Review

Long Non-Coding RNAs in Cardiac Remodeling

Shutong Shen^a Huimin Jiang^{b,c} Yihua Bei^{d,e} Junjie Xiao^{d,e} Xinli Li^a

^aDepartment of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing,

^bClinical Laboratory Center, Beijing Hospital of Traditional Chinese Medicine, Beijing, ^cDepartment of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, Beijing, ^dCardiac Regeneration and Ageing Lab, School of Life Science, Shanghai University, Shanghai,

^eShanghai Key Laboratory of Bio-Energy Crops, School of Life Science, Shanghai University, Shanghai, China

Key Words

Long non-coding RNAs • Cardiac remodeling • Hypertrophy • Apoptosis

Abstract

Cardiac remodeling occurs after stress to the heart, manifested as pathological processes, including hypertrophy and apoptosis of cardiomyocytes, dysfunction of vascular endothelial cells and vascular smooth muscle cells as well as differentiation and proliferation of fibroblasts, ultimately resulting in progression of cardiovascular diseases. Emerging evidence has revealed that long non-coding RNAs (lncRNAs) acted as powerful and dynamic modifiers of cardiac remodeling. lncRNAs including Chaer, Chast, Mhrt, CHRF, ROR, H19, and MIAT have been implicated in cardiac hypertrophy while NRF, H19, APF, CARL, UCA, Mhrt and several other lncRNAs (n379599, n379519, n384640, n380433 and n410105) in cardiomyocyte loss and extracellular matrix remodeling. In addition, MALAT1 and TGFB2-OT1 have been reported to contribute to vascular endothelial cells dysfunction while lincRNA-p21 and lnc-Ang362 to vascular smooth muscle cells proliferation. Thus, manipulation of lncRNA expression levels through either the inhibition of disease-up-regulated lncRNAs or increasing disease-down-regulated lncRNAs represents novel therapeutic strategies for cardiac remodeling.

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Introduction

Cardiovascular diseases, especially coronary atherosclerotic disease and heart failure (HF), affect more than 20% of the population aged 40 and over. Though the clinical management is improving, mortality rates of HF remain about 50% within 5 years of diagnosis, making HF a leading cause of morbidity and mortality in industrialized countries [1, 2]. Cardiac remodeling, which refers to changes that result in the rearrangement of normal structures of the heart and vessel [3], is a chronic maladaptive process characterized

S. Shen and H. Jiang contributed equally to this work.

Dr. Xinli Li and Dr. Junjie Xiao

Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029 and Cardiac Regeneration and Ageing Lab, School of Life Science, Shanghai University, 333 Nan Chen Road, Shanghai 200444 (China)
E-Mail xinli3267_nj@hotmail.com/junjiexiao@shu.edu.cn

by progressive myocardial hypertrophy, apoptosis, ventricular dilatation, fibrosis, vascular dysfunction, finally resulting in HF [4, 5]. Preventing or reversing cardiac remodeling is a key strategy for the treatment of HF [6] and further efforts are highly needed to explore the mechanisms underlying cardiac remodeling.

Non-coding RNAs (ncRNAs) cover more than 98% of the human genome [7]. Among which, small ncRNAs, such as microRNAs (miRNAs, miRs), have been intensely investigated for many years while studies on long ncRNAs (lncRNAs) just started in recent years. LncRNAs are defined as transcripts that are longer than 200 nucleotides and do not code for proteins in most cases, but basepair with DNA or RNA in a sequence-specific manner, thus regulating gene expression. LncRNAs can be classified into 4 main categories based on the gene-regulating mechanism: i) signal lncRNA, which can regulate gene expression in a time and space manner; ii) decoy lncRNA, which can titrate transcription factors and other proteins away from chromatin, or titrate miRNAs out from their target; iii) guide lncRNA, which can recruit chromatin modifying enzymes to target genes, either in cis (near the site of lncRNA production) or in trans to distant target genes; and iv) scaffold lncRNA, which can facilitate the assembling of multiple proteins to form ribonucleoprotein (RNP) complexes, which may act on chromatin, affecting histone modifications [7-12].

Emerging data have shown that lncRNAs play a role in both the development and pathology of cardiovascular system, providing novel insights and therapeutic targets for cardiovascular diseases. Here we reviewed the progress of lncRNAs' roles in cardiac remodeling and HF, especially the interaction between lncRNAs and other RNAs, mainly miRNAs and mRNAs (Table 1 and Fig. 1).

LncRNAs in cardiac hypertrophy

Cardiac hypertrophy is an initially adaptive response to stress or volume overload stimuli, reducing the increased wall tension and helping to maintain cardiac output [3]. The adaptive process is beneficial and can improve muscular economy at the very start, however, persistent exposure of the heart to increased load would lead to the impairment of cardiac microcirculation, resulting in tissue hypoxia and a subsequent loss of cardiomyocytes [13, 14], ultimately resulting in HF. With the advent of high-throughput RNA sequencing, a number of studies have been carried out to investigate the role of lncRNAs in cardiac hypertrophy.

Chaer

Two high-throughput RNA sequencing studies revealed approximately 15 differentially regulated lncRNAs in mouse cardiac hypertrophy model [15, 16]. Among them, *Chaer* (Cardiac Hypertrophy-Associated Epigenetic Regulator) can directly interact with the catalytic subunit of polycomb repressor complex 2 (PRC2), thereby inhibiting histone H3 lysine 27 methylation at the promoter regions of genes involved in cardiac hypertrophy and thus contributing to the development of cardiac hypertrophy [17]. Along with other PRC2-interacting lncRNAs, such as *Fendrr* and *Bvht*, which have been shown to be important in epigenetic programming during heart development, *Chaer* is also an epigenetic regulatory lncRNAs. Since *Chaer*-PRC2 interaction is only transiently enhanced at the onset of hypertrophy, while the downstream effect of this interaction seems to be long lasting in mouse transverse aortic constriction (TAC) model, inactivation of *Chaer* in the stressed heart may serve as a novel therapy for pathological remodeling in hypertrophic cardiomyopathy.

Mhrt

LncRNA *Mhrt* (Myosin Heavy Chain Associated RNA Transcripts) is the first example of lncRNA serving as chromatin remodelers and it can inhibit cardiac hypertrophy in pathological remodeling. *Mhrt* directly interacts with a histone acetylation factor named *Brg1* and antagonizes the function of *Brg1*, which is activated as a chromatin-remodeling factor

Table 1. An overview of lncRNAs in cardiac remodeling

lncRNAs	Models	Pathological processes	Targets	Reference
Chaer	TAC mouse	Cardiomyocyte hypertrophy	PRC2	17
Mhrt	TAC mouse	Cardiomyocyte hypertrophy	Brg1	18
Chast	TAC mouse	Cardiomyocyte hypertrophy	Pleckstrin homology domain-containing protein family member 1	20
CHRF	AngII-treated mouse	Cardiomyocyte hypertrophy and apoptosis	miR-489	21
ROR	Phenylephrine-treated cardiomyocytes	Cardiomyocyte hypertrophy	miR-133	22
H19	Phenylephrine-treated cardiomyocytes	Cardiomyocyte hypertrophy	miR-675	23
MIAT	AngII-treated mouse and cardiomyocytes	Cardiomyocyte hypertrophy	miR-150	24
NRF	H ₂ O ₂ -treated cardiomyocytes and ischaemia/reperfusion mouse	Cardiomyocyte necrosis	miR-873	28
H19	H ₂ O ₂ -treated cardiomyocytes	Cardiomyocyte necrosis	miR-103/107	29
APF	Anoxia/reoxygenation cardiomyocytes and ischaemia/reperfusion mouse	Cardiomyocyte autophagy	miR-188-3p	30
CARL	Anoxia-treated cardiomyocytes	Mitochondrial fission and cardiomyocyte apoptosis	miR-539	31
UCA1	H2O2-treated cardiomyocytes	Cardiomyocyte apoptosis	p27	32
Mhrt	Doxorubicin-treated cardiomyocyte	Cardiomyocyte apoptosis	Nrf2	33
n379599, n379519, n384640, n380433, n410105	Cardiac fibroblasts	Myofibroblast differentiation	not mentioned	34
MALAT1	Hypoxia-treated HUVECs	ECs proliferation	not mentioned	35
TGFB2-OT1	LPS-treated & oxLDL-treated HUVECs	ECs autophagy and inflammation	miR-3960, miR-4459, miR-4488	36
lncRNA-p21	VSMCs	VSMCs apoptosis and proliferation	p53	37
lncAng362	AngII-treated VSMC	VSMCs proliferation	miR-221 and miR-222	38

TAC, Transverse aortic constriction; AngII, Angiotensin-2; ECs, Endothelial cells; VSMCs, Vascular smooth muscle cells; HUVECs, Human Umbilical Vein Endothelial Cells

by stress to trigger aberrant gene expression and cardiomyopathies [18, 19]. The reciprocal Mhrt-Brg1 inhibition constitutes a negative feedback circuit in maintaining cardiac function. It is worth mentioning that Mhrt directly interacts with the helicase core of Brg1, implying Mhrt-helicase interaction may be a new mechanism by which lncRNA controls chromatin structure.

Chast

Chast (Cardiac Hypertrophy-Associated Transcript) is another pro-hypertrophic lncRNA which shows a cis-regulatory action on the gene located on the opposite strand, named Plekhhm1. Chast was found to be specifically up-regulated in hearts from both mouse TAC model and aortic stenosis patients. Further studies mechanistically revealed that Chast negatively regulated Plekhhm1, thus impeding cardiomyocyte autophagy and driving hypertrophy, while Chast expression was induced partly by the pro-hypertrophic transcription factor NFAT [20]. Further studies also showed that Chast had a strong effect on pathways associated with cardiac muscle morphogenesis, cardiomyopathies, and Wnt signaling by bioinformatic analysis while activation of Wnt signaling has been described as a cause of cardiac hypertrophy.

CHRF

Unlike the gene- or chromatin- regulation effect of other lncRNAs, CHRF (Cardiac Hypertrophy-Related Factor) was found to function as a sponge of miRNA. CHRF was found to be up-regulated in both hypertrophic mouse heart and human HF samples as well. In *vitro* studies mechanistically indicated that CHRF played an anti-hypertrophic role by down-regulating miR-489 expression level while miR-489 had a pro-hypertrophic effect by increasing its target gene Myd88, which could down-regulate the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway [21].

Fig. 1. LncRNAs in cardiac remodeling.

ROR

LncRNA ROR has been reported to contribute to cardiac hypertrophic responses by acting as a sponge of miR-133, whose expression was increased while ROR was knocked down. In line with this, over-expression of miR-133 also prevented the elevation of ROR. The ROR/miR-133 negative feedback circle protected cardiomyocytes from phenylephrine-induced cardiomyocytes hypertrophy [22].

H19

LncRNA H19 was firstly verified to be up-regulated in pathological cardiac hypertrophy and HF by the RNA-sequencing approach [15]. A gain-of-function and loss-of-function study performed *in vitro* further indicated that H19 protected cardiomyocytes from phenylephrine-induced hypertrophy through miR-675. Furthermore, CaMKII δ , a direct target of miR-675, partially mediated the effect of H19 on cardiomyocyte hypertrophy [23].

MIAT

In an AngII-induced cardiac hypertrophy mouse model, lncRNA MIAT (Myocardial Infarction-Associated Transcript) was significantly increased and was necessary for cardiac hypertrophy. MIAT over-expression in H9C2 cells significantly reduced the miR-150 expression and MIAT acted as a sponge of miR-150 during the development of hypertrophy [24].

LncRNAs in post-ischemic remodelling, mainly cardiomyocytes loss and extracellular matrix remodeling

In addition to cardiac hypertrophy, post-ischemic remodeling, mainly manifested as the loss of cardiomyocytes and extracellular matrix remodeling, is also a common kind of cardiac remodeling. Ischemia injury releases reactive oxygen species and causes inflammation in the heart, leading to dysfunction of the energy metabolism of cardiomyocytes and finally resulting in autophagy, apoptosis or necrosis of the cardiomyocytes [25-27]. Loss of cardiomyocytes further contributes to systolic dysfunction and extracellular matrix remodeling. Several lncRNAs have been reported to participate in this process.

NRF and H19 in myocardial necrosis

LncRNA NRF (Necrosis-Related Factor) was able to induce cardiomyocyte necrosis and exacerbate ischemia/reperfusion injury in H₂O₂-treated cardiomyocytes and myocardial infarction mice by sponging miR-873 and its target gene RIPK1 (Receptor-Interacting serine/threonine-Protein Kinase 1)/RIPK3 (Receptor-Interacting serine/threonine-Pro-

tein Kinase 3) [28]. Besides NRF, H19 also inhibited H₂O₂-induced cardiomyocyte necrosis *in vitro* by serving as a sponge for miR-103/107 and it can further regulate FADD, a target gene of miR-103/107 [29].

APF in myocardial autophagy

LncRNA APF (Autophagy Promoting Factor) acted as an enhancer of the miR-188-3p/ATG7 axis both *in vitro* and *in vivo*, regulating autophagy. APF knockdown by APF siRNA exhibited a significant reduction in myocardial infarction sizes and the amelioration of myocardial function in the ischemia/reperfusion mouse hearts by targeting miR-188-3p and ATG7 [30].

CARL, UCA and Mhrt in myocardial apoptosis

LncRNA CARL (Cardiac Apoptosis-Related LncRNA) inhibited anoxia-induced mitochondrial fission and apoptosis in cardiomyocytes by impairing miR-539-dependent downregulation of PHB2 [31]. Besides that, lncRNA UCA1 (Urothelial Carcinoma-Associated 1) contributed to cardiomyocyte apoptosis by suppressing p27 expression *in vitro* [32]. Moreover, the Mhrt/Nrf2 pathway was also reported to participate in the regulation of doxorubicin-induced cardiomyocyte apoptosis [33].

LncRNAs (n379599, n379519, n384640, n380433 and n410105) regulate ECM remodeling

A deep sequencing and genome-wide transcriptome analysis of RNAs from cardiac samples of 15 patients with ischemic cardiomyopathy (ICM) and 15 controls identified 35 lncRNAs that displayed a strong positive correlation with extracellular matrix (ECM) protein-coding genes and further gain- and loss-of-function studies in cardiac fibroblasts identified that 5 of the 35 lncRNAs (n379599, n379519, n384640, n380433 and n410105) participated in the TGF- β pathway to modulate the expression of ECM genes and myofibroblast differentiation [34].

LncRNAs in dysfunction of vascular endothelial cells and smooth muscle cells

Vascular remodeling, mainly characterized by vascular endothelial cells (VECs) dysfunction and vascular smooth muscle cells (VSMCs) proliferation, is closely linked to numerous pathological processes such as arteriosclerosis, thrombus formation and plaque erosion, leading to acute myocardial infarction or chronic ischemic heart disease. LncRNAs have also been reported to participate in the regulation of vascular remodeling.

MALAT1 and TGFB2-OT1 in VECs dysfunction

LncRNA MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) has been found to be highly expressed in VECs and the expression of MALAT1 was significantly increased the proliferating VECs in hypoxic conditions. Additionally, MALAT1 improved blood flow in recovery and capillary density after hindlimb ischemia, implying the angiogenesis effect of MALAT1 in the ischemic heart [35].

LncRNA TGFB2-OT1 (TGFB2 Overlapping Transcript 1) was also shown to be involved in VEC dysfunction. TGFB2-OT1 in HUVECs could regulate the levels of miR-3960, miR-4459 and miR-4488 and then regulate the expression of the miRNA targets CERS1, NAT8L and LARP1, of which NAT8L and CERS1 may participate in autophagy by regulating mitochondrial function. Moreover, over-expression of TGFB2-OT1 could induce IL-6 and IL-8 production in VECs, which indicates that TGFB2-OT1 can trigger the inflammation linkage reaction [36].

LincRNA-p21 and Lnc-Ang362 in VSMCs proliferation

LincRNA-p21 has been reported to be dramatically down-regulated in an animal model of atherosclerosis, and it could repress VSMC cell proliferation and induce apoptosis *in vitro*

using loss- and gain-of-function approaches. Furthermore, lincRNA-p21 was proven to be a promising transcriptional target of p53, which could feed back to enhance p53 transcriptional activity. Finally, lincRNA-p21 expression was significantly decreased in coronary artery tissues of coronary artery disease patients. These data elucidated an important role and a proper mechanism of lincRNA-p21 in angiogenesis [37]. Besides that, another study found that lnc-Ang362 was responsible for AngII-induced VSMC proliferation by targeting miR-221 and miR-222, implying that lnc-Ang362 is a therapeutic target of AngII-associated cardiovascular disease [38].

lncRNAs in genetic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) represents a most common genetic cardiomyopathy and is also a leading cause of cardiac sudden death in young people [39]. Although a total of 1400 mutations in more than 10 genes have been identified as genetic variants responsible for HCM pathology, the predominant mechanisms underlying the pathogenesis of HCM is still unknown. Since lncRNAs are involved in a variety of pathologically processes of HCM, such as varying degrees of myocardial hypertrophy, cardiomyocyte disarrangement as well as interstitial fibrosis [40, 41]. The lncRNA expression profile of HCM patients has been screened by microarray and related pathologic pathways were further analyzed by Gene ontology (GO) enrichment and KEGG analysis. They found that lncRNAs were involved in the pathogenesis of HCM, mainly through pathways underlying ribosome and oxidative phosphorylation [42]. Furthermore, another study identified 2 specific mitochondrial lncRNAs named uc004cov.4 and uc022bqu.1 as potential useful clinical biomarkers for hypertrophic obstructive cardiomyopathy (HOCM) [43].

Conclusions

lncRNAs could regulate multiple pathological processes of cardiac remodeling, including myocardial hypertrophy, autophagy, necrosis, apoptosis, fibrosis as well as vascular cell apoptosis and proliferation. Therefore, to manipulate lncRNA expression levels through either the inhibition of disease-up-regulated lncRNAs or increasing disease-down-regulated lncRNAs represents novel therapeutic strategies for cardiac remodeling. To date, various studies have been successfully performed in modulating lncRNAs in animal models by loss- and gain-of-function approaches; however, due to the innate immunity response and unpredictable toxicity of lncRNAs, no clinical trial has been performed. Nevertheless, anti-miR-122 has come to a phase II clinical trial in the treatment of hepatitis C virus infection [44, 45], indicating the possibility of lncRNAs. In the future, with the development of sequencing and interfering technology, more lncRNAs associated with cardiac remodeling will be revealed, and more meaningful translational studies are highly needed.

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Disclosure Statement

The authors declare there are no conflicts of interest.

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