Review

Noncoding RNAs in Cardiac Hypertrophy and Heart Failure

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Abstract: Heart failure is a major global health concern. Noncoding RNAs (ncRNAs) are involved in physiological processes and in the pathogenesis of various diseases, including heart failure. ncRNAs have emerged as critical components of transcriptional regulatory pathways that govern cardiac development, stress response, signaling, and remodeling in cardiac pathology. Recently, studies of ncRNAs in cardiovascular disease have achieved significant development. Here, we discuss the roles of ncRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) that modulate the cardiac hypertrophy and heart failure.

Keywords: heart failure; cardiac hypertrophy; noncoding RNAs

1. Introduction

Cardiac hypertrophy is an essential milestone of many heart diseases, including hypertension [1], myocardial infarction (MI) [2], and aortic stenosis [3,4]. It may be the initial adaptive response to maintaining cardiac function; sustained hypertrophy is often accompanied by maladaptive cardiac remodeling that ultimately leads to heart failure and sudden death [5,6]. Many effective cardiovascular drugs, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibition, are available for patients with heart failure with reduced ejection fraction (HFrEF) [7–9]. However, few evidence-based therapeutic plans are available for heart failure with preserved ejection fraction (HFpEF), acute heart failure, or the preventive management of individuals with cardiovascular risk factors [10,11]. Thus, delaying or preventing heart failure is increasingly important in patients at risk, and should be prioritized in future research studies. One way to achieve this goal is to block or reverse pathological cardiac hypertrophy in heart failure.

At the cellular level, cardiac hypertrophy is featured by increased cardiac myocyte size, sarcomere assembly, and fetal cardiac gene re-expression. Pathological stimuli induce these alterations by activating intracellular signaling pathways and transcriptional mediators in cardiac myocytes [6,12]. Hence, cardiac hypertrophy is associated with changes in gene expression.

In recent years, the development of next-generation sequencing technologies has led to an explosion of newly identified noncoding RNAs (ncRNAs), such as microRNAs (miRNAs), linear long noncoding RNAs (lncRNAs), and circular noncoding RNAs (circRNAs). Unlike messenger RNAs (mRNAs), ncRNAs do not encode proteins, but rather act as epigenetic regulators [13], post-transcriptional modifiers [14], and translational coordinators of gene expression [15,16]. Mounting evidence highlights the aberrant expression of ncRNAs in cardiac development and cardiac diseases using RNA-sequencing technologies and genomewide profiling approaches. For example, the expression of 43 out of 428 miRNAs, including miR-1, -19, -133, and -108, is altered in human heart disease [17]. Ounzain et al. revealed hundreds of novel heart-specific lncRNAs with potential roles in pathological remodeling in a mouse myocardial infarction (MI) model [18]. Tan et al. provided a

detailed circRNA expression landscape in human hearts [19]. Dong et al. established a functional paradigm for identifying novel circRNAs in human dilated cardiomyopathy [20]. ncRNAs may provide therapeutic targets and serve as biomarkers in diagnosis and prognosis [21–23]. The development of RNA interference (RNAi) drugs, which use the recently discovered endogenous short interfering RNA pathway, suggests that therapy with ncRNAs is a new frontier of disease treatment [24]. However, the role and function of ncRNAs in cardiac hypertrophy and heart failure remain to be illustrated. Here, we review the potential roles of these three classes of well-described ncRNAs as potential targets for therapy.

2. Biogenesis and Function of ncRNAs

On the basis of the length of nucleotides, ncRNAs are categorized into small (<200 bp) and long (>200 bp) RNAs. Small RNAs, comprising 19–25 bp miRNAs, target RNA stability and translation, while long RNAs are composed of linear long noncoding (lncRNAs) and circular (circRNAs) RNAs [16,25].

2.1. MiRNAs

MiRNAs are endogenous, single-stranded, small noncoding RNA molecules that suppress gene expression at the post-transcriptional level by targeting specific mRNAs [26]. RNA polymerase II transcribes miRNA genes to generate primary transcripts (pri-miRNAs). Drosha crops pri-miRNAs into precursor miRNAs (pre-miRNAs), which are exported from the nucleus to the cytoplasm by Exportin-5. Lastly, pre-miRNAs are cleaved by the RNase III enzyme dicer to produce mature miRNAs. miRNAs can direct the RNA-induced silencing complex (RISC) to downregulate gene expression by post-transcriptional mechanisms: mRNA cleavage or translational repression (Figure 1A) [27,28].

2.2. LncRNAs

Most lncRNA species are transcribed by polymerase II. Like mRNAs, many lncRNAs display 5′-end CpG islands and 3′-end poly(A) tails. Unlike mRNAs, they are inefficiently processed and retained in the nucleus, whereas others are spliced and exported to the cytoplasm [29,30]. LncRNAs are important players in a wide range of biological processes by targeting proteins and other RNAs to regulate splicing, translation, and mRNA decay. Moreover, lncRNAs can bind multiple proteins to regulate chromatin modification, genetic imprinting, and cell cycle control. LncRNAs are divided into four archetypes on the basis of their molecular functions: (1) as signals, lncRNA expression can reflect the combinatorial actions of transcription factors or signaling pathways to regulate gene regulation by space and time; (2) as decoys, lncRNAs can titrate transcription factors and other proteins from chromatin or titrate protein factors into nuclear subdomains; (3) as guides, lncRNAs may recruit chromatin-modifying enzymes to target gene promoters in either the Cis or Trans of target genes in the distance; (4) as scaffolds, lncRNAs may nucleate multiple proteins to affect histone modifications [31,32] (Figure 1B).

2.3. CircRNAs

CircRNAs range from hundreds to a few kilobases of nucleotides in length. They are generally produced from exon regions and introns, exon–introns, and tRNA intron regions of protein-coding genes. They circularize the 3′ and 5′ ends of the RNAs [33,34]. CircRNAs are generated from exons or introns through multiple mechanisms, and most circRNAs are stable and conserved across different species. CircRNAs can act as miRNA sponges and inhibit the activity of one or multiple miRNAs. For example, circRNA ciRS-7 harbors more than 70 conventional miR-7-binding sites, and it was identified as a miR-7 inhibitor [35,36]. CircRNAs can also interact with RNA-binding proteins and function as regulators of splicing and transcription; for instance, circMbl is strongly and specifically bound by MBL proteins [37] and serves as protein scaffold or modifier during parental gene expression [38,39]. Most circRNAs do not appear to be involved in gene expression,

but a few, mainly intron circRNAs, may regulate the expression of host genes, such as ci-ankrd52 [40]. Some circRNAs can also be translated into proteins to regulate gene expression (Figure 1C) [41–43]. Yang et al. found that circ-fbxw7 can encode a 21-kDa protein (fbxw7-185aa) through an internal ribosome entry site (IRES) [44]. In addition, compared with miRNAs and lncRNAs, circRNAs are more stable and have longer half-lives, making them abundant in extracellular fluid and easy to detect, indicating that circRNAs can be a better choice for biomarkers of cardiovascular diseases [45–47].
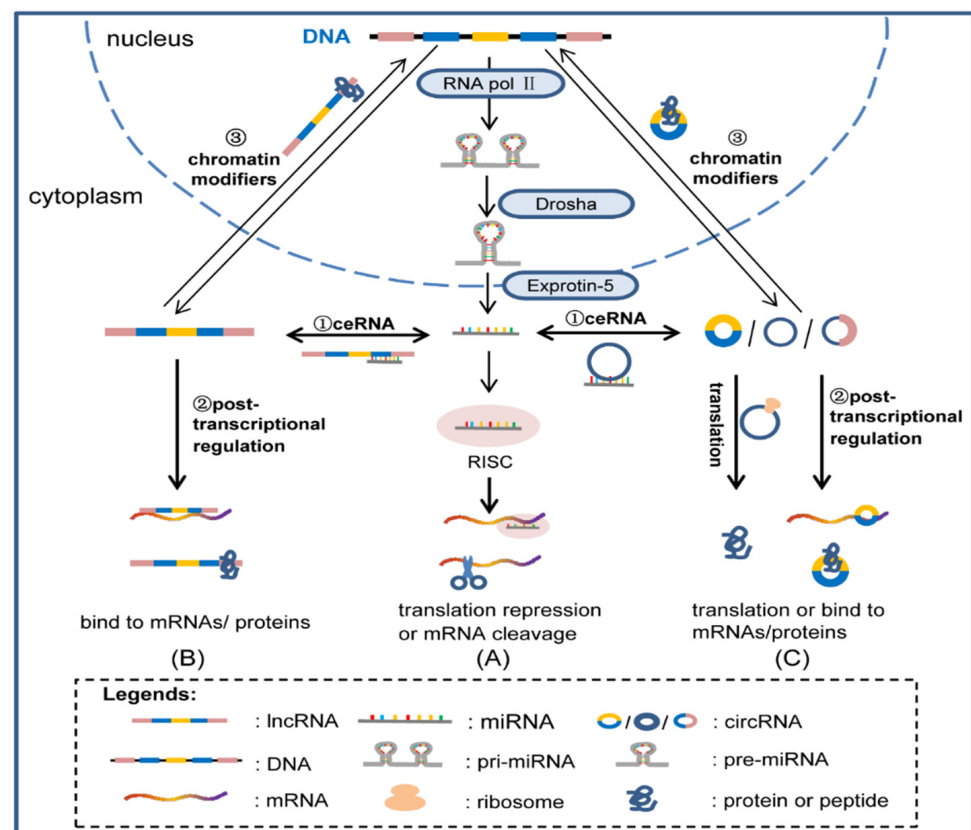

Figure 1. Biogenesis and function of ncRNAs. ncRNA genes are transcribed by RNA Pol II to generate pri-RNAs. Drosha crops pri-RNAs into pre-RNAs, and pre-RNAs are exported from nucleus to cytoplasm by Exportin-5. (**A**) miRNAs direct RISC to downregulate gene expression by mRNA cleavage or translation repression. (**B**) LncRNAs act as signals, and decoy proteins and other RNAs to regulate translation. LncRNAs can bring together multiple proteins to affect histone modifications. (**C**) CircRNAs act as miRNA sponges and interact with RNA binding proteins, and function as protein scaffolds and modifiers of parental gene expression. CircRNAs can also be translated into proteins.

3. Roles and Mechanism of ncRNAs in Cardiac Hypertrophy and Heart Failure

Cardiac hypertrophy is an early milestone before degeneration to heart failure and a significant risk factor for subsequent cardiac morbidity and mortality. Pathologic cardiac hypertrophy is controlled at three levels: extracellular hypertrophic stimulus signal, cytoplasmic signal transduction, and nuclear gene transcription and post-transcription [48].

3.1. MiRNAs

MiRNAs modulate gene expression at the post-transcriptional level via the activation of intracellular signaling, such as the hypertrophic Ca^{2+} signaling pathway (Figure 2A). Catecholamine stimulates β-adrenoceptors (β-ARs) to activate Gs proteins and generate the second messenger cyclic adenosine monophosphate (cAMP). cAMP binds to and activates protein kinase A (PKA) to phosphorylate Ca^{2+} signaling proteins, such as L-type calcium channel (LTCC), ryanodine receptor (RyR), and sarcoplasmic reticulum Ca^{2+}-

ATPase (SERCA), thereby increasing intracellular Ca^{2+} concentration ($[Ca^{2+}]i$). Intracellular Ca^{2+}, in turn, activates Ca^{2+}-dependent calcineurin (CN) and calmodulin (CaM)-dependent kinase II (CaMKII). CN and CaMKII activate transcription factors such as nuclear factor of activated T cells (NFAT) and histone deacetylase (HDAC), respectively, to induce the expression of genes involved in hypertrophy [49,50].
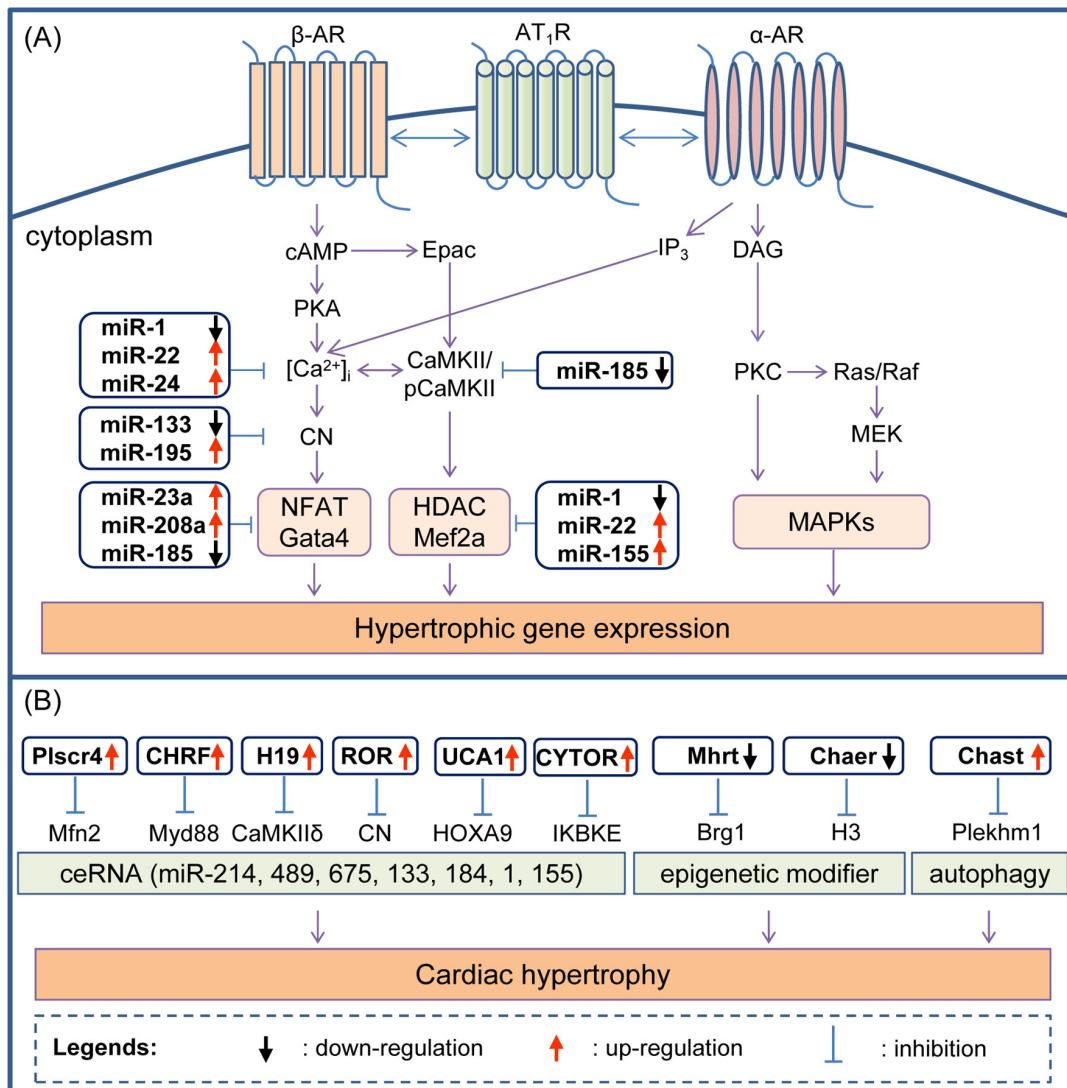

Figure 2. Interaction of partial ncRNAs in cardiac hypertrophy and heart failure. (**A**) MiRNAs regulate hypertrophic Ca^{2+} signaling pathway; (**B**) lncRNAs exert splicing regulation and translational regulation through competing endogenous RNA (ceRNA) mechanism. β-AR, β-adrenoceptors; AT1R, angiotensin II type-1 receptor; α-AR, alpha-adrenergic receptor; cAMP, cyclic adenosine monophosphate; PKA, activates protein kinase A; $[Ca^{2+}]i$, intracellular Ca^{2+} concentration; CN, calcineurin; NFAT, nuclear factor of activated T cells; Gata4, GATA-binding factor 4; Epac, exchange factor directly activated by cAMP; CaMKII, calmodulin dependent kinase II; pCaMKII, the phosphorylation of CaMKII; HDAC, histone deacetylase; Mef2a, myocyte-specific enhancer factor 2A; IP3, inositol 1, 4, 5-trisphosphate; DAG, dystrophin-associated glycoprotein; PKC, protein kinase C; Ras, Ras family of small GTPases; Raf, Raf proto-oncogene serine/threonine-protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; MAPKs, mitogen-activated protein kinases; Mfn2, mitofusin-2; Myd88, myeloid differentiation primary response gene 88; CaMKIIδ, calmodulin dependent kinase IIδ; HOXA9, homeobox A9; IKBKE, I-kappa-B kinase epsilon; H3, histone H3; Plekhm1, Pleckstrin homology domain-containing protein family M member 1.

Multiple miRNAs are involved in regulating hypertrophy-related pathways. The over-expression of miR-1 attenuates cardiomyocyte hypertrophy in cultured neonatal rat cardiomyocytes and the intact adult heart by downregulating the expression of CaM, GATA-binding factor 4 (Gata4), Mef2, and the CN-NFAT and CaMKII-HDAC transcriptional pathways [51]. Increased miR-22 impairs Ca^{2+} loading into the sarcoplasmic reticulum (SR) and suppresses peroxisome proliferator-activated receptor (PPAR), estrogen-related receptor (ERR), sirtuin 1 (SIRT1), and HDAC [52,53]. MiR-24, a junctophilin-2 (JP2) suppressor, is upregulated in hypertrophy and failing cardiomyocytes [54]. MiR-24 suppression stabilizes JP2 expression and protects the ultrastructure of T-tubule and SR junctions from Ca^{2+} disruption [55]. The downregulation of miR-133 leads to the enhancement of transcriptional repression of CN-NFAT [56]. MiR-195 is upregulated during cardiac hypertrophy, leading to pathological cardiac growth and heart failure in transgenic mice through activated calcineurin A (CnA) [57]. The upregulation of MiR-23a targets NFATc3 directly to promote cardiac hypertrophy [58]. The downregulation of miR-208a is required for the proper expression of cardiac transcription factors Gata4, homeodomain-only protein (Hop), and gap junction protein connexin40 (Cx40) [59]. MiR-185, which is downregulated in hypertrophic hearts, plays an antihypertrophic role by directly targeting CaMKIIδ, NFATc3, and Na^{+}-Ca^{2+} exchanger gene (NCX1) [60]. The loss of miR-155 protects the heart from pathological cardiac hypertrophy and failure by targeting the suppressor of cytokine signaling 1 (Socs1) [61,62]. MiRNAs are also involved in signaling pathways other than the hypertrophic Ca^{2+} signaling pathway. Transforming growth factor β1 (TGF-β1)-regulated miR-27b targets PPAR-γ in cardiac hypertrophy [63]. MiR-214 provokes cardiac hypertrophy by repressing the enhancer of homolog 2 (EZH2) [64]. MiR-206 mediates cardiac hypertrophy by inhibiting Forkhead box protein P1 (FoxP1) [65]. MiR-223 directly targets cardiac troponin I-interacting kinase TNNI3K and downregulates cardiac troponin I (cTnI) phosphorylation to suppress cardiomyocyte hypertrophy [66]. Chronic kidney disease can result in left ventricular hypertrophy, in which the expression of miR-30 is downregulated. The knockdown of miRNA-30 in cardiomyocytes leads to hypertrophy by upregulating calcineurin signaling [67].

One of the characteristics of miRNA regulation is that more than one miRNA can affect a single mRNA; for example, many of the above miRNAs were involved in the hypertrophic Ca^{2+} signaling pathway. The other characteristic of miRNA regulation is that one miRNA can influence several targets, such as miR-21. MiR-21 is highly expressed in all main types of cardiovascular cells, and the biological functions of miR-21 were investigated well in cardiovascular disease [68,69]. Depending on cell-specific expression, miR-21 can either protect against hypertrophy and apoptosis [57,70,71] or promote cardiac fibrosis and cardiac hypertrophy in fibroblasts [72]. Danish Sayed et al. identified that miR-21 mediates cardiomyocyte outgrowth by targeting gene SPRY2 [73]. However, miR-21 is upregulated in fibroblasts but not cardiomyocytes in the pressure-overloaded heart model [72]. Silencing of miR-21 in fibroblasts reduces ERK-MAP kinase activity by inhibiting sprouty homolog 1 (Spry1), preventing interstitial fibrosis, and attenuating cardiac dysfunction [72].

3.2. LncRNAs

The role of lncRNAs in myocardial hypertrophy has also been extensively studied. As shown in Figure 2B, some lncRNAs can exert splicing and translational regulation through competing endogenous RNA (ceRNA) mechanisms in hypertrophic responses. Jiang et al. detected 16,044 lncRNAs, and established a lncRNA profile of the heart and 29 other tissue types [74]. Approximately 14.7% (2353) of lncRNAs can only be detected in the heart, called heart-specific (HS) lncRNAs. In addition, 1.7% (273) of lncRNAs are expressed in the heart at least five times more than they are in all other tissue types, and 30.1% (4828) of lncRNAs are expressed in the heart at least five times more than the average levels in all other tissue types, which are considered to be heart-enriched (HER) lncRNAs and heart-enhanced (HEH) lncRNAs, respectively. The total number of HS, HER, and HEH is 7454 (46.5%), named heart-elevated (HE) lncRNAs.

LncRNAs can modulate gene expression via several mechanisms, including signaling induced by transcription factors, sponging miRNAs, recruiting chromatin-modifying enzymes, and modifying genomic components [75,76]. Moreover, more than 100 uncharacterized short open reading frames were detected in lncRNA genes, which suggest lncRNAs may be translated into potential micropeptides [77,78].

LncRNA Plscr4 acts as an endogenous sponge of miR-214, the suppresser of mitofusin2 (Mfn2), to maintain mitochondrial homeostasis and exert an antihypertrophic effect in Ang II-treated cardiomyocytes and TAC-induced cardiac hypertrophy [79]. Similarly, lncRNA cardiac hypertrophy related factor (CHRF) acts as an endogenous sponge of miR-489, which regulates the expression of myeloid differentiation primary response gene 88 (Myd88) to facilitate hypertrophy [80]. LncRNA H19 regulates functionality on miR-675 to increase CaMKIIδ expression at both the mRNA and the protein level, leading to enhanced cardiomyocyte hypertrophy [81,82]. The expression of lncRNA ROR negatively correlates with miR-133, enhancing the hypertrophic Ca^{2+} signaling pathway after phenylephrine treatment [83]. The LncRNA of paternally expressed imprinted gene 10 (PEG10) is upregulated in mice with cardiac hypertrophy. PEG10 can regulate the expression of homeobox A9 (HOXA9) to aggravate cardiac hypertrophy; the silence of HOXA9 reverses the cardiac hypertrophy in cardiomyocytes by over-expressing PEG10 [84]. The lncRNA UCA1 can promote the progression of cardiac hypertrophy as an endogenous sponge of miR-184 to enhance the expression of HOXA9 [85]. The expression of miR-1 is negatively correlated with the expression of UCA1 [86]. The lncRNA cytoskeleton regulator RNA (CYTOR), serving as a miR-155 sponge to counteract miR-155-mediated repression of I-kappa-B kinase epsilon (IKKBKE), plays a protective role in I kappa-B kinase (IKKi) and nuclear factor kappa-B (NF-κB) signaling pathway [87].

Some lncRNAs are involved in hypertrophic processes through chromatin remodeling mechanisms. The lncRNA Mhrt antagonizes the function of Brg1, a chromatin-remodeling factor, which is activated by stress to trigger aberrant gene expression, and cardiac hypertrophy and failure [88]. The Chaer lncRNA directly interacts with polycomb repressor complex 2 (PRC2) catalytic subunit through a 66-mer motif and subsequently inhibits histone H3 lysine 27 methylation for epigenetic reprogramming at hypertrophic genes [89]. LncRNAs can regulate cell autophagy. The lncRNA Chast negatively regulates the expression of the autophagy regulator Pleckstrin homology domain-containing protein family M member 1 (Plekhm1) to drive hypertrophy [90]. The long noncoding myosin heavy chain associated RNA transcript Mhrt779 is markedly upregulated under TAC surgery. However, Mhrt779 displays a minimal increase associated with the lower expression of the Nppa and Myh7 genes in the exercise hypertrophy preconditioning group. Silencing of Mhrt779 attenuates the antihypertrophic effect, and overexpression enhances the antihypertrophic effect. Mhry779 can bind Brg1 to inhibit the activation of the Hdac2/Akt/GSK3β pathway induced by pressure overload, acting as an anti-hypertrophic effect [91].

3.3. CircRNAs

In 2016, the expression profile of circRNAs in adult mouse hearts was plotted [92]. Jacobi et al. compiled a catalog of 575 candidate circRNAs, and many of these candidates coincided with disease-associated gene loci. For instance, a significant number of candidates originate from the Ryr2, Hectd1, and Ppp2r3a gene loci that are linked to cardiovascular diseases. Wu et al. performed deep RNA-sequencing on ribosomal-depleted RNA isolated from 12 human hearts, 25 mouse hearts, and across a 28-day differentiation time-course of human embryonic stem cell-derived cardiomyocytes. Top highly expressed circRNAs are related to cardiac genes, including Titin (TTN), RYR2, and DMD. The most abundant cardiac-expressed circRNA is a cytoplasmic localized single-exon circSLC8A1-1 [19]. Werfel et al. performed RNA-Seq analysis of ribosome-depleted libraries from rats (neonatal and adult), mice (sham or TAC), and humans (failing, nonfailing). They observed dozens of circRNAs arising from the TTN gene in all three species, which is known to undergo highly complex alternative splicing during heart maturation. They observed extensive

differential regulation of TTN circRNAs between neonatal and adult rat hearts, suggesting that circRNA formation could be involved in the regulation of titin splicing [93]. Meng et al. reported that circRNAs are differentially expressed in cardiac hypertrophic cells cultured in the presence of high and normal levels of D-glucose. Five circRNAs, namely, ciRNA261, ciRNA26, circRNA1191, circRNA4251, and circRNA6913, are significantly different. These circRNAs have more than 60 targeted miRNAs, suggesting that they may play a role in myocardial hypertrophy and serve as biomarkers [94]. In 2020, circRNA microarrays on plasma samples obtained from three patients with HF and three healthy controls were investigated. HF patients display 477 upregulated circRNAs, and 219 downregulated circRNAs compared with healthy controls [95]. Yang et al. showed that 401 out of 3323 circRNAs were dysregulated in left ventricular specimens collected from 8-week-old mice with isoproterenol hydrochloride-induced cardiac hypertrophy compared with the controls. Of these, 303 circRNAs were upregulated, and 98 were downregulated [96].

Until now, few studies have fully explained the mechanisms of circRNA in myocardial hypertrophy, especially circRNA related to the Ca^{2+} signaling pathway. MicroRNA-133a (miR-133a) is well-recognized in cardiac hypertrophy [97,98]. Lim et al. found that miR-133a was highly enriched in the fraction of circSlc8a1 pull-down [99]. Next, they show that knockdown of circSlc8a1 attenuates pressure-overload induced cardiac hypertrophy, whereas overexpression of circSlc8a1 results in heart failure. Further research shows circSlc8a1 functions through miR-133a and its downstream targets, including serum response factor (Srf), connective tissue growth factor (Ctgf), adrenoceptor beta 1 (Adrb1), and adenylate cyclase 6 (Adcy6). Meanwhile, circNcx1 (a circRNA transcribed from the sodium/calcium exchanger 1 (ncx1) gene, which is also called solute carrier family 8 member A1 (slc8a1) gene), was able to regulate cardiomyocyte apoptosis by targeting miR-133a-3p-CDIP1 in 2018 [100], but whether it can regulate myocardial hypertrophy by targeting miR-133a is still unknown. circ-HIPK3 affects the concentration of Ca^{2+} in the cytoplasm by the miR-17-3p/ADCY6 axis [101], and the level of circ-HIPK3 in the heart was increased by adrenaline via transcription factor cAMP-responsive element-binding protein 1 (CREB1). The downregulation of circ-HIPK3 can alleviate fibrosis and maintain cardiac function post-MI in mice. Deng et al., therefore, concluded that the increased circ-HIPK3 acts as a helper for adrenaline, but is harmful to the heart in the long run, which may be an ideal therapeutic target of HF. Xu et al. found that circHIPK3 regulates pressure overload-induced cardiac hypertrophy by sponging miR-185-3p and modulating CaSR in neonatal mouse cardiomyocytes [102]. Mouse homolog circ-SIRT1 (mmu_circ_0002354) was downregulated in Ang II-treated H9c2 cells and TAC induced mice model. circ-SIRT1 deficiency was conducive to CH formation, and the overexpression circ-SIRT1 elevates SIRT1 expression by competitively binding with miR-3681-3p/miR-5195-3p or recruits USP22 to stabilize SIRT1 protein in hiPSCCMs [103]. Moreover, many circRNAs can affect ejection fraction, such as heart-related circRNA (HRCR) and circRNA_000203 [104,105], and ejection fraction is closely related to myocardial contractility, which can be affected by Ca^{2+}. Therefore, we suspect that these circRNAs may reduce the ejection fraction by regulating the Ca^{2+} signaling pathway. This conjecture needs experimental validation.

4. Discussion

The expression of ncRNAs is significantly altered in various cardiac diseases and is an adaptive regulation of the body. Research on ncRNAs in heart failure has rapidly expanded from the initial discovery of the abnormal expression of miRNAs to the role of the newer types of ncRNAs: lncRNAs and circRNAs. More results indicate that ncRNAs play an essential function in heart failure [106–108], and the interaction of circRNA/lncRNA/miRNA may provide new ideas for the treatment of heart failure [109]. It is conceivable that modulating ncRNAs may provide potential therapeutic values. First, dysregulated ncRNAs expression could be used as biomarkers to diagnose different kinds of cardiac diseases. Second, ncRNAs could also be potential targets for disease therapies. RNA-targeted therapies provide new ideas for drug discovery involving chemically modified oligonucleotides

and novel target-binding motifs [110]. RNA-based drugs have conceptual and practical advantages compared to conventional chemistry-based drugs or antibodies. However, the regulation of ncRNAs is not well-characterized. Additional hurdles also need to be addressed before clinical application, such as off-target effects and potential toxicity [111].

Earlier, ncRNAs were thought of as useless RNAs. ncRNAs act as essential regulators that mediate their functions through complex mechanisms. Recent studies have also indicated that some ncRNAs could be translated into small peptides to regulate gene expression. The roles of peptides encoded by lncRNAs or circRNAs were primarily verified on cancers [112–114], but not in cardiac hypertrophy. This review summarized the current understanding of ncRNAs biogenesis and global mechanisms in cardiac hypertrophy and heart failure. The incorporation of ncRNAs within cardiac gene regulatory networks represents a novel venue for therapeutic intervention in clinical heart failure.

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