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EDITORIAL

MicroRNAs as mediators of cardiovascular disease: Targets to be manipulated

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Abstract

Cardiovascular disease has been the leading cause of death worldwide for the last few decades. Even with the rapid progression of the biomedical field, conquering/managing cardiovascular disease is not an easy task because it is multifactorial disease. One of the key players of the development and progression of numerous diseases is microRNA (miRNA). These small, non-coding RNAs bind to target mRNAs to inhibit translations of and/or degrade the target mRNAs, thus acting as negative regulators of gene expressions. Accumulating evidence indicates that non-physiological expressions of miRNAs contribute to both development and progression of cardiovascular diseases. Since even a single miRNA can have multiple targets, dysregulation of miRNAs can lead to catastrophic changes of proteins that may be important for maintaining physiologic conditions of cells, tissues, and organs. Current knowledge on the role of miRNAs in cardiovascular disease is mostly based on the observational data such as microarray of miRNAs in animal disease models, thus relatively lacking insight of how such dysregulation of miRNAs is initiated and regulated. Consequently, future research should aim to elucidate the more comprehensive mechanisms of miRNA dysregulation during pathogenesis of the cardiovascular system so that appropriate counter-measures to prevent/manage cardiovascular disease can be developed.

Key words: Cardiovascular diseases; MicroRNA; Heart; Endothelial cells; Smooth muscle cells

Core tip: Accumulating evidence indicates that microRNAs (miRNAs) play important roles in the development and progression of cardiovascular diseases. To date, observational studies such as miRNA-profiling in diseased animals and/or patients have provided valuable information regarding their roles in cardiovascular diseases. For example, dysregulated miRNAs under pathologic conditions have been identified, and their possible targets, whose down-regulation may have contributed to the development of corresponding disease, have been examined. Nevertheless, future studies should

be more focused on identifying key mechanisms of miRNA dysregulation during pathogenesis of the cardiovascular system so that optimized counter-measures to prevent/manage cardiovascular disease can be designed and developed.

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INTRODUCTION

Despite enhanced understanding of the pathogenesis of cardiovascular system, it still is challenging to manage/treat cardiovascular disease, making the cardiovascular disease leading cause of death worldwide. Cardiovascular disease is a multifactorial disease having number of risk factors such as obesity, hypertension, dyslipidemia, and diabetes. Development and progression of cardiovascular disease has been associated with non-coding RNA-mediated change of gene expressions that are critical for the maintenance of cardiovascular system[1]. Over the last few decades, small, non-coding microRNAs (miRNAs) have emerged as critical players in controlling physiological and pathological processes, and accumulating evidence indicates that the development and progression of cardiovascular disease are also regulated by miRNAs[2-4]. Since the field of miRNA-dependent physiologic/pathologic regulation of cardiac cells, or the heart, evolves rapidly, it is always high time to overview the field and to re-adjust the strategies for the future studies.

CARDIOVASCULAR DISEASE AND MICRORNA

MicroRNAs are single-stranded RNAs that bind to the complementary sequences present on the 3'UTR (untranslated region) of target mRNAs, subsequently suppressing target protein expressions[5]. Since an individual miRNA targets multiple mRNAs, the manipulation of miRNAs can have a significant impact on intracellular networks. Such concept of miRNA-dependent regulation of cellular signaling has been empirically proved in various diseases including cardiovascular disease[4,6,7]. For example, pertaining to the role of miRNAs in coronary artery disease, miR-21 has been reported to be up-regulated in atherosclerotic plaques, and knockdown of miR-21 using anti-sense oligonucleotide reduced neointima formation in balloon injured animals[8]. For the case of remodeling process after myocardial infarction, miR-29 family has been reported to be down-regulated in the region of fibrous tissue formation and extracellular matrix deposition, increasing expressions of its target genes such as fibrillin and various isotypes of collagens[9]. As to the vascular inflammation and miRNA, endothelial cell enriched miR-126 inhibited vascular adhesion molecule 1 (VCAM-1) expression and decreased leucocyte binding to activated endothelial cells[10]. Furthermore, miR-195 significantly down-regulated production of inflammatory cytokines such as interleukin 1 beta (IL-1β), IL-6, and IL-8 in vascular smooth muscle cells[11]. In some cases, miRNAs have impact on more than one aspects of cardiovascular system to develop pathologic conditions. For example, patients with hypertension are at an increased risk of cardiovascular disease[12], and the etiology of hypertension encompasses abnormally increased vascular tone, endothelial dysfunction, and cardiac hypertrophy, and miRNA-dependent regulation has been implicated in all of these conditions[13]. These examples clearly demonstrate that miRNAs play important roles in modulating pathophysiologic function of cardiovascular system.

TYPICAL PATTERN OF STUDY ON CARDIOVASCULAR DISEASE AND MICRORNA

As described above, numerous studies have elucidated the role of miRNAs in cardiovascular disease and provided valuable information for further research. For most of studies focusing on the role of miRNAs in disease, (1) identification of miRNA in a specific disease, (2) target identification of the miRNA, and (3) functional validation of the targets using gain and/or loss of function approaches are the reoccurring theme of the studies. As an example, a previous study examined the role of miRNA in cardiac hypertrophy[14]. In that particular study, (1) pro-hypertrophic miRNAs (miR-212/132) were identified; (2) their functional role was evaluated by either overexpressing or knockout them; and (3) FoxO3 was identified as their target. However, there are relatively few studies provided information on (1) what kind of stimulus induce or repress expression of a specific miRNA; and (2) how that stimulus operates remains insufficient regarding the role of miRNAs in cardiovascular disease. It is important that future studies also focus on this type of information to establish an effective miRNA-based therapeutic strategy.

INVESTIGATING REGULATION OF SPECIFIC MIRNAS UNDER PARTICULAR PATHOLOGIC CONDITIONS

Although there are studies focused on bona fide transcriptional regulation of miRNAs[15,16], what may be also useful to develop therapies and/or therapeutic strategies for cardiovascular disease is to elucidate

how specific miRNAs are regulated under a particular pathologic condition. For example, miR-1, one of the most enriched miRNAs in heart, has been associated with different types of heart diseases. The expression of miR-1 has been reported to be decreased in cardiac hypertrophy and atrial fibrillation[17,18], while increased expression of miR-1 was observed in heart failure[19]. Although these findings clearly state that miR-1 play crucial roles in modulating multiple cardiovascular diseases, they do not provide information on how such bi-directional regulation of miR-1 expression is achieved. The importance of elucidating the mechanisms of particular miRNAs under specific circumstance comes from the uncertainty, at least for now, of using miRNAs as therapeutic tools. One of the most recent clinical trials utilizing miRNA-based therapeutic approach is the use of miravirsen, a locked nucleic acid-modified DNA phosphorothioate antisense oligonucleotide designed to neutralizing miR-122, for the treatment of hepatitis C virus (HCV)[20]. Although miravirsen reduced the level of HCV RNA in a dose-dependent fashion without viral resistance, there remain some issues related to the role of miR-122 in other physiologic and/or pathologic conditions. For example, low expression level of miR-122 in hepatocellular carcinomas (HCCs) has been associated with a poor prognosis[21], and deletion of miR-122 in mouse resulted in hepatosteatosis, hepatitis, and HCC-like tumor development[22]. These studies indicate that the potential benefits and drawbacks of using miravirsen must be carefully weighed during further clinical development. Furthermore, optimized means of effective miRNA delivery to target tissues or organs are yet to be developed. Although a number of different approaches to facilitate effective miRNA delivery, such as nanotechnology-based[23], lipid-based[24], and virus-based miRNA delivery systems[25], have been designed, there still remains issue of toxicity which often led to ultimate death of animals and target specific delivery[26,27]. Thus, as contingency strategy, it may be necessary to start to find means of regulating specific miRNAs *in situ* other than delivering exogenous miRNAs to effectively utilize miRNAs as potent therapeutic target for treating diseases.

ALTERNATIVE APPROACHES TO MODULATE EXPRESSIONS OF MIRNAS

One of the alternative approaches to modulate *in vivo* miRNA expression is using small molecules to regulate expressions of miRNAs[28]. The very first evidence was demonstrated by the study of Gumireddy *et al*[29]. In that particular study, the authors identified 2 small molecules as selective and effective inhibitors of miR-21 expression[29]. Few years later, small molecule-induced up-regulation of miRNA, miR-122, was also demonstrated[30]. Recently, a compound called Rubone has been reported to induce miR-34a expression, suppressing growth of HCC[31]. Another strategy for inhibiting the production of mature miRNAs involves inhibition of Dicer, miRNA processing nucleases. It has been reported that streptomycin prevented the processing of pre-miR-21 by binding to the Dicer processing site[32]. Additionally, the processing of pre-miR-372 and 373 by Dicer was also significantly inhibited by small molecule inhibitors[33]. The structural characteristics of miRNA, such as stem loops in pre-miRNAs and the bulges in miRNAs, are suspected to enable them to be targeted by small molecules[34,35]. In conjunction with such effort to find small molecules that modulate miRNA expressions, computer-aided approaches are getting attentions in RNA-targeting lead compound (small molecule) identification[36,37]. These *in silico* approaches are expected to improve the pipelines in a cost-effective way compared to the traditional approaches that are usually expensive and time-consuming.

CONCLUSION

Diverse roles of miRNAs in physiologic and/or path-ophysiologic conditions make them a very attractive modality to manage/treat multifactorial diseases such as cardiovascular disease. Nevertheless, using miRNAs as a therapeutic drug faces a major obstacle of developing efficient delivery methods. Consequently, finding means of regulating specific miRNAs is important to effectively utilize miRNAs as potent therapeutic target for treating diseases. Elucidating detailed mechanisms by which miRNAs are regulated under physiologic and/or pathologic conditions is imperative to design novel and potent miRNA-based therapeutic strategy. Especially for the case of using small molecules to modulate miRNA expressions, more structural and thermodynamic information on the interaction of those two molecules are required. Given the importance of miRNAs in pathogenesis of cardiovascular diseases and the promise they hold as viable therapeutic modality, miRNA-based therapeutics are expected to revolutionize the way of treating cardiovascular diseases in near future.

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