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MicroRNA: A new therapeutic strategy for cardiovascular diseases

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A B S T R A C T

Myocardial infarction, atherosclerosis, and hypertension are the most common heart-related diseases that affect both the heart and the blood vessels. Multiple independent risk factors have been shown to be responsible for cardiovascular diseases. The combination of a healthy diet, exercise, and smoking cessation keeps these risk factors in check and helps maintain homeostasis. The dynamic monolayer endothelial cell integrity and cell–cell communication are the fundamental mechanisms in maintaining homeostasis. Recently, it has been revealed that small noncoding RNAs (ncRNAs) play a critical role in regulation of genes involved in either posttranscriptional or pretranslational modifications. They also control diverse biological functions like development, differentiation, growth, and metabolism. Among ncRNAs, the short interfering RNAs (siRNAs), and microRNAs (miRNAs) have been extensively studied, but their specific functions remain largely unknown. In recent years, miRNAs are efficiently studied as one of the important candidates for involvement in most biological processes and have been implicated in many human diseases. Thus, the identification and the respective targets of miRNAs may provide novel molecular insight and new therapeutic strategies to treat diseases. This review summarizes the recent developments and insight on the role of miRNAs in cardiovascular disease prognosis, diagnostic and clinical applications.

Key words: MicroRNAs, Endothelial cells, Cardiac fibrosis, Atherosclerosis, Myocardial infarction, Stroke, Hypertension.

Abbreviations: ATH, atherosclerosis, ALDH2, aldehyde dehydrogenase 2, BMP, bone morphogenetic protein, Bcl-2, B-cell lymphoma, CAD, coronary artery diseases, CDC42, cell division cycle 42, CPCs, cardiac progenitor cells, CM, cardiomyopathy, CCL2, chemokine (C–C motif) ligand 2, CircRNAs, circular RNAs, CTGF, connective tissue growth factor, Cx40, Connexin 40, DCM, diabetic cardiomyopathy, DGCR8, DiGeorge critical region 8), DLK1, δ-like 1 homology, Dyrk, dual specificity tyrosine regulated kinase, EC, endothelial cell, ECM, extra cellular matrix, Erk, extracellular signal-regulated kinase, eNOS, endothelial nitric oxide synthase, FGF, fibroblast growth factor, FOXO3, forkhead box O-3, Grb2, growth factor receptor-bound protein 2, GATA4, gata binding protein 4, HGF, hepatocyte growth factor, HSP70, heat-shock protein 70, HSF1, heat-shock factor 1, HUR, human antigen R, IGFR1, insulin growth factor 1 receptor, ICAM, intercellular adhesion molecule, LDLs, low-density lipoproteins, MMP, Matrix metalloproteinase, mRNA, messenger RNA, MiRNA, MicroRNA, MAPK, mitogen-activated protein kinases, MCP1, monocyte chemo attractant protein1, MEF2A, myocyte enhancer factor 2A, MI, myocardial infarction, NOS2, nitric oxide synthase 2, ncRNA, noncoding RNA, NF-KB, nuclear factor κB, NR3C2, nuclear receptor subfamily 3 group C member 2, PAD, peripheral artery diseases, PPARγ, peroxisome proliferator-activated receptor γ, PTBP1, polypyrimidine tract-binding protein 1, PTEN, phosphatase and tensin homolog, PiRNA, piwi-interacting RNAs, PI3K, phosphatidylinositol-3-kinase, PH, pulmonary hypertension, RAA, renin–angiotensin–aldosterone, rRNA, ribosomal RNA, Rho, ras homology gene family, RISC, RNA inducing silencing complex, scaRNAs, small cajal body specific RNAs, SMA-α, smooth muscle actin-α,

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snoRNAs, small nucleolar RNAs, STK35, serine/threonine-protein kinase 35, tRNA, transfer RNA, TRBP, transactivation response RNA binding protein, TGFβ, transforming growth factor β, TNNI3K, cardiac troponin-I3 interacting kinase 3, VCAM, vascular cell adhesion molecule, VEGF, vascular endothelial growth factor, VSMCs, vascular smooth muscle cells.

Introduction

Heart diseases are the leading cause of death in the United States and around the world [1]. Hypertension, tobacco exposure, high cholesterol, obesity, diabetes, unhealthy diets, and alcohol seem to have an additive effect for the causation of cardiac diseases. Myocardial infarction (heart attacks), cerebrovascular disease (stroke), atherosclerosis, and hypertensions (raised blood pressure) are the most common cardiovascular diseases, which involve heart and blood vessels. Number of recent studies has shown that miRNAs are essential for the normal development and physiology of various organs, including the heart. Studies have also started to characterize the link between microRNAs (miRNAs) and different aspects of cardiac pathogenesis such as chamber morphogenesis, conduction, and contraction. Moreover, congenital anomalies of the heart can be associated with the dysregulation of specific miRNAs [2].

Recently, investigators have demonstrated that RNA functions not only as an intermediate molecule between DNA and protein, but is also involved in the complicated process of gene regulation and expression. Some of the RNAs are the functional molecules that are not capable of translating into proteins. Hence, these RNAs are called noncoding RNAs (ncRNAs). Among the several classes of ncRNAs, miRNA is the most extensively studied and has gained prominence in current research. These ncRNAs are found within intergenic or intragenic regions of host genes, which make up approximately 10% of the human genome [3]. Recently, a rapid progress has been made in profiling miRNA and reported it in various diseases and cell types. MiRNAs are involved in a number of biological processes, including cell proliferation, apoptosis, stress response, hematopoiesis, and oncogenesis. Studies have highlighted that miRNA could be a potential molecular therapeutic strategy for various diseases, including heart diseases [4]. MiRNAs are tissue and lineage specific, and many more to be discovered. The recently developed high-throughput approaches revealed the miRNA size, their target, and the connectivity of the miRNA-dependent regulatory network. One step further, the expression levels of miRNAs and their decay rates have been identified in individual cell types. These works together help us to understand miRNA-dependent gene regulation to study the response of the entire network. Studies have shown that miRNAs stably regulate many developmental and cellular processes, including numerous eukaryotic plants, and mammals with vary in expression at extracellular and intracellular fractions [5]. During the past decade, numerous research articles have shown a wide knowledge about the basic mechanisms of miRNAs, biogenesis and its functions in the circulatory system. This review will discuss the biosynthesis of the miRNA and its functional role in cardiovascular diseases, as well as the challenges in miRNA-based therapy.

Noncoding RNAs

The ncRNAs are the functional entity of a cell in regulating the gene expression. These regulatory RNAs have function but do not encode proteins. In 1950s, discoveries of ribosomal RNA (rRNA) and transfer RNA (tRNA) are known as the principle RNA molecules that participate in gene expression. In the early 1980s, the existence of small nuclear RNAs (snRNAs) was discovered. Recently, the other ncRNAs, such as small cajal body specific RNAs (scaRNAs), small nucleolar RNAs (snoRNAs), long noncoding RNAs (lncRNAs), piwi-interacting RNAs (piRNAs), and circular RNAs (circRNAs) were discovered for the labile genes. The discovery of miRNAs was a huge revolution because it depicted their importance of posttranscriptional events in gene expression, particularly in eukaryotic organisms [6].

SiRNAs

The siRNAs are small double-stranded RNAs and well studied among the ncRNAs of approximately 20–25 base pair (bp) in length. The major role of siRNA is to involve in RNA interference (RNAi) pathway in regulating the gene expression. This RNAi-mediated gene regulation can be executed by either siRNA or miRNA, but there are subtle differences between the 2. However, siRNA based strategies have some disadvantages, mostly RNase susceptibility. The use of RNAi-based therapeutics from a clinical standpoint, is a new platform that is steadily developing [7].

PiRNAs

Comprising a length of approximately 24–30 bp. PiRNAs are the Dicer-independent ncRNAs that associated with PIWI subfamily proteins. PiRNAs are highly abundant in germ cells. Some are involved in the formation of heterochromatin or RNA destabilization, which mediates gene silencing [8].

SnoRNAs

SnoRNAs are intermediate-sized ncRNAs (60–300 bp) responsible for posttranscriptional modifications and assist in folding and stability of rRNA [9].

Sca-RNAs

The scaRNAs (60–425 bp) are a subset of snoRNA family, which is large family of conserved ncRNAs that primarily guide biochemical modifications of particular nucleotides (e.g., methylation and pseudouridylation) of rRNAs and snoRNAs. Without the specific modifications controlled by the scaRNAs, the spliceosome fails to function properly [10].