Noncoding RNA Modulation for Cardiovascular Therapeutics

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Abstract

Cardiovascular diseasesare multifactorial diseases that involve alteration of multiple genes and subsequent phenotypic changes. Non-coding RNAs regulate gene expression, affecting many physiological and pathophysiological processes in humans. Accumulating evidence indicates that noncoding RNA, such as microRNAs, expression profile changes can lead to cardiovascular diseases. This article reviews the current findings regarding the roles of noncoding RNAs in cardiovascular diseases, and strategy to modulate them for therapeutics.

Introduction

By a simple definition, noncoding RNAs are group of RNAs that are transcribed but not translated into proteins. They can be classified into small and long ncRNAs based on their sizes. Small ncRNAsarencRNAs shorter than 200 nucleotides long, and long ncRNAsare ncRNAs composed of 200 or more nucleotides. Small ncRNAs can be further categorized into subcategories such as miRNAs, short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs), short hairpin RNAs (shRNA), and other short RNAs based on length, function and subcellular localization. The significant role of ncRNAs in pathologic conditions has been under spotlight because phenotype changesunder pathologic conditions are more than often regulated by the alteration of gene expressions in an ncRNA-dependent manner [1]. As a good example, the role of microRNAs (miRNAs), a well-known example of small ncRNAs, in cardiovascular diseases has been one of the growing areas of interest for the last few decades [2,3]. Since cardiovascular disease is one of the leading causes of death worldwide being a serious burden to public health and economy in general, reviewing the previous studies elucidating the role of ncRNA in cardiovascular disease is aclinically meaningful step to design an effective therapeutic strategy for cardiovascular disease by modulating key ncRNAs.

LncRNAsmodulate mRNA turnover, translation, and silencing and they can alsofunction as asponge for miRNA in the cytoplasm. In the nucleus, lncRNAs can function as decoys for transcription factor suppressing transcription or serve as a scaffold for RNA-protein complex promoting transcriptional activity. RNP: ribonucleoprotein. In case of miRNAs, they can inhibit the expression of target genes by either degrading target mRNA or suppressing translation (Figure 1).
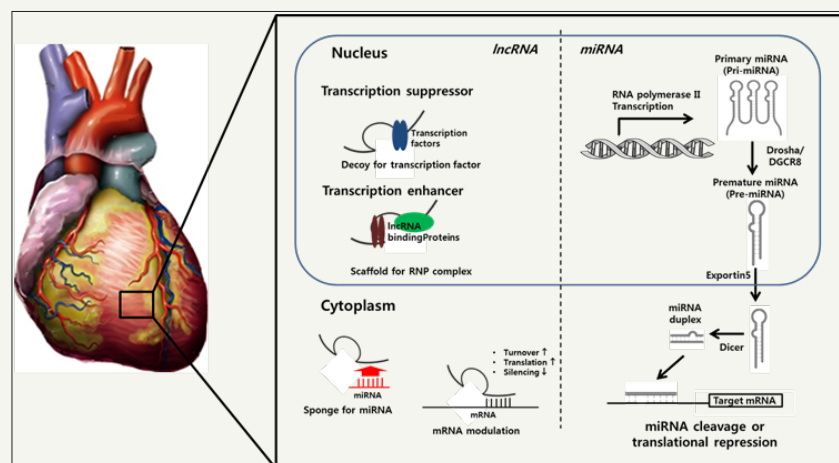

Figure1: Examples of biological function of ncRNAs in the heart.

Modulation of Mirnas in Cardiovascular Disease

MicroRNAs are small non-coding RNAs that are approximately 18-25 nucleotides long which negatively regulate target gene expression at the post-transcriptional level [4]. The followings are few selected examples of miRNAs modulation for cardiovascular disease.

miR-133a

MicroRNA-133a has been known to regulate cardiac hypertrophy. However, the underlying mechanisms have not been fully elucidated. Our research group recently found one of the underlying mechanisms of how miR-133a regulates cardiac hypertrophy. According to our findings, miR-133a prevents norepinephrine-induced hypertrophy of cardiomyocyte by targeting protein kinase C (PKC) δ and Gq, both are involved in the downstream signaling pathways of the α1-adrenergic receptor [5]. These results demonstrated the therapeutic potential of miRNAs as an effective agent to control cardiac hypertrophy.

miR-17-3p

MicroRNA-17 regulates cardiac fibroblast senescence so that miR-17-3p diminishes cardiac aging in mice [6]. Additionally, delivery of exogenous miR-17 protected cardiomyocytes from apoptosis by targeting the apoptotic protease activating factor 1 (Apaf-1), which relays apoptotic signals via formation of apoptosome [7].

miR-132

Ischemia-reperfusion (IR) injury of the heart induces Ca2+ overload in cardiomyocytes, leading to eventual apoptosis. During IR-injury, the expression of Na-Ca exchanger 1 (NCX1), which regulates intracellular Ca2+level, is down-regulated causing Ca2+ overload. By delivering miR-132 targeting NCX1, the increase of intracellular Ca2+, apoptotic molecules such as Bax and cytochrome C, and the number of apoptotic cells were effectively suppressed [8], indicating that the potential of miR-132 as an effective anti-apoptotic agent in cardiac disease.

Long Noncoding Rnas (Lncrnas) in Cardiac Disease

LncRNAs are a class of noncoding RNAscomposed of 200 or more nucleotides that participate in multiple biological processes. Thanks to the RNA sequencing technology, the number of lncRNAs with known sequence is rapidly increasing [9]. However, exact role and function of lncRNA are largely unknown and there are only few studies examined the role of lncRNA in cardiac disease. The followings are few selected findings of the role of lncRNAs in cardiac fibrosis as relevant examples.

H19

LncRNA H19 is the first lncRNA discovered and is paternally imprinted [10]. Overexpression of H19 has been reported to attenuate phenylephrine-induced cardiomyocyte hypertrophy [11], while the expression of H19 was increased in activated cardiac fibroblast in another study [12]. Such discrepancy of H19

expressions in those studies may have come from the type of cells they investigated. Investigating whether the expression of H19 in cardiomyocytes and cardiac fibroblasts is regulated by different mechanisms will be an interesting subject for further studies. According to the above mentioned study reported the increase of H19 in activated cardiac fibroblast, transforming growth factor (TGF) increased the expression of H19 and it lead to cardiac fibroblast proliferation and fibrosis by down-regulating the expression of dual-specificity phosphatase 5 (DUSP5), a nuclear phosphatase that negatively regulates ERK1/2-mediated prohypertrophic signaling [13]. Since TGF is a major mediator of cardiac fibroblast activation and fibrosis [14] and TGF signaling is one of the signaling pathways that induce H19 expression [15], TGF-induced increase of H19 seems to be well grounded. However, a detailed mechanism of how H19 suppresses the expression of DUSP5 is still lacking and it needs to be further elucidated.

MIAT (myocardial infarction associated transcript)

MIAT was first discovered as a gene (FLJ25967) carrying a single nucleotide polymorphism (SNP, rs2301523) significantly associated with MI [16]. Later, a clinical study demonstrated that MIAT was a significant predictor of left ventricular (LV) dysfunction [17]. Additionally, MIAT has been reported to be involved in high glucose-mediated microvascular dysfunction where it acted as a competing endogenous RNA (ceRNA) sponging miR-150-5p in retinal endothelial cells [18]. According to a very recent study conducted by Qu et. al. [19] increased MIAT expression in MI was accompanied by increased furin and TGF- expression, while associated with decreased expression of miR-24 [19]. For the underlying mechanism, the authors identified the role of MIAT as a miRNA sponge for miR-24 in cardiac fibroblast. Furin is a proprotein convertase, produces biologically active TGF-b by cleaving pro-TGFb [20], and it has been reported to be one of the direct targets of miR-24 [21]. Therefore, by decreasing the availability of miR-24, which targets furin, MIAT can increase the amount of functional furin, and this leads to increased production of bioactive TGFb, a major pro-fibrotic cytokine. Furthermore, by demonstrating that siRNA-mediated down-regulation of endogenous MIAT significantly attenuated cardiac fibrosis and improved cardiac function, that particular study provided strong evidence that MIAT plays an important role in the development of cardiac fibrosis, and therapeutic potential of modulating lncRNA in cardiac fibrosis as well.

CHAST (cardiac hypertrophy-associated transcript)

In 2016, Viereck and colleagues elucidated the role of lncRNA ENSMUST00000130556 in the development of cardiac hypertrophy by studying a whole-genome lncRNA profile in pressure overload-induced hypertrophic mouse hearts, and name it cardiac hypertrophy-associated transcript (CHAST) [22]. Autophagy, a conserved catabolic process where cellular components are degraded in the lysosome [23], has been linked to the development of cardiac hypertrophy by previous studies demonstrated that ablation of key mediators of autophagy, such as

Atg5 and Vps34, resulted in severe cardiac hypertrophy [24,25]. In their study, Viereck and colleagues showed that CHAST attenuated the expression of pleckstrain homology domain-containing protein family M member 1 (Plekhm1), which modulates the fusion of autophagosome and lysosome [26], leading to decreased autophagic activity and increased cardiac hypertrophy. They also found that the gene encoding CHAST partially overlapped the gene encoding Plekhm1 in antisense and the expression of Plekhm1 was inversely correlated to that of CHAST, indicating CHAST has a cis-regulatory effect on the Plekhm1 located on the opposite strand. Furthermore, overexpression of CHAST was sufficient to induce cardiomyocyte hypertrophy in vitro and in vivo, while GapmeR (a chimeric antisense oligonucleotide having locked nucleic acid (LNA)-flanked complementary DNA sequence to target, forms DNA/RNA heteroduplex susceptible to ribonuclease H-induced degradation) mediated silencing of CHAST attenuated the development and progression of pressure overload-induced cardiac hypertrophy. Considering that pro-fibrotic state of the heart precedes the development of LV hypertrophy or clinically detectable cardiac fibrosis [27], the results of the study by Viereck et. al. [22] strongly suggested and provided some critical evidence that CHAST is also a potent regulator of cardiac fibrosis.

Conclusion and Perspectives

Accumulating evidence suggests that ncRNAs are deeply involved in the development and progression of cardiovascular diseases. Pathologic alteration of ncRNA expression levels can exacerbate or attenuate cardiovascular dysfunction. Although therapeutic use of ncRNAs such as miRNAs is achievable and has demonstrated some encouraging results [28,29], unsolved problems such as low cellular uptake, off-target effects, and instability in serum [30] has to be resolved.As an alternative, a small molecule-mediated approach to modulate the expression of endogenous miRNAs has been tried [31,32]. This new approach to regulate endogenous miRNAs using small moleculesmay help to developimproved means to treat cardiovascular diseases.

Acknowledgements

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