Non-coding RNAs in Physiological Cardiac Hypertrophy

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Abstract

Non-coding RNA (ncRNA) is a class of RNAs that are not act as translational protein templates. They are involved in the regulation of gene transcription, RNA maturation and protein translation, participating in a variety of physiological and physiological processes. NcRNAs have important functions, and are recently one of the hotspots in biomedical research. Cardiac hypertrophy is classified into physiological cardiac hypertrophy and pathological cardiac hypertrophy. Different from pathological cardiac hypertrophy, physiological cardiac hypertrophy usually developed during exercise, pregnancy, normal postnatal growth, accompanied with preservation or improvement of systolic function, while no cardiac fibrosis. In this chapter, we will briefly introduce the definition, characteristics, and functions of ncRNAs, including miRNAs, lncRNAs, and circRNAs, as well as a summary of the existing bioinformatics online databases which commonly used in the study of ncRNAs. Specially, this chapter will be focused on the characteristics and the underlying mechanisms about physiological cardiac hypertrophy. Furthermore, the regulatory mechanism of ncRNAs in physiological hypertrophy and the latest research progress will be summarized. Taken together, exploring physiologic cardiac hypertrophy-specific ncRNAs might be a unique research perspective that provides new point of view for interventions in heart failure and other cardiovascular diseases.

Keywords

Physiological cardiac hypertrophy · NcRNAs · MiRNAs · LncRNAs · CircRNAs

1 Introduction

Non-coding RNAs (ncRNAs) are a class of RNAs that are not act as a template for translation proteins. They are involved in the regulation of mRNA translation, RNA splicing, DNA replication repair, gene transcription, development, and cell differentiation [1, 2]. Besides, it is closely related to the occurrence, development, progression, treatment, and diagnosis of various diseases [3–5]. NcRNAs can be divided into two broad categories depending on their biological functions: house keeping non-coding RNAs and regulatory

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non-coding RNAs. Among them, house keeping non-coding RNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs). Non-coding RNAs with regulatory effects can be divided into two subclasses (short non-coding RNAs and long non-coding RNAs) according to the length of the transcription product. Short non-coding RNAs include piRNAs, microRNAs (miRNAs, miRs), siRNAs, and among them, miRNAs are the most widely studied. Long non-coding RNA (lncRNA) refers to a class of non-coding RNAs that lack an >100 amino acids open reading frame and larger than 200 nucleotides, and their structure and function are diverse and complex [3]. In addition, linear products (miRNAs, lncRNAs) and circular RNA (circRNAs) can be classified according to the linearity or circularity of the transcription product. A large number of non-coding RNAs are detected in tissues and body fluids. In the cardiovascular system, ncRNAs are also key regulators involved in regulation of cardiac-related gene expression, and significantly affecting cardiac homeostasis maintenance and heart function [6–10].

Cardiac hypertrophy is classified as physiological cardiac hypertrophy and pathological cardiac hypertrophy [11]. Pathological cardiac hypertrophy is an injury response that occurs when the heart is overloaded, mainly due to increased myocardial cell volume, interstitial and perivascular fibrosis, loss of cardiomyocytes, increased collagen, and myofibroblasts activation. Eventually lead to myocardial structure disorder, reduced contractility, myocardial contraction and diastolic dysfunction. Pathological cardiac hypertrophy is considered to be an independent risk factor for increased morbidity and mortality of cardiovascular disease [12]. Different from pathological cardiac hypertrophy, physiological cardiac hypertrophy does not cause pathological changes such as loss of cardiomyocytes, decline of cardiac function, and aggravation of cardiac fibrosis [13, 14]. On the contrary, physiological cardiac hypertrophy is a protective response, which refers to the heart under the action of various physiological factors, such as regular exercise training and pregnancy [15]. During the progression of physiological hypertrophy, the area of cadiomyocytes, the volume of the heart, and the weight of the heart are increasing. In the meantime, the contractility function of heart also improved, however, there was no process of fibrosis. Previous studies have shown that physiological cardiac hypertrophy factors are resistant to persistent pathological stimuli, can inhibit ventricular remodeling and ameliorate heart failure [16–18]. Therefore, exploring the key regulatory factors of physiological cardiac hypertrophy is of great significance for the prevention and treatment of heart failure [15, 19].

2 Non-coding RNAs

2.1 MicroRNAs

MicroRNAs (miRNAs, miRs) are a class of ncRNAs of about 22 nucleotides in length that bind to messenger RNA via complementary or partial complementary base pairing. Degradation of mRNA, inhibition of mRNA translation is involved in the regulation of gene expression. MiRNAs need to undergo post-transcriptional modification [20]. The primary miRNAs (pri-miRNAs) transcribed by RNA polymerase II are processed to produce precursor miRNAs (pre-miRNAs), which are finally cleaved into mature miRNAs by RNase III enzyme DICER in the cytoplasm [21, 22]. MiRNAs can form RNA-induced silencing complexes (RISCs) with some proteins such as Argonaute protein family AGO2. Generally, the function of miRNAs is mainly determined by the function of their target genes. Different miRNAs can have different functions in the same tissue, and the same miRNA can also perform different functions in different tissues [4, 23, 24].

In cardiovascular system, miRNAs are involved in the cardiovascular development and the occurrence and development of cardiovascular diseases [7, 25, 26]. MiRNAs have been reported being involved in the regulation of almost all cardiovascular-related cells, such as endothelial cells, cardiomyocytes, smooth muscle cells, fibroblasts, etc., which play important regu-

latory roles in various cardiovascular diseases [27–29]. For example, miR-1, miR-133, miR-145, and miR-34 have been reported to negatively regulate the pathological hypertrophy of cardiomyocytes [30–36]. In contrast, miR-208a, miR-155, miR-199a have a pro-effect on the development pathological hypertrophy [37–41]. Besides, miRNAs can target specific transcription factors to indirectly regulate the expression of channel genes, thereby modulating cardiomyocytes excitability. MiR-122 can regulate the metabolism of NO by regulating its target gene L-arginine transporter 1 (SLC7A1), which leads to endothelial cells dysfunction [42]. MiR-122, as well as miR-33 may participate in the modulation of lipid homeostasis *in vivo*, and thus involved in the regulation of atherosclerosis [43, 44]. In addition, circulating miRNAs have been intensively studied as biomarkers in the cardiovascular system [6, 45]. Collectively, as potential biomarkers and therapeutic targets, miRNAs have prospective applications for cardiovascular diseases diagnosis and prognosis.

2.2 Long Non-coding RNAs

Long non-coding RNAs (LncRNAs) refer to a class of non-coding RNAs that are transcribed over 200 nucleotides in length. Similar to miRNAs, lncRNAs usually do not encoding proteins. LncRNAs are mostly transcribed by RNA polymerase II, can be spliced, and have 5′-terminal capped structure and 3′-terminal poly-A tail. Some lncRNAs also have splicing processes similar to mRNA biogenesis. The expression of lncRNAs are different among different tissues. Moreover, the same tissue or organ at different developmental stages, the expression of lncRNAs can also be different. Therefore, lncRNAs exhibit obvious tissue specificity and space-time specificity. Recent years, various functions of lncRNA have been discovered, which play an important role in gene transcription, protein translation, protein localization, stem cell pluripotency and modulation the progression of human diseases. It is valuable for diagnosis, treatment and prognosis evaluation of diseases [46]. Interestingly, recent studies have found that some lncRNAs can encode small peptides and exhibit their mode of action through translated products [47, 48].

In the cardiovascular system, lncRNAs have been reported to be involved in the occurrence and development of various diseases [10, 49–51]. For example, lncRNA Chaer was found to be enriched in the heart, and directly interacting with the catalytic subunit of PRC2, disrupting the PRC2-targeted genome site, thereby inhibiting histone H3K27 methylation in the promoter region of cardiac hypertrophy-related genes. Inhibition of Chaer in the heart can alleviate the pathogenesis of cardiac hypertrophy and improve cardiac function [52]. Besides, lncRNA Chrf, lncRNA mhrt have been reported to be involved in the regulation of pathological cardiac hypertrophy [53, 54]. Additionally, lncRNA Mexis, and lncRNA p21 regulate atherosclerosis [55, 56]. Furthermore, meg3, which is highly expressed in cardiac fibroblasts, is down-egulated in cardiac remodeling. And knockdown of meg3 would inhibit p53 binding to the promoter region of MMP-2, consequently blocking TGF-β1-induced MMP-2 expression and preventing cardiac fibrosis [57]. Moreover, lncRNA MIAT was found to promote cardiac fibrosis by up-regulating TGF-β1 by sponge miR-24 [58]. It is worth noting that, similar to miRNAs, the expression level of lncRNAs in serum have also been found to be closely associated with cardiovascular diseases. Therefore, lncRNAs can also be used as biomarkers for disease diagnosis. For instance, the expression level of lncRNA Lipcar was significantly different in patients with and without ventricular remodeling after myocardial infarction, suggesting that Lipcar might be a valuable biomarker of the progression of cardiac remodeling [59].

2.3 Circular RNAs

Circular RNAs (circRNAs) were first discovered in plant viruses in 1976, but did not receive much attention for decades. Due to the limitations of detection techniques and algorithms, it has long been believed that circular RNA is a small amount

of splicing by-products present in mammals and does not have biological functions. Until recent years, with the breakthrough in high-throughput sequencing technology and bioinformatics analysis algorithms, a large number of circular RNAs were discovered in mammals [60–62]. In 2013, Hansen et al. discovered circRNA CDR1as has an important role. Since then, more and more circRNA studies have shown that circRNA is involved in the regulation of many important biological processes [63, 64]. Several mode of actions of circRNAs have been identified by multiple functional and mechanism studies [65–68]. Among them, the most well investigated action was that circRNA can be used as an endogenous miRNA sponge [63, 64, 69]. Besides, circRNA can interact with functional proteins and regulate gene transcription [70, 71]. What's more, some circRNAs have coding potential, which can be translated into small peptides or proteins [72–74]. The expression of circRNA in different species, tissues and cells is different, and it is closely related to the occurrence of various diseases such as tumors, nervous system diseases and metabolic diseases [75–77]. It is worth noting that because of its cell/tissue specificity and evolutionary conservation, circRNAs are of great potential as clinical therapeutic targets.

In cardiovascular, similar to miRNAs and lncRNAs, circRNAs are also involved in the regulation of many cardiovascular diseases [77, 78]. In the myocardial ischemia model, circRNA CDR1as (also known as ciRS-7) can be used as an endogenous sponge of miR-7a, aggravating myocardial apoptosis and myocardial infarct size [79]. CircRNA mm9_circ_016597 (MFACR) can also be used as miR-652-3p sponge to mediate mitochondrial division and cardiomyocytes apoptosis induced by myocardial ischemia-reperfusion injury [80]. CircRNA circ-Ttc3 plays a protective role in myocardial infarction, and reduces ATP depletion and apoptosis in cardiomyocytes [81]. The main mechanism is that circ-Ttc3 regulates the expression of downstream target genes Arl2, and protects cardiomyocytes from apoptosis via sponging miR-15b. CircRNA mm9_circ_012559 (also known as HRCR) is down-regulated in heart failure mice [82]. HRCR act as miR-223 sponge to inhibit miR-223 activity, which in turn aggravates the development of pathological cardiac hypertrophy and heart failure. In addition to cardiomyocytes, circRNAs also found to involved in the regulation of non-cardiomyocytes. Circ_000203, and circ_010567 have been reported to act as miRNA sponges that regulate cardiac fibroblasts or endothelial cells [83, 84]. However, act as miRNA sponge is only one of the mechanisms by which circRNAs take part in biological roles. CircRNAs function as protein sponges have also been investigated in cardiovascular system. In doxorubicin-induced cardiomyopathy, the circRNA Amotl1 can promote the phosphorylation of AKT and its nuclear transfer by binding AKT1 and PDK1, thereby alleviating cardiomyocytes apoptosis and myocardial injury [85]. In cardiac senescence, circRNA circ-Foxo3 binds and inhibits the migration of anti-aging and anti-stress proteins (ID-1, E2F1, FAK, HIF1α) from cytoplasm into nucleus and mitochondria, and thus mediating cardiac senescence [86]. In atherosclerosis, the circRNA circANRIL can bind to PES1 protein and promote p53 activation, play a role in aggravating apoptosis and suppression proliferation of vascular smooth muscle cells and macrophages, which ultimately play an important role in protecting atherosclerosis [70]. What is noteworthy is that except act as the key regulators of cardiac development and heart disease, circRNAs are also associated with cardiac regeneration. Super-enhancer (SEs)-related circRNA circNfix have been reported that knockdown of circNfix promotes cardiac regeneration by inhibiting Ybx1 ubiquitin-dependent degradation, increasing miR-214 activity [87].

3 Current Bioinformatics Tools in ncRNA Studies

A large number of ncRNAs have been identified, and the function of most ncRNAs has not been well documented. In ncRNA studies, RNA-sequencing and microarray are the most commonly used detection methods. A large number of statistically significant differential ncRNAs

have been identified. Typically, sequencing data is validated by quantitative real-time PCR designed with specific primers. In the meantime, the application of bioinformatics is crucial for study of the function of ncRNA, especially in the prediction of function, exploration of interaction networks, and the relationship between ncRNAs and the occurrence and development of specific diseases. Therefore, a large number of Bioinformatic platforms have been developed and widely used. A summary about online databases is given in the Table 8.1.

4 NcRNAs Are Key Regulators of Physiological Cardiac Hypertrophy

4.1 Characteristics of Physiological Cardiac Hypertrophy

Endurance exercise have been reported to benefit whole body metabolism, however, the underlying mechanisms still largely remained unknown [15, 88–91]. Physiological cardiac hypertrophy usually occurs during exercise, pregnancy, and normal postnatal growth. Physiological hypertrophy includes exercise-induced physiological cardiac hypertrophy and pregnancy hypertrophy. Physiological cardiac hypertrophy is characterized by preservation or improvement of cardiac systolic function, without cardiac fibrosis. Especially, physiological hypertrophy is a reversible benign adaptive change that does not lead to pathological ventricular remodeling and heart failure [92]. When physiological cardiac hypertrophy occurs, the marker genes, such as ANP, BNP, β-MHC, of pathological remodeling do not increase. In addition, different from pathological cardiac hypertrophy, genes encoding Ca^{2+}-handling proteins did not change when physiological cardiac hypertrophy occurred.

The IGF1-PI3K-AKT signaling pathway is regarded as a key signaling pathway in regulating the development of physiological cardiac hypertrophy [93, 94]. Studies have shown that serum IGF1 levels are elevated in athletes with physiological cardiac hypertrophy, and also insulin-like growth factor-binding protein 2 (IGFBP2) plays an important role in the development of pregnancy hypertrophy [95, 96]. Insulin binds to and activates the insulin receptor, which recruits and phosphorylates the insulin receptor substrate 1 (IRS1) and insulin receptor substrate 2 (IRS2). These proteins activate the PI3K-AKT1 signaling pathway to promote cardiac physiological growth. Mouse-specific knockout of IRS1 or IRS2 can prevent exercise-induced physiological cardiac hypertrophy [97]. In addition, IGF1 activates the downstream signaling pathway by binding to and activating the IGF1 receptor IGF1R [98]. IGF1R is also essential for exercise-induced physiological cardiac hypertrophy. The catalytic subunit of PI3K, p110α, is a key molecule of physiological cardiac hypertrophy. When p110α knockout, IGF1R will not lead to the development of physiological hypertrophy. While activate p110α, the heart can demonstrate physiological growth spontaneously, and resist heart failure [99, 100]. Serine/threonine-protein kinases 1 (AKT1) is one of 3 closely related AKTs (AKT1, AKT2 and AKT3). The phosphorylation level of AKT1 is dynamically changed in exercised rats, AKT1 down-regulated in the first week, and then specifically increased phosphorylation level of AKT1 Ser-473 in the third week [101]. The expression of AKT decreased during pregnancy and then returned to normal levels after post portum delivery [102]. These all suggest that AKT plays an important role in physiological cardiac hypertrophy [103]. Besides, transcription factors C/EBPβ and CITED4 have been reported to be involved in the regulation of physiological cardiac hypertrophy. When physiological cardiac hypertrophy occurs, C/EBPβ is down-regulated, while CITED4 is up-regulated, which promotes cardiomyocytes proliferation and hypertrophy [18]. And moreover, thyroid hormone is also involved in the regulation of physiological cardiac hypertrophy [104, 105]. Thyroid hormone is closely associated with the development of physiological cardiac hypertrophy in cardiomyocytes via activating the PI3K/AKT/mTOR signaling pathway [106, 107].

Table 8.1 Summary of online databases associated with ncRNAs

NcRNAs	Database name	Description	Website	References
miRNAs	miRBase	MiRBase database is a comprehensive database that provides published miRNA sequence data, annotations, predicted target genes	http://www.mirbase.org	[116–118]
	RNAhybrid	RNAhybrid is a miRNA target gene prediction software developed based on the secondary structure of miRNA and target genes	https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid/	[119]
	starBase	The database analyzed the interaction among miRNAs lncRNAs, circRNAs, protein and mRNAs, and analyzed the ceRNA mechanism. The database mainly contains information of three species: human, mouse and nematode	http://starbase.sysu.edu.cn/	[120, 121]
	ChIPBase	By integrating clip-seq and chip-seq data, the transcription and post-transcriptional regulation of microRNA were provided, and the regulatory network of transcription factor, microRNA and target genes was provided	http://rna.sysu.edu.cn/chipbase/	[122, 123]
	Targetscan	Targetscan database was developed for target prediction of miRNAs	http://www.targetscan.org/	[124]
lncRNAs	LNCipedia	LNCipedia includes a total of 146,742 human annotated lncRNA transcripts, all of which contain annotated information such as sequence, genomic location, and sources	https://lncipedia.org/	[125–127]
	Linc2GO	The database is intended to provide comprehensive functional annotations of human lncRNAs. MicroRNA-mRNA and microRNA-lncRNA interaction data were integrated to generate functional annotations of lncRNA based on the "ceRNA hypothesis"	https://omictools.com/linc2go-tool	[128]
	Noncode	NONCODE is intended to provide ncRNA annotation, which includes coding capability assessment, location information, expression information and potential functionality, and co-expression	http://www.noncode.org	[129–134]
circRNAs	circBase	This database collects thousands of circRNAs expressed in animals. This database allows users to search, browse, and download corresponding circRNAs	http://www.circbase.org/	[135]
	CIRCpedia v2	The database allows users to search, browse, and download circRNAs with expression characteristics of various cell types/tissues, including disease samples	http://www.picb.ac.cn/rnomics/circpedia/	[136]
	CircInteractome	The database allows users to prediction and map binding sites for RBPs and miRNAs on reported circRNAs	https://circinteractome.nia.nih.gov	[137, 138]
	circBank	The circBank database applied a novel nomenclature of human circRNAs and provides information about circRNAs sequences, miRNA-circRNA interactions, circRNA coding potential and conservation between human and mouse	http://www.circbank.cn/	[139]

4.2 NcRNAs and Physiological Cardiac Hypertrophy

To well investigate the underlying mechanism of physiological cardiac hypertrophy, it is usually use exercise training (running or swimming) to induce physiological cardiac hypertrophy. Currently, in the exercise-induced physiological cardiac hypertrophy model, miR-126, miR-144, miR-145, miR-21, miR-29a, miR-29c, miR-27a and miR-27b were found to be up-regulated, while miR-1, miR-124, miR-133a, miR-133b and miR-143 were found to be down-regulated [108–111]. However, none of these studies performed further mechanism researches to investigate why and whether these miRNAs are specific regulated during physiological hypertrophy. Moreover, none of those miRNAs have been checked their effects on cardiomyoytes growth and proliferation, which are considered to be the specific function in exercise-induced physiological hypertrophy [18]. The function of miR-222 and miR-17-3p on physiological cardiac hypertrophy is a relatively in-depth study of miRNAs [17, 112]. MiR-222 was significantly up-regulated in physiological cardiac hypertrophy both induced by swimming and running. Increased miR-222 can promote cardiomyocytes hypertrophy and proliferation through regulating its target genes p27, Hmbox1, HIPK1 and HIPK2. And it is necessary to increase the level of miR-222 in exercise-induced physiological cardiac hypertrophy. It is worth noting that cardiac-specific overexpression of miR-222 has a protective effect on ventricular remodeling induced by cardiac ischemia-reperfusion injury in mice, which can significantly improve cardiac function and ameliorate myocardial fibrosis [17]. In addition, miR-17-3p was also found to be significantly elevated in physiologically induced cardiac hypertrophy either induced by swimming or running. MiR-17-3p can also promote cardiomyocytes proliferation by directly acting on its target gene TIMP3, as well as indirectly inhibit PTEN and activate AKT signaling pathway to promote cardiomyocytes hypertrophy. Similar to miR-222, up-regulation of miR-17-3p can alleviate ventricular remodeling and heart failure caused by myocardial ischemia-reperfusion injury [112]. Besides, cardiac-specific overexpression of miR-223 exhibited significant physiological cardiac hypertrophy, and up-regulation of miR-223 in rat cardiomyocytes induced physiological growth through activation of AKT signaling pathway [113]. Moreover, miR-199-sponge transgenic mice can lead to physiological cardiac hypertrophy [114]. However, the roles of lncRNAs and circRNAs in physiological cardiac hypertrophy have not been reported. Therefore, further investigations to elucidate the underlying mechanisms of lncRNAs and circRNAs in physiological cardiac hypertrophy is of great significance.

5 Conclusion and Future Perspectives

With the deepening of research, more and more ncRNAs have been identified to be associated with cardiovascular physiology and pathology. The regulation of ncRNA expression levels is expected to become a new strategy for the treatment of heart diseases clinically in future. Although current experiments targeting ncRNAs for treatment of cardiac diseases that have been successfully used in animal models, the clinical treatment of pathological cardiac hypertrophy and heart failure progresses very slowly. Detailed studies about miR-222 and miR-17-3p specifically associated with physiological cardiac hypertrophy indicate that key factors of physiological cardiac hypertrophy might be resistant to sustained pathological hypertrophy stimuli, and changes in physiological hypertrophy-specific miRNAs can improve ventricular remodeling and further ameliorate heart failure. This suggests that exploring physiologic cardiac hypertrophy-specific ncRNAs might be a unique research perspective that provides new strategies for interventions in heart failure and other cardiovascular diseases. However, the research on key lncRNAs and circRNAs related to physiological cardiac hypertrophy has not been reported, and these still need to be further explored and studied in the future. Interestingly, it is worth mentioning

that miR-222 and miR-17-3p are also sharing the same target gene TIMP3 in pulmonary arterial smooth muscle cells [115]. Although the specific relationship between miR-222 and miR-17-3p in cardiomyocytes is not clear, it is certain that there is definitely intrinsic connection between them. Therefore, future studies on the regulatory networks of ncRNAs among physiological specific miRNAs, lncRNAs and circRNAs will not only illuminate the molecular mechanisms but also provide us new therapeutic targets for cardiac diseases from the perspective of protecting the heart.

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