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REVIEW

Role of noncoding RNAs in regulation of cardiac cell death and cardiovascular diseases

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Abstract Loss of functional cardiomyocytes is a major underlying mechanism for myocardial remodeling and heart diseases, due to the limited regenerative capacity of adult myocardium. Apoptosis, programmed necrosis, and autophagy contribute to loss of cardiac myocytes that control the balance of cardiac cell death and cell survival through multiple intricate signaling pathways. In recent years, noncoding RNAs (ncRNAs) have received much attention to uncover their roles in cell death of cardiovascular diseases, such as myocardial infarction, cardiac hypertrophy, and heart failure. In addition, based on the view that mitochondrial morphology is linked to three types of cell death, ncRNAs are able to regulate mitochondrial fission/fusion of cardiomyocytes by targeting genes involved in cell death pathways. This review focuses on recent progress regarding the complex relationship between apoptosis/necrosis/autophagy and ncRNAs in the context of myocardial cell death in response to stress. This review also provides insight into the treatment for heart diseases that will guide novel therapies in the future.

Keywords miRNAs · Cardiomyocyte death · Apoptosis · Necrosis · Autophagy · Heart diseases

Introduction

Heart diseases remain serious problems that lead to increasing morbidity and mortality globally. Given that mammalian heart has limited regenerative capacity, the maintenance of cardiac homeostasis is particularly important. Excessive cell death in the heart has been implicated to be a critical factor resulting in many cardiovascular diseases [1, 2], such as cardiac hypertrophy, coronary artery disease, myocardial infarction (MI), and heart failure. The loss of cardiomyocytes involves a variety of cell death/survival processes, including apoptosis, necrosis, and autophagy, which are regulated by different pathways when the heart faces stress stimuli, intracellular biochemical components, and so on [3]. Over the last few decades, the regulatory mechanisms of cardiomyocyte death have been explored in order to improve the function of the failing myocardium. As a primary source for ATP and reactive oxygen species production in cardiomyocytes [4], the morphology of mitochondria is tightly linked with the cell death processes.

In recent years, growing number of studies indicate that non-coding RNAs (ncRNAs), especially microRNAs (miRNAs), are associated with cell death signaling, and they play essential roles in initiation and progression of heart diseases [5–7]. NcRNAs are a class of RNAs, which originate from genome that generally not translated into proteins. They are classified into two subgroups according to their length: long ncRNAs contain more than 200 nucleotides (lncRNAs); and short ncRNAs (<200 nucleotides), including miRNAs, piwi-interacting RNAs (piRNAs), short interfering RNAs (siRNAs), and others [8]. Among them, miRNAs is a class of small (22–24 nt) and highly conserved ncRNAs, which bind to the 3′ or 5′ untranslated regions (UTRs) of mRNA through complementary base pairing, and thus mediates posttranscriptional gene silencing by inhibiting protein

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translation or targeting mRNA degradation [9, 10]. The biogenesis of miRNA has been reviewed in detail by Berezikov and Graves et al. [11, 12]. Increasing evidences have widely revealed that many miRNAs are involved in the regulation of cardiomyocyte death pathways during heart diseases progression. Based on these findings, many miRNA-based therapeutic strategies have been directed towards reducing the extent of heart injury and improving the function of failing myocardium. However, the knowledge on contribution of other types of ncRNAs in regulating cell death in cardiovascular diseases remains fairly limited so far. In this review, we highlight the role of ncRNAs in regulating various myocardial cell death pathways that control cardiac physiological and pathological balance, and the potential therapeutic approaches for regulation of ncRNAs in heart diseases are also discussed.

NcRNAs in apoptosis-related cardiovascular diseases

The cell death network comprises of three different modes: apoptosis, autophagy, and necrosis [13, 14]. Among them, apoptosis, also referred as programmed cell death, is a highly conserved and regulated process that is relatively well defined [14]. Apoptosis is activated through two distinct pathways, the extrinsic death receptor pathway and intrinsic mitochondrial pathway, and followed by the structural changes, such as cell shrinkage, plasma membrane blebbing, nuclear condensation, and DNA fragmentation leads to complete demolition of the cell [15].

The extrinsic pathway of apoptosis is mediated via the death receptor (e.g., Fas, TNFR) located on the plasma membrane, where these receptors bind to their ligands (e.g., FasL, TNF-α) to form the death-inducing complex (DISC) that activates caspase-8. The activation of caspase-8 then leads to activation of downstream effector caspase-3 and caspase-7, which degrade proteome and drive cells to death [16]. On the other hand, the intracellular stress signals (e.g., hypoxia, acidosis, oxidative stress, DNA damage) stimulate the pro-apoptotic Bax and Bak in the outer membrane of mitochondria to release cytochrome c into the cytosol [17]. In turn, the downstream caspase-9 and its effector caspase-3 and caspase-7 are activated [18]. In the intrinsic mitochondrial pathway, the changes in the morphology of mitochondria can influence the apoptosis process [19].

Studies have implicated that apoptotic cell death contributes to cardiac pathologies that are associated with disorder of gene expression [20]. In recent years, abundant of miRNAs have been identified as an important contributor in the cell death network during the pathogenesis of myocardial disorders (Table 1). For instance, miR-1 is down-regulated in human infarcted hearts [21], and overexpression of miR-1 in cardiomyocytes can increase apoptosis under oxidative stress by targeting and reducing anti-apoptotic Bcl-2 [22]. In addition, the knockdown of miR-1 can suppress the cardiac arrhythmias [23]. It is well known that miR-133 can antagonize apoptosis triggered by H_2O_2 by negatively regulating caspase-9 expression [24], while overexpression of miR-133a protects heart against myocardial fibrosis [25]. A recent study found that miR-181c is involved in TNF-α-induced apoptosis and leads to heart failure by targeting Bcl-2 [26]. Besides, miR-21, miR-30, miR-199a, and miR-320 positively modulate the apoptotic program of heart by targeting different apoptosis-related proteins [27–30]. Recently, Wang et al. demonstrated that reactive oxygen species (ROS) can oxidatively modify miR-184, and the modified miR-184 misrecognizes Bcl-xL and Bcl-w, which are not its native targets [31]. Further experiments in mouse model of MI proved that the mismatch of oxidized miR-184 with Bcl-xL and Bcl-w contributes to ROS-induced lesions in myocardial tissue.

The mitochondrial apoptotic pathway is under the control of multiple miRNAs in the heart. It is well known that mitochondria constantly undergo fusion and fission in response to the changes coming from surrounding environments. In fact, mitochondrial fusion and fission are able to inhibit or trigger apoptosis in cardiomyocytes, respectively [32, 33]. Emerging evidences demonstrate that mitochondrial dynamics regulate cardiac function and susceptibility to injury [15]. For instance, the activation of dynamin-related protein-1 (Drp1) is required for mitochondrial fission during apoptosis [34], and knockdown of Drp1 in vivo can reduce infarct size after ischemia/reperfusion injury in adult mice [19]. In addition, miR-30 family regulates mitochondrial apoptotic pathway by suppressing the expression of p53, which targets Drp1 [35]. Wang et al. reported that miR-499 levels are down-regulated in the area at risk for ischemic injury in the heart, and overexpression of miR-499 can decrease the severity of MI through inhibiting the calcineurin-mediated dephosphorylation of Drp1 [36]. Mitofusion1 (Mfn1) is one of the mitochondrial dynamics-related protein that can prevent mitochondrial fission and cell death in cardiomyocytes [37]. In the mouse model of MI, miR-140 suppresses Mfn1 expression by directly binding to its 3′UTR [38]. Pink1 is a Ser/Thr kinase, which is tightly associated with the mitochondrial fusion and fission machinery [39]. Recently, Li and his colleagues exhibited an interplay between E2F1, miR-421, and Pink1, and this network is responsible for the abnormal mitochondrial morphology and myocardial apoptosis [40]. MiR-421 induces mitochondrial fragmentation, apoptosis and myocardial infarction by suppressing Pink1 translation. In the mitochondrial network, another signaling pathway composed of miR-361 and prohibitin 1 (PHB1), initiates mitochondrial fission and apoptosis, and protects heart from ischemia injury [41]. A study found that NFAT4/miR-324-5p/Mtfr 1 (mitochondrial fission regulator 1) axis

Table 1 Summary of ncRNAs linked to apoptosis in CVDs

ncRNAs	Targets/CVDs	Pro- or anti-apoptosis	References
miR-1	Bcl-2/MI	Promotes apoptosis	[22]
miR-133a	Caspase-9/MI	Inhibits apoptosis	[24]
miR-17-92 cluster	STAT3/MI, HF	Induces apoptosis	[63, 64]
miR-21	Bcl-2/MI	Anti-apoptotic	[65]
miR-30	P53/MI	Anti-apoptotic	[35]
miR-199a	Hif1α, Sirt1/MI	Anti-apoptotic	[29]
miR-320	Hsp20/MI	Pro-apoptotic	[30]
miR-149	Puma/MI	Decreases apoptosis	[66]
miR-761	Mff/MI	Promotes apoptosis	[67]
miR-499	Calcineurin/MI	Inhibits apoptosis	[68]
miR-214	Pten/MI	Anti-apoptotic	[69]
miR-145	Bnip3/MI	Decreases apoptosis	[70]
miR-378	Caspase-3/MI	Anti-apoptotic	[71]
miR-195	Sirt1/lipotoxic cardiomyopathy	Pro-apoptotic	[72]
miR-34a	Sirt1/coronary artery disease	Promotes apoptosis	[73]
miR-184	Bcl-xL, Bcl-w/MI	Pro-apoptotic	[31]
miR-140	Mfn1/MI	Induces apoptosis	[38]
miR-421	Pink1/MI	Promotes apoptosis	[4]
miR-324-5p	Mtfr 1/MI	Anti-apoptotic	[42]
miR-361	Phb1/MI	Pro-apoptotic	[41]
miR-208a	GATA4/DOX cardiotoxicity	Promotes apoptosis	[45]
miR-532-3p	ARC/DOX cardiotoxicity	Pro-apoptosis	[46]
LncRNA-CARL	miR-539, Phb2/MI	Inhibits apoptosis	[56]
CircRNA-HRCR	miR-223, arc/cardiac hypertrophy	Anti-apoptotic	[60]

participates in abnormal mitochondrial function [42]. Overexpression of miR-324-5p leads to reduction of apoptosis and infarct sizes in ischemia/reperfusion (I/R) injury animal model. Despite, many miRNAs have been identified to regulate the balance between cell survival and cell death in cardiomyocytes, the molecular mechanisms of mitochondrial network in heart remain largely explored.

Several miRNAs have been identified to protect heart from the cardiomyocyte death induced by doxorubicin (DOX), a drug widely used in cancer treatment. But this drug is associated risk of congestive heart failure [43, 44]. For instance, antagomir-based silencing of miR-208a or miR-532-3p attenuates DOX-induced myocyte apoptosis and cardiotoxicity [45, 46]. Meanwhile, overexpression of miR-21 or miR-30 inhibits DOX-induced apoptosis in cardiac cells [47, 48]. These studies shed light on new therapeutic strategies to overcome the DOX-induced cardiotoxicity during cancer therapy.

The other classes of ncRNAs such as lncRNAs and circular RNAs (circRNAs) are described as new regulators of the apoptosis pathway in cardiovascular diseases. LncRNAs are a set of RNAs with more than 200 nt in length with rare protein-coding potential, which are located throughout the whole genome [49]. It displays many cellular functions, such as capturing miRNAs, guiding transcription factors (TFs), and affecting the three-dimensional structure of chromatin [50, 51]. LncRNAs participate in various biological processes, including chromatin modification, genomic imprinting, and cell fate determination, and so on [52, 53]. For instance, lncRNA-Braveheart and Fendrr play critical roles during cardiomyocyte differentiation [54, 55]. However, the knowledge of influence of lncRNAs in cardiomyocytes death remains limited. Recently, Wang et al. demonstrated that a cardiac apoptosis-related lncRNA (CARL) acts as an endogenous miR-539 sponge [56]. MiR-539 directly targets prohibitin 2 (PHB2), which is a subunit of the prohibitin complex. The enforced expression of PHB2 blocks mitochondrial fission and apoptosis, as well as reduces infarct sizes in the mice of I/R model [56]. In this context, CARL is able to suppress mitochondrial fission and apoptosis by regulating the miR-539/PHB2 pathway. Another class of ncRNA, circRNAs, was discovered by Hsu et al. decades ago [57] that have 3′ and 5′ ends joined together to form a closed continuous loop. Recent findings reveal that they participate in multiple cellular processes [58]. CircRNA functions as a competing endogenous RNAs to miRNAs through complementary base pairing [59]; however, the functions of circRNAs in the cardiomyocyte death yet to be studied. So far, only one circRNA (heart-related circRNA, HRCR) is identified as a potential modulator of the apoptosis pathway

[60]. In this study, HRCR acts as an endogenous miR-223 sponge by directly binding to miR-223 and inhibiting its activity. MiR-223 is known to promote cardiac hypertrophy and heart failure by targeting the anti-apoptotic protein Arc (apoptosis repressor with CARD domain), which is highly expressed in the heart and known to suppress apoptosis in cell [61, 62].

NcRNAs regulate cardiovascular sensitivity to necrosis

Necrosis is morphologically characterized by increased cell volume, organelles swelling, disruption of the plasma membrane, and leakage of intracellular contents [74]. For a long time, necrosis was commonly viewed as a passive, accidental, and unregulated event. In recent years, accumulating evidence indicates that necrosis can also be programmed by cells (Fig. 1). Recently, a relatively new form of necrosis termed programmed necrosis or necroptosis is identified, which exhibits a unique signaling pathway that requires receptor interaction protein kinase 1 and 3 (RIP1 and RIP3) [74, 75]. The necroptosis pathway is induced by a set of death receptors (e.g., TNFR1, TNFR2, and Fas) in certain cell types when apoptotic cell death is blocked [76, 77]. Upon death receptor ligation, RIP1 and RIP3 are catalytically phosphorylated and form a necrosome, which consequently initiates necroptosis, when caspase-8 is inactivated [74]. Necrostatin-1 (Nec-1) has the capability to inhibit necroptosis through disturbing RIP1 and RIP3 interactions [78]. Besides, opening of mitochondrial permeability transition pore (mPTP) in the inner mitochondrial membrane can also contribute to necrotic cell death, which is accompanied by the loss of the electrical potential difference and mitochondrial swelling [79].

In cardiomyocyte, the necrosis-induced release of cellular contents triggers inflammatory reaction and pathological consequences, such as MI, heart failure, and stroke [79]. Ischemic injury often leads to hypoxia, increased levels of intracellular calcium and depletion of ATP, which subsequently causes opening of the mPTP. Cyclophilin D, a peptidyl–prolyl isomerase, is a critical regulator of mPTP [80]. Schinzel et al. reported that the suppression of cyclophilin D in mice reduces the infarct size after I/R injury and also

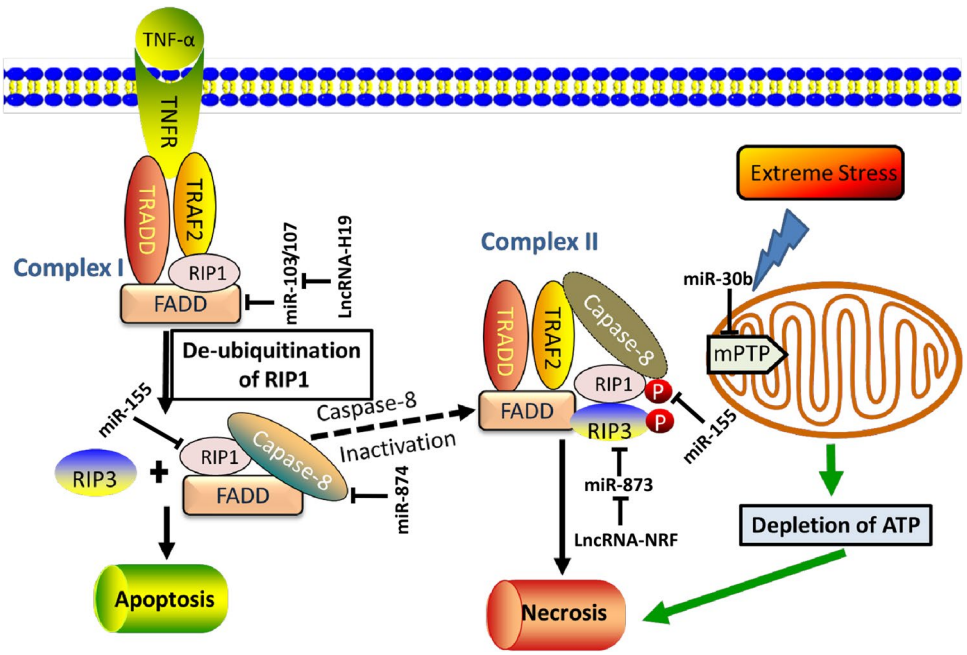

Fig. 1 Non-coding RNAs regulate necrosis signaling. Currently, necrosis is triggered through two pathways. The first pathway, also named necroptosis, involves death receptors, including TNFR1, TNFR2, and Fas. For example, upon binding its agonist TNF-α, TNFR1 can modulate either apoptotic or necrotic cell death by recruiting complex I. The complex I contains TNFR1, TRADD, RIP1, TRAF2, and FADD. This complex leads to de-ubiquitination of RIP1 releases RIP1 to the cytoplasm, and activates the formation of complex II (composed of TRADD, RIP1, RIP3, TRAF2, FADD, and caspase-8). The caspase-8 activity determines whether cells undergo apoptosis or necroptosis, because caspase-8 is able to cleave RIP1. The activation of caspase-8 induces apoptosis. When caspase-8 is blocked, RIP1 is not cleaved; instead, it recruits RIP3 and leads to the phosphorylation of the two kinases. Subsequently, necroptosis is initiated. On the other hand, excessive stimulation (e.g. Ca^{2+}, oxidative stress) leads to opening of mPTP in the inner mitochondrial membrane. MPTP is regulated by cyclophilin D and its opening results in depletion of ATP, which consequently activates mitochondrial necrosis pathway. The ncRNAs regulating these key components of necrotic/necroptotic are shown in the diagram. TNFR1, TNF-α receptor 1; TRADD, TNFR1-associated death domain protein; TRAF2, TNF receptor-associated factor 2

promotes resistance to permeability transition in mitochondria [81]. Recent study unveiled that miR-30b inhibits the translation of cyclophilin D and thus it can impair cyclophilin D-induced necrotic cardiomyocyte death [82]. In addition, E2F1 negatively controls the expression of miR-30b in vitro and in vivo [82]. These findings suggest that a novel necrosis-modulating signaling axis is composed of E2F1, miR-30b, and cyclophilin D. Current knowledge about the role of ncRNAs in regulating myocardial necrosis is relatively limited. Cardiomyocyte progenitor cells (CMPCs) provide a potential cell source for the generation of injured myocardium. Liu et al. found that miR-155 expression is increased in CMPCs when they are exposed to H_2O_2, and overexpression of miR-155 in vitro triggered anti-necrotic responses through blocking RIP1 [83]. This finding revealed a promising therapeutic target for transplantation therapy. In recent years, several research groups provide a new insight into the complex signaling mechanisms that regulated the pathogenesis of cardiomyocyte necrosis. The expression of miR-874 is up-regulated by necrotic damage induced by H_2O_2 in cardiomyocytes. Under vivo condition, the knockdown of miR-874 decreased the necrotic cells and improved cardiac function following I/R injury to the heart. Further study revealed that miR-874 directly targets caspase-8, which antagonizes necrosis via cleaving the RIP1 and RIP3. In addition, a transcription factor, Foxo3a, can repress miR-874 expression, which is evident from both Foxo3a transgenic and knockout mice studies [84]. FADD (Fas-associated protein with death domain) negatively regulates the formation of RIP1-RIP3 complex and necrosis [85]. MiR-103/107 influences H_2O_2-induced cell necrosis and myocardial infarct sizes in the heart by interfering the regulation of FADD expression. A bioinformatic study found that lncRNA-H19 contains complementary sites for miR-103/107. The enforced expression and knockdown of H19 in vitro proved the negative correlation between the expression of H19 and sensitivity of cells to necrotic mode of death. These results support a novel model regulating cardiomyocyte necroptosis, which is composed of H19, miR-103/107 and FADD [86]. Another example of miRNAs contributing to necroptosis in the heart is miR-2861 [87]. In this study, miR-2861 is found to inhibit ANT1 and promotes necrotic cell death in cardiomyocytes. ANT1 (adenine nucleotide translocator 1) is a mitochondrial protein involved in cellular energy metabolism [88], which protects cardiomyocyte from necrosis and MI. The level of miR-2861 is increased under severe oxidative stress induced necrosis, and knockdown of miR-286 can protect heart from the progression of myocardial necrosis by blocking the miR-286 induced degrading ANT1 mRNA. Recently, a new p53/lncRNA-NRF/miR-873/RIP pathway draws people's concern, which provides a new insight into the programmed necrotic cell death during the cardiac pathological process [89]. In this signaling pathway, p53 transcriptionally activates lncRNA-NRF expression. NRF works as an endogenous sponge of miR-873, which suppresses translation of RIP1//RIP3. Thus, the upregulation of lncRNA-NRF leads to increased necrotic cell death in cardiomyocytes and myocardial infarct size upon I/R injury. Experiments carried out in vivo also confirmed this necrotic pathway.

NcRNAs regulate cardiomyocyte autophagy

Autophagy is a conserved intracellular recycling process during which non-functional proteins and organelles are delivered to lysosomes for degradation [90]. This process is mediated by the formation of double-membrane vesicles, termed autophagosomes, which is initiated by vesicle nucleation and elongation involving Beclin-1, Vps34, Atg proteins, etc. [91]. Autophagosomes fuse with the lysosome to form an autolysosome, resulting in breakdown of its contents, after autophagosomes sequester long-lived proteins and damaged organelles such as mitochondria [90, 91]. The produced macromolecules are then recycled and released into the cytosol for reuse in biosynthetic pathways. Autophagy is regulated through two major pathways-mTOR (mammalian target of rapamycin) and Beclin-1 in response to stress signals (e.g., starvation, ROS, and protein aggregates).

Autophagy usually serves to maintain the homeostasis in cells. The dysfunction of autophagy is responsible for cardiovascular disorders. For example, dysfunction of autophagy can influence the renewal of mitochondria in the cardiomyocytes, and that causes deficit in the energy demand of the heart [92]. So far, multiple miRNAs have been linked to the autophagy pathway and cardiac pathologies (Table 2). Inhibition of the mTOR activity is able to prompt autophagy, and its inhibition exhibits a beneficial effect in the animal model of MI [93]. The overexpression of miR-99a attenuated mTOR activity, which led to decreased infarct size and improved cardiac function after MI [94]. Recently, Su et al. reported that miR-221 interferes autophagic balance and cardiac remodeling by modulating the p27/CDK2/mTOR axis in the failing heart [95].

On the contrary, activation of autophagy by Beclin-1 was demonstrated to induce cell death and disorder of the heart. For instance, ARC acts as an inhibitor of Beclin-1 and it decreases autophagic cell death and MI size in pressure-overload-induced heart failure [96]. Bioinformatic analysis and further experiments revealed that miR-325 conveyed the autophagic pathway by targeting ARC. Interestingly, miR-325 acts as a downstream of transcription factor E2F1. Another study found that Angiotensin II-induced down-regulation of miR-30a leads to up-regulation of Beclin-1 and excessive autophagy. This

Table 2 NcRNAs regulating necrosis and autophagy of cardiomyocytes

ncRNAs	Targets/CVDs	Effects on necrosis/autophagy	References
miR-155	Rip1/MI	Decreases necrosis	[83]
miR-30b	Cyclophilin D/MI	Inhibits necrosis	[82]
miR-874	Caspase-8/MI	Promotes necrosis	[84]
miR-2861	Ant1/MI	Promotes necrosis	[87]
lncRNA-H19	miR-103/107, FADD/MI	Anti-necrosis	[86]
lncRNA-NRF	miR-873, RIP/MI	Pro-necrosis	[89]
miR-99a	mTOR/MI	Activates beneficial autophagy	[94]
miR-22	PPAR-α/MI	Decreases beneficial autophagy	[101]
miR-221	P27/heart failure	Decreases autophagy	[95]
miR-212/132	Foxo3a/cardiac hypertrophy	Inhibits beneficial autophagy	[99]
miR-451	Tsc1/cardiac hypertrophy	Inhibits harmful autophagy	[100]
miR-325	Arc/MI	Promotes autophagy	[96]
miR-30a	Beclin-1/cardiac hypertrophy	Decreases harmful autophagy	[97]
miR-34a	Atg9a/cardiac hypertrophy	Inhibits harmful autophagy	[103]
miR-497	Lc3b, Bcl2/MI	Anti-autophagic	[104]
lncRNA-APF	miR-188-3p, Atg7/MI	Promotes autophagy	[102]

consequently results in defective autophagy mediated hypertrophy in cardiomyocytes response to Angiotensin II. Experiments in vitro revealed that miR-30a mimics can reverse the effects of Angiotensin II-induced cardiac hypertrophy by suppressing expression of Beclin-1 [97].

The expression of miR-212/132 family is upregulated in failing human hearts [98, 99]. In animal models, the knockout of miR-212/132 protects the cardiac function from pressure-overload-induced heart failure. In contrast, cardiomyocyte-specific overexpression of miR-212/132 impairs normal autophagic response and caused hyperactivation of pro-hypertrophic calcineurin/NFAT pathway through negatively regulating FOXO3 expression. In another study, miRNA microarrays on heart tissue from hypertrophic cardiomyopathy patients and healthy donors revealed that the level of miR-451 is decreased under diseased condition [100]. However, the enforced expression of miR-451 accelerates cardiac hypertrophy via targeting TSC1 (tuberous sclerosis complex 1), which is a known positive regulator of autophagy. Recently, Gupta et al. identified that miR-22 acts as an inhibitor of cardiac autophagy, and miR-22 is considered as a promising prognostic and therapeutic tool for MI patients [101]. The latest evidence shows that lncRNAs also participate in the regulation of cardiomyocyte autophagy. Wang et al. screened in cardiac tissue and found an lncRNA named as lncRNA-APF (autophagy promoting factor) [102]. APF is significantly up-regulated upon anoxia/reoxygenation, and this lncRNA consist of a binding site of miR-188-3p. A series of further experiments revealed that APF, miR-188-3p, and ATG7 constitute a novel regulating axis of autophagic program in the heart and this axis has influence on the autophagic cell death and myocardial infarction.

Crosstalk between three types of cell death

Under different levels of stresses, apoptosis, autophagy, and necrosis occur, respectively. In general, autophagy is induced under condition of mild stress, whereas apoptosis happens under condition of increasing and progressive stress, resulting in release of cytochrome *c* from mitochondria. Under further extreme stress, necrosis takes place along with ATP depletion [105]. During the cell death processes, mitochondria often functions as a switch between autophagy and apoptosis [105]. Some common cellular stressor factors can trigger signaling pathways that regulate apoptosis and autophagy. For instance, ROS induces autophagy through affecting the activity of Atg4 [106], meanwhile, ROS also plays critical role in apoptosis [107]. In addition, some node genes of signaling pathways, such as Beclin-1/Bcl-2 [108], p53 [109], caspase-8, as well as Atg5/FADD [110], act as switch between apoptosis/autophagy/necroptosis. The case of Bcl-2 family members such as Bax/Bak, the silencing of Bax/Bak causes resistance to mPTP opening and necrosis [111], while Bax and Bak are known to activate apoptosis upon I/R injury. Another study reported that Nix, a Bcl-2 family protein, could mediate apoptosis or necrosis depending on its cellular localization [112].

In the context, miRNAs targeting these node genes or different transcripts sharing a common binding site to the same miRNA are speculated to regulate the crosstalk between apoptosis, autophagy, and necroptosis. However, miRNAs contributed to the crosstalk on cardiac cell survival still remain relatively unknown. For example, Sirt1 is a miR-34a target, and that is able to influence apoptosis via p53 and ROS signaling pathway. In addition, Sirt1 is involved in autophagy via regulating the activity of p53 and

FoxO TFs [113]. A recent study found that let-7b inhibits apoptosis and autophagy of human mesenchymal stem cells transplanted into I/R injured heart by suppressing caspase-3 [114]. Li et al. reported that miR-497 can enhance cell apoptosis and reduce autophagy by targeting anti-apoptotic Bcl2 and autophagic gene LC3B [104]. The silencing of miR-497 ameliorated myocardial A/R and I/R injury in vitro and in vivo, respectively. Likewise, miR-153 regulates the survival of cardiomyocytes under oxidative stress condition through modulating apoptosis and autophagy by directly targeting Mcl-1 [115].

Future outlook

Cardiovascular diseases are complex, which involve multiple cellular processes, including cardiomyocyte death, during the disease progression. Based on the studies presented in this review, ncRNAs play essential role in cell survival and death by modulating apoptosis, necrosis, and autophagy processes in cardiomyocytes, and they exhibit enormous potential to treat cardiac diseases in the clinical application (Tables 1, 2; Fig. 1). Experiments on several animal models have validated that blocking of apoptosis or necrosis could be an effective therapeutic strategy for heart diseases. Given that ncRNA mimics or inhibitors can be easily synthesized and transfect cells with low toxicity in vivo, ncRNAs offer promising therapeutic targets in human to treat heart diseases. However, many questions and challenges remain to be solved in the development of ncRNA-based therapy, e.g., the off-target effects. Currently, some of the identified cardiovascular-related miRNAs have been used as diagnostic biomarkers in cardiac pathology [116]. For instance, circulating miR-126 and miR-145 are decreased in patients with coronary artery disease compared to healthy human [117]. However, further studies are still required to explore the complex mechanisms connecting ncRNAs and different mode of cardiac cell death during different myocardial pathological conditions.

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Compliance with ethical standards

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