

Non-coding RNA in Cardiovascular Diseases and Therapeutic Potential

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Cardiovascular diseases (CVDs) remain a predominant cause of disability and death in the world, although much progress has been made in the clinical settings, such as angiotensin receptor blockades, statins, and antiplatelet drugs, to decrease the incidence of CVDs in past two decades. An estimated 17 million people died of CVDs every year, especially, for which age is a key risk factor. The aging heart possess the characteristic of some adverse changes, for instance, diastolic dysfunction, increased cardiac fibrosis, left ventricular hypertrophy, etc. A report from world health organization (WHO) reveals that high blood pressure, abnormal blood lipids, tobacco use, physical inactivity, obesity, and unhealthy diets are the major risk factors, which could lead to approximately 75% of CVDs. Furthermore, impaired cardiovascular function often closely link to myocardial infarction (MI), heart failure, hypertension, atherosclerosis, coronary artery disease, atrial fibrillation, and dyslipidaemia. Enormous research effort has been directed in this field to identify underlying pathophysiological aspects of CVDs. Nevertheless, more mechanisms still need be investigated to enhance the development of efficient diagnostic and therapeutic strategies targeting CVDs.

Noncoding RNAs (ncRNAs) are a class of small RNAs originally from genome not translated into proteins, while only a minority of mammalian genome is responsible for protein-coding genes. Noncoding RNAs are regarded as fundamental of gene regulation machinery, and participate in a wide range of biological and pathological process, including chromatin remodeling, gene transcription, mRNA splicing, protein translation [1]. It can be divided into two subgroups: short ncRNAs (<30 nucleotides long), including microRNAs (miRNAs), piwi-interacting RNAs (piRNAs) and short interfering RNAs (siRNAs); and long ncRNAs longer than 200 nucleotides (lncRNAs) [2]. Recently, ncRNAs have been established as key players in regulating cardiovascular disease. Different ncRNA subgroup performs multiple functions. For instance, miRNAs play vital roles in cardiac signaling and transcriptional pathway during cardiac development and disease. The functions of lncRNA focus on regulation of epigenetic level, transcriptional level and posttranscriptional level in cardiac remodeling and as a novel marker in predicting cardiovascular disease. Furthermore, the cross-talk between miRNAs and lncRNAs provides new insights into regulation pathophysiological conditions of the heart [3].

Myocardial infarction (MI) is a common cardiovascular event induced by myocardial ischaemia accompany by loss of large amount of myocardium and reducing blood supply to the heart, which results in an intense inflammatory reaction, cardiac cell death, tissue damage ventricular malfunction, and heart failure [4]. Prevention of cell death and generation of new cardiac tissue are the approaches to the treatment of MI, that can be regulated by miRNAs or lncRNAs [4]. Boon et al. review that miRNAs can impair or promote cardiomyocyte survival,

such as some miRNAs were reported to induce cardiomyocyte cell death after ischaemia-reperfusion, while several other miRNAs contributed to protect cardiomyocyte from injury by attenuating infarct size and improving heart function; miRNAs can also enhance proliferation capacity of cardiomyocytes and regeneration of heart after damage in new birth mice, promote growth of new blood vessels that supply sufficient blood for regeneration of cardiac tissue after MI injury, and modulate cardiac differentiation capacity of adult progenitor cells, such as miR-499, which promotes reprogrammed of fibroblast to cardiomyocyte [5]. Interestingly, in another review, Goretti and colleagues proposed that miRNAs is great valuable for risk stratification and as prognostic biomarkers for MI, hence miRNAs will be a promising tool to move personalized medicine a step forward [6]. However, study is still at its start step about the pathogenesis of lncRNAs in MI. lncRNAs are found to be as high risk factors with up-expression in MI, or target the aberrant mRNAs at the early stage of reperfusion in the infarct region [7].

Cardiac hypertrophy is characterized as a complicate process of heart structure remodeling and a variety of functions changes resulting from an increased workload under physiological or pathological conditions [8]. Pathological cardiac hypertrophy generally refers to enlargement of cardiomyocyte size, disarrangement of myofibril, abnormal expression of protein and reactivation of fetal gene, and these factors are considered as high risk for heart failure and life threatening arrhythmias [9,10]. Recently, as the development of epigenetic study, miRNAs and lncRNAs are considered to be important regulators of cardiac remodeling. miRNA antagomir can induce cardiac hypertrophy by a single infusion in mice. Moreover, miRNAs were reported as an inducer and paracrine mediators of cardiac hypertrophy to inhibit of cardiac contractility by suppress sarcoplasmic reticulum calcium uptake pump, reduce in fibrosis and normalization of cardiomyocyte size [11]. Even more, reactivation of fetal miRNAs expression show a similarity with re-expression of fetal protein, which contributes to decrease contractile function of ventricular myocardium in failure heart [12]. Recently, as a number of lncRNAs are identified by deep-sequencing in diseased heart (adult hypertrophied heart, ischaemic heart etc.), the roles of lncRNA in cardiovascular diseases have been raised concern. lncRNAs have been established as signature of heart disease under pathological conditions, reference parameters of cardiac function and dimension, modulation of heart development, and an endogenous sponge for miRNAs [13].

Atherosclerosis (AS), one of the major forms of CVDs, is a pathological condition characterized by chronic cholesterol accumulation and lipid induced inflammation within the arterial wall, which lead to arterial remodeling and infiltration of leukocyte cells. During the initiation and progression of AS, complex interaction of diverse types of cells

and modified lipoproteins occurs, including macrophages, dendritic cells, vascular smooth muscle cells (VSMCs) and endothelial cells. The atherosclerotic process involves four steps: macrophage foam cell formation, fatty streak accumulation, migration and proliferation of VSMC, and fibrous cap formation. Recent studies have found that altered ncRNA expression is related to the functions of different cell types and lipid metabolism, thereby controlling the atherosclerotic process. A variety of miRNAs have been demonstrated to play a critical role in AS, for instance, miR-122, miR-33, miR-144, and miR-106 are reported to be related to lipoprotein metabolism [14-17]. Moreover, miR-126, miR-181b, and miR-21 are described in endothelial dysfunction [18-20]; miR-143/145 cluster, miR-29, and let-7 family are identified as key players in VSMC regulation [21-23]; miR-125a-5p is important during macrophage activation [24]. Besides, several lncRNAs are proved to be correlated with the severity of AS, such as tie-1AS lncRNA [25], ANRIL [26], lnc-Ang362 [27].

Given the emerging importance in multiple cardiac pathophysiological conditions, ncRNAs provide promising therapeutic targets. On the other hand, miRNAs between species are conserved, indicating that the involved biological pathways also might be conserved. Although recent available studies highlight the prospect of ncRNA-based therapies in CVDs and its potential has been demonstrated in animal models, the clinical application of ncRNAs has been limited so far. One of the clinical trials is the role of miRNAs as predictive biomarkers to monitor disorders of heart such as myocardial infarction. In addition, both oligonucleotide miRNA mimics and antisense oligonucleotide antagomirs can be easily synthesized, packaged within exosomes or microvesicles, and transfect cells with low toxicity in vivo. Therefore, ncRNAs would provide valuable diagnostic approaches that take into account individual cardiovascular risk factors in the future.

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