

miRNAs as Biomarkers for Diagnosis and Assessment of Prognosis of Coronary Artery Disease

Sabina Shrestha, Liqun Ren*, Rajan Vaidya

Department of Cardiology, Zhongda Hospital, Affiliated to Southeast University, Nanjing, China
Email: *rlq6345@126.com

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Abstract

Atherosclerosis, stable myocardial infarction (MI), non-stable MI are the most common manifestations of coronary artery disease (CAD). CAD is one of leading causes of substantial morbidity and mortality in the global scenario. There are several biomarkers and methods for the diagnosis of CAD such as cardiac specific troponin, electrocardiogram (ECG), CT angiography. Recently, many studies have shown that miRNAs are involved in regulation of gene expression on post-transcriptional level by inhibiting translation protein from mRNA that miRNAs dysregulated in the plasma of patients with CAD (cases). These suggested miRNAs can be detected in circulating blood which might be a diagnostic and prognostic biomarker for CAD. Besides these studies, there is an additional need in studies about miRNAs family, so that miRNAs might serve as potential therapeutic target in the treatment of CAD, as well as other complex diseases. In this review, we have summarized some studies as miRNAs as diagnostic and assessment of prognosis biomarker in patients with CAD.

Keywords

Coronary Artery Disease, miRNA, Myocardial Infarction

1. Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality and morbidity worldwide, accounting for 14% of all deaths and is predicted to remain so until 2030 [1]. It is estimated that nearly one half of all middle-aged men and one third of middle-aged women in the United States will develop some form of the disease [2]. CAD is the number one killer in the developed

world, with over 7.4 million deaths attributed to CAD in 2012 [3]. In the United States, it is estimated that one in seven deaths is due to heart disease. In addition, heart disease is the primary cause of death in women, taking more lives than all cancers combined [4]. Coronary artery disease is also known as coronary heart disease (CHD), ischemic heart disease (IHD), atherosclerotic heart disease or coronary atherosclerotic disease. The main forms of coronary artery disease are: Chronic stable angina and acute coronary syndromes. The main three acute coronary syndromes are: Unstable angina, myocardial infarction (MI) and sudden cardiac death.

1.1. MicroRNAs

MicroRNAs (miRNAs) are small, single-stranded, nonprotein-coding RNAs of about less than 22 nucleotides. To date, more than hundreds of miRNA molecules have been identified in the human genome that plays key roles in a broad range of physiologic and pathologic processes [5]. It also hold capacity as novel biomarkers for clinical diagnosis which can be found in a number of bodily fluids, including blood, urine, saliva, plasma and serum that is protected from degradation in the circulation through association with lipids, proteins or micro-particles, interpreting them as disease biomarker candidate. miRNAs have been progressively occupied in the regulator of various biological processes which includes cell differentiation, cell proliferation, cell growth and apoptosis, and numerous pathological processes, such as cancer, Alzheimer's disease and cardiovascular disease [6].

1.2. Biogenesis Pathway of miRNAs

In nucleus the canonical miRNAs are processed from primary miRNAs (pri-miRNAs) which are synthesized from DNA by enzyme protein coding RNA polymerase II transcripts. Pri-miRNAs are folded and formed into hairpin structures, then are cleaved by ribonuclease III known as Drosha with cofactor DGCR8 (DiGeorge syndrome chromosomes region 8) that forms the microprocessor complex (Drosha-DGCR8 complex) which processes pri-miRNAs to preliminary miRNAs (pre-miRNAs) of 70 - 100 nucleotides. Pre-miRNAs are transported into cytoplasm by exportin-5, where they are cleaved by Dicer, ribonuclease III and cofactor TRBP and formed to yield miRNAs duplexes which are shorter, double standard immature miRNAs, where one strand is selected to work as mature miRNAs while other strand is degraded. Following all pathway processing, miRNAs are assembled into Ribonucleoprotein (RNP) complexes known as micro-RNPs (mi RNPs) and also known as miRNAs induced silencing complexes (miRISC). During these processes, miRNAs are considered as proteins of the Argonaute protein family (AGO) that undergo conformational changes to allow binding of miRNAs duplex. [AGO proteins works in mRNAs, miRNAs and siRNAs (small interfering RNA) pathways and in mammals, only 4 types of AGO proteins works in miRNAs repression]. Into RISC, the miRNAs

present the seed sequence at an interface where they can interact at the region of miRNAs with in 3'-UTR region of mRNA target gene [7]. The mature miRNA within the RISC complex expressions its monitoring character in the cytoplasm as well as in the nucleus [8] In the cytoplasm targeted mRNA 3'UTRs with corresponding sequence display translational repression, sometimes multiple miRNAs target a single mRNA and vice versa [9] [10].

1.3. miRNAs in Cardiovascular Disease

In the cardiovascular system, miRNAs are not only important for heart and vascular development but also play an essential role in cardiac pathophysiology, such as arrhythmia, ischemia and coronary atherogenesis [11]. There are many studies done regarding clinical relevance of miRNAs in cardiovascular disease (CVD). Some studies revealed that miRNAs function as regulators of metabolic pathways such as lipid metabolism and glucose homeostasis, which are highly involved in vascular disease. Besides their role in metabolism, miRNAs are also key regulators in vascular cells and endothelial cells (EC) [12]. A era ago, the first in vivo description of the relevance of miRNAs in heart disease was made in cardiac hypertrophy and Heart failure of mice and humans [13]. Shortly afterward, Ikeda *et al.* for the first time showed that miRNA expression profiles are specifically altered in different entities of heart disease comprising distinct changes of single miRNA expressions [14]. Certain studies results reflect the tissue- and cell type-specific regulation of miRNAs and gave rise to screening projects to identify single miRNAs in CVD, their mode of function, and importantly, their potential for clinical application [11].

1.4. miRNAs in Coronary Artery Disease

Atherosclerosis is a major contributor to CAD and MI and eventually leads to CVD. The complex balance of pro- and antiangiogenic signaling pathways is dysregulated that results in pathological angiogenesis and vascular inflammation, which contribute to the development and progression of CAD and dysregulated levels of specific miRNAs were identified compared with healthy controls [15].

1.5. miRNAs as Circulating Biomarkers

The release of miRNAs into the bloodstream, has presented the possibility to non-invasively detect circulating miRNAs and to use them as disease biomarkers. As opposed to their cellular origin, miRNAs are well-known as extracellular messengers and detectable in peripheral blood [16]. This study evaluated that miRNAs characterized by a remarkably stable structure, which prevents them from early degradation [17].

Apart from their diagnostic potential to identify cardiovascular disease esp. CAD in acute phase, miRNAs have been analysed for their ability to predict future cardiovascular adverse events among general population (controls) and in

CAD patients (cases) [18] [19].

2. Discussion

Some studies have been investigated the diagnostic and prognostic role of miRNAs in CAD patients as shown and summarized in **Table 1**: Guo D evaluated serum miR-145 lower in CAD patients especially ST elevated MI CAD which suggests that downregulation of miR-145 plays a critical role in pathogenesis of atherosclerotic plaques which is main form for development of CAD. This study also correlated miR-145 with risk factors of CAD. However, this study also has its limitations due to expensive investigation method, time limitation and a small sample size. This study couldn't demonstrate the primary mechanism behind the association between lower miR-145 levels and CAD severity. Besides these limitations, this study may have extensive clinical implications in diagnosis as well as therapy of CAD [20]. Fichtlscherer assessed several miRNAs in stable CAD patients under drug therapy and healthy people among large study. They found that serum levels of miR-133 and miR-208a were higher in the CAD group, while the levels of miR-145, miR-155, miR17, miR-126 and miR-92a were lower in CAD group. This study demonstrated the reliable measurement of circulating miRNAs and also addressed the levels and regulation of vascular and muscle derived miRNAs which shows miRNAs that are highly expressed by endothelial cells can be detected in high concentrations in the blood circulation. Besides that, the mechanisms underlying the dysregulation, as well as the putative impact of the changes in circulating miRNAs levels in the physiology or pathophysiology have to be determined. For further effective analysis, prospective large-scale studies are required to determine the potential use of circulating endothelial or vascular miRNAs as biomarkers and risk factors for the of development of CAD [21]. Liu H's study shows expression levels of miR208a and miR 370 with high lipid profile are significantly higher in CAD patients which demonstrate potential diagnostic tools for CAD and for further management for CAD patients. This study could be helpful, as it shows combination of two or more than two miRNAs could be effective for diagnosis of CAD. However, further investigations are needed to establish suitable combination miRNAs for early diagnosis of CAD [22]. Weber's study is done into whole blood sample to measure levels of miRNAs in CAD patients and healthy population. This study determined the downregulation of miRNAs in CAD patients, is involved in inflammation or is compensatory response to this process. For further study, a larger sample size is required, so that chronic CAD will continue contribute to determine disease process so that therapeutic and preventative strategies can be determined [23]. Liu F. demonstrated the relationship between miR-17-92 family and lipid metabolism .Many previous studies determined this miR-17-92 cluster family, and has already studied and reported to play important roles in regulating diverse cell activities including angiogenesis and cancer [24]. This study suggested that miR-17-92 may play important roles in the

Table 1. Summary of relevant studies investigating miRNAs in CAD.

<i>AUTHOR</i>	<i>TYPE AND STUDY POPULATION</i>	<i>SPECIMEN</i>	<i>MAIN miRNAs INVESTIGATED</i>	<i>MiRNAs ANALYSIS METHOD</i>	<i>CHIEF FINDING</i>
GUO D, <i>et al.</i> [20]	67 CASES (CAD PATIENTS), 28 CONTROLS (NON-CAD)	PLASMA	miR-145	RT-qPCR	HIGHER IN CAD PATIENTS
FITCHLSCHERER <i>et al.</i> [21]	8 CASES (STABLE CAD PATIENTS), 20 CONTROLS (NON-CAD)	PLASMA AND SERUM	miR-208a, miR-133, miR-145, miR-155, miR-17, miR-126, miR-92a	RT-qPCR	miR-208a, miR-133-[HIGHER IN CAD PATIENTS], miR-145, miR-155, miR-17, miR-126, miR-92a [LOWER IN CAD PATIENTS]
LIU H, YANG N, FEI Z, <i>et al.</i> [22]	95 CASES (CAD PATIENTS), 50 CONTROLS (NON-CAD)	PLASMA	miR-208a, miR-370	RT-qPCR	HIGHER IN CAD PATIENTS
WEBER <i>et al.</i> [23]	10 CASES (CAD PATIENTS), 15 CONTROLS (NON-CAD)	WHOLE BLOOD SAMPLE	miR-145, miR-19a, miR-484, miR-155, miR-150, miR-378	RT-qPCR	LOWER IN CAD PATIENTS
LIU F <i>et al.</i> [24]	81 CASES (CAD PATIENTS), 50 CONTROLS (NON-CAD)	PLASMA	miR-18a, miR-92a, miR-106b, miR-17	RT-qPCR	miR-17 HIGHER IN CAD PATIENTS WITH INCREASED LIPID PROFILE, miR-92a, miR-106b LOWER IN CAD PATIENTS WITH INCREASED LIPID PROFILE.
MINAMI <i>et al.</i> [26]	44CASES (STABLE CAD PATIENTS), 22 CONTROLS (NON-CAD)	PLASMA	miR-221, miR-222	RT-qPCR	HIGHER IN CAD PATIENTS
ZHANG <i>et al.</i> [27]	149 CASES (STABLE CAD PATIENTS), 22 CONTROLS (NON-CAD)	PLASMA	miR-6090, miR-4516	RT-qPCR	miR-6090, miR-4516 CAN BE USED AS REFERENCE GENES FOR PLASMA miRNAs ANALYSIS IN STABLE CAD.

Continued

CORSTEN, <i>et al.</i> [28]	32 CASES (ACUTE MI), 36 CONTROLS (NON-CAD)	PLASMA/WHOLE BLOOD SAMPLE	miR-208b, miR-499	RT-qPCR	HIGHER IN MI PATIENTS
WANG <i>et al.</i> [29]	33 CASES (ACUTE MI), 33 CASES (NON-ACUTE MI), 30 CONTROLS (NON-CAD)	PLASMA	miR-208a, miR-499, miR-1, miR-133a	RT-qPCR	HIGHER IN ACUTE MI PATIENTS
DONG J <i>et al.</i> [30]	161 CASES (STABLE CAD PATIENTS), 149 CONTROLS (NON-CAD)	PLASMA	miR-61, miR-33a, miR-103a, miR-122	RT-qPCR	HIGHER IN CAD PATIENTS
MENNO H <i>et al.</i> [31]	25 CASES (STABLE ANGINA), 25 CASES (UNSTABLE ANGINA), 20 CONTROLS (NON-CAD)	PLASMA	miR-135a, miR-147	RT-qPCR	miR-135a HIGHER AND , miR-147 LOWER IN STABLE ANGINA AND UNSTABLE ANGINA PATIENTS

process of angiogenesis following acute MI, thus exhibiting higher or lower expression in plasma of CAD patients [25]. Minami and colleagues, evaluated serum miR-221 and miR-222 in patients with stable CAD and non-CAD patients and found that these miRNAs were significantly higher in CAD patients. Due to some limitations of the present study, including the small number of CAD patients taking each low statin therapy. In addition, this study did not perform miR 221 and miR 222 functional analysis of Endothelial progenitor cells (EPCs)[only this study investigated in vitro model]. Therefore further studies will be needed to determine a mechanism that these miRNAs expression regulated EPCs biology in CAD patients [26]. Zhang evaluated that miR 6090 and miR 4516 determined reference miRNAs for quantitative polymerase chain reaction (qPCR) analysis of plasma miRNA in stable CAD and healthy population. In this study ,there exist certain limitations, such as small sample size and miRNAs isolation method for CAD patients only, which could be expensive [27]. Corsten demonstrated that miR 208b and 499 are highly elevated in Acute MI where cardiac damage are severely occurred which initiates massive release of cardiomyocyte specific miRNAs into blood circulation so that these miRNAs into blood circulation so that these miRNAs are higher with CAD patients than in healthy populations [28]. Wang measured several serum miRNAs in patients with acute and non-acute MI, and healthy population. In this study, Wang selected 4 different miRNAs (miR-208a, miR-499, miR-1, miR-133a), among them they found that miR-208a was undetectable in blood in non-acute MI patients and healthy population but was increased in the patients with acute MI, within 4 hours after symptoms start in which only 85% of this patients had elevated se-

rum troponin, and remaining 3 miRNAs levels also higher in the patients with acute MI, compared with non-acute MI patients and healthy populations. This study suggest that miRNAs may leak into blood during the early stage of myocardial injury. Microvesicles (exosomes, ectosomes, or microparticles) are small vesicles of endocytic origin released by normal healthy or damaged cells and are reported to be present in the peripheral blood. More evidence reveals that miRNAs are present in microvesicles that remains to be seen whether cardiac-origin miRNAs released from damaged myocardium are in the form of microvesicles when they enter into circulating blood. Due to small sample study this research limitations exists [29]. Dong J study shows increased expression level of miR24, miR33a, miR103a, miR 122 in peripheral blood mononuclear cells of CAD patients with high level of lipid profile. This suggests a lipometabolism-related miRNAs in peripheral blood mononuclear cells which may emerge as an efficient biomarker for preventive, diagnostic and therapeutic approaches for CAD [30]. Menno H shows that miRNA can possibly be used to identify patients with CAD (atherosclerosis) and also for patients at a risk of acute coronary syndromes. This study can be considered as a principle study of mRNA in specific blood cell types from individual patients with CAD (including all kinds of cardiovascular diseases) [31].

All above mentioned studies were performed by Reverse transcription quantitative polymerase chain reaction (RT-qPCR) which is a widely-used method to estimate expression levels of circulating miRNAs for CVD and other complex diseases [32]. It is an important technology to study circulating miRNAs high sensitivity of RT-qPCR and demands a suitable reference gene to correct the non-biological variation.

3. Conclusion

miRNA expression profile, whether it expressed lower or higher, is associated with cardiovascular diseases, which can serve as a biomarker for diagnosis as well as assessment of prognosis of CVD, especially CAD. This review suggested miRNAs in CAD yield enormous potential to serve as clinically applicable diagnostic and prognostic biomarkers. miRNA expression contour is related with some cardiovascular diseases, signifying their character as a novel biomarkers as well as potential treatment targets for cardiovascular diseases. In additional kind of miRNA expression may help to describe their role in improving both the diagnostic and therapeutic methods to stratifying CAD burden in the general population. The use of several miRNAs as biomarkers has encouraged significant attention in scientists and it can be expected that in the future some miRNAs might become useful biomarkers for prognosis and effective treatment to CAD as well other various kind of disease. But there are some limitations to this study, regarding small sample size, time limitations, as well as expensive methods. Thus, there is a need for further study to obtain information about new multi-center human studies with larger sample size and new technique which includes

rapid and inexpensive methods for analyzing miRNAs.

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Abbreviations

CAD: Coronary artery disease,
ECG: Electrocardiogram,
MI: Myocardial infarction,
CHD: Coronary heart disease,
IHD: Ischemic heart disease,
miRNAs: MicroRNAs,
pri-miRNAs: Primary micro RNAs,
pre-miRNAs: Preliminary miRNAs,
DGCR8: DiGeorge syndrome chromosomes region 8,
RNP: Ribonucleoprotein,
miRISC: miRNAs induced silencing complexes,
AGO: Argonaute protein family,
siRNAs: Small interfering RNA,
CVD: Cardiovascular disease,
EC: Endothelial cells,
RT-qPCR: Reverse transcription quantitative polymerase chain reaction.