Noncoding RNAs and Heart Failure

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Abstract

Heart failure (HF) is a leading cause of death worldwide and is still growing. Thus, it's critical to understand the molecular causes of HF and develop effective therapies to treat HF. Recently, scientists and clinicians identified that noncoding RNAs play important roles in pathogenesis of HF. Some of noncoding RNAs can serve as novel biomarkers for HF and some of them contribute to the progression of HF. In addition, noncoding RNAs can be related to well-known HF risk factors, such as hypertension, diabetes etc. In this review, we sought to summarize current knowledge about noncoding RNAs and noncoding RNAs mediated regulation of HF and its risk factors.

Keywords

Noncoding RNA · Heart failure · Regulation · Risk factors

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1   Introduction

Accompanied with the development of genomic sequencing, the biology and functions of noncoding RNAs (ncRNAs), which were considered as genetic waste, have been gradually revealed. From human genome project, people have known that about 98% of human genome do not encode proteins [1], thus, the roles of ncRNAs, which are not translated into proteins, have drawn intensive attention and have been extensively studied since then. With great efforts from both basic and translational researchers, ncRNAs have been linked to human physiology and diseases, including HF [2].

Heart failure (HF) is a stage that heart is unable to pump enough blood to meet physical demand of human body. While there are some advances in treating HF, the current mortality of HF is still very high due to poor understanding of the cellular and molecular causes of HF, which is an unmet medical need worldwide [3]. Fortunately, recent studies have revealed that ncRNAs might contribute to pathologies of HF [4]. More importantly, modulation of ncRNA has been shown to ameliorate HF [4]. In addition, some specific circulating ncRNAs in peripheral blood have been shown to serve as novel biomarkers for HF [5, 6]. In this chapter, we will review the functions of ncRNAs in development of HF and summarize ncRNA biomarkers for HF (see summary of Fig. 12.1).

Fig. 12.1 Overview of noncoding RNAs in development of HF
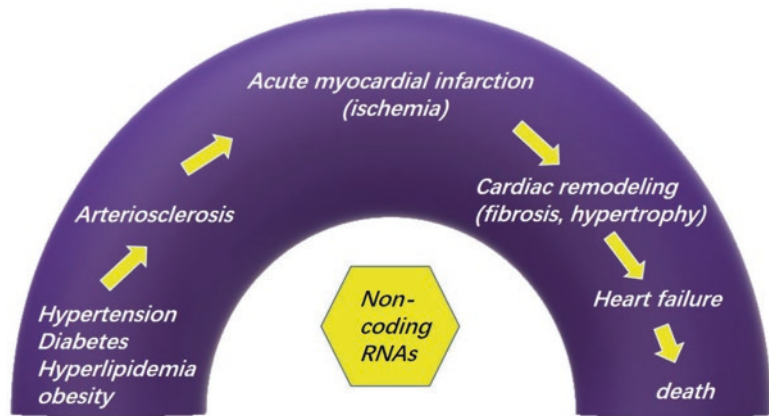
1.1 Members of ncRNAs

To date, ncRNAs mainly refer to microRNA (miRNA), long-noncoding RNA (lncRNA), and circular RNA (circRNA). miRNAs, considered as small ncRNA as well, consist of less than 200 nucleotides while lncRNAs are usually more than 200 nucleotides and regarded as large ncRNA. miRNAs are relatively stable and easy to measure in both tissues and body fluids. Furthermore, miRNA have been proven as a reliable therapeutic agent to treat cardiovascular disease [7]. Based on their genomic location, lncRNAs are grouped into five subclasses: (1) sense, transcribed from the same strand of the nearest protein-coding gene,and can be exonic, intronic, or both; (2) antisense, transcribed from the opposite strand of the surrounding protein-coding gene; (3) intronic, totally transcribed from an intronic region of protein-coding gene with the same direction; (4) intergenic, located between two protein-coding genes; (5) bidirectional, share the same premotor with coding genes, but transcribed from the opposite direction. lncRNAs have been shown to play a role in cardiovascular disease, the dysregulation of lncRNAs are commonly linked to exacerbation of cardiovascular functions [8, 9]. Uniquely, with a 5′ to 3′-phosphodiester bond, circular RNA forms a circular structure. Besides, no 5′ or 3′ free terminus enables its superior stability in cells. Though less well-known than miRNA and lncRNA, circular RNAs have been emerging as a novel biomarker and therapeutic target for treatment of HF [10].

1.2 General Functions of ncRNAs

In canonical way, miRNAs suppress specific gene by binding to partial complemental to 3′-untranlational region (UTR) of mRNA [11]. Furthermore, scientists found that miRNAs can target other ncRNAs, like rRNAs, tRNAs, and even other miRNAs [12]. And miRNAs are able to modulate gene expression in transcription level [13] or suppress both transcription and translation [14]. Unlike miRNAs, the functions of lncRNAs vary. It is mainly classified into signal, decoy, guide, and scaffold aspects [15]. Later, researches demonstrate an unexpected mechanism of lncRNAs by acting as a molecular sponge to miRNAs [16]. Surprisingly, some lncRNAs were recently reported to encode small peptides [17]. Despite more and more researchers have proved important functional role of lncRNAs, our understanding about lncRNAs remains limited. Compared with miRNA and lncRNA, circRNAs are less known. It is believed that circRNA also works as miRNA sponge [18] and regulates the transcription [19]. But further studies are needed to unveil the functional role of this special molecules in our bodies.

1.3 Noncoding RNAs Therapies: Promising but Challenging

Considerable researches have shown miRNA is a potential therapeutic target in cardiovascular disease. However, targeting a single miRNA may

result in altering multiple targets, which greatly limits its efficacy as a therapeutic agent [20]. LncRNAs mediate multiple functional regulations in heart. Unlike miRNAs, lncRNAs are less conserved, thus, it is difficult to study their potential functions in human bodies with animal models [21]. Taken together, while ncRNAs can contribute to progression of HF, it is still challenging to utilize them as therapeutic targets to treat HF.

2   Noncoding RNAs in Risk Factors for Heart Failure

2.1   Hypertension

Significantly, patients with high blood pressure more likely suffer from heart failure. Also, noncoding RNAs play   roles in pathogenesis and progression of hypertension [22]. Researchers figure out that miRNAs contribute to hypertension by their effects on rein-angiotensin-aldosterone system (RAAS), endothelial cells and vascular smooth muscle cells (VSMCs) [22, 23]. And circulating microRNAs are considered as modulators, like miR-181a, and biomarkers, like miR-505, for hypertension [24]. In a profile of long noncoding RNAs, 235 long noncoding RNAs were found deregulation and the lncRNA-XR007793 participates in remodeling of VSMCs, thus results in hypertension [25]. Similarly, lncRNA GAS5 and lncRNA AK098656 take part in pathogenesis of hypertension by vascular remodeling via their effects on VSMCs [26, 27]. Besides, circular RNA is believed to take part in hypertension pathogenesis and couples of circular RNA profiles were carried to figure out those deregulated. For instance, Wu et al. reported 13 downregulated and 46 upregulated circRNAs in hypertension patients. Then they validated circRNA has-circ-0005870 was significantly downregulated in hypertensive patients and hypothesized a has-circ-0005870-miRNA-mRNA network with utilization of Gene Oncology and KEGG analysis [28]. Whereas, more specific mechanism of circular RNAs in hypertension remains to be told.

2.2   Diabetes

Considerable clues have implied diabetes a risk factor for cardiovascular disease, including heart failure [29]. At the meantime, noncoding RNAs act as regulators of diabetes. MicroRNAs modulate Beta cells development (like miR-106b and miR-222), insulin sensitivity (like miR-103 and miR-107), resistance (like miR-190b), production (like miR-124a), secretion and insulin signaling (like miR-128a) [30]. In addition, miRNAs are involved in diabetic complications, like diabetic retinopathy, diabetic nephropathy, diabetic microvascular kidney disease and diabetic wound healing, etc. [31]. LncRNA can modulate diabetic related metabolism through interact with miRNA. For example, lncRNA Gomafu, by sponging miR-139-5p, upregulates Foxo1 expression to accelerate hepatic insulin resistance [32]. Similarly, circular RNA Crd1as regulates insulin transcription and secretion by sponging miR-7 [33]. Furthermore, circular RNAs, for instance, circHIPK3 and ciRS-7/CDR1as, are involved in regulations of beta-cell activities under diabetic conditions [34].

2.3   Hyperlipidemia

As known, hyperlipidemia puts risk on the occurrence of heart failure [35]. Therefore, promising treatment for hyperlipidemia is in great need. Excitedly, the researches of noncoding RNA shed new lights on solutions to hyperlipidemia. Of note, inhibition of miR-33a/b raises plasma HDL and reduces VLDL triglyceride levels, which may provide a novel therapy for hyperlipidemia [36]. And microRNA-24 contributes to hepatic lipid accumulation and hyperlipidemia by repressing insulin-induced gene 1 [37]. MicroRNA -30c decreases lipid synthesis through both MTP (microsomal triglyceride transfer protein)-dependent and MTP-independent manners, thus, reduces hyperlipidemia [38]. At the same time, long noncoding RNA takes part in process of lipid metabolism. A liver-enriched long noncoding RNA, lncLSTR, enhances triglyceride clearance by modulating

the bile acid pool [39]. The long non-coding RNA LeXis, behaves a mediator of a transcriptional regulation to cholesterol hemostasis by liver X receptors (LXRs) [40]. Unlike miRNA and lncRNA, there is still few researches to unveil the relation between circular RNA and hyperlipidemia and further recognition remains in infancy.

2.4 Obesity and Others

Plenty of clinical trials have proved that obesity causes rising risk to heart failure [41]. And noncoding RNAs influence the pathogenesis of obesity as well. Micro RNAs function as a stimulator or a repressor to the differentiation of adipocytes, which directly link to the development of obesity [42]. There are two kinds of adipose tissue in our body: white adipose tissue (WAT) which acts as largest energy storage, and brown adipose tissue (BAT) which consumes energy to produce enough heat in case of low body temperature. And modulation of WAT and BAT associates with process of obesity tightly [42]. Elevating the level of miR-34a is found to inhibit BAT formation then promote obesity happening. On the opposite, downregulation of miR-34a increases browning marker UCP1 and additional browning in brown fat [43]. It implies that inhibits the expression of miR-34a may be a new treatment for obesity. Similarly, miR-378 regulates BAT expansion and obesity resistance [44]. LncRNA is also a regulator of adipogenesis and controls the differentiation of preadipocytes [45]. For example, lncRNA Blnc1 is able to protect cold-induced thermogenesis and browning and impede obesity-associated brown fat whitening [46]. And lncRNA H19 was found inverse correlations with BMI in humans [47]. In addition, noncoding RNAs are involved in other risk factors for heart failure, like hyperuricemia and aging. It's reported that miR-34a suppresses the expression of human urate anion exthanger 1(URAT1) and decreases the excretion of uric acid [48]. And lncRNA is of potential to act as diagnostic and therapeutic targets to impede age associated pathologies and prolong lifespan [49].

2.5 Acute Myocardial Infarction-Induced HF

Acute myocardial infarction (AMI) refers to acute death of the myocardium because of sudden and lasting insufficient blood supply to the heart. The risk factors we mentioned above contributes to the development of atherosclerosis accumulatively. And the most common cause of AMI is the rupture of unstable atherosclerosis plaques in coronary, which lead to cardiac ischemia and damage [50]. Horribly, this is not the end. Following the AMI, heart failure which means not enough blood pumped to meet body's need happens.

2.5.1 Arteriosclerosis

In atherosclerosis, endothelial maladaptation to disturbed blood flow at bifurcations courses slight endothelial apoptosis and chronic inflammatory process. Besides, overloading subendothelial lipoprotein retention leads to macrophage failure [51].

From the very beginning, exosome-mediated miR-155 from smooth muscle cells to endothelial cells impairs the junctions and the integrity of endothelial cells, causing increasing endothelial permeability, and results in endothelial injury [52]. In endothelial maladaptation, miR-103 impedes endothelial cells proliferation and accelerate endothelial DNA damage by preventing lncRNA WDR59 interact with Notch1-inhibitor to interrupt Notch1-induced EC proliferation, rather than targeting at conventional protein-coding RNAs [53]. In endothelial inflammation, couples of noncoding RNAs are involved and nuclear factor-κB pathway is widely regulated in this process. MiR-103 mediated suppression of Krüppel-like factor 4 raises monocyte adhesion to ECs by promoting nuclear factor-κB-dependent endothelial C-X-C motif chemokine 1 expression [54]. Increasing miR-146a mediates the suppression of NF-κB–mediated inflammation by cellular apolipoprotein E [55]. Suppression of miR-499 expression upregulates programmed cell death 4 (PDCD4) expression and ameliorates endothelial inflammatory damage by inhibiting NF-κB/TNF-α signaling pathway [56]. In

macrophage, miR-33 regulates its autophagy and reduce lipid droplet catabolism [57]. And miR-155 inhibits the transformation of macrophage into foam cells through activating cholesterol ester hydrolase (CEH) signaling pathway, then eases atherosclerosis [58].

Long noncoding RNA regulates the atherosclerosis circuit as well [59]. On the one hand, lncRNA plays a role in atherosclerosis-associated cell proliferation. LncRNA-p21, which is downregulated in a atherosclerosis plaques of an animal atherosclerosis model mice, increases p53 transcriptional activity by binding to a p53 repressor MDM2, therefore regulates p53-dependent cell proliferation [60] . Smooth muscle enriched long noncoding RNA (SMILR) is identified to be a driver of SMCs proliferation and upregulated in unstable atherosclerosis plaques in human samples [61]. Similarly, knockdown the long noncoding RNA-RNCR3, which is upregulated in cultured ECs and VSMSs with ox-LDL treated, inhibits the proliferation and migration of ECs and VSMCs by acting as a ceRNA to compete with miR-185-5p [62]. On the other hand, lncRNA is involved atherosclerosis-associated inflammation. Compared with control mice, researchers find MALAT1-deficient mice showed more severe plaque size and higher infiltration of inflammatory CD45 cells [63]. Another research discovers that MALAT1 is associated with immune system which mediates atherosclerosis. In parallel with the former research, the MALAT1-deficient mice show increased plaque area. Furthermore, massive deregulations of immune system happen. Serum levels of IFN γ, TNF, IL6 are increasing and macrophages in bone marrow cells and splenocytes of MALAT1-deficient mice are undergoing a series of immunological disturbance [64].

Tough less well known as microRNA and lncRNA, circular RNA shouldn't be ignored in regulation of atherosclerosis pathogenesis. Holdt et al. find that Circular RNA ANRIL increases p53 activation and induces nucleolar stress by targeting ribosomal RNA maturation and regulating pathways of atherogenesis, thus promotes apoptosis and inhibits proliferation, which slow down the process of atherosclerosis [65].

However, Song et al. gave opposite opinion about circRNA ANRIL. They found that atherosclerotic plaques and thrombi showed up in over-expressed circRNA ANRIL group while didn't in under-expressed circRNA ANRIL group. Furthermore, compared with model group, the levels of indicators pointed to atherosclerosis were decreased in low-expressed circRNA ANRIL group while the opposite outcome in over-expressed circRNA ANRIL group. So they claimed that high expression level of circRNA ANRIL may lead to atherogenesis [66]. The controversy remains to be further discussed and solved by more powerful researches data.

2.5.2   Ischemia
Usually, the coronary arteries can be restricted or totally blocked by the embolus caused by the unstable plaque in atherosclerosis, resulting in the insufficient blood supply for myocardium, which is termed cardiac ischemia.

In ischemic heart disease, cell death is caused by couples of reasons, such as lack of oxygen, insufficient adenosine triphosphate (ATP) and mitochondrial impairment, etc. [67] As known, mitochondria is a factory generated power, termed ATP, to meet body's physiological demand, which highlights the importance of mitochondrial function. As widespread regulators, microRNAs are involved in mitochondrial function in cardiac ischemia. Downregulation of miRNA-361 showed talent in reducing mitochondrial fission and apoptosis by clearing the repression of prohibitin1 (PHB1), resulting smaller myocardial infarction sizes after operation causing ischemia performing [68]. Hong et al. reported that miRNA-143 impaired mitochondrial membrane by downregulating the expression of protein kinase Cepsilon in both ischemia model in vivo and in vitro [69]. Apart from mitochondrial dysfunction, cardiomyocytes apoptosis, a kind of programmed cell death, is an important process in cardiac ischemia. Artificial modulation of the miRNA expression is able to improve the apoptotic cell death, thus increases cardiac function in ischemic heart disease. He et al. reported that suppression of miRNA-124 with AMO124 decreased the apoptotic cell death

by targeting STAT3 protein in a mice model of MI and neonatal rat ventricular myocytes (NRVMs) treated with H2O2 as well. Besides, AMO124 is of ability to ameliorate mitochondrial dysfunction in NRVMs with H_2O_2 treatment [70]. Tang et al. observed that miRNA-150 regulated cardiomyocyte death in ischemic injury. They revealed that miRNA-150 directly repress the expression of the pro-apoptotic gene egr2, a zinc-binding transcription factor triggered by ischemia, and p2x7 (pro-inflammatory ATP receptor) during ischemic injury [71]. Interestingly, Huang et al. explored the effect of combination of miRNA-21 and miRNA-146a to cardiac function and apoptosis in a mice model of AMI. In this research, they found that it augmented the effect to decrease apoptosis under ischemia when combined miRNA-21 and miRNA-146a together, compared with each of them respectively [72].

Long noncoding RNA was little known in the onset of myocardial ischemia. To explore more lncRNAs with potential to regulate the development of cardiac ischemia, couples of researches were carried out. As a case, Saddic et al. measured the lncRNAs in left ventricular tissue in patients before and after cardiopulmonary bypass carrying ischemia insult. Then they obtained a list of deregulated lncRNAs which may point to regulators for cardiac ischemia. Furthermore, for the reason that lncRNAs tightly links with neighboring coding genes in co-expression, regulation and even functions, they figured out neighboring coding genes of these deregulated lncRNAs modulates the stress and immune response and mRNA co-expressed with them played roles in metabolism and heart physiology as well. Last but not least, they claimed differentially expressed lncRNAs with transcription factor binding sites enrichment were associated with ischemia injury [73]. They have showed us lncRNA is related to ischemic heart disease and metabolism, stress and immune response may be the field lncRNA interrupts in cardiac ischemia. However, specific mechanism lncRNA regulates ischemia process rely on other researches. Gong et al. reported that knockdown of lncRNA H19 promoted hypoxia-induced injury in H9c2 cells by up-regulating

miR-139. And repression of Sox8, the target of H19, activates the PI3K/AKT/mTOR pathway and MAPK, then ameliorates hypoxia-induced cell injury. The H19-miR-139-Sox8-PI3K/AKT/mTOR and MAPK axis shows us alternative mechanism of lncRNA in cardiac ischemia [74]. Interestingly, they also observed the overexpression of H19 reversed the down-expression of SERCA2a which was induced by hypoxia and promoted contractility [74]. More specifically, targeting SERCA2a as H19 did, Zhang et al. reported that lncRNA ZFAS1 exacerbated contractile dysfunction in mouse models of myocardial infarction. According to the research, ZFAS1 was able to binding to SERCA2a protein and repress its expression so as to alter the transient of Ca^{2+}, which caused intracellular Ca^{2+} overload, then contributed to cardiac contractile dysfunction [75]. Modulation of ZFAS1 provides us a new potential therapy to battle with ischemia-induced heart failure by elevating contractile function.

A microarray expression profile of circular RNAs by *Wu* et al. showed differential expression of circular RNAs in myocardial tissue during AMI-induced HF, comparing with transcriptome profiles of hypertrophy one. And they found a handful of deregulated circular RNAs showed up in this process, which meant circular RNAs were involved in post-AMI regulation at least [76]. But how does circular work in cardiac ischemia? *Wang* et al. reported that a mitochondrial fission and apoptosis-related circular RNA MFACR regulated cardiomyocytes death. MFACR downregulated miR-652-3p, which suppressed the expression MTP18. And MTP18 increased mitochondrial fission and promoted cardiomyocyte apoptosis. Taking together, the MFACR-miRNA-652-3p-MTP18 axis is crucial to the regulation of mitochondrial fission and cardiomyocyte apoptosis in an ischemia/reperfusion model [77]. Li et al. found that a circular RNA NCX1, which was transcribed from the sodium/calcium exchanger 1 gene, acted as a miRNA-133a-3p sponge, thus weaken the effect of miRNA-133a-3p to suppress the expression pro-apoptotic gene cell death-inducing protein (CDIPI). As a result, less apoptosis and ischemic

myocardial injury happen when knockdown the expression of circNCX1 [78]. This circRNA-miRNA interaction shows us a novel mechanism of circular RNA modulating manner in cardiac

ischemia disease. However, specific signal pathway involved in circular RNA regulation is under to be unpacked.

Alteration of noncoding RNAs in risk factors of heart failure

	MiRNA [Refs.]	LncRNA [Refs.]	CircRNA [Refs.]
Hypertension	miR-181a [24] miR-505 [24]	lncRNA-XR007793 [25] lncRNA GAS5 [26] lncRNA AK098656 [27]	has-circ-0005870 [28]
Diabetes	miR-106b miR-222 miR-103 miR-107 [30] miR-190b miR-124a miR-128a	lncRNA Gomafu [32]	circHIPK3 [33, 34] ciRS-7/CDR1as [33]
Hyperlipidemia	miR-33a/b [36] microRNA-24 [37] MicroRNA-30c [38]	LncRNA LSTR [39] LncRNA LeXis [40]	–
Obesity	miR-34a [43] miR-378 [44]	lncRNA Blnc1 [46] lncRNA H19 [47]	–
Hyperuricemia	miR-34a [48]	–	–
Age	–	–	–
Genders	–	–	–
Arteriosclerosis	miR-155 [52] miR-103 [53, 54] miR-146a [55] miR-499 [56] miR-33 [57] miR-155 [79]	lncRNA-p21 [60] SMILR [61] RNCR3 [62] MALAT1 [63, 64]	ANRIL [65]
Ischemia	miRNA-361 [68] miRNA-143 [69] miRNA-124 [70] miRNA-150 [71] miRNA-21 [72] miRNA-146a [72]	H19 [74] ZFAS1 [75]	MFACR [77] NCX1 [78]

3   Noncoding RNAs as Pivotal Roles in HF Remodeling

The two most common modes of myocardial remodeling are cardiac hypertrophy and myocardial fibrosis in heart failure. In the compensatory phase of cardiac hypertrophy, the cardiomyocyte increases its size to enhance the contractile force against abnormal resistance and maintain the blood supply to meet the body's demand. If the pathological resistance persists, however, the increasing size of myocardial cells leads to an elevation in oxygen consumption, which results in a relatively insufficient blood supply from the

coronary arteries, which causes the myocardial contractility to decrease and lack of blood supply to maintain normal pump function of heart. Myocardial fibrosis is characterized by excessive deposition of the extracellular matrix, which leads to a decrease in myocardial compliance. And the decreasing myocardial compliance causes reducing myocardial contractility and insufficient blood pumped to maintain the physiological needs. It is meaningful to slow down, even reverse these pathological processes in case of occurrence of heart failure. And researchers have found that noncoding RNAs are involved in

cardiac remodeling and present a novel therapeutic strategy for heart failure [80].

3.1   Cardiac Hypertrophy

Cardiac hypertrophy is a maladaptation to overload pressure. At the very beginning, cardiomyocytes change into larger size to strengthen the contractibility so as to output enough blood volume to meet body's need against the unusual obstruction, which termed compensate phase. But cardiomyocytes will not be of ability to cope with long-term lasting overload pressure and insufficient blood supplied, then leads to heart failure, which we term it decompensate phase. In decompensate phase, though no enough blood supplement, cardiomyocytes still try to suit the abnormal pressure condition, resulting in pathological hypertrophy. Attenuating this maladaptation has been proved a promising therapeutic method and thus reduces heart failure suffering. Researchers found that noncoding RNAs were able to regulate the process of hypertrophy and modulation of specific noncoding RNAs showed satisfied outcome against hypertrophy [80].

Micro RNA can alter the genes expression that have been pointed to cardiac hypertrophy, thus ameliorate heart failure [81]. And miRNA can modulate hypertrophy through various of signal pathways. For instance, Tijsen et al. observed that miR-15 was a negative regulator to hypertrophy by inhibiting TGFβ signaling pathway [82]. Li et al. generated miR-199-sponge transgenic mice and figured out that the absence of endogenous miR-199 induced physiological cardiac hypertrophy [83]. Later, they showed more details about miR-199 in another research. They found that miR-199 acted as a negative regulator of cardiac autophagy by targeting GSKβ/mTOR complex signaling, then induced cardiac hypertrophy [84]. Sassi et al. reported that inhibition of miR-29 attenuated cardiac hypertrophy and improved cardiac function by abolishing activating effect of miR-29 on Wnt signal pathway [85]. Besides, miRNA can play as a mediator in modulation of cardiac hypertrophic pathogenesis. Huang et al. revealed that

miR-18 acted as a mediator in regulation. In this process, P53 activation promoted heat shock factor 1(HSF1) expression and IGF-IIR-induced cardiomyocytes hypertrophy by downregulating miR-18 [86]. Right ventricular hypertrophy (RVH) is mainly caused by pulmonary arterial hypertension (PAH). So miRNA involved in PAH affects the pathogenesis of RVH indirectly [87]. Brock et al. reported that suppression of miR-20a with antagomiR-20a attenuated right ventricular hypertrophy by upregulating the expression bone morphogenetic protein receptor type 2(BMPR2), which is related with PAH occurrence [88]. Similarly, Baptista et al. observed that miR-424(322) upregulated BMPR2 pathway activity by targeting smad ubiquitination regulator factor1 (SMURF1) in right ventricular hypertrophic models. Besides, they revealed that the level of miR-424(322) was parallel to the severity of heart disease, which enabled miR-424(322) an novel prognostic biomarker [89].

Long noncoding RNA is an important regulator in cardiac hypertrophy development as well. Viereck et al. observed that a long noncoding RNA, selected by global lncRNA expression profiling in cardiac hypertrophy mice heart tissue and named Chast (cardiac hypertrophy-associated transcript) promoted cardiac hypertrophy. Overexpression and suppression of Chast induced cardiac hypertrophy and attenuated pressure overload-induced pathological hypertrophy respectively. In mechanism, Chast inhibited cardiomyocyte autophagy and led to hypertrophy by targeting Pleckstrin homology domain-containing protein family M member 1 [90]. And lncRNA can interact with miRNA in this regulation. Wang et al. firstly reported this novel hypertrophy regulating mechanism. They revealed that long noncoding RNA CHRF (cardiac hypertrophy related factor) functioned as an endogenous sponge of miR-489, which was found to be involved in cardiac hypertrophy pathogenesis. Furthermore, suppression of miR-489 target gene Myd88 attenuated hypertrophic response [91]. Taken together, they found a lncRNA-miRNA-miRNA target genes axis in cardiac hypertrophy regulation at first. Since then, this regulation pattern was reported in dozens of researches, like

lncRNA XIST-miR-101-TLR2 axis [92], MIAT-miR-93-TLR4 (toll like receptor 4) axis [93] etc. Differently, *Liu* et al. observed that long noncoding RNA H19 and its encoded miR-675 cooperated in cardiac hypertrophy regulation. They found that H19 overexpression attenuated hypertrophy while H19 suppression promoted hypertrophy. Furthermore, inhibition of miR-675 abolished the inhibitory effect of H19 on hypertrophy. Next, they figured out that miR-675 targeted CaMKIIδ directly in regulation of cardiac hypertrophy [94]. Overall, they showed us a lncRNA together with its own encoding miRNA regulating the process of cardiac hypertrophy.

Compared with miRNA and lncRNA, Circular RNA is much less reported in cardiac hypertrophic regulation. However, scientists do find its role in this modulation process. Wang et al. reported that a heart-related circular RNA (HRCR) impeded cardiac hypertrophy. They found miR-233 was a positive regulator of cardiac hypertrophy while HRCR functioned as a miR-233 sponge. As a result, HRCR blocked adverse effect of miR-233 on myocardium by modulating ARC, a downstream target of miR-233 which mediated cardiac hypertrophy induction [95]. For limited recognition, there are still lots of challenges on the way to unveil the secret of circular RNA in cardiac hypertrophy pathogenesis.

3.2   Cardiac Fibrosis

Similarly, cardiac interstitial fibrosis leads to left ventricular dysfunction resulting in the occurrence of heart failure [96]. Abundant research has provided evidences for the cellular and molecular mechanisms behind these pathological changes and the pathways by which it renders an adverse effect on cardiac function [97].

In particular, Thum T's research shows that microRNA-21 (miR-21, also known as Mirn21) was involved in the regulation of the ERK-MAP kinase signaling pathway in cardiac fibroblasts, affecting global cardiac structure and function. MiR-21 levels are selectively up-regulated in the failing heart fibroblasts, enhancing ERK-MAP kinase activity through suppression of sprouty homologue 1 (Spry1). Therefore, in response to cardiac pressure overload in cardiac fibrosis, miR-21 is specifically enriched in cardiac fibroblasts facilitating fibroblast survival and growth factor secretion [98]. In Lorenzen's study, furthermore, miR-21 silencing in vivo prevented the development of Ang II-induced cardiac fibrosis [99]. Another well-studied miRNA involved in cardiac fibrosis is microRNA-101, which has been found to inhibit post-infarction myocardial fibrosis and improve left ventricular compliance through the FBJ osteosarcoma gene/transforming growth factor-1 pathway. Overexpression of miR-101a can respite interstitial fibrosis and the failure of cardiac function, demonstrating miR-101a therapeutic potential for cardiac disease associated with fibrosis [100]. Other cardiomyocyte-enriched miRNAs, such as miR-378 and miR-133a, are also involved in cardiac fibrosis. Among them, miR-378 is secreted by cardiomyocytes after mechanical stress and acts as an inhibitor of excessive myocardial fibrosis through a paracrine mechanism [101]. And overexpression of miR-133 in the heart can prevent fibrosis without affecting the degree of hypertrophy during left ventricular pressure overload [102] or in a mouse model of type 1 diabetes [103].

In addition to microRNA, many long noncoding RNAs were found to be involved in cardiac fibrosis with the advancement of bioinformatics analysis of microarray data [104]. For example, using an integrated genomic screen, Thum T's research group characterized Wisper (Wisp2 super-enhancer–associated RNA) as a cardiac fibroblast–enriched lncRNA regulating cardiac fibrosis after damage. Of note, ASO-mediated silencing of Wisper mitigated MI-induced fibrosis and cardiac dysfunction *in vivo*. Furthermore, its binding to TIA1-related proteins enables it to control the expression of profibrotic forms of lysine hydroxylase 2, which involves collagen cross-linking and matrix stabilization [105]. At the same time, the CF-rich lncRNA maternal expression gene 3 (MEG3) has also been found participating in the regulation of cardiac fibrosis. Researchers figure out that Meg3 regulated the matrix metalloproteinase-2 (MMP-2) production

in vitro, and that GapmeR-mediated silencing of Meg3 in CFs resulted in Mmp-2 transcription decrease, which, in turn, depending on P53 activity both in the absence and in the presence of transforming growth factor-β I [106]. In addition to the above lncRNA, by using microarray data for bioinformatics analysis, the researchers also found lncRNA NONMMUT022555, named profibrotic lncRNA (PFL), and found that PFL is increased in the hearts of mice in response to myocardial infarction (MI) and in the fibrotic cardiac fibroblasts (CFs). Further studies indicate that overexpression of PFL promotes fibroblast-myofibroblast transformation and fibrosis in CFs by regulating let-7d. PFL acts as a competitive endogenous RNA (ceRNA) for let-7d, thereby reducing the expression and activity of let-7d, and inhibition of let-7d leads to fibrosis of CFs [107]. Collectively, a growing number of studies have revealed the key role of lncRNAs in the regulation of fibrosis in vitro and in vivo in CFs,

identifying new roles in the development of cardiac fibrosis and potential new targets for preventing cardiac remodeling.

As other ncRNAs, Circular RNA also plays a role in the regulation of cardiac fibrosis [108]. For instance, CircRNA_010567 was found to be significantly up-regulated in the circRNA expression profiles of cardiac and cardiac fibroblasts (CF) in Ang II treated diabetic mice. Bioinformatics analysis pointed out that circRNA_010567, sponge miR-141 and miR-141 directly target TGF-β1. In addition, functional experiments showed that circRNA_010567 silencing up-regulated miR-141 and down-regulated TGF-β1 expression, and inhibited fibrosis-associated protein excision in CFs, including Col I, Col III and α-SMA [109]. Regrettably, little is known about the mechanistic function of circRNAs in the heart or vessels, which needs to be determined in future studies.

Noncoding RNAs involved in cardiac hypertrophy and fibrosis

	MiRNA	LncRNA	CircRNA
Hypertrophy	miR-15 [82] miR-199 [83] miR-29 [85] miR-18 [86] miR-20a [88] miR-424(322) [89]	Chast [90] CHRF [91] XIST [92] MIAT [93] H19 [94]	HRCR [95]
Fibrosis	miR-21 [98, 99] miR-101a [100] miR-378 [101] miR-133a [102, 103]	Wisper [105] MEG3 [106] PFL [107]	CircRNA_010567 [109]

4   Conclusion

Heart failure is a worldwide problem that threatens patients' lifespan. The cognition of noncoding RNA has shown us their expression patterns, regulation modes and roles in heart failure and heart failure related risk factors as well. And noncoding RNA provides a novel potential therapy, diagnostic implication and prognostic prediction. In human being research, some noncoding RNAs have proved to be potential biomarkers for heart, such as miRNA-19b, miRNA-148-3b, miRNA-409-3p, lncRNA

LIPCAR etc. [110–112]. However, the sample amounts involved in these researches are limited and there is no multiple centers research yet. As a result, the conclusions they draw may ignore the existence of bias. As for noncoding RNA therapy in human, it still stays infancy. No matter technical safety nor ethical issue is a stumbling block at present.

Overall, identification of noncoding RNA in heart failure benefits the treatment for heart. And there is still a long way to go before universal clinical utilization against heart failure.

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