyltransferase 8-like [GCN5-related, putative] (NAT8L), and La ribonucleoprotein domain family, member 1 (LARP1) [30]. Consistently, TGFB2-OT1 increased ATG13 to promote the autophagy in HUVECs by sponging miR-4459 [31]. MALAT1, which contains potential miR-558 binding sites, increased autophagy of cardiomyocyte by inhibiting the expression of miR-558 targeting unc-51-like kinase 1 (ULK1) in isoproterenol (ISO)-treated H9c2 cells, while these effects were reversed by knockdown of MALAT1 [32]. In another study, it was proposed that MALAT1 regulated autophagy in myocardial I/R injury by inhibiting miR-204, which exert function through regulating microtubule-associated protein 1 light chain 3 (LC3-II) and need further study [33]. LncRNA AK088388 was found to regulate autophagy in cardiomyocytes by acting as an endogenous RNA sponge of miR-30a under H/R conditions. Inhibition of AK088388 increased the levels of miR-30a and attenuated the expression of Beclin-1 and LC3-II, which led to a sharp reduction in cardiomyocyte damage and autophagy [34]. The level of lncRNA urothelial carcinoma-associated 1 (UCA1) was decreased in both H/R treated H9c2 cells and I/R injured heart, which caused the up-regulation of miR-128 and reduced the target heat shock protein 70 (HSP70). Interestingly, morphine post-conditioning reversed the levels of UCA1, miR-128, and HSP70, attenuating cell autophagy and cardiac injury [35]. Knockdown of AK139328 inhibited apoptosis and autophagy of cardiomyocyte in I/R injury diabetic mice. The AK139328 contained a binding site for miR-204-3p has been reported to play an essential role in autophagy and apoptosis [36].

2.3. Necrosis

Necrosis is a pathological process of cardiac disease and is most prominent in myocyte injury [37]. The lncRNA nuclear respiratory factor (NRF) plays a critical role in the regulation of cardiomyocyte necrosis by competing with miR-873, which in turn regulates the receptor-interacting serine/threonine-protein kinase 1/ receptor-interacting serine/threonine-protein kinase 3 (RIPK1/RIPK3) pathway in cardiomyocytes treated with H_2O_2 [38]. In another study, H19 bound directly to miR-103/107, suppressing its expression and targeting Fas-associated protein with death domain (FADD) to control cardiomyocyte necrosis in H_2O_2 treated H9c2 cells and a mouse I/R model [39].

2.4. Proliferation and migration

The proliferation and migration of ECs and VSMCs were involved in vascular remodeling, which were also regulated by lncRNAs. For instance, smooth muscle and endothelial cell-enriched migration/differentiation-associated long noncoding RNA (SENCR) inhibits high glucose induced VSMCs proliferation and migration by down-regulated the expression of forkhead box O(FoxO)1 and transient receptor potential canonical (TRPC)6 [40]. Silencing SENCR promotes proliferation and migration of ECs by inhibiting CC chemokine ligand 5 (CCL5) and CX3CL1 expression [41]. Smooth muscle enriched smooth muscle-induced lncRNA enhances replication (SMILR) derived smooth muscle cell proliferation by controlling the hyaluronan synthase 2 (HAS2) expression [42]. LncRNA antisense non-coding RNA in the INK4 locus (ANRIL also known as CDKN2B-AS) could reduce the proliferation of VSMCs by inhibiting the INK4/ARF/p53 pathway [43]. Over-expression of ANRIL contributes to proliferation of VSMCs accompanied by down-regulation of miR-181a and up-regulation of Sirtuin 1 (SIRT1) [44]. In another research, over-expression of ANRIL promotes the proliferation of ECs by sponging miR-181b, activating nuclear factor-kappa B (NF-κb) signaling [45]. Many studies confirmed that the lncRNA/circRNA-

miRNA-mRNA axis was also involved in proliferation and migration of proliferation and migration of ECs and VSMCs. Lnc-Ang362 exerts a coregulatory function with neighboring genes (miR-221 and miR-222). These two miRNAs were overexpressed in response to angiotensin II (Ang II) and co-transcribed with Ang362 to regulate the proliferation of VSMCs. The knockdown of Ang362 inhibited proliferation of VSMCs by attenuating expression of miR-221/222 and minichromosomal maintenance 7 (Mcm7) [46]. LncRNA myocardial infarction-associated transcript (MIAT) knockdown was found to inhibit the proliferation and migration of ECs. Moreover, MIAT can regulate ECs function by sponging miR-150-5p and directly targeting vascular endothelial growth factor (VEGF) [47]. Knockdown of the lncRNA Retinal non-coding RNA3 (RNCR3) decreased ECs and VSMCs proliferation in aortic atherosclerotic lesions in vivo, inhibited the proliferation and migration of ECs and VSMCs, and promoted apoptosis. This fact indicates the participation of RNCR3 sponging miR-185-5p, targeting kruppel-like factor 2 (KLF2) in vascular dysfunction [48]. LncRNA taurine up-regulated gene 1 (TUG1) promoted the proliferation and migration of VSMCs by increasing fibroblast growth factor 10 (FGF10) by sponging miR-145-5p [49]. LncRNA XR007793 expression was significantly increased in injured rat aortic cell. XR007793 regulates VSMCs dysfunction by negatively regulating miR-23b and then directly targeting FoxO4 [50]. H19 is the host gene of miR-675, the release of miR-675 could target the phosphatase with tensin homology (PTEN) to promote VSMCs proliferation in vitro and increase restenosis in vivo [51]. In CoCl2 -induced cardiac stem cells hypoxia injury, MALAT1 drastically increased and inhibiting miR-155 by targeting MEF2A [52]. The over-expression of NR_045363 enhanced cardiomyocyte proliferation after MI by directly suppressing the expression of miR-216a and subsequently increasing the level of its target Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3) [53]. In TNF-α exposed HUVECs, the expression of TCONS_00024652 was upregulated by reduction of miR-21 expression, promoting cell proliferation, migration, and angiogenesis [54]. Hsa_circRNA-0054633 expression increased under high-glucose conditions. Decreased hsa_circRNA-0054633 expression led to high-glucose-induced ECs dysfunction. Researchers also observed that circRNA-0054633 inhibited miR-218 and promoted the expression of roundabout 1 (ROBO1) and heme oxygenase 1 (HO-1) to elevate ECs proliferation and migration [55]. Hsa_circ_0007422 (SATB2) was implicated in proliferative VSMCs. SATB2 and miR-939 do not mutually coregulate each other, but SATB2 affected the level of stromal interaction molecule 1 (STIM1), which is the miR-939 target gene. These findings suggested that SATB2 affected differentiation, proliferation, apoptosis, and migration of VSMCs through miR-939/STIM1 [56]. CircWDR77 acted as a miR-124 sponge in VSMCs induced by high glucose and targeted fibroblast growth factor 2 (FGF2) to regulate VSMCs proliferation and migration [57].

2.5. Fibrosis

Cardiac fibrosis the excessive activation of (mostly) resident CFs and plays a vital part in regulating heart function in the development of HF. In ISO-induced cardiac fibrosis, the level of growth arrest-specific 5 (GAS5) was downregulated, while the level of miR-21 was upregulated. Overexpression of GAS5 blocked the activation of CFs by negatively regulating miR-21 targeting PTEN [58]. Another interesting study reported that MIAT and miR-29a interacted with each other and played an important role in the control of fibrosis in hypertrophic cardiomyopathy [59]. In addition, MIAT was also found to promote collagen accumulation and fibroblasts proliferation through sponging miRNA-24, which targets Furin and transforming growth factor-β1 (TGF-β1) in MI-induced cardiac fibrosis. In a diabetic animal model and Ang II-induced CFs, knockdown of lncRNA H19 increased miR-455 levels, which decreased synthesis of fibrosis-related proteins including collagen I, III, and α-smooth muscle actin (α-SMA) by targeting connective tissue growth factor (CTGF) [60]. In MI heart and Ang II-treated CFs, the level of MALAT1 was upregulated when the expression of miR-145 was downregulated, and the downregulated miR-145 increased TGF-β1 activity resulting in fibroblast proliferation, collagen production, and α-SMA expression. This effect was reversed by MALAT1 knockdown [61]. The lncRNA pro-fibrotic lncRNA (PFL) is involved in cardiac fibrosis, which is also associated with TGF-β1 axis. PFL was found to be upregulated in TGF-β1-treated CFs and MI mice. PFL exerts its pro-fibrotic function through negative regulation of anti-fibrotic miRNA let-7d. Inhibition of let-7d resulted in cell proliferation and fibroblast-myofibroblast transition by targeting the platelet-activating factor receptor (Ptafr). Increased expression of let-7d improved cardiac function and attenuated cardiac fibrosis after MI. These studies indicate that PFL is a novel therapeutic target for cardiac fibrosis [62]. High expression of lncRNA n379519 was observed in the MI mice and TGF-β1-induced CFs. Knockdown of n379519 significantly downregulated the expression of fibrosis genes (collagen 3A1, collagen 8A1, and fibronectin) and α-SMA, and inhibited cardiac fibrosis by sponging miR-30 [63].

Similarly, circRNA_000203 and circRNA_010567 were also significantly over-expressed in Ang II-treated CFs and diabetic mouse myocardium. CircRNA_000203 contains two potential binding sites for miR-26b-5p, whose targets are human type I collagen α2 (Col1a2) and CTGF which exert pro-fibrosis effects [64]. CircRNA_010567 contained complementary binding sites with miR-141 acting as miRNA sponges, targeting the TGF-β1 pathway to participate in the pathogenesis of myocardial fibrosis. Moreover, circRNA_010567 knockdown increased miR-141 expression and suppressed collagen I, collagen III, and α-SMA through the TGF-β1 pathway. Overall, the circRNA_010567-miR-141-TGF-β1 axis is a promising therapeutic target that regulates myocardial fibrosis in cardiomyopathy [65].

3. LncRNA/circRNA-miRNA-mRNA axis in CVDs

CVDs is complex and includes disorders of the heart and blood vessels including atherosclerosis, MI, cardiac hypertrophy and HF, and cardiomyopathy. Non coding RNAs such as lncRNA, circRNA, miRNA are changed in response to the certain stresses and involved in the pathology of CVDs (Tables 1, 2).

3.1. Atherosclerosis

Atherosclerosis, one of the most common vascular abnormalities, is a member of progressive vascular disease characterized by inner narrow artery due to the abnormal lipid metabolism and inflammation [66]. Several research groups investigated the role of lncRNAs in oxidized low-density lipoprotein (ox-LDL)-induced atherosclerosis cell model. MALAT1 expression was upregulated in ox-LDL-treated ECs and could protect ECs by competing with miR-22-3p and up-regulating its target, CXC chemokine receptor 2 (CXCR2), which is involved in the AKT pathway [67]. In addition, H19 was also upregulated in ox-LDL-treated Raw264.7 cells and blood samples from patients with atherosclerosis, indicating it was associated with inflammation. H19 could upregulate anti-inflammatory cytokines (IL-4, IL-10)/CD163 and downregulate pro-inflammatory cytokines (TNF-α, IL-1β)/CD68 via inhibition of miR-130b [68]. H19 can also enhance proliferation and decrease apoptosis in ox-LDL-induced human aorta (HA)-VSMCs. This is achieved by inhibiting miR-148b, causing a negative feedback to promote wnt family member 1 (WNT1) expression [69]. Similarly, the lncRNA GAS5 has been shown to promote an inflammatory response in ox-LDL induced macrophages, as well as upregulate matrix metalloproteases (MMPs) by sponging miR-221 [70]. Knockdown of GAS5 inhibited inflammatory injury in PA-treated H9c2 cells by sponging miR-26a targeting high mobility group box 1 (HMGB1) and NF-κb [71]. Other studies have shown that GAS5 transcription was affected by the rs145204276 polymorphism. In ECs, high glucose caused a significant increase in GAS5 and its target gene programmed cell death 4 (PDCD4) via negatively regulating miR-21, which influenced proliferation and apoptosis

Table 1
LncRNA-miRNA-mRNA axis in CVDs.

Disease	Expression	LncRNA	miRNA	mRNA	Function	Ref
Atherosclerosis	↓	HULC	miR-9	DNMT	Apoptosis (−)	[21]
	↓	TUG1	miR-62a	–	Apoptosis (+)	[22]
	↑	MALAT1	miR-22-3p	CXCR2	Apoptosis (+);proliferation (−)	[67]
	↑	H19	miR-130b	–	Inflammation (+)	[68]
	↑	H19	miR-148b	WNT1	Apoptosis (+);proliferation (−)	[69]
	↑	GAS5	miR-221	MMP	Inflammation (+)	[70]
	↑	GAS5	miR-26a	HMGB1/NF-B axis	Inflammation (+)	[71]
	↑	GAS5	miR-21	PDCD4	Apoptosis (+);proliferation (−)	[72]
	↑	MIAT	miR-181b	STAT3	Apoptosis (−);proliferation (+)	[73]
	↑	XIST	miR-320	NOD2	Apoptosis (+)	[74]
	↑	MEG3	miR-223	NLRP3	Inflammation (+)	[75]
	↑	MEG3	miR-21	RhoB and PTEN	Proliferation (−)	[76]
	↑	DIGIT	miR-134	Bmi-1	Apoptosis (−);migration (+)	[77]
	↑	SIRST1 antisense	miR-22	Sirt1	Proliferation (+);migration (+)	[78]
	↑	RP5-833A20.1	miR-382-5p	NFIA	Inflammation (+)	[79]
MI	↓	FTX	miR-29b-1-5p	Bcl2l2	Apoptosis (−)	[18]
	↑	MALAT1	miR-145	Bnip3	Apoptosis (+)	[25]
	↑	APF	miR-188-3p	ATG7	Autophagy (+)	[29]
	↑	MALAT1	miR-204	LC3-II	–	[33]
	↑	AK088388	miR-30a	Beclin-1 and LC3-II	Apoptosis (+);autophagy (+)	[34]
	↓	UCA1	miR-128	HSP70	Autophagy (−)	[35]
	↑	AK139328	miR-204-3p	–	Apoptosis (+);autophagy (+)	[36]
	↓	NRF	miR-873	RIPK1/RIPK3	Necrosis (+)	[38]
	↓	H19	miR-103/107	FADD	Necrosis (−)	[39]
	↑	MALAT1	miR-320	PTEN	Apoptosis (+)	[81]
	↑	MALAT1	miR-125	JMJD6	Proliferation (+);migration (+)	[82]
	↑	MALAT1	miR-133	NLRP3 inflammasome	–	[83]
	↑	MALAT1	miR-144	Brg1	–	[84]
	↑	MALAT1	miR-203	–	–	[85]
	↓	HOTAIR	miR −125	MMP2	Apoptosis (−);proliferation (+)	[86]
	↓	HOTAIR	miR -519d-3p	–	Apoptosis (−)	[87]
	↑	H19	miR-675	PPARα	Apoptosis (+);inflammation (+)	[88]
	↓	H19	miR-200a-3p	SIRT1	Proliferation (+);migration (+)	[89]
	↑	H19	miR-139	Sox8	Apoptosis (−);migration (+)	[90]
	↓	H19	miR-29b-3p	cIAP1	Apoptosis (−)	[91]
	↑	MEG3	miR-183	P27	Apoptosis (+);migration (−)	[92]
	↑	MEG3	miR-22	HMGB1	Proliferation (−)	[93]
	↓	TUG1	miR-145-5p	Binp3	Apoptosis (+);migration (−)	[94]
	↓	TUG1	miR-124	Hic-5	Apoptosis (−);migration (+);proliferation (+)	[95]
Hypertrophy And heart failure	↑	ROR	miR-133	–	Hypertrophy (+)	[99]
	↑	CHRF	miR-93	Akt3	Hypertrophy (+)	[100]
	↑	CHRF	miR-489	MyD88	Hypertrophy (+)	[101]
	↓	HOTAIR	miR-19	PTEN	Hypertrophy (−)	[102]
	↑	MIAT	miR-150	P300	Hypertrophy (+)	[104]
	↑	MIAT	miR-93	TLR4	Hypertrophy (+)	[105]
	↑	Plscr4	miR-214	Mfn2	Hypertrophy (−)	[106]
	↑	H19	miR-675	CaMKIIδ	Hypertrophy (−)	[107]
	↑	XIST	miR-101	TLR2	Hypertrophy (+)	[108]
	↑	XIST	miR-330-3p	S100B	Hypertrophy (−)	[109]
	↑	CASC15	miR-432-5p	TLR4	Hypertrophy (+)	[110]
	↑	UCA1	miR-184	HOXA9	Hypertrophy (+)	[111]
Cardiomyopathy	↑	H19	miR675	PA2G4	Apoptosis (+)	[113]
	↓	H19	miR675	VDAC1	Apoptosis (−);inflammation (−)	[114]
	↑	MIAT	miR-22-3p	DAPK2	Apoptosis (+)	[115]
	↓	HOTAIR	miR-34a	SIRT1	Apoptosis (−)	[116]

↑: Increase, ↓: Decrease, +: Promotion, −: Inhibition.

[72]. Furthermore, the lncRNA MIAT act as a competing endogenous RNA (ceRNA) to increase expression of STAT3 by sponging miR-181b in HA-VSMCs and U937 cells treated with ox-LDL [73]. Knockdown of the lncRNA X-inactive specific transcript (XIST) played a protective role in ox-LDL exposed HUVECs by modulating miR-320 targeting nucleotide-binding oligomerization domain 2 (NOD2) [74]. Moreover, maternally expressed gene 3 (MEG3) promoted ox-LDL induced ECs pyroptosis by endogenously competing with miR-223, and then enhancing NLRP3. Meanwhile, melatonin inhibits the expression of pyroptosis-related genes in high-fat diet-treated ApoE(−/−) mice through affecting MEG3-miR-223-NLRP3 axis [75]. In addition, MEG3 also was increased in ECs after treatment with TNF-α and inhibited ECs proliferation and type I collagen, type V collagen, and proteoglycan expression partly by suppressing miR-21 levels, targeting GTPase ras homolog gene family, member B (RhoB) and PTEN [76]. Silencing LncRNA divergent to GSC induced by TGF-b family signaling (DIGIT) attenuated cell growth, migration, and tube formation. Interestingly, it was also found that DIGIT stimulated apoptosis in human microvascular endothelial cells 1 via regulation of Bmi-1 expression by suppressing miR-134 [77]. The axis of SIRT1 antisense lncRNA/miR-22 targeting SIRT1 regulated senescence, proliferation, and migration in nicotinamide phosphoribosyltransferase (NAMPT)-treated endothelial progenitor cells [78]. RP5-833A20.1 was overexpressed in human acute monocytic leukemia macrophage-derived foam cells and increased the expression of miR-382-5p by suppressing downstream target gene nuclear factor IA (NFIA) to regulate cholesterol homeostasis and inflammatory responses [79].

Table 2
The circRNA–miRNA–mRNA axis in CVD.

Cell dysfunction/disease	Expression	circRNA	miRNA	mRNA	Function	Ref
Apoptosis	↑	circNCX1	miR-133a-3p	CDIP1	Promoted cardiomyocyte apoptosis and I/R injury	[20]
	↑	has-circ-0010729	miR-186	HIF-1α	Inhibited apoptosis and promoted proliferation	[26]
	↑	cZNF609	miR-615-5p	MEF2A	Inhibited cell proliferation and promoted cell apoptosis	[27]
Proliferation	↑	has-circ-0054633	miR-218	ROBO1, HO1	Protected endothelial cell dysfunction	[55]
	↑	circ-SATB2	miR-939	STIM1	Promoted proliferation and migration	[56]
	↑	circ-WDR77	miR-124	FGF-2	Promoted proliferation of VSMCs	[57]
Fibrosis	↑	circ-000203	miR-26b-5p	Col1a2 and CTGF	Inhibited anti-fibrosis effect	[64]
	↑	circ-010567	miR-141	TGF-β1	Promoted fibrosis	[65]
MI	↑	CDR1as	miR-7a	PARP, SP1	Increased cardiac infarct size and promoted apoptosis	[96]
	↑	MFACR	miR-652-3p	MTP18	Upregulated mitochondrial fission and apoptosis	[97]
Hypertrophy and HF	↓	HRCR	miR-223	ARC	Suppressed cardiac hypertrophy	[112]

↑: Increase, ↓: Decrease.

3.2. Myocardial infarction

MI is common in CVDs and one of the leading causes of morbidity and mortality [80]. It had been found that some miRNAs, lncRNAs and circRNAs are associated with incurrences of MI. Many studies have shown that MALAT1 over-expression is linked to pathogenesis in MI and myocardial I/R injury. The axis of MALAT1-miR-320-PTEN could promote myocardial apoptosis in an MI mouse model [81]. Suppression of MALAT1 could inhibit cardiac progenitor cell (CPC) proliferation by sponging miR-125 targeting jmjC domain-containing protein 6 (JMJD6) with CoCl2-induced hypoxia [82]. The other three studies proposed that MALAT1 serves as a ceRNA to inhibit miR-133 by targeting nod-like receptor protein-3 (NLRP3) inflammasome and inhibit miR-144 by targeting brahma-related gene 1 (Brg1), as well as inhibit miR-203 in myocardial I/R injury [83–85] . However, all presented proposals need further experimental research to confirm. Interestingly, in H9c2 cells under oxidative stress, a network of HOX antisense intergenic RNA (HOTAIR), miR-125 and matrix metalloproteinase 2 (MMP2) is involved in regulating cardiomyocyte proliferation and apoptosis [86]. Knockdown of HOTAIR caused a reduction in MMP2 expression, which was reversed by an inhibitor of miR-125. In addition, HOTAIR also exert anti-apoptosis of cardiomyocyte partly through inhibition of miR-519d-3p [87]. Many recent studies have shown that H19 affects multiple functions of cells through interaction with many different miRNAs. In myocardial I/R injury mice and oxygen-glucose deprivation and reperfusion treated cardiomyocytes, both lncRNA H19 and its encoded miR-675 levels increased by negatively regulating poly ADP-ribose polymerase (PPAR)α [88]. On the other hand, inhibition of H19 has been shown to reduce proliferation and migration of CPCs by sponging miR-200a-3p targeting SIRT1 during CoCl2 induced hypoxia, where the regeneration of CPCs plays a vital role in the process of heart failure after MI [89]. In addition, H19 knockdown can promote the hypoxia-induced injury role of miR-139, inhibit Sox8 expression, and further increase hypoxia-induced cell injury via mitogen-activated protein kinase and the PI3K/AKT/mTOR pathway [90]. Interestingly, down-regulated H19 increased the expression of miR-29b-3p, and then H19 modulated the expression of cellular inhibitor of apoptosis protein 1 (cIAP1) through miR-29b-3p in hypoxic postconditioning treated aged cardiomyocytes [91]. Moreover, the MEG3 sponging of miR-183 targeting P27 axis participated in cell migration and invasion, as well as apoptosis, and the MEG3 sponging miR-22 targeting HMGB1 axis is involved in CPC proliferation induced by 0.5% O2 [92,93]. Two independent experiments demonstrated that TUG1 promoted hypoxia-induced myocardial injury in H9c2 via inhibition of miR-145-5p and miR-124, leading to the up-regulation of BNIP3 and hydrogen peroxide-inducible clone-5 (Hic-5), respectively [94,95]. Those LncRNA-miRNA-mRNA axes may provide the therapeutic target or strategy for MI.

CircRNA cerebellar degeneration-related protein 1 transcript (Cdr1) as functioned as a sponge of miR-7a to promote cardiac injuries by suppressing the activity of miR-7a and upregulating the expression of miR-7a targets such as PARP and SP1 [96]. Mitochondrial fission and apoptosis-related circRNA (MFACR) modulates mitochondrial fission and apoptosis by acting as a sponge of miR-652-3p. Mitochondrial protein 18 (MTP18), which is the downstream target of miR-652-3p, is a nuclear gene involved in mitochondrial fission, apoptotic cardiomyocyte death, and MI [97]. Thus, the Cdr1as-miR-7a-PARP/SP1 or MFACR-miR-652-3p-MTP18 axis may be as a potential therapeutic target for MI.

3.3. Hypertrophy and heart failure

Cardiac hypertrophy is a response triggered by a wide variety of stimuli, including hemodynamic overload, neurohormonal activation and ischemia. Thought to be initially adaptive, this response involves structural, morphological, and functional changes in cardiac myocytes, including increases in cell size, thereby provoking an overall growth in heart mass and leading to the HF [98].

Previous studies showed that the lncRNA regulator of reprogramming (ROR) plays essential roles in the pathogenesis of cardiac hypertrophy. In a hypertrophic mouse model and cardiomyocytes treated with phenylephrine (PE), the expression of lncRNA-ROR was upregulated, while decreased levels attenuated the response of cardiac hypertrophy. LncRNA-ROR promoted cardiac hypertrophy by acting as a sponge for miR-133, which is known as an anti-hypertrophic miRNA [99]. LncRNA cardiac hypertrophy related factor (CHRF) can bind directly to miR-93 and act as an endogenous miR-93 sponge to inhibit its activity. Knockdown of CHRF protected cardiac hypertrophy by reversing the effect on miR-93 which resulted in decreased expression of Akt3 [100]. In another study, CHRF was found to be upregulated in hypertrophic hearts in both murine and human HF samples and served as a sponge for miRNA-489 by targeting myeloid differentiation primary response gene 88 (Myd88) to induce cardiomyocyte hypertrophy [101]. In transverse aortic constriction (TAC) surgery-induced cardiac hypertrophy and Ang II-treated cardiomyocytes, HOTAIR was significantly decreased when the expression of miR-19 increased. Overexpression of HOTAIR plays a protective role in hypertrophy by sponging miR-19 targeting PTEN [102]. MIAT was also overexpressed in AngII-induced cardiac hypertrophy and promoted pathological progression by inhibiting the expression of miR-150 [103]. Consistently, MIAT exerted a protective effect in hypertrophy via up-regulation of P300, a target of miR-150, which was also reported to play an important role in hypertrophy [104]. In addition, MIAT functioned as a molecular sponge of miR-93, whose downstream target is toll-like receptor 4 (TLR4) [105]. Furthermore, LV et al. revealed that overexpression of the lncRNA Plscr4 reduced hypertrophic growth in Ang II-treated cardiomyocytes and hypertrophic mouse hearts, resulting in the protection of cardiac function and inhibition of cardiac fibrosis. The Plscr4 acted as an endogenous sponge of miR-214 and could stimulate the expression of mitofusin 2 (Mfn2) and attenuate hypertrophy [106]. Moreover, H19 and its encoded miR675 are both upregulated in TAC

surgery induced hypertrophy heart and PE treated cardiomyocytes and inhibited cardiomyocyte hypertrophy by targeting Ca2 + /calmodulin-dependent protein kinase II delta (CaMKIIδ) [107]. In the latest study, in both cardiomyocyte treated with PE and in mouse models confronted with TAC surgery, the levels of XIST were significantly upregulated which aggravated pathological hypertrophy development by suppressing miR-101 targeting TLR2 [108]. In contrast, XIST also could attenuate cardiomyocyte hypertrophy by sponging miR-330-3p targeting S100B [109]. Knockdown of lncRNA CASC15 can decrease hypertrophic factors including atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), and β-myosin heavy chain (β-MHC) in vivo and in vitro. CASC15 performs as a ceRNA of miR-432-5p and forms a negative feedback loop with TLR4 to participate in the pathology of cardiac hypertrophy [110]. The lncRNA UCA1 downregulated miR-184 through targeting homeobox A9 (HOXA9) in PE-treated hypertrophic cardiomyocytes and TAC induced hypertrophic heart [111]. It was also reported that heart-related circRNA (HRCR) increased the level of ARC by sponging miR-223, which decreased hypertrophy in a mice model in vivo and in cardiomyocytes in vitro [112].

3.4. Cardiomyopathy

Cardiomyopathy, a group of diseases that affect the myocardium, often leads to cardiovascular events-related death or progressive heart failure-associated disability. Understanding the effect of lncRNA–miRNA–mRNA axis on the pathophysiology of cardiomyopathy favor the development of novel therapeutic strategies.

In a previous study, Zhang et al. found that in a rat model of adriamycin-induced dilated cardiomyopathy, the lncRNA H19 was overexpressed in myocardial tissue. Moreover H19 promoted cardiomyocyte apoptosis by upregulating miR675, which targets expression of the anti-apoptosis gene proliferation-associated protein 2G4 (PA2G4) to exert its function [113]. This study indicated that the H19/miR-675/PA2G4 axis could be useful as a new therapeutic strategy for treating adriamycin-induced dilated cardiomyopathy. In another study, high-glucose conditions resulted in the downregulation of H19 and promoted cardiomyocyte apoptosis by inhibiting miR675. Other study showed that voltage-dependent anion channel 1 (VDAC1), a key protein in the process of apoptosis and is mediated by the mitochondria, could be inhibited by lncRNA H19/miR-675 and involved in apoptosis in diabetic cardiomyopathy [114]. MIAT exerts its function by sponging miR-22-3p and directly targeting death-associated protein kinase 2 (DAPK2), which leads to cardiomyocyte apoptosis in the pathogenesis of diabetic cardiomyopathy [115]. It was shown that overexpression of lncRNA HOTAIR inhibits streptozotocin-induced oxidative injury, inflammation, and apoptosis in vitro. Moreover, HOTAIR plays a crucial role in high-glucose-induced cardiomyocyte injury in H9c2 by acting as a sponge of miR-34a targeting SIRT1 [116].

4. Conclusion and outlook

In the past decade, ncRNAs have become one of the most widely examined research areas of the development of CVDs. However, the regulation of lncRNAs and circRNAs in disease conditions and their potential as therapeutic or diagnostic indicators of CVDs is in its early stage. The regulatory network of lncRNA/circRNA–miRNA–mRNAs needs to be advanced with more novel discoveries. In this review, we summarized lncRNA–miRNA–mRNA axes by cell dysfunction and development of CVDs.

Several phase I and II clinical trials have revealed the potential for the development of miRNA and lncRNA-based therapeutics. These developments have provided a foundation for future applications of ncRNAs for treating CVDs, regulatory networks of lncRNA/circRNA–miRNA–mRNA might also be improved with additional avenues of research. The research scenario includes: (1) complex crosstalk among lncRNAs/circRNAs, miRNAs, and mRNAs, and underlying regulatory mechanisms yet to be discovered; (2) the identification of ncRNAs and their targets in a tissue-specific or cell-type-specific manner, as potential therapeutics is desirable. Finally, (3) challenge to integrate laboratory and clinical research and translate experimental results into clinical applications, which can be employed in large-scale clinical studies.

In this nascent field, continuous efforts will be needed to incorporate ncRNAs into clinical practice. In-depth studies will provide a foundation for the development of clinical diagnoses and treatment options, utilizing lncRNA/circRNA–miRNA–mRNA axes in CVDs.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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