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Review Article

The Therapeutic Effects and Role of MiRNAs in Coronary Artery Disease: A Systemic Review

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Cardiovascular diseases are the most common causes of human morbidity and mortality despite significant therapeutic improvements by surgical or pharmacological approaches in the last decade. MicroRNAs (miRNAs) have a significant role in diseases development or response to treatment. In this review, we summarized the role of miRNAs in the pathogenesis or the treatment of coronary artery disease (CAD). We searched four electronic databases (PubMed, Ensemble, Science Direct and Ensemble) with no date limit. All of the selected articles investigated microRNAs activity and/or therapeutic approaches related to CAD. The exclusion criteria were a sample size <100 patients, editorials, and other diseases and comorbidities. With these criteria, we identified 52 prospective studies published in the last decade with a total of around 20,000 participants. Most of the studies support the concept that alterations in miRNAs activity levels might be associated with the risk of CAD development. Here, the current knowledge about the miRNAs biology, and the clinical advantage of miRNAs modulation as therapeutics in cardiovascular system are reviewed and discussed.

Keywords: Coronary artery disease, miRNAs, therapeutic

Heart diseases are the leading cause of death all around the world. Hypertension, different addictions such as alcohol and tobacco, obesity and diabetes, unhealthy diets and high cholesterol levels, are the important factors that could increase the cardiac diseases risk (1). Heart or cardiac disease is a term used to describe a large family of conditions that affect the myocardial muscle. All the disorders that fall under this category include blood vessel illnesses such as coronary artery disease (CAD), heart rhythm conditions (arrhythmias), and all the other types of cardiomyopathies (2-3). CAD, secondary to coronary atherosclerosis, also known as ischemic heart disease, is the most common type of cardiovascular disease which causes death globally. More than 80% of sudden cardiac deaths in the world are caused by CAD, and the remaining 20% of cases are caused by other diseases including left ventricular hypertrophy, congenital heart disease, cardiomyopathies, aortic valve disease and other types of cardiac disorders (4). Based on the familial pedigree, twin-concordance, and adoption studies, CAD has a significant hereditary component especially in the younger generation (5). Ensuing epidemiological studies to uncover the other etiology of heart disease significantly reduced the

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mortality rates through the identification of hypertension, and dyslipidemia as major, modifiable CAD risk factors (6-7). Understanding the underlying molecular and cellular mechanisms may contribute to the prevention of cardiovascular diseases (4, 8).

A family of small regulatory RNA molecules known as microRNAs (miR; miRNAs), which could act as a "fine tuner" or even as an on/off switch of gene expression (9), act in the regulation of diverse aspects of cardiac function (10-11). MiRNAs has been shown to be essential for the correct physiology and development of the cardiovascular system (2). Recently, various studies have illustrated alterations in miRNAs expression levels in human heart conditions such as myocardial infarction (MI) (12)(10), cardiac hypertrophy and fibrosis (13), and developmental heart disease (14). They showed that the expression of numerous miRNAs is changed in such pathological processes and that different types of heart disease are associated with abnormal miRNAs expression (15-17). In this review, we summarized the role of miRNAs in heart development and vascular system as two main factors of congenital disabilities and adult morbidity and mortality (18-19).

Methodology and search strategy

The search was performed in four electronic databases: PubMed, SNPedia, Ensemble, and ScienceDirect. They were published between 2005 and 2017 and included a total of around 20,000 participants. The main search terms included: coronary artery disease (CAD) and miRNA. Two steps of selection screening were accomplished; the first screening selection was based on the article's title, and the abstract of articles was the second one.

All of the articles involved in miRNAs activity and/or therapeutic approaches were selected. The selection focused on miRNAs relationship with CAD. The exclusion criteria were a sample size of <100 patients, editorials and other diseases and comorbidities.

Identification of studies

The initial electronic search identified 400 articles based on mentioned points. After exclusion of duplicates, approximately 200 articles with 150 contributions were considered irrelevant based on our concept. The selection was therefore reduced to 52 full-text articles. Finally, all the selected manuscripts were included in this review.

The biology of miRNAs

MiRNAs are highly conserved RNAs, which have 18–25 nucleotides length, regulate expression or turn on/off the specific target gene. MiRNAs may be located within the genome as intronic miRNAs where they can be processed from introns of protein-coding gene transcripts, or may be transcribed under the control of their own promoters as intergenic miRNAs (20). MiRNAs bind to the 3'-untranslated region (UTR) of specific mRNAs according to the complementarity of the nucleotide sequences and inhibit translation or promote target mRNAs degradation (21). Approximately 2,500 miRNAs have been identified in the human genome; More than 60% of human protein-coding genes have been under selective pressure to maintain pairing to miRNAs (2, 22). MiRNAs can have control on the various stages of embryonic heart development, and their downstream targets are shown to be involved during embryonic heart development (23-24).

MiRNAs biosynthesis and function

The biosynthesis of miRNAs is a sophisticated multi-step process that begins within nucleus, and the maturation process ends in the cytoplasm of the cell. The synthesis process starts from the miRNA genes that are transcribed either by RNA polymerase II or III which are organized in clusters for the transcriptional regulation arising out of introns of protein-coding genes. The pri- miRNAs are cleaved by the microprocessor enzyme complex DROSHA and DGCR8 (DiGeorge Critical Region 8), and the cleaved precursor miRNA (pre-miRNA) molecule which contains a local hairpin structure with approximately 100 bp in length is created (25). Then, the pre-miRNAs are exported from the

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nucleus into the cytoplasm through nuclear pores via a GTP-GDP gradient by the exportin-5 enzyme (26). In the cytoplasm, DICER, derived from an RNA III family, interacts with another protein partner transactivation response RNA-binding protein (TRBP), cleaves the pre-miRNAs into short double-stranded RNA; this ultimately form of mature miRNA has a hairpin loop of 33 bp (27). Overexpression and suppression of miRNAs revealed the importance of miRNAs in pathophysiology. Since the discovery of physiology of miRNAs, numerous clinical researches were performed on the relationship of cardiovascular diseases and miRNAs.

MiRNAs in cardiac function

Recent studies have shown that miRNAs play an essential role in some biological processes such as cells' proliferation and differentiation, and apoptosis. Thus, they could be associated with important global diseases such as cancer or cardiovascular diseases (28-29). According to Sanger Institute and miRNA databases (http://www.sanger.ac.uk, http://www.mirbase.org) more than 1500 miRNAs have been identified in humans. Current databases report 1600 precursors and 2042 mature miRNA sequences in the human genome. Among them, a subset of miRNAs including miR-1, miR-133, miR-206, and miR-208 are muscle tissue-specific and have been called myomiRs (30-31). MiR-206 is one of the most studied and best characterized miRNA to date, which is specifically expressed in skeletal muscle (23). MiR-206 is a member of the miR-1 family, and the gene for miR-206 is located between the interleukin- 17, and the polycystic kidney and hepatic disease 1 genes in human (Chr 6), with highly conserved sequence (32). Further, a recent report indicated that circulating miR-1, which is released into the blood stream via exosomes in mice with an acute MI, suppresses the expression of the SDF-1 receptor CXCR-4 in bone marrow mononuclear cells. This might contribute to the increased bone marrow -cell mobilization elicited by an acute ischemic episode, such as MI. These studies implicate that exosomes-mediated communication mechanisms may play a significant role in disease dissemination, cardiac repair, and regeneration (33) (31). MiRNAs changes can be considered as a biomarker for the diseases including cardiac related diseases. Several accurate and complex interactions among a wide range of cells including fibroblasts, cardiomyocytes, endocardial, epicardial and vascular cells, and cells of the conduction system are required for the correct heart formation (31). Many miRNAs play a role in some aspects of cardiovascular remodeling. For example, miR-21-3p is involved in sepsis-associated cardiac dysfunction, miR-433 exerts a role in cardiac fibrosis (34), miR-33 and miR- 145/143 have been associated with atherosclerosis, miR-21 and miR-320 are important in CAD, and miR-1 and miR-133 are involved in heart failure, while miR-222 protects against pathological cardiac remodeling (2). Table 1 represents the most relevant miRNAs involved in left ventricular remodeling process.

The biological characteristics of miR-155

MiR-155 is located on chromosome 21, and is processed from an exon of a non-coding RNA which is transcribed from the B-cell integration cluster (BIC). The association between CAD and miR-155

Table 1. Representation of the most relevant miRNAs reported during different phases of left ventricular remodeling process and the associated heart defects

Heart defects	miRNAs			
Myocardial ischemia (MI)	miR-24	miR-214	miR-126	miR-499
Cardiac hypertrophy	miR-21	miR-195	miR-199	miR-208
Cardiac fibrosis	miR-21	miR-29 family		miR-208
Cardiac arrhythmia	miR-1	miR-133	miR-17-2	

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has been studied extensively. MiR-155 was among the miRNAs highly expressed in patients with high risk for cardiac death. Zhu's research group also showed a significant concentration of miR-155 in CAD patients' plasma (18). They suggested that elevation in miR-155 levels contributes to the prevention of atherosclerosis development via targeting mitogen-activated protein kinase 10 (*MAP3K10*). Interestingly, miR-155 was found to be either upregulated in CAD patients and promote disease development, or was found to prevent CAD by being downregulated (2).

MiRNAs regulate muscle development

Two miRNAs, miR-1 and miR-133, are co-transcribed from a single locus and are uniquely expressed in skeletal and cardiac muscle cells and their progenitors. Furthermore, miR-1 can promote the differentiation of skeletal muscle from myoblast precursors by targeting myocyte enhancer factor 2C (*MEF2C*) that further drives miR-1 expression. This miRNA induces the muscle cell differentiation, and the misexpression of this single miRNA in fibroblasts contributes largely to the cell programing toward muscle cells formation. Misexpression of miR-1 in human embryonic stem cells causes them to favor the muscle cell fate. MiR-1 overexpression in developing mouse heart muscle leads to the premature cell cycle exit, providing therefore an example of a tissue-specific regulator of the cell cycle. On the contrary, a decrease of miR-1 expression level in the cell causes cardiac developmental defects and persistent postnatal cardiomyocyte karyokinesis.

Interestingly, miR-1 and miR-133 also may direct pluripotent cells to form mesoderm while actively suppressing alternative lineages. According to the results of many studies, miR-133 acts in partial opposition to miR-1, by promoting the expansion of muscle progenitor cells and terminal differentiation prevention, which may be activated by miR-133 mediated cyclin D2 and serum response factor (SRF) repression. Thus, these two coexpressed miRNAs have an accurate balancing and regulating effect on cardiac and skeletal muscle cell proliferation or differentiation through the establishment of feed-forward and feedback loops integrated into known muscle cell networks and cell-cycle regulatory pathways (35). MiR-1 and miR-133 are among a cohort of numerous miRNAs whose transcription is directed by and dependent on the developmental regulator SRF (36). In the absence of SRF, mesoderm differentiation is weak and delayed. Development of mesoderm progenitors can be partially rescued by forced expression of either miR-1 or miR-133 in cells (37).

MiRNAs and therapeutic options

MiRNAs could be of clinical value in the context of cardiovascular diseases, both as therapeutic targets and as biomarkers to follow disease diagnosis and prognosis. The therapeutic potential of miRNAs in cardiovascular diseases was first proposed in the light of results from animal studies that unveiled important roles of miRNAs in several contexts of cardiac development and disease. Knockout of *DICER1* showed a phenotype change in cardiomyocytes, smooth muscle cells, and endothelial cells leading to heart defect (3, 38). It can therefore be concluded that miRNA reestablishment to normal levels may exert a therapeutic effect in the context of cardiac disease (39).

In principle, one of the advantages of the miRNAs as therapeutic tools in cardiovascular diseases is their ability to target various factors in an established biological context. Because of the intrinsic nature of miRNAs, several miRNAs targets may be downregulated by a single mature molecule, increasing the likelihood of affecting multiple components within a biological pathway. Indeed, there are molecular tools that can affect simultaneously several miRNAs, and consequently further increasing the range of biological action. The design of specific inhibitory molecules, called miRNA sponges, may allow the inhibition of several miRNAs, with a very high efficacy and the ability to specifically modify the dynamics of any pathway

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(40). Furthermore, inducing gain- or loss-of-function is technically more feasible, both *in vivo* and *in vitro*, using miRNAs rather than mRNA or DNAs, and miRNAs show higher stability (40-41). Therapeutic inhibition of miRNAs in cardiovascular diseases is currently based on the fact that specific microRNAs have been investigated and their role as fundamental regulators of distinct phases of embryonic heart development has been demonstrated, and they were also described in the pathogenesis of different remodeling processes. Interestingly, loss of function approaches could be planed using miRNAs sponges as inhibitory tools in order to block specifically those miRNAs related to a defined aspect of cardiovascular diseases development in order to attenuate the response to cardiac injuries (42-43).

The 2-*O*-methyl modification often has been used to reach high oligonucleotide stability and efficacy. A cholesterol construct with enhanced cellular uptake ability was described, and this approach has been used to target cardiac tissue *in vivo*. Recently, an excellent historical description of miRNA therapeutic development was provided (44). The group of Stoffel reported for the first time that mammalian miRNAs can be knocked down in the presence of cholesterol-conjugated antagomirs inhibiting miR-122, a liver-specific miRNA (45). In addition, the investigation of the knockdown output of many other antagomirs showed that the use of cholesterol-based chemistry through intravenous injection was also able to knockdown miRNAs expression in cardiac tissue (46). Care et al. employed a similar strategy with an antagomir against miR-133, and obtained cardiac hypertrophy in mice (46). In a therapeutic approach, Thum et al. showed the success of using an antagomir against fibroblast-enriched miR-21 to prevent cardiac fibrosis (44). These primary results were followed by many other successful studies using miRNA inhibitors to affect cardiovascular function. Relatively, miR-155 was described as a a prognostic marker candidate for cardiac death. Decreased miR-155 serum levels, along with increased expression of the target gene SH2-containing inositol 5'-phosphatase 1 (SHIP-1) was linked to reduced incidence of periprocedural MI, reduced levels of cardiac troponin I as well as inflammatory cytokines (INF-γ, TNF-α, and IL-6) after rosuvastatin treatment in patients with acute coronary syndromes who received percutaneous coronary intervention . Therefore, the beneficial effect of rosuvastatin might be at least partially due to the suppression of the miR-155/SHIP-1 signaling pathway.

MiRNA therapeutics targeting cardiac hypertrophy and fibrosis

Care et al. were among the pioneers who used an antagomir to inhibit a miRNA involved in cardiac hypertrophy (46). They implanted subcutaneous osmotic minipumps in mice for a continuous delivery of a cholesterol-based antagomir targeting miR-133. After a month of infusion, cardiac hypertrophy increase was observed upon echocardiographic analysis, suggesting that miR-133 mimics may be of therapeutic relevance. Cardiac fibrosis development is often linked to cardiac stress including pathological cardiomyocyte hypertrophy. Cardiac fibroblasts are enriched with certain miRNAs, such as miR-21, which regulates the ERK–MAP kinase signaling pathway via targeting sprouty-1, a negative regulator of fibroblast growth factor receptor signaling pathway (47-48).

MiR-21*

Cardiac fibroblasts were shown to secrete exosomes enriched with miR-21* as a crucial paracrine signaling mediator of cardiac hypertrophy. MiR-21* was shuttled to cardiomyocytes affecting the expression of the miR-21* target genes within them and leading to cellular hypertrophy. Pharmacological inhibition of miR-21* obtained by injection of an "antagomiR-21*" attenuated the development of cardiac hypertrophy in mice infused with angiotensin II (AngII) (33, 49). These findings illustrate that investigations on exosome-mediated communication systems may lead to the discovery

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of novel mechanisms contributing to the cardiac failure. Exosomes can also exert beneficial actions (50).

MiR-132

The mentioned studies consistently implicate the transfer of one or more miRNAs in action elicited by the exosomes. Some reports have shown that miRNAs could be transfered between cells without identifying the method of transportation from one cell type to the other. For instance, the pro-angiogenic activity of pericytes depends on miR-132 which they produce and release, especially in response to hypoxia (49). Interestingly, it was demonstrated that both ischemic and healthy human and mouse cardiomyocytes are able to release exosomes-like vesicles *in vivo* (51).

Conclusion

This systematic review has sought to highlight the role of miRNAs in the cardiovascular system and the identification of putative therapeutic strategies to treat cardiovascular diseases. Studies to fully exploit the potential miRNA therapeutic approaches are still needed. Despite remarkable successes in the treatment and prevention of CAD in the past decades, it is still the leading cause of death and premature disability in the United States and other developed countries (52). Therefore, more comprehensive studies of underlying mechanisms of miR-155 as well as other critical miRNAs involvement in CAD are needed.

Conflict of interest

The authors declared no conflict of interest.

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