Molecular Therapy
Nucleic Acids
Review

Autophagy in cardiovascular diseases: role of noncoding RNAs

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Cardiovascular diseases (CVDs) remain the world's leading cause of death. Cardiomyocyte autophagy helps maintain normal metabolism and functioning of the heart. Importantly, mounting evidence has revealed that autophagy plays a dual role in CVD pathology. Under physiological conditions, moderate autophagy maintains cell metabolic balance by degrading and recycling damaged organelles and proteins, and it promotes myocardial survival, but excessive or insufficient autophagy is equally deleterious and contributes to disease progression. Noncoding RNAs (ncRNAs) are a class of RNAs transcribed from the genome, but most ncRNAs do not code for functional proteins. In recent years, increasingly, various ncRNAs have been identified, and they play important regulatory roles in the physiological and pathological processes of organisms, as well as in autophagy. Thus, determining whether ncRNA-regulated autophagy plays a protective role in CVDs or promotes their progression can help us to develop ncRNAs as therapeutic targets in autophagy-related CVDs. In this review, we briefly summarize the regulatory roles of several important ncRNAs, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), in the autophagy of various CVDs to provide a theoretical basis for the etiology and pathogenesis of CVDs and develop novel therapies to treat CVDs.

Autophagy is a dynamic equilibrium process that removes damaged cell inclusions or organelles in a lysosomal-dependent way and plays a critical role in maintaining cellular homeostasis.[1] Autophagy processes can be classified as chaperone-mediated autophagy, microautophagy, and macroautophagy depending on their physiological functions and delivery routes.[2] Among these processes, macroautophagy is the most common and deeply studied process. In this review, "autophagy" refers to macroautophagy, and this process involves the following steps: (1) initiation: after receiving external stimuli, phagophores are formed in the cytoplasm; (2) elongation: vesicles extend to wrap damaged organelles; (3) closure: vesicles are sealed into double-membrane autophagosomes; (4) maturation: autophagosomes combine with lysosomes to form autolysosomes; and (5) degradation: cytoplasmic materials are degraded by lysosomal acid hydrolases, and the products are transported to the cytoplasm for reuse.[3]

Autophagy is highly conserved in evolution. More than 30 autophagy-related genes (ATGs) have been identified in yeast, many of which have mammalian orthologs. ATGs regulate the occurrence of autophagy in a coordinated manner. Among them, beclin-1 (the mammalian ortholog of yeast ATG6) was first discovered as an important autophagosome initiation regulator that forms a class III phosphatidylinositol 3-kinase (PI3K) complex with hVsp34, p150 (Vps15), and ATG14, while the level of LC3-II (ATG8-II) is directly proportional to the autophagosome number. Thus, beclin-1 and the LC3-II/LC3-I ratio are the most widely used autophagy markers.[4] Activation of the autophagy machinery is regulated by two central modulators, mTOR (mammalian target of rapamycin) and AMPK (adenosine 5′-monophosphate [AMP]-activated protein kinase). mTOR can integrate upstream signals, such as PI3K/Akt and mitogen-activated protein kinase (MAPK)/Erk1/2 signaling, and function as a metabolic sensor to negatively regulate autophagy. AMPK can be activated at a high cellular AMP/ATP ratio, and it is an important mediator for maintaining cellular energy homeostasis. AMPK inhibits mTOR kinase activity by phosphorylating the tuberous sclerosis 1/2 (TSC1/2) complex and activates autophagy. Moreover, AMPK can phosphorylate Unc-51-like autophagy-activating kinase 1 (ULK1) to activate the class III PI3K complex.[5–7]

Cardiovascular diseases (CVDs) remain the world's leading cause of death, as more people die from CVDs each year than from any other cause. Cardiomyocyte autophagy helps maintain normal metabolism and functioning of the heart. Importantly, an increasing body of evidence supports the dual role of autophagy in the pathogenesis of CVDs.[8,9] Under physiological conditions, moderate autophagy helps maintain metabolic balance in cells through the degradation and recycling of damaged organelles and proteins, in addition to promoting myocardial survival. However, excessive or insufficient autophagy may lead to disease. Under pathological conditions, autophagy strives to ensure cell survival, but when it fails to exert its protective effect, autophagic cell death occurs. Noncoding RNAs (ncRNAs) are a class

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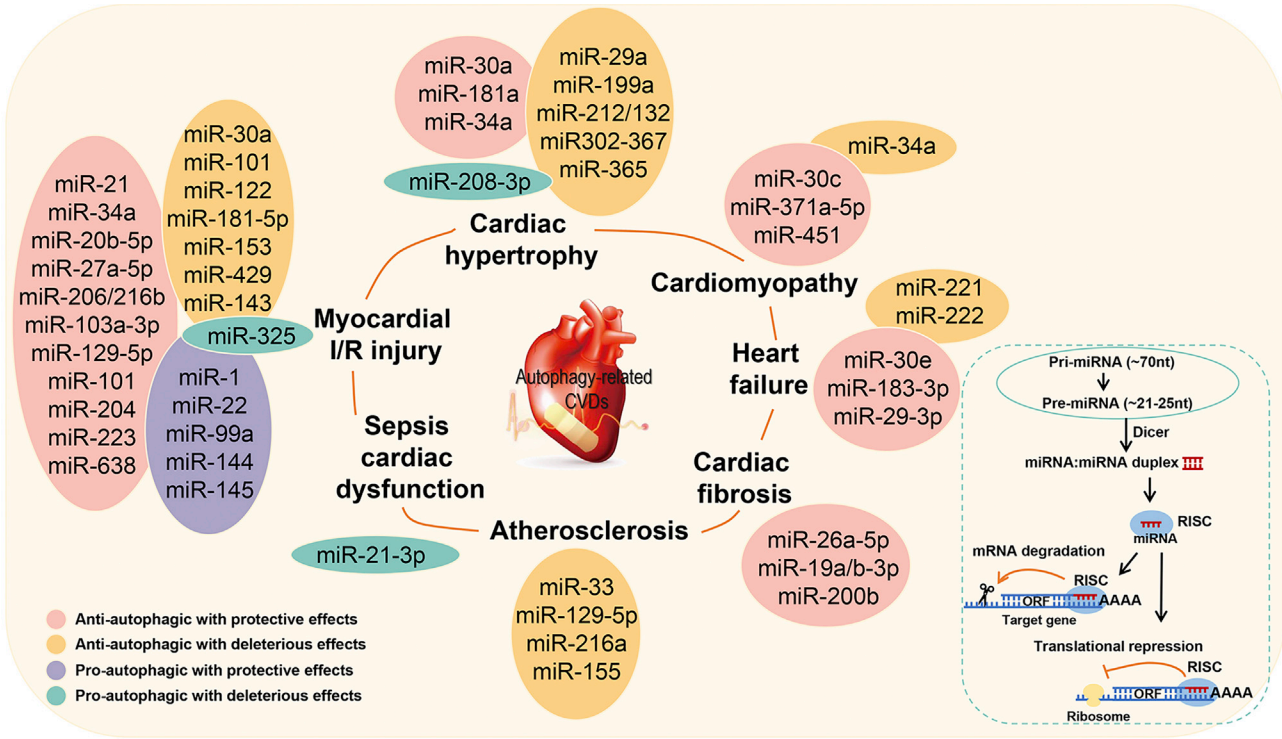

Figure 1. Regulatory roles of miRNAs in cardiac autophagy and related CVDs

miRNAs negatively regulate gene expression by completely or partially base pairing with the 3′ UTR region of the target gene, leading to the cleavage/degradation of mRNA transcripts or protein translation repression. See text and Table 1 for detailed molecular mechanism explanations. Pink oval represents anti-autophagic miRNAs with protective effects in CVDs; yellow oval represents anti-autophagic miRNAs with deleterious effects; purple oval represents pro-autophagic miRNAs with protective effects in CVDs; green oval represents pro-autophagic miRNAs with deleterious effects in CVDs.

of RNAs transcribed from the genome, but most ncRNAs do not code for functional proteins. In recent years, a large number of diverse ncRNAs have been identified, and they play important regulatory roles in the physiological and pathological processes of organisms, as well as in autophagy.[10–12] In this review, we briefly summarize the regulatory roles of several important ncRNAs, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), in the autophagy of various CVDs to provide a theoretical basis for the etiology and pathogenesis of CVDs and to facilitate the development of novel therapies for the treatment of CVDs.

miRNAs and autophagy

miRNAs constitute a class of single-stranded ncRNA molecules with lengths of 19–24 nt, and they negatively regulate gene expression at the post-translational level by completely or partially base pairing with the 3′ UTR region of the target gene, which leads to the cleavage/degradation of mRNA transcripts or protein translation repression (Figure 1). Subsequent studies have shown that a few miRNAs can also bind to the 5′ UTR or even the coding regions to exert their functions.[13,14] Typically, each miRNA can have multiple target genes, and, conversely, several miRNAs can regulate the same gene. This complex regulatory network not only can regulate the expression of multiple genes through one miRNA, but it also can finely regulate the expression of a gene through the combination of several miRNAs. Recent studies have found that miRNAs participate in the regulation of autophagy by regulating the expression of ATGs and play an important role in the development of organisms and the occurrence of CVDs. Significantly, it has been found that autophagy not only has different characteristics in different physiological states but also has different effects on cardiomyocytes in different states. The first reported autophagy-related miRNA contributing to cardiac pathologies was miR-204, which plays a role during myocardial ischemia/reperfusion (I/R) injury.[15] Since then, many dysregulated autophagic miRNAs (see Table 1 and Figure 1 for a complete list) have been implicated in various CVDs.

miRNAs, autophagy, myocardial infarction (MI), and myocardial I/R injury

Autophagy plays a key role in maintaining energy production and myocardial viability during myocardial ischemia.[69] Reperfusion therapies, including thrombolysis, interventional treatment, and coronary artery bypass grafting can benefit patients with MI by restoring blood flow. However, subsequent I/R injury increases the risk of cardiac dysfunction, heart failure (HF), and death. In the early stage of myocardial ischemia, starvation occurs owing to the lack of cellular nutrients. In this stage, autophagy recovers amino acids to synthesize the proteins necessary for survival and degrades damaged organelles, thereby

Table 1. Dysregulated miRNAs and their roles in autophagy during the progression of CVDs

miRNAs	Roles in autophagy	Target genes/signaling pathways	Outcomes	Refs.
Myocardial infarction/injury				
miR-20b-5p	anti-	ULK1	↓ H/R-induced injury	16
miR-21	anti-	Akt/mTOR	↓ myocardial apoptosis	17
miR-27a-5p	anti-	Atg7	↓ hypoxia-induced injury	18
miR-34a	anti-	TNF-α	↓ myocardial I/R injury	19
miR-101	anti-	DDIT4	↓ myocardial I/R injury	20
miR-103a-3p	anti-	Atg5	↓ H/R-induced apoptosis	21
miR-129-5p	anti-	ATG14	↓ H_2O_2-induced apoptosis	22
miR-188-3p	anti-	ATG7	↓ myocardial I/R injury	23
miR-204	anti-	LC3-II	↓ myocardial I/R injury	15
	anti-	SIRT1	↓ H/R-induced injury	24
miR-206/216b	anti-	Atg13	↓ myocardial I/R injury	25
miR-223	anti-	PARP-1	↓ H/R-induced injury	26
miR-638	anti-	ATG5	↓ myocardial apoptosis	27
miR-30a	anti-	Beclin1	↑ myocardial injury	28
miR-101	anti-	RAB5A	↑ myocardial apoptosis	29
miR-122	anti-	PTEN/PI3K/AKT	↑ myocardial apoptosis	30
miR-153	anti-	Mcl-1	↑ myocardial apoptosis	31
miR-181b-5p	anti-	Hspa5	↑ myocardial apoptosis	32
miR-429	anti-	MO25/LKB1/AMPK	↑ myocardial I/R injury	33
miR-143	anti-	Atg7	↓ CPC survival	34
miR-1	pro-	PIK3CA	↓ myocardial injury	35
miR-22	pro-	p38α	↓ myocardial apoptosis	36
miR-145	pro-	Akt3/mTOR signaling	↓ myocardial apoptosis	37
	pro-	Angpt2	↓ myocardial I/R injury	38
	pro-	FRS2	↓ myocardial I/R injury	39
miR-144	pro-	mTOR	↓ myocardial I/R injury	40
miR-99a	pro-	mTOR/P70/S6K	↑ cardiac function	41
miR-325	pro-	ARC	↑ myocardial I/R injury	42
Cardiac hypertrophy				
miR-30a	anti-	Beclin1	↓ myocardial hypertrophy	43
miR-34a	anti-	ATG9A	↓ myocardial hypertrophy	44
miR-181a	anti-	ATG5	↓ myocardial hypertrophy	45
miR-29a	anti-	PTEN/AKT/mTOR	↑ cardiac hypertrophy	46
miR-199a	anti-	GSK3β/mTOR signaling	↑ cardiac hypertrophy	47
miR-212/132	anti-	FoxO3/calcineurin signaling	↑ cardiac hypertrophy	48
miR302-367	anti-	PTEN/PI3K/AKT/mTORC1	↑ cardiac hypertrophy	49
miR-365	anti-	Skp2	↑ cardiac hypertrophy	50
miR-208-3p	pro-	PDCD4	↑ myocardial hypertrophy	51
Cardiac fibrosis				
miR-19a/b-3p	anti-	TGF-βRII	↓ cardiac fibrosis	52
miR-26a-5p	anti-	ULK1	↓ cardiac fibrosis	53
miR-200b	anti-	–	↓ cardiac fibrosis	54

(*Continued on next page*)

Table 1. *Continued*

miRNAs	Roles in autophagy	Target genes/signaling pathways	Outcomes	Refs.
Heart failure				
miR-29-3p	anti-	SPARC	↓ cardiomyocytes apoptosis	55
miR-30e	anti-	Beclin1	↓ heart failure	56
miR-183-3p	anti-	BNIP3L	↓ Chronic systolic heart failure	57
miR-221	anti-	p27/CDK2/Mtor axis	↑ heart failure	58
miR-222	anti-	p27	↑ heart failure	59
Cardiomyopathy				
miR-451	anti-	TSC1	↓ hypertrophic cardiomyopathy	60
miR-30c	anti-	BECN1	↓ diabetic cardiomyopathy	61
miR-371a-5p	anti-	BAG3	↓ takotsubo cardiomyopathy	62
miR-34a	anti-	–	↑ diabetic cardiomyopathy	63
Atherosclerosis				
miR-33	anti-	Abca1/Atg5/Lamp1/Prkaa1	↑ atherosclerosis	64
miR-129-5p	anti-	Beclin1	↑ atherosclerosis	65
miR-155	anti-	ATG5	↑ oxidant-induced injury	66
miR-216a	anti-	Beclin1	↑ atherosclerosis	67
Sepsis cardiac dysfunction				
miR-21-3p	pro-	SORBS2	↑ cardiac dysfunction	68

reducing myocardial damage and apoptosis and maintaining cardiac function.[32] During reperfusion, because of the activation of the above autophagy pathways, increased levels of reactive oxygen species (ROS) induce mitochondrial damage, which in turn can promote autophagy. This vicious cycle leads to excessive activation of autophagy and accelerates damage to cardiomyocytes and enlargement of infarct size.[22]

Anti-autophagic miRNAs with beneficial impacts

Various miRNAs have been found to exert a protective effect against myocardial injury by inhibiting excessive autophagy. It has been reported that miR-34a and miR-101 can attenuate myocardial I/R injury through suppressing autophagy by targeting tumor necrosis factor α (TNF-α) and DNA damage-inducible transcript 4 (DDIT4), respectively.[19,20] mTOR plays a vital role in autophagy regulation, in that it negatively regulates autophagy by inhibiting ULK1, and the mTOR-dependent pathway is regulated by PI3K/Akt and MAPK/Erk1/2 signaling. Overexpression of miR-21 activates the Akt/mTOR pathway, inhibits the autophagic activity, and decreases myocardial apoptosis, thus protecting H9c2 cells against hypoxia/reoxygenation (H/R) injury.[17] In human umbilical vein endothelial cells (HUVECs) with H/R injury, propofol treatment inhibits autophagic cell death through the upregulation of miR-20b-5p and downregulation of ULK1. In contrast, in propofol-preconditioned HUVECs with H/R injury, ULK1 overexpression promotes cell autophagy and apoptosis and restrains the protective effect of miR-20b-5p.[16] In neonatal rat cardiomyocytes and H9c2 cells, it is thought that miR-223 represses hypoxia-induced apoptosis and overactivated autophagy through the Akt/mTOR pathway by targeting PARP-1.[26] ATG proteins are essential for autophagic flux. ATG13 is vital for the activation and stability of ULK1 together with the scaffold protein FIP200, and this complex is important for membrane nucleation. Ding et al.[25] reported that histamine increases miR-206 and miR-216b expression, and these molecules work in combination to downregulate ATG13, leading to the reduction of autophagy. Moreover, they demonstrated that ATG13 can interact with Fas-associated protein with death domain (FADD) to activate the caspase-8 apoptosis pathway. Thus, the miR-206-216b/ATG13 axis mediates the prohibitive role of histamine in MI-induced autophagy activation and myocardial apoptosis.[25] ATG14 is required for the membrane targeting of the PI3KC3-C1 complex and the induction of autophagy. Zhang et al.[22] revealed that ATG14 is a direct target of miR-129-5p, and ATG14 inhibition due to miR-129-5p overexpression suppresses H_2O_2-induced autophagy and apoptosis in H9c2 cells through the activation of the PI3K/Akt/mTOR pathway. Among the 41 ATG proteins, ATG5 and ATG7 are indispensable for autophagic vesicle formation.[70] miR-103-3p and miR-638 both suppress cardiomyocyte autophagy and apoptosis by targeting ATG5.[21,27] miR-27a-5p and miR-188-3p attenuate hypoxia- or A/R-induced cardiomyocyte injury by inhibiting ATG7.[18,23] Furthermore, SIRT1 and LC3-II have been recognized as potential targets of miR-204 to mediate the cardioprotective role of miR-204 on I/R-induced cardiomyocytes apoptosis through the repression of autophagy.[15,24]

Anti-autophagic miRNAs with deleterious impacts

A few miRNAs contribute to myocardial I/R injury through the suppression of autophagy initiation and autophagic flux. Beclin-1, the mammalian homolog of yeast Atg6, was the first identified mammalian autophagy protein that promotes autophagosome formation. miR-30a

is highly enriched in exosomes in acute MI patients.[28] Either inhibition of exosome release or miR-30a increases the levels of beclin-1, Atg12, as well as the LC3-II/LC3-I ratio, thus maintaining the autophagic response and attenuated apoptosis in cardiomyocytes after hypoxia.[28] In hypoxic H9c2 cells, miR-122 is significantly upregulated, and overexpression of miR-122 aggravates the effects of hypoxia on increased cell apoptosis through inhibition of the PTEN/PI3K/Akt pathway.[30] Hspa5 is an endoplasmic reticulum (ER) stress chaperone synchronously with LC3-II and is cardioprotective.[32] miR-181b-5p contributes to starvation-induced cardiomyocyte autophagy and apoptosis by directly targeting Hspa5 through the PI3K/Akt/mTOR pathway.[32] In addition, the inhibition of miR-429 by antagomir transfection enhances autophagy and suppresses apoptosis through the MO25/LKB1/AMPK signaling pathway, whereas the overexpression of miR-429 by mimic transfection has the opposite effects.[33] miR-101 can target Ras-related protein Rab-5A (RAB5A), a small GTPase that can interact with hVPS34 and beclin-1 to induce autophagosome formation, while the inhibition of miR-101 ameliorates myocardial ischemic injury though the induction of cardiomyocyte autophagy.[29] Oxidative stress can activate autophagy to clear damaged cells, and such autophagy may delay cell death and maintain cellular homeostasis. Zou et al.[31] reported that miR-153 suppresses cardiomyocyte autophagy and reduces cell survival upon oxidative stimuli by attenuating Mcl-1 expression. Moreover, they found that the silencing of miR-143 upregulates Atg7 expression and promotes the autophagy of c-kit$^+$ cardiac progenitor cells (CPCs) exposed to H_2O_2.[34] Moreover, the transplantation of c-kit$^+$ CPCs with miR-143 inhibitor improves cell survival and enhanced therapeutic efficiency in MI.[34]

Pro-autophagic miRNAs with beneficial impacts

Many miRNAs activate cardiomyocyte autophagy through upregulation of ATGs, such as beclin-1, and LC3, and by promoting the formation of autophagosomes, thus improving the cardiac function. For instance, miR-99a overexpression prevents cardiomyocyte apoptosis and enhances autophagy through the mTOR/P70/S6K signaling pathway, thus exhibiting a protective role against MI and ameliorating the subsequent cardiac remodeling.[41] Similarly, miR-22 can protect cardiomyocytes from starvation-induced injury through the promotion of autophagy and inhibition of apoptosis by targeting p38α.[36] The upregulation of miR-1 upon paeonol treatment suppresses the expression of PIK3CA, enhances autophagy, and mitigates the cardiac dysfunction induced by epirubicin.[35] By targeting mTOR, miR-144 mediates the cardioprotective role of remote ischemic preconditioning in I/R injury.[71] Intravenous administration of miR-145 could accelerate the transition of LC3-I to LC3-II and enhance cardiomyocyte autophagy to reduce myocardial I/R injury.[39] In this study, fibroblast growth factor receptor substrate 2 (FRS2) was determined as a target of miR-145. In addition, angiopoietin-2 (Angpt2) and the Akt3/mTOR pathway also function as downstream targets of miR-145 to mediate its protective role in MI through the induction of autophagy.[37,38]

Pro-autophagic miRNAs with deleterious impacts

Moreover, miRNA can promote autophagy through the downregulation of anti-autophagic proteins, leading to increased MI size and even the development of cardiac failure. Bo et al.[42] reported that the E2F1-miR-325-ARC axis play an important role in the regulation of autophagy during H/R and I/R. In stress-induced HF, ARC transgenic (Tg) mice exhibited reduced autophagy and MI area. E2F1 facilitates the expression of miR-325 to inhibit ARC. Consequently, ARC is unable to repress the autophagic program, thus enhancing autophagy and aggravating myocardial I/R injury.[42]

miRNAs, autophagy, and cardiac hypertrophy

Cardiac hypertrophy is a compensatory response to pressure overload, and it manifests as thickening of the left ventricular (LV) wall, enlarged cardiomyocyte size accompanied by cytoskeletal remodeling, and upregulated fetal gene expression. Sustained hypertrophic growth often causes HF and even sudden death, leading to a poor prognosis. An excessively activated autophagy level may be involved in the pathophysiological process of cardiac hypertrophy. Moreover, deficient autophagy has also been observed in the process.

Anti-autophagic miRNAs with beneficial impacts

Ang II is an important factor leading to hypertension and cardiac hypertrophy. Pan et al.[43] found that Ang II induces excessive cardiomyocyte autophagy through the downregulation of miR-30 expression and upregulation of its target gene beclin-1, and this excessive autophagy mediates the development of cardiac hypertrophy. ATG9 is a key transmembrane autophagic protein involved in the regulation of autophagosome formation. Huang et al.[44] reported that miR-34a can suppress ATG9A expression by directly binding to its 3′ UTR. miR-34a inhibition or ATG9A overexpression enhances the autophagic activity and aggravates Ang II-induced myocardial hypertrophy.[44] Similarly, miR-181a mediates Ang II-induced myocardial hypertrophy by enhancing ATG5-stimulated autophagy.[45]

Pro-autophagic miRNAs with deleterious impacts

However, Wang et al.[51] reported increased levels of miR-208a-3p in Ang-II induced H9c2 cardiomyocytes and aggravated autophagy through the inhibition of programmed cell death protein 4 (PDCD4) and upregulation of ATG5. Thus, miRNA (miR-208-3a) or its downregulation (miR-30a/miR-34a/miR-181a) can trigger the autophagy cascade in a direct or indirect manner, and the excessive degradation of organelles and proteins eventually leads to cardiac hypertrophy.

Anti-autophagic miRNAs with deleterious impacts

Both in transverse aortic constriction (TAC) surgery mice and Ang II-stimulated H9c2 cells, miR-29a has been found to be upregulated, and the inhibition of miR-29a can partially mitigate Ang II-induced hypertrophy.[46] The overexpression of miR-29a promotes cardiac hypertrophy through the suppression of PTEN, thus activating the AKT/mTOR pathway and inhibiting autophagy.[46] Interestingly, miR302-367 has been identified as another upstream regulator of PTEN and PI3K/AKT/mTORC1 signaling to inhibit autophagy and promote cardiac hypertrophy.[49] Skp2 is sufficient to promote autophagy through mTORC1 inhibition, and miR-365 negatively modulates autophagy in hypertrophic cardiomyocytes by targeting Skp2.[50]

miR-199a Tg mice had significantly larger hearts and lower autophagy levels.[47] When these mice were treated with rapamycin, an autophagy inducer, the autophagic activity was enhanced, and cardiac hypertrophy improved. Furthermore, when stimulated with the lysosomal inhibitor chloroquine, the LC3 ratio and the p62 of the Tg and control mice were upregulated, indicating that miR-199 did not inhibit lysosomal degradation but the formation of autophagic vesicles. Mechanically, miR-199 targets the pro-autophagic and antihypertrophic GSK3β to activate mTOR signaling and inhibit autophagy.[47] The overexpression of GSK3β enhanced the autophagy level and attenuated the hypertrophic responses in the miR-199 Tg mice.[47] Similarly, miR-212/132 directly targeted the anti-hypertrophic and pro-autophagic FoxO3 transcription factor to impair autophagic response and activate calcineurin/NFAT signaling, leading to pathological cardiac hypertrophy.[48] In summary, the above miRNAs can inhibit autophagy, and lower levels of autophagy activity block their protective effect, thereby promoting the occurrence and development of cardiac hypertrophy.

miRNAs, autophagy, and cardiac fibrosis

Cardiac fibrosis refers to the proliferation of fibroblasts in the heart and their transformation into myofibroblasts, which leads to excessive deposition of collagen fibers in the extracellular matrix of the myocardium, accompanied by dysregulation of collagen types and disordered arrangement. The occurrence of various CVDs, such as atrial fibrillation (AF), ischemic cardiomyopathy, chronic HF, and hypertensive heart disease, is inseparable from myocardial fibrosis.

Anti-autophagic miRNAs with beneficial impacts

TGF-β1 plays an important role in fibrogenesis, which promotes COL1A2 and fibronectin synthesis and activates autophagy in human cardiac fibroblasts.[52] Low expression levels of miR-19a-3p/19b-3p were observed in HF patients' plasma. miR-19a-3p/19b-3p overexpression attenuates autophagy and ameliorates the fibrosis induced by TGF-β1. Further functional studies have demonstrated that miR-19a-3p/19b-3p suppresses autophagy-mediated fibrogenesis by targeting TGF-βRII mRNA.[52] miR-26a-5p directly interferes with ULK1 and reduces the transformation of LC3-I to LC3-II, which simultaneously inhibits the collagen expression in cardiac fibroblasts.[53] miR-200b is negatively regulated by DNA (cytosine-5-)-methyltransferase 3 alpha (DNMT3A) and represses cardiac fibroblast autophagy during cardiac fibrosis.[54] Collectively, the above miRNAs can inhibit autophagy and exhibit a cardioprotective effect during fibrogenesis in the heart.

miRNAs, autophagy, and HF

HF is the end stage of many CVDs caused by ventricular filling or impaired ejection capacity due to abnormal heart structure and function, which seriously affects the quality of life and prognosis of patients.

Anti-autophagic miRNAs with beneficial impacts

The clinical application of doxorubicin for treating human tumor diseases is limited by its cardiotoxicity effect, which can cause cardiomyopathy and congestive HF. Angiotensin converting enzyme 2 (ACE2) can metabolize a variety of vasoactive peptide substrates for HF therapy.[72,73] Lai et al.[56] reported that exogenous administration of recombinant human ACE2 suppressed the harmful side effects of doxorubicin and improved LV function by upregulating miR-30e expression, inhibiting the expression of its target gene beclin-1 and reducing the LC3-II/LC3-I ratio. Therefore, ACE2 attenuates doxorubicin-induced cardiac dysfunction by preventing autophagy-induced cardiomyocyte apoptosis in a miR-30e/beclin-1 signaling pathway.[56] Likewise, vagus nerve stimulation, an emerging method for chronic systolic HF (CSHF) treatment, improves the cardiac function in CSHF through the upregulation of miR-183-3p, which represses the BNIP3L-mediated autophagy.[57] The cardioprotective miR-29b-3p targeting secreted protein acidic and rich in cysteine (SPARC) is downregulated in HF patients and hypoxia-induced H9c2 cells, and it attenuates the autophagy and apoptosis of cardiomyocytes by inhibiting TGF-β1/Smad3 activation.[55]

Anti-autophagic miRNAs with deleterious impacts

Conversely, both cardiac-specific overexpression of miR-221 and miR-222 provoke cardiac dysfunction and HF.[58,59] Mechanically, direct suppression of the cyclin-dependent kinase inhibitor p27 by miR-221/222 leads to mTOR activation and autophagic flux impairment, resulting in pathological cardiac remodeling.[58,59] Hence, the basal autophagy is extremely important for maintaining normal cardiac function and structure. The modulation of miR-221/222 levels may provide new targets and strategies for HF treatment.

miRNAs, autophagy, and cardiomyopathy

Cardiomyopathies are a group of heterogeneous heart diseases that lead to abnormal mechanical and electrical activities of the heart owing to different pathogenies, including genetic, infection, metabolism, and endocrine, and they manifest as improper ventricular hypertrophy or dilation.[74] Severe cardiomyopathy can cause cardiovascular death or progressive HF.

Anti-autophagic miRNAs with beneficial impacts

Hypertrophic cardiomyopathy (HCM), a common inherited disease caused by mutations in the MYH7 and MYBPC3 genes, is defined by unexplained myocardial hypertrophy and a high risk of sudden cardiac death. In the hearts of HCM, miR-451 is downregulated, and the level of autophagy is increased.[60] Forced expression of miR-451 *in vitro* significantly inhibits the formation of autophagosomes and decreases the surface area of cardiomyocytes. miR-451 can directly bind to the 3′ UTR of TSC1, which is a negative regulator upstream of mTORC1, suggesting that TSC1 may be a potential target for miR-451 to regulate autophagy in HCM.[60]

Diabetic cardiomyopathy (DCM) is one of the common complications of diabetes, and it is characterized by myocardial hypertrophy and contractile dysfunction. Nandi et al.[75] found that miR-133a was less expressed in the cardiomyocytes of patients with diabetic HF than in healthy cardiomyocytes. miR-133a can inhibit cardiomyocyte autophagy by targeting beclin-1 and LC3B. In addition, the

mTOR activity in patients with diabetic HF was found to be significantly lower than that in healthy people. These findings demonstrate that the attenuation of miR-133a and mTOR inhibition may be the mechanisms of autophagy induction and hypertrophy in DCM.[75] In diabetic (*db*/*db*) hearts, miR-30c expression is attenuated, and autophagy is induced.[61] Overexpression of miR-30c results in reduced BECN1 levels and autophagy, thus improving cardiac function and structure. Similarly, miR-30 inhibition raises the levels of BECN1 and autophagy and aggravates cardiac abnormalities. Furthermore, SP1, an important transcription factor involved in the regulation of energy metabolism, has been revealed to be an upstream activator of miR-30c. Taken together, this study demonstrates that in *db*/*db* hearts, elevated free fatty acids downregulate SP1, leading to lower levels of transcribed miR-30c and, subsequently, increased levels of BECN1 and autophagic flux, which contribute to the pathological process of DCM.[61]

Takotsubo cardiomyopathy (TCM) is an acute heart syndrome first described by Sato et al. in 1990[76]. It is characterized by transient reversible LV wall motion dysfunction but without coronary artery abnormality.[77] This disease, also called broken heart syndrome, usually occurs in people with emotional changes or excessive stress. d'Avenia et al.[62] found that excessive epinephrine induced ERK phosphorylation-dependent β-catenin nuclear translocation in cardiomyocytes, resulting in increased miR-371-5p expression. Although miRNA can suppress the target protein level by binding to the 3′ UTR of the target mRNA, a growing body of evidence has indicated that miRNA can also stimulate gene expression at the post-translational level through multiple mechanisms.[62] As revealed in this study, miR-371a-5p binds to the 3′ UTR of Bcl2-asscociated athanogene 3 (BAG3), leading to increased BAG3 protein expression. BAG3 is a member of the BAG family of auxiliary chaperones that interact with ATPase domain of HSP70. BAG is strongly expressed in cardiomyocytes and participates in molecular chaperone-mediated autophagy. The absence of BAG in mice can cause fatal cardiomyopathy. TCM patients often exhibit the g2252c mutation in BAG3 3′ UTR, which results in the inability of miR-371a-5p to bind to the 3′ UTR of BAG3 and, thus, induces an altered response to epinephrine stimulation, which may be a new mechanism of TCM pathogenesis.[62]

Anti-autophagic miRNAs with deleterious impacts

In contrast, Ni et al.[63] indicated that miR-34a was upregulated and autophagy was impaired in high-glucose-induced cardiomyocytes and in diabetic hearts. Dihydromyricetin can restore impaired autophagy by reducing miR-34a levels, thus decelerating the development of DCM.[63]

miRNAs, autophagy, and atherosclerosis (AS)

AS is a chronic inflammatory process characterized by lipid accumulation and inflammatory cell infiltration. The stability of atherosclerotic plaque is the main risk factor for coronary heart disease and stroke. Recent studies have found that autophagy plays an important role in regulating the formation of AS and the stabilization of atherosclerotic plaques.[78,79] When stimulated by AS risk factors, such as oxidized low-density lipoprotein (ox-LDL) and ROS, endothelial cells (ECs) undergo a stress-repairing autophagic process, which can degrade the damaged organelles in the cell and protect ECs from inflammation and oxidative stress. However, defective autophagy can cause the apoptosis of ECs, resulting in a loss of endothelial integrity to facilitate local lipid deposition, plaque instability, and even acute coronary occlusion and sudden death.

Anti-autophagic miRNAs with deleterious impacts

miR-129-5p is increased both in ApoE$^{-/-}$ mice supplied with a high-fat diet and human aortic ECs treated with ox-LDL, which impairs the protective effects of EC autophagy against AS by suppressing the translation of beclin-1.[65] miR-216a may be a regulator linker between endothelial dysfunction and autophagy, and it can induce ox-LDL aggregation and monocyte adhesion in HUVECs through suppression of the expression of beclin-1 and ATG5.[67] In senescent HUVECs, miR-216a downregulation enhances the autophagic activity and reduces ox-LDL uptake and THP-1 adhesion, thereby exerting a protective anti-atherogenic role against ox-LDL treatment.[67]

In ox-LDL-exposed HUVECs, miR-155 expression is significantly increased, and inhibition of miR-155 inhibits autophagic activity. miR-155 can promote the ox-LDL-induced autophagy of HUVECs by enhancing LC3 levels and reducing p62 levels.[80] Moreover, miR-155 directly targets FADD to inhibit the apoptosis of RAW264.7 macrophage cells and the formation of atherosclerotic plaque.[81] However, in an H_2O_2-induced oxidative stress EC model, miR-155 downregulation promoted the proliferation of ECs and decreased intracellular ROS injury by modulating the expression of ATG5.[66]

Impaired cholesterol metabolism and defective efferocytosis contribute to AS. In macrophages, miR-33 targets key autophagic regulators to reduce the clearances of lipid droplets and apoptotic cells.[64] Furthermore, miR-33 regulation of autophagy acts upstream of ATP-binding cassette transporter A1 (ABCA1) to control cholesterol efflux, whereas miR-33 inhibition restores defective autophagy and promotes efferocytosis, lysosomal biogenesis, and apoptotic degradation to reduce plaque necrosis in atherosclerotic *Ldlr*$^{-/-}$ mice.[64] Collectively, these data reveal that miR-33 regulates cellular cholesterol homeostasis and AS through autophagy.

miRNAs, autophagy, and sepsis cardiac dysfunction

Sepsis is a systemic inflammatory response syndrome caused by infection, and its further development is among the main causes of death in intensive care units. Sepsis cardiac dysfunction is a severe complication of sepsis, and it is one of the main factors that determine the outcome and prognosis of sepsis. Recent studies have shown that inflammation, EC damage, oxidative stress, mitochondrial dysfunction, cardiomyocyte autophagy, and apoptosis play important roles in sepsis cardiac insufficiency.[82,83]

Pro-autophagic miRNA with deleterious impact

Wang et al.[68] established a murine model of sepsis cardiac dysfunction exposed to lipopolysaccharide (LPS) and identified a remarkable

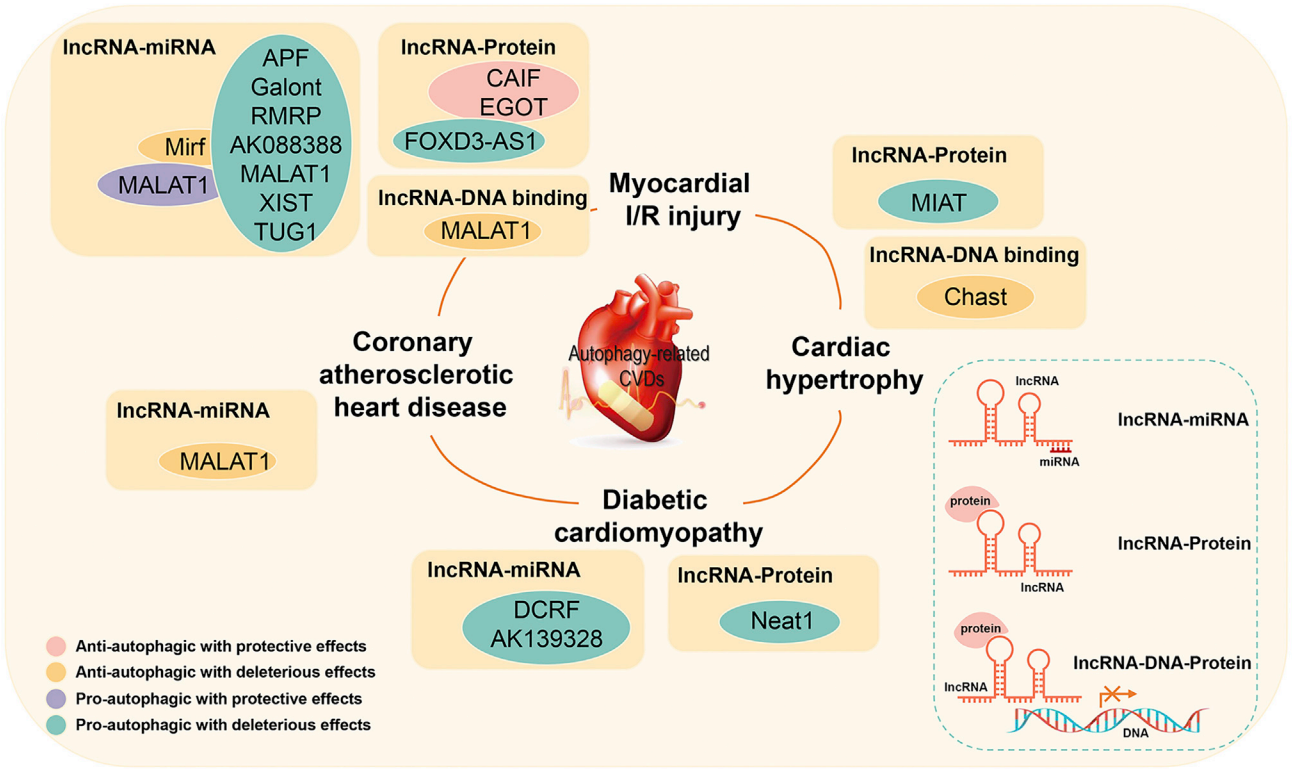

Figure 2. Regulatory roles of lncRNAs in cardiac autophagy and related CVDs

The molecular mechanisms of lncRNAs are shown. lncRNAs can function as a sponge for miRNAs or as a scaffold by interacting with proteins such as transcription factors or components of chromatin-modifying complexes to activate or repress gene expression. lncRNAs can also bind to specific protein to modulate their activity or alter their localization. See text and Table 2 for detailed molecular mechanism explanations. Pink oval represents anti-autophagic lncRNAs with protective effects in CVDs; yellow oval represents anti-autophagic lncRNAs with deleterious effects; purple oval represents pro-autophagic lncRNAs with protective effects in CVDs; green oval represents pro-autophagic lncRNAs with deleterious effects in CVDs.

increase in miR-21 in the myocardium of LPS-treated mice through microarray analysis. Inhibition of miR-21-3p with antagomiR prevents mitochondrial ultrastructural damage and autophagy, attenuates LPS-induced cardiac dysfunction, and improves the survival of mice treated with LPS *in vivo*. However, forced expression of miR-21-3p by using agomiR exacerbates sepsis-associated cardiac dysfunction through the suppression of SORBS2. Additionally, the receiver operating characteristic curve (0.939) suggests that miR-21-3p might be a specific predictor of the development of cardiac dysfunction in septic patients, thus providing a new strategy for disease treatment.[68]

lncRNAs and autophagy

lncRNAs are a class of RNA molecules with lengths greater than 200 nt, and they can regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels, in addition to directly modulating protein activity.[84] The mechanisms of lncRNA action are extremely complex and have not been fully elucidated yet. According to existing studies, the mechanisms of lncRNAs can be classified into multiple types, including the following ones: (1) transcriptional interference, (2) induced chromatin remodeling and histone modification, (3) binding to specific protein to modulate their activity or alter their localization, and (4) miRNA sponge (Figure 2).[85] Among these, serving as a competing endogenous RNA (ceRNA) is the most well-described mechanism through which lncRNAs can attenuate the activity of miRNA via sequestration, leading to elevated expression of the miRNA target gene. In a microarray study, 1,249 lncRNAs were identified as being differentially expressed in Ang II-induced cardiomyocyte autophagy, thus pointing to the existence of a correlation between abnormal lncRNA expression and autophagy in the heart.[86] In a microarray analysis of H9c2 myocytes exposed to H/R, the lncRNA E230034O05Rik (HRIM) was found to play a pro-autophagic role to reduce the viability of myocytes.[87] Nevertheless, H19 demonstrably protected mice against acute MI by activating autophagy.[88] Thus far, numerous lncRNAs (see Table 2 and Figure 2 for a complete list) have been found to exert different effects in CVD occurrence either through pro- or anti-autophagy.

lncRNAs, autophagy, MI, and myocardial I/R injury

lncRNA-miRNA sponging

Pro-autophagic lncRNAs with deleterious impacts. The first reported lncRNA that regulates autophagy and cell death in the heart was AK079427 in 2015, and it was named autophagy

Table 2. Dysregulated lncRNAs and their roles in autophagy and in the progression of CVDs

LncRNAs	Roles in autophagy	Binding partners/downstream targets	Action modes	Outcomes	Refs
Myocardial infarction					
APF	pro-	miR-188/ATG7	miRNA sponge	↑ cell death	23
Galont	pro-	miR-338/ATG5	miRNA sponge	↑ cell death	89
RMRP	pro-	miR-206/ATG3 PI3K/Akt/mTOR pathway	miRNA sponge	↑ myocardial I/R injury	90
TUG1	pro-	miR-142-3p/HMGB1, Rac1	miRNA sponge	↑ myocardial I/R injury	91
XIST	pro-	miR-133a/SOCS2	miRNA sponge	↑ myocardial I/R injury	92
AK088388	pro-	miR-30a/Beclin1	miRNA sponge	↑ cardiomyocyte damage	93
Mirf	anti-	miR-26a/USP15	miRNA sponge	↑ ischemic myocardial injury	94
MALAT1	pro-	miR-20b/Beclin1	miRNA sponge	↑ cardiomyocyte injury	95
	pro-	miR-558/ULK1	miRNA sponge	↓ cardiomyocyte apoptosis	96
	anti-	EZH2 protein TSC2 promoter	transcriptional suppression	↑ cardiomyocyte apoptosis	97
CAIF	anti-	p53 protein/myocardin	transcriptional suppression	↓ myocardial infarction	98
EGOT	anti-	cyclin D1 protein PI3K/Akt/mTOR pathway	modulate protein activity	↓ hypoxia-induced injury	99
FOXD3-AS1	pro-	NF-κB/COX-2/iNOS pathway	modulate protein activity	↑ myocardial I/R injury	100
HRIM	pro-	–	–	↓ myocytes viability	87
H19	pro-	–	–	↓ acute myocardial infarction	88
Myocardial hypertrophy					
Chast	anti-	Plekhm1	transcriptional suppression	↑ cardiac remodeling	101
MIAT	pro-	mTOR, AMPK	modulate protein activity	↑ myocardial hypertrophy	102
Diabetic cardiomyopathy					
DCRF	pro-	miR-551b-5p/PCDH17	miRNA sponge	↓ cardiac function	103
AK139328	pro-	miR-204-3p	miRNA sponge	↑ myocardial I/R injury	104
Neat1	pro-	Foxo1	modulate protein activity	↑ myocardial I/R injury	105
Coronary atherosclerotic heart disease					
MALAT1	anti-	miR-15b-5p/MAPK1 mTOR pathway	miRNA sponge	↑ atherosclerosis	106

promoting factor (APF). Through *in vitro* and *in vivo* analyses, APF has been demonstrated to play a pro-autophagic role during I/R-induced MI by targeting miR-188-3p and the autophagy promoting gene ATG7.[23] lncRNAs can be positive regulators of mRNA targets by sponging miRNAs and preventing them from completing their regulatory roles. miR-188-3p has been found to be involved in the regulation of ATG7 expression, and APF directly binds to miR-188-3p to block its ability to suppress autophagy and cell death.[23] Similar to APF, other lncRNAs have also been confirmed to promote autophagic cell death in myocardial I/R injury through the lncRNA-miRNA-mRNA axis. GATA1-activated lncRNA (Galont) can sponge miR-338 to promote the expression of its downstream target ATG5 and autophagic cell death after anoxia/reoxygenation (A/R) stimuli.[89] The enforced expression of the lncRNA component of mitochondrial RNA processing endoribonuclease (RMRP) aggravates hypoxia-induced injury by regulating the activity of miR-206 and the expression of its target ATG3.[90] Recently, the miR-133a/SOCS2 axis has been demonstrated to convey the autophagic signal of lncRNA XIST. miR-133a directly targets SOCS2 to suppress apoptosis and autophagy and promote cell viability.[92] XIST knockdown inhibits autophagy and cell apoptosis through the downregulation of miR-133a and attenuation of the MI area after I/R injury.[92]

HMGB1 and Rac1 are important autophagy-inducing proteins associated with the mTOR signaling pathway.[91,107,108] Interestingly, miR-142-3p regulates both HMGB1 and Rac1; therefore, both of them are upregulated by lncRNA taurine upregulated gene 1 (TUG1) when it interacts with miR-142-3p, thus stimulating autophagic cell death in response to I/R.[91] In addition, beclin-1 has been determined to be a direct target of both miR-30a and miR-20a-5p, as suggested by their opposite expression change trends after treatment and dual-luciferase assay verification.[93,95] Simultaneously, lncRNA AK088388 and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) have been revealed to positively regulate the de-repression of beclin-1 by sponging miR-30a and miR-20a-5p, separately.[93,95] Thus, the axes of AK088388/miR-30a and MALAT1/miR-20b contribute to beclin-1-mediated autophagy in cardiomyocyte injury.

Pro-autophagic lncRNAs with beneficial impacts. In response to stress, either extremely low autophagy levels or overactivation of autophagy is harmful to cells. Significantly, a certain level of basic

autophagy is necessary for cell survival. In contrast to the previously described function of driving autophagic cell death,[95] according to Guo et al.,[96] MALAT1 promoted ULK1-mediated protective autophagy and facilitate myocardial protection in isoproterenol (ISO)-infused MI hearts by sponging miR-558. Initially, autophagy inhibitors 3-methyladenine (^{3}M) and chloroquine were used to verify the protective role of autophagy in ISO-treated H9c2 cells; that is, autophagy inhibition enhanced the expression levels of the death substrate PARP and increased cell apoptosis. Silencing of MALAT1 increased miR-558 expression and decreased the level of the miR-558 target ULK1, leading to the suppression of autophagy and increased cell death. However, overexpression of MALAT1 sponged miR-558 and upregulated ULK1 to promote the protective autophagy.[96] Taken together, these experiments revealed the protective role of the MALAT1/miR-558/ULK1 pathway against ISO-induced cardiomyocyte injury in a mitochondrial-dependent way.[96]

Anti-autophagic lncRNAs with deleterious impacts. According to Liang et al.,[94] the lncRNA 2810403D21Rik/Mirf may be a potential therapeutic target for autophagy-related heart diseases. Mirf was upregulated, and Mir26a was significantly downregulated in the ischemic heart and cardiomyocytes. Moreover, *in vivo* silencing of Mir26a reduced autophagy levels and aggravated the impairment of cardiac function. However, overexpression of Mir26a could activate cardiomyocyte autophagy by targeting Usp15, thereby reducing ischemic stress-induced cardiomyocyte death.[94] Mirf exerted its ceRNA mechanism to target and regulate the activity of Mir26a, thus inhibiting cardiomyocyte autophagy. In contrast, Mirf loss significantly upregulated the expression of Mir26a, activated autophagy, and ultimately reduced the ischemia-induced cardiac injury and improved mice cardiac function.[94] Taken together, Mirf acts as an anti-autophagy molecule through the Mir26a/Usp15 axis to exacerbate ischemic cardiac injury.

lncRNA-protein interaction and regulation

Anti-autophagic lncRNAs with beneficial impacts. Wang and colleagues[109] identified a lncRNA called CAIF that can inhibit cardiomyocyte autophagy and protect mouse heart against IR injury. Myocardin is a transcriptional coactivator of the serum response factor and is especially expressed in cardiac and smooth muscle cells. Through *in vitro* and *in vivo* studies, Wang and colleagues[109] first demonstrated that myocardin positively regulates the induction of the autophagic process and cardiomyocyte death and promotes MI. Moreover, beclin-1 was revealed as the potential target of myocardin. Second, the transcription factor p53 can bind to myocardin promoter and activate its transcription. In contrast, CAIF can directly bind to p53 and block the p53-mediated transcription of myocardin, resulting in the downregulation of myocardin expression, which in turn inhibits cardiomyocyte autophagy. Wang and colleagues revealed the important role of the CAIF-p53-myocardin regulatory axis in cardiomyocyte autophagy, and they provided a potential therapeutic target for autophagy-related CVDs.

The expression of lncRNA EGOT was found to significantly decrease in H9c2 cells suffering from hypoxia.[99] Moreover, EGOT was found to mediate the protective effects of the recombinant human brain natriuretic on hypoxia-induced injury in H9c2 cells by regulating the expression of cyclin D1 and activating the PI3K/AKT/mTOR pathway with reduced apoptosis and autophagic levels.[99]

Pro-autophagic lncRNAs with deleterious impacts. In oxygen glucose deprivation (OGD)/R-induced H9c2 cells, lncRNA FOXD3-AS1 was found to increase, and its overexpression aggravated myocardial IR injury by promoting autophagy through the activation of the nuclear factor κB (NF-κB)/COX-2/inducible NO (nitric oxide) synthase (iNOS) signaling pathway.[100] However, the administration of ^{3}M downregulated the associated proteins and reversed the aggravation of cardiac myocyte damage.[100]

lncRNA-DNA binding and chromatin remodeling

lncRNAs can regulate epigenetic modifiers, such as DNMTs and EZH2, to induce chromatin remodeling and histone modification. Epigenetic changes to certain genes are involved in the progression of CVDs. For instance, lncRNA MALAT1 can recruit EZH2 to induce H3K27me3 modification in the TSC2 promoter region, thus repressing its transcription, while TSC2 overexpression inhibits mTOR signaling and activates autophagy. Therefore, the increased MALAT1 expression induced by H/R injury inhibits cardiomyocyte proliferation and enhances apoptosis through autophagy inhibition by regulating TSC2-mTOR signaling activity.[97]

lncRNAs, autophagy, and cardiac hypertrophy

lncRNA-transcription regulation

Viereck et al.[101] observed a significant upregulation of Chast (cardiac hypertrophy-associated transcript) in cardiomyocytes from TAC mice as well as in hypertrophic heart tissue from aortic stenosis patients. They identified the roles of Chast in impeding autophagy and promoting cardiac hypertrophy by conducting overexpression and silencing experiments. Mechanistically, Chast is activated by the well-defined pro-hypertrophic transcription factor NFAT. In addition, Chast is partially transcribed from the opposite strand of the protein-coding gene Plekhm1, which can intensely repress the transcription of Plekhm1. The silencing of Plekhm1 results in reduced autophagic capacity and hypertrophic responses. This reveals a transcriptional regulation circuit of the lncRNA Chast in autophagy and cardiac hypertrophy.

lncRNA-protein interaction

The lncRNA MIAT (MI-associated transcript) has been initially reported to play a role in MI, and its over-expanding role in other diseases has been recently revealed.[110] MIAT mediates the inhibitory effect of berberine on cardiac hypertrophy by regulating autophagy.[102] MIAT knockdown alleviates the hypertrophic responses and the relative protein levels of phosphorylated (p-)mTOR, p-AMPK, and LC3 in H9c2 cells treated with Ang II.

lncRNAs, autophagy, and DCM

lncRNA-miRNA sponging

The lncRNA DCRF (DCM-related factor) was first described as being upregulated in DCM in a microarray-based screen for dysregulated lncRNAs in diabetic hearts with pathological remodeling versus

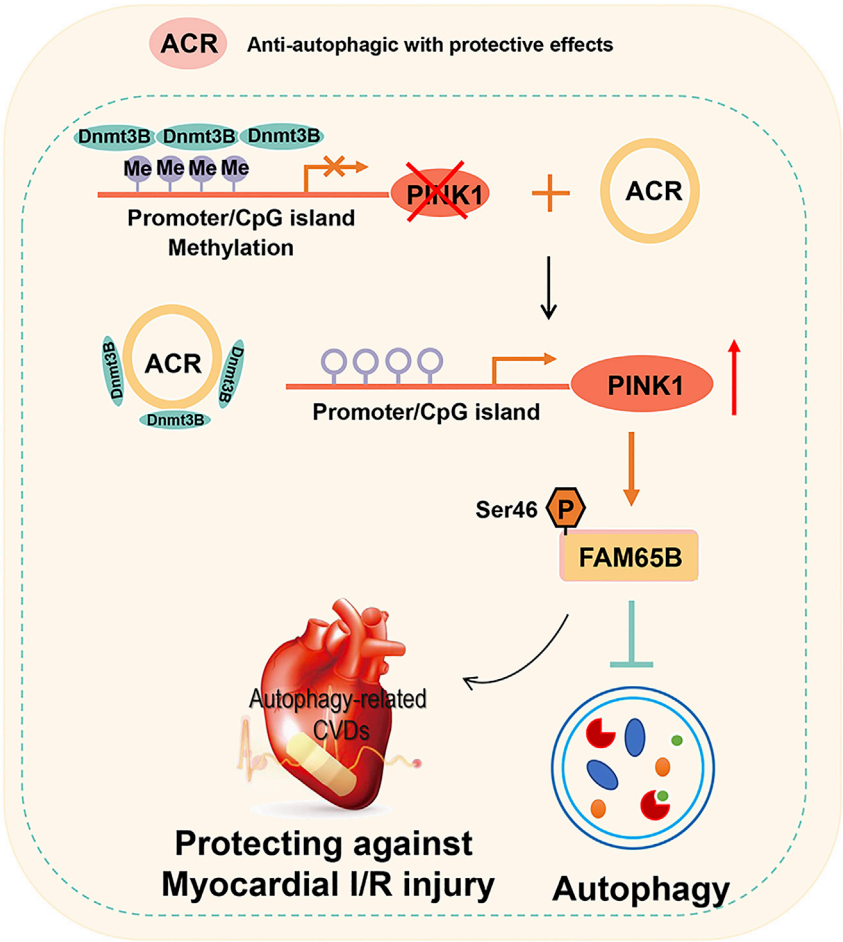

Figure 3. Mechanism diagram of circRNA ACR in myocardial I/R injury

Though directly binding to Dnmt3B, ACR inhibits PINK1 methylation and promotes PINK1 expression, which facilitates the phosphorylation of FAM65B at Ser46, resulting in reduced autophagy and myocardial I/R injury.

normal hearts.[103] DCRF knockdown significantly relieved high glucose-induced cardiomyocyte autophagy and improved histological abnormalities and cardiac function in diabetic rats. When functioning as a ceRNA, DCRF can increase the expression of PCDH17 through miR-155b-5p sponging and consequently impel autophagy.[103] Thus, it can be thought that the DCRF/miR-155b-5p/PCDH17 axis contributes to the progression of DCM.

Similarly, by using a microarray approach to compare the lncRNA transcriptome of I/R injury in diabetic mice and normal mice, Yu et al.[104] identified the overexpression of AK139328 in diabetic mice. A subsequent molecular mechanism investigation revealed that AK139328 knockdown blunted cardiomyocyte autophagy and attenuated myocardial I/R injury through direct sponging of miR-204-3p.[104] Nevertheless, the target protein-coding gene of miR-204-3p has not been studied.

lncRNA-protein interaction

Through *ex vivo* and *in vivo* analyses, Ma et al.[105] demonstrated the participation of the lncRNA nuclear-enriched abundant transcript 1 (Neat1) in diabetic rats with I/R injury. Neat1 was found to exacerbate cardiomyocyte injuries through the activation of myocardial apoptosis and autophagy, as indicated by the elevated fluorescent LC3 puncta and increased levels of autophagy-related proteins. Furthermore, Neat1 promoted the autophagy level by upregulating the expression of Foxo1, a transcription factor that modulates physiological functions through the transcription and transmission of various growth factors and cytokine signals.[105]

lncRNAs, autophagy, and coronary atherosclerotic heart disease

The MALAT1/miR-15b-5p/MAPK1 axis has been described in coronary atherosclerotic heart disease, and according to this description, MALAT1 directly targets miR-15b-5p to amplify MAPK1 expression.[106] Subsequently, this signal axis triggers the mTOR signaling pathway to enhance the progression of coronary atherosclerotic heart disease. In contrast, MALAT1 inhibition promotes the autophagy of endothelial progenitor cells and increases cell viability, thereby protecting mice against AS.[106]

circRNAs and autophagy

circRNAs are covalently closed cyclic RNAs with high frequencies of eukaryotic transcripts, and they can act as miRNA sponges to regulate splicing or transcription and the expression of parental genes. Recent studies have demonstrated their critical roles in neurological disorders, infectious diseases, cancers, and CVDs.[111] As an important process of cellular physiological activity, the relationship between autophagy and circRNAs has been studied. In 2017, Yao and colleagues[112] first reported that circHIPK2 can modulate astrocyte activation through cooperation between autophagy and ER stress by targeting the MIR124-2HG/SIGMAR1 axis. Subsequently, many circRNAs have been identified to regulate autophagy through the sponging of miRNAs in various cancers.[113–116]

Thus far, only two studies have examined the autophagy-related circRNAs in cardiovascular pathologies. Different from their most common regulatory mechanism of miRNA sponges, these two circRNAs exert their functions through interactions with proteins. Wang and colleagues[117] reported that an autophagy-related circRNA called ACR participated in regulating autophagy in a myocardial I/R injury model (Figure 3). ACR expression decreased significantly in cardiomyocytes after A/R treatment. ACR overexpression reduced the

accumulation of GFP-LC3 puncta, expression levels of LC-II, and numbers of autophagic vesicles in A/R-treated cells, indicating that ACR inhibited A/R-induced autophagy and mitophagy in cardiomyocytes. Through transcriptome microarray analysis, they revealed that ACR can inhibit PINK1 methylation and promote PINK1 expression by directly binding to Dnmt3B. Furthermore, Wang and colleagues[117] demonstrated that PINK1 regulates the autophagy pathway *in vitro* and *in vivo*. To identify the mechanism through which PINK1 regulates autophagy, the interaction between PINK1 and FAM65B was tested with western identification after co-immunoprecipitation. Based on mass spectrometry analysis and antibody verification, S46 was proved to be the PINK1 site for targeting FAM65B. PINK1 can facilitate the phosphorylation of FAM65B, thus inhibiting cardiomyocyte autophagy and protecting cells during myocardial I/R injury. The other one is circRNA ZNF 292, which can alleviate OGD-induced ischemic injury, including apoptosis and autophagy, in H9c2 cells by targeting BNIP3 through Wnt/β-catenin and mTOR activation.[118] Overall, these findings reveal novel roles of circRNA ARC and ZNF292 in regulating autophagy and their potential applications as therapeutic targets in the treatment of CVDs.

Clinical relevance of ncRNAs in CVDs

Due to the lack of effective therapeutic targets, the global morbidity and mortality of CVDs are increasing year by year. Nevertheless, it is inspiring that the research on ncRNAs, which play a critical regulatory role in gene expression in the physiology and pathophysiology of cardiovascular system, has developed rapidly, and the potential of ncRNAs for the diagnosis and treatment of CVDs is supported by multiple studies. We searched the https://clinicaltrials.gov database for publicly available studies by the keywords associated with ncRNAs, and then the clinical trials details were downloaded. At the time of our search, there were 939 studies found for miRNA, 100 of which were CVDs related; 48 studies were found for lncRNAs, 7 of which were CVDs related; and 7 studies were found for circRNAs, 2 of which were CVDs related. Given the high tissue specificity and stability of ncRNAs, as well as their easy access for monitoring, it is reasonable that most of the above trials are diagnostic, where ncRNAs are used as novel clinical biomarkers for CVDs diagnosis. Furthermore, with the development of gene-based technologies including RNA interference (RNAi) and antisense oligonucleotides, a lot of therapeutic clinical trials using ncRNAs as treatment targets and therapeutics have begun.[119,120] Thus, ncRNAs are worth looking forward to for their use in elucidating the pathogenesis of certain CVDs and becoming novel diagnostic biomarkers and intriguing targeted therapeutic tools.

ncRNAs as CVD biomarkers

Although cardiac troponin I (cTnl), creatine kinase isoenzyme (CK-MB), and brain natriuretic peptide (BNP) have been widely used in the diagnosis of myocardial ischemia, MI, and HF, more stable and specific disease diagnostic markers still need to be explored widely. At present, a number of studies focus on mining ncRNAs in body fluids as CVD biomarkers and are carried out for clinical research in a population.

ncRNAs can be used to screen and distinguish biomarkers in the diagnosis of CVDs. Screening of differentially expressed miRNAs in the blood of healthy people and patients with HCM identified that 12 miRNAs were significantly elevated in the plasma of patients. Among them, only circulating miR-29a was significantly correlated with both hypertrophy and fibrosis, indicating it as a potential diagnosis biomarker for cardiac remodeling assessment in HCM.[121] miR-423-5p was tested as a specific biomarker for clinical HF, the levels of which are related to N-terminal pro-BNP (NT-proBNP) and New York Heart Association (NYHA) classification.[122] As acute MI is a cardiovascular event with high mortality, a rapid diagnostic method with high sensitivity and specificity is urgently needed. Of the six acute MI-relevant miRNAs, circulating miR-22-5p and miR-122-5p are promising diagnostic biomarkers, and the joint detection of them increased the distinguished sensitivity (98.6%) between acute MI patients and healthy controls.[123] Moreover, a full-featured microwell detector has been developed to rapidly detect miRNAs in plasma for CVD diagnosis, which can simplify the detection steps and eliminate human errors.[124] Analysis of miRNAs in the plasma of patients with HF with reduced or preserved LV ejection fraction (HFrEF versus HFpEF) revealed that miR-125a-5p, miR-190a, miR-550a-5p, and miR-638 can be used to distinguish these two subtypes of HF.[125] BNP and NT-proBNP are the gold standards for clinical diagnosis of HF, with high sensitivity but poor specificity. In addition, multi-miRNA panels in combination with NT-proBNP can significantly improve the specificity and accuracy in identifying nonacute HF with HFpEF.[126]

Mitochondrial lncRNA LIPCAR is differentially expressed between patients with or without LV remodeling after MI, and it is also independent of other risk markers associated with future cardiovascular mortality, suggesting that it may be used as a biomarker of cardiac remodeling and predict survival in patients with HF.[127] Other lncRNAs such as CoroMarker and PPARδ are useful biomarkers for coronary artery disease (CAD) diagnosis.[128] As for disease classification, lncRNA uc004cov.4 and uc022bqu.1 can distinguish the obstructive HCM from the nonobstructive subtype.[129] de Gonzalo-Calvo et al.[130] reported for the first time that lncRNA SENCR can be used as a potential candidate molecular marker for evaluating the efficacy of individualized treatment of type 2 diabetes mellitus (T2DM) patients with pioglitazone, a thiazolidinedione insulin sensitizer that improves LV diastolic function in T2DM patients. To date, lncRNA prostate cancer antigen-3 (PCA3) is the first and only ncRNA that has been approved by the US Food and Drug Administration (FDA) for routine clinical diagnosis of prostate cancer.[131] Thus, whether lncRNA can be used in clinical diagnosis of CVDs remains to be further verified.

Distinct from miRNAs and lncRNAs, the closed ring structure makes circRNAs more stable and have more advantages in the application as clinical diagnostic markers.[132] Salgado-Somoza et al.[133] reported that circRNA MICRA is differentially low in patients with HF after acute MI (EF of $\leq$40%), and a bootstrap internal validation revealed that MICRA was selected in 86% of the models to be an optimal predictive

marker, which is completely comparable to the traditional NT-proBNP and has high diagnostic value. So far, lots of circRNAs have been identified and verified as potential biomarkers to diagnose CVDs, such as hsa_circ_0124644 and hsa_circ_ 11783-2 for CAD, hsa_circ_ 081881 for acute MI, hsa_circ_ 025016 for postoperative AF, and so on. Nevertheless, only with multi-center clinical trials with larger sample size can we more convincingly confirm the role of ncRNAs in the diagnosis of CVDs. Additionally, more basic studies are needed to clarify the biological role of ncRNAs in the occurrence and development of CVDs.

Therapeutic targeting of ncRNAs in CVD preclinical studies and clinical trials

In addition to their roles as potential biomarkers, ncRNAs also represent targets for new therapeutic approaches and attractive tools.[134,135] In 2018, the first RNAi drug patisiran (reduces *TTR* levels) was approved by the FDA for the treatment of neurodegenerative disease hereditary transthyretin amyloidosis, marking the dawn of a new era of clinical application of RNA as a target and tool.[136] Recently, cobomarsen (also termed MRG-106; miRagen Therapeutics), a locked nucleic acid (LNA)-based oligonucleotide against miR-155, has entered a phase II clinical trial in patients with cutaneous T cell lymphoma, mycosis fungoides subtype (ClinicalTrials.gov: NCT03837457), and a phase I clinical trial in patients with different leukemia/lymphoma (ClinicalTrials.gov: NCT02580552). Among other miRNA candidates, MRG-201 (remlarsen; miRagen Therapeutics), a miR-29 mimic, is currently undergoing a phase II clinical trial in participants with cutaneous fibrosis (ClinicalTrials.gov: NCT03601052). Moreover, MRG-201 has the potential clinical application in a number of pathological fibrotic conditions, including cardiac fibrosis.

At present, a larger number of preclinical studies on ncRNA-based therapeutics for the treatment of CVDs are under way, and some of them have entered clinical trials. For example, miR-33a/b is involved in the regulation of lipid metabolism.[137,138] Preclinical studies have shown that silencing miR-33 with anti-miR-33 in non-human primates can effectively reduce the plasma very-low-density lipoprotein (VLDL) and raise the high-density lipoprotein (HDL) level without significant side effects, indicating that miR-33 has the potential to become a therapeutic target for the treatment of AS and dyslipidemia.[139,140] Other therapeutic candidates such as LNA antimiR-21 for cardiac fibrosis treatment, antimiR-208 for cardiac remodeling treatment, and antimiR-15 for MI treatment are expected to become a hotspot in clinical research.[134] Recently, MRG-110 (LNA antimir-92) aimed for HF indication has just completed the phase I clinical trial (ClinicalTrials.gov: NCT03603431) by intradermal injection in heathy volunteers. The small interfering RNA (siRNA) drug inclisiran (ALN-PCS) is directed against proprotein convertase subtilisin-kexin type 9 (PCSK9) mRNA to reduce LDL cholesterol (LDL-C) level, which is high cardiovascular risk of AS and CAD.[141] In the phase II clinical trial (ClinicalTrials.gov: NCT02597127 and NCT03060577) of inclisiran injection in participants with atherosclerotic CVDs, the serum LDL-C levels were decreased, and the tolerance was acceptable, and now a phase III clinical trial (ClinicalTrials.gov: NCT03705234) is under way to assess its effect on clinical outcomes among people with CVDs. In future studies, the combination of high-throughput sequencing and CRISPR-Cas9 gene editing technologies will help to quickly screen ncRNAs that play critical roles in CVDs. However, although having good prospects, there are still some issues to be solved in clinical trials: (1) for lncRNA and circRNA with poor conservation among species, it is necessary to find appropriate preclinical animal models; (2) ncRNAs are widely distributed, and thus drug delivery systems that specifically target heart tissue are in need of development; and (3) the *in vivo* safety of the currently used ncRNA mimics or inhibitors, such as anti-miR, antagomir, LNA oligonucleotides, and viral vectors, should be verified.

Conclusions

The normal progress of material synthesis and catabolism maintains the human body's homeostasis. Autophagy is one of the important metabolic pathways that removes dysfunctional organelles, misfolded proteins, and macromolecules in eukaryotic cells, thus realizing the efficient and stable operation of the intracellular environment. Autophagy is critical for cardiovascular system homeostasis and closely related to CVDs, including myocardial I/R injury, cardiac hypertrophy, HF, cardiomyopathy, and AS. This systematic review, despite focusing on the ncRNA regulation field, indicates that autophagy plays a dual role in CVD pathology. Moderate levels of autophagy can protect cells from apoptosis and help maintain normal cardiovascular metabolism by degrading and recycling damaged organelles and aging proteins. However, excessive autophagy can destroy the essential cell components necessary for cell survival and cardiac contraction, and insufficient autophagy can lead to the accumulation of damaged organelles and redundant proteins, which are detrimental to myocardial cells and contribute to disease progression. Thus, regulators of autophagy, such as mTOR, AMPK, and others, can be used as targets to prevent or treat CVDs. So far, drugs such as rapamycin (an mTOR inhibitor), histone deacetylase inhibitors, and spermidine have been demonstrated to be useful for improving cardiovascular functions and decelerating the progression of CVD in animal models through modulation of autophagy.[142–145] However, the clinical evaluation of autophagy-targeting drugs within the cardiovascular system is limited owing to the lack of drug compounds that specifically regulate autophagy in heart and non-invasive biomarkers that reflect their effects on autophagy.[146]

In recent years, various pieces evidence have indicated that ncRNA-mediated post-transcriptional regulation of gene expression represents an integral part of the autophagy regulatory network and has a substantial effect on autophagy-related diseases.[147] Therefore, determining whether ncRNA-regulated autophagy plays a protective role against CVDs or promotes the progression of CVDs can facilitate the development of ncRNAs as therapeutic targets in the treatment of autophagy-related CVDs. For instance, CAIF is a novel lncRNA with protective effects on MI through the inhibition of autophagy, and patients with end-stage cardiomyopathy exhibit downregulated CAIF levels.[98] Additionally, ATG5-associated lncRNA Chast has been tested to verify the relationship between autophagy dysregulation

and CAD.[148,149] These results suggest that autophagy-regulating ncRNAs can potentially serve as novel targets in the development of diagnostic and therapeutic agents. Moreover, it is reasonable to think that the mechanism research on autophagy and ncRNAs can provide new strategies for the prevention and treatment of CVDs.

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AUTHOR CONTRIBUTIONS

J.G. and K.S. conceived this article. X.C. and C.S. collected the related papers. J.G. wrote the manuscript. K.S. drew the figures. Y.W. and P.L. helped to revise the manuscript and do the final editing.

DECLARATIONS OF INTERESTS

The authors declare no competing interests.

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