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Minireview

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Circulating microRNAs in cardiovascular diseases: recent progress and challenges

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Abstract

MicroRNAs (miRNAs) are a relatively novel class of non-protein coding small RNA molecules (20–24 nucleotides) which have been shown as promising biomarkers for several diseases, including cardiovascular diseases. Circulating miRNAs can be detected in plasma or serum and are very stable to degradation. This protection is due to their association with RNA-binding proteins and lipoprotein complexes or enclosure into different types of extracellular vesicles. This minireview assesses the current knowledge of circulating miRNAs in cardiovascular diseases.

Keywords: microRNA, essential hypertension, coronary artery disease, myocardial infarction, heart failure

Introduction

Cardiovascular diseases (CVDs) is an umbrella type term under which a group of disorders of the heart and blood vessels are united: coronary heart disease, cerebrovascular disease, raised blood pressure (hypertension), peripheral arterial disease, rheumatic heart disease, congenital heart disease, heart failure, deep vein thrombosis and pulmonary embolism.

Nowadays, great promises in CVDs diagnosis and therapeutics comes from microRNAs (miRNAs). miRNAs signify small RNA molecules involved in post-transcriptional regulation of gene expression and were first identified in 1993 by two different groups (Lee et al. and Wightman et al.) in the nematode *C. elegans* [1, 2]. In 2014, Friedländer et al. reported more than 1000 validated human miRNA, stating that "the complement of human miRNA genes is substantially larger than anticipated"[3]. MicroRNAs proved to be involved in a large variety of biological processes and moreover, circulating miRNAs have been shown to be cargos for extracellular vesicles [4]. Circulating miRNAs are protected from degradation due to the membrane of at least three types of extracellular vesicles (classified according to and mode of release): exosomes, microvesicles, or apoptotic bodies [5]. In addition, it was shown that HDL can also transport endogenous miRNAs in the form of stable complexes having much lower dimensions comparative with extracellular vesicles [6]. miRNAs presence in serum or plasma is considered as the future hope for a non-invasive diagnostic screening for multiple diseases including CVCs. This mini-review aims to syn-

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thesize the most recent advances regarding circulating miRNAs as putative biomarkers in CVCs.

Coronary artery disease

Coronary heart disease (CAD) is the most common cause of death in Europe and US. Recently, Sayed et al. evaluated and suggest the potential roles of circulating miR-149, miR-424 and miR-765 as non-invasive biomarkers for the diagnosis of coronary artery disease in middle-aged patients [7]. In geriatric patients, Ali Sheikh et al. reported that plasma levels of miR-765 and miR-149 might be used as noninvasive biomarkers for the diagnosis of coronary artery disease [8].

Eight miRNAs (miR-223, miR-3135b, miR-133a-3p, miR-2861, miR-134, miR-191-3p, miR-3679-5p, miR-1229) were found to be significantly increased in plasma of patients suffering from coronary artery calcification. Four of these miRNAs (miR-2861, 134, 1229 and 3135b) were correlated with the degree of coronary artery calcification [9]. Moreover, it was suggested that miR-100 may be released into the coronary circulation and, therefore, may be useful as a biomarker proving the relationship between plasma miRNAs and vulnerable coronary plaque [10].

Interestingly, the possible contribution of miRNAs serum levels in risk stratification of future cardiovascular events was recently evaluated and miRNA-197 and miRNA-223 were identified as predictors of cardiovascular death in patients with coronary artery disease [11].

Ren et al. evaluated the circulating miRNA signature, consisting of the plasma miR-106b/25 cluster, miR-17/92a cluster, miR-21/590-5p family, miR-126* and miR-451 suggesting that they may become a valuable biomarker for vulnerable coronary artery disease [12]. In addition, to discriminate between stable and vulnerable coronary artery disease patients Niculescu et al. demonstrated the utility of miR-486, miR-92a which were highly expressed in vulnerable patients sera [13]. Also, the cardiovascular events in patients with stable coronary artery disease might be predicted through the evaluation of circulating microvesicles containing miR-126 and miR-199a [14]. Fukushima et al. have also identified a specific miRNA signature in plasma of patients with heart failure. Plasma concentrations of miR-126 were up-regulated with the improvement of the NYHA class from IV to III and were negatively correlated with age [15]. Ellis at al. also studied the diagnostic utility of microRNAs in differentiating between patients with heart failure and other dyspnea patients and found that miR-103, miR-142-3p, miR-30b, and miR-342-3p, were differentially expressed between HF and control, COPD, and other breathless patients.

Myocardial infarction

Acute myocardial infarction (MI) remains a principal cause of morbidity and mortality worldwide and therefore, rapid and correct diagnosis plays a critical role in its treatment and prognosis. Detection of miRNAs in serum or plasma of patients who suffered MI hold great promise if it will be proven to reflect cardiac injury.

Several plasma and serum miRNA signatures were found in recent years as being of interest for early detection of MI. Thus, in the following, some of them will be brought to light. Several studies found elevated levels of miR-1, miR-499, miR-208a, miR-423 in the plasma and serum of MI patients [16-19]. Apparently, circulating miR-499 will be used as a clinical marker for acute MI as it is considered by Zhang et al. having a great value in the diagnosis and prognostic prediction of acute MI [20]. Moreover, Liu et al. confirmed the predictive values of plasma miR-1, miR-208 and miR-499 in acute MI in a recent study [21]. Also, plasma levels of other heart-associated miRNAs were assessed and their results indicated that miR-133a, miR-208b might evoke tantalizing questions, especially miR-133a which is also elevated in heart failure [22, 23]. In addition, Long et al. showed that increased miR-1 and decreased miR-126 were found in the plasma from patients with acute MI after the onset of symptoms [18].

In the aforementioned studies, the circulating miRNAs were originating in the injured heart muscle. In search of miRNAs specific for MI and which are not related to the injury of the myocardium, other 121 significantly deregulated miRNAs were identified in a detailed analysis and miR-1291 and miR-663b were shown to have the highest sensitivity and specificity [24].

Heart failure

Over 23 million adults worldwide have been diagnosed with heart failure with a mortality rate of ~50% within 5 years of diagnosis [25]. Li and colleagues identified cardiac fibroblast-derived circulating miRNAs: miR-660-3p, miR-665 and miR-1285-3p which were found to be upregulated in chronic heart failure and correlated to its severity [26]. Cardiac fibrosis is regarded as an important hallmark of heart failure. miR-

503 has been found to be up-regulated in mouse hearts and responsible to promotes cardiac fibrosis. Therefore, it was proposed as a promising therapeutic target for reducing cardiac fibrosis in an animal model by Zhou et al. [27]. Another study identified and validated seven miRNAs in the plasma of patients with heart failure (miR-423-5p, miR-18b*, miR-129-5p, miR-1254, miR-675, HS_202.1, and miR-622), among which mature miR-423-5p was most strongly related to the clinical diagnosis of heart failure [28].

Essential hypertension

Hypertension represents one of the leading risk factors for global mortality mainly to the severe complications such as coronary heart disease and ischemic or hemorrhagic stroke. Globally, its overall prevalence was around 22% in 2014 according to WHO. Currently, several circulating miRNAs were found to be associated with hypertension. Yang et al. investigated the circulating level of hsa-miR-505 and found significantly elevated levels in the male hypertensive patient. He concluded that hsa-miR-505 may be involved in the pathogenesis of hypertension [29]. miR-130a and miR-195 were also shown to be involved as contributors of hypertension in patients with metabolic syndrome [30]. Cengiz et al. studied for the first time the plasma miRNA profile for hypertensive patients, by comparison to white coat hypertension patients [31]. miR-21, miR-122, miR-637, and let-7e expression levels were significantly upregulated in the plasma samples of hypertensive patients group while miR-122 and miR-637 expressions were significantly upregulated in the white coat hypertension group [31].

Although the information regarding the miRNAs involvement in hypertension is scarce at the moment, encouraging evidence will accumulate over the years. This is the beginning of the assessment of circulating miRNA as biomarkers for hypertension.

Conclusion

Recently, miRNAs have been suggested as novel biomarkers for diagnosis and potential therapeutic targets for treatment. A number of miRNA-targeted therapies are currently in clinical trials (e.g. for cancer and hepatitis C); however, the circulating miRNAs in CVDs are yet to be studied in greater depth and represent a great expectation for future therapies in cardiology.

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