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What are microRNAs?

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Abstract

MicroRNAs (miRNAs) are short regulatory noncoding endogenous RNA species that are involved in virtually all cellular processes. Intriguingly, they are highly conserved among species and very rarely harbor genetic variants, underlining their important role during the evolution of species. miRNAs fine-tune and regulate proteins involved in all main processes, including cell signaling pathways, as well as cellular functions and developmental steps. miRNAs are expressed in all organs and cells, and multiple functional aspects of miRNAs underscore their key role in physiology and pathophysiology. The development of novel molecular biology tools contributed to the recent successes in miRNA research. Moreover, miRNAs emerge as interesting biomarker candidates in cardiovascular disease, but also as therapeutic targets. Finally, so-called long noncoding RNAs regulate gene and protein expression and are also briefly discussed in this short review article. ■ *Heart Metab*. 2014;65:34-36

Keywords: cardiac remodeling; cardiovascular disease; heart failure; microRNA

Biogenesis and importance of microRNAs

MicroRNAs (miRNAs) are endogenous, small (≈22 nucleotides) noncoding RNAs that are highly conserved among species and regulate expression of target mRNAs[1] by binding to their 3' untranslated region (UTR), followed by translational repression.[2] In rare cases, miRNAs can also target 5'UTR or coding regions. miRNAs are indeed ubiquitously expressed, but may differ in expression patterns.[3] In the cardiovascular system, miRNAs have an enormous gene regulatory potential, and play key roles in the physiology and pathophysiology of the entire cardiovascular system.[4,5]

miRNAs originate from transcripts that are either coexpressed with the host gene transcript or located in intergenic regions of the genome.[1,5] Initially, the early transcript, called "primary (pri)-miRNA," is processed within the cellular nucleus by the ribonuclease III enzyme Drosha and the double-stranded RNA-binding protein DGCR8 into a so-called precursor (pre)-miRNA (a short hairpin RNA molecule) and thereafter exported to the cytosol by exportin-5.[1,6,7] Within the cytosol, there is a digestion of pre-miRNA into small mature RNA molecules by the endonuclease Dicer, followed by binding to the RNA-induced silencing complex (RISC) complex. During cardiovascular development and in disease, there are significant changes of miRNA expression profiles leading to derailed orchestration of cardiovascular genes.[5]

MicroRNAs as therapeutic targets in cardiovascular disease

Cardiac miRNA is necessary for a balancing and buffer system to regulate protein expression, in order to maintain homeostasis in the heart. A disturbed balance of miRNA expression occurs in almost all cardiovascular pathologies.[5,8-13] Major cardiovascular disorders with deregulated miRNA expression include

Abbreviations

AMI: acute myocardial infarction; **CAD:** coronary artery disease; **miRNA:** microRNA

cardiac fibrosis,[8] cardiac hypertrophy,[14] arrhythmias, heart failure[5], myocardial ischemia,[5] or myocarditis.[5] Details of the current knowledge in miRNA regulation in cardiovascular disease has recently been reviewed.[5,15-17] There are now numerous studies in animal models that have employed synthetically modified oligonucleotides directed against endogenous miRNAs, of which several are highlighted as follows.

Carè et al found a cholesterol-based antagomir targeting miR-133 that resulted in cardiac hypertrophy.[18] da Costa Martins et al showed involvement of miRNAs in cardiac hypertrophy, eg, miR-199b is a direct calcineurin/nuclear factor of activated T cells (NFAT) target that increases in expression during mouse and human heart failure, thus being a potentially interesting target for therapies.[19] Our group showed that blockade of miR-21 inhibits the development of cardiac fibrosis.[8] Indeed, cardiac fibroblasts are enriched with certain miRNAs, such as miR-21. In addition, other cell types, such as endothelial cells, express miR-21; miR-21 antagonism blocks endothelial–mesenchymal transition in transforming growth factor β–treated endothelial cells, resulting in reduced fibrosis development. Bonauer et al inhibited miR-92a to induce neovascularization after hindlimb ischemia and myocardial infarction,[9] whereas comparable results by the blockade of another endothelial-enriched miRNA mir-24 were shown by Fiedler et al.[10]

MicroRNAs as biomarkers in cardiovascular disease

Surprisingly, it is possible to detect circulating miRNAs in serum/plasma, suggesting that they may serve as potential biomarkers for diseases and/or may have paracrine effector capacity. Circulating miRNAs are protected from RNase-dependent degradation by several mechanisms, including their inclusion in microvesicles, exosomes, and apoptotic bodies, and by formation of protein-miRNA complexes resistant to degradation. There is now ample evidence for the diagnostic use of circulating miRNAs as biomarkers, but here only a few studies can be highlighted. For instance, in patients with diabetes or coronary artery disease (CAD), reduced levels of miR-126 are observed, whereas cardiac muscle-enriched miRNAs (miR-133a, miR-208a) tended to be higher in patients with CAD.[20] In patients with acute myocardial infarction (AMI), the muscle-enriched miRNA miR-1 was significantly upregulated in the circulation compared with non-AMI controls. Our group has also shown increased plasma miRNA post-AMI as well as some prognostic value of selected circulating miRNAs in terms of predicting future death (Widera et al[21]). During viral myocarditis, mild elevation of miR-208b and miR-499 was found.[22] A recent study found circulating long noncoding RNAs to be of diagnostic and predictive value in post-MI and heart failure patients.[23]

Outlook and conclusions

There are three major important points on the usefulness of miRNAs that I wish to explicitly highlight:

1. miRNA research has identified a *new layer of mechanistic complexity* in genome research, and has opened a new angle on how to identify new and potentially important mechanisms of cellular functions. Multiple novel pathways involving not only miRNAs, but also regulatory upstream mechanisms as well as downstream target networks, have only been identified because of miRNA research activities.
2. miRNAs emerged as *drug-able targets,* which, within a couple of years, made their way into clinical phase 1 and 2 trials, and have an enormous future therapeutic potential. Research has started using small and large animal models of diseases and, indeed, recently, the first miRNA therapeutic study in patients with hepatitis C has been published with many other ongoing clinical miRNA studies (www.clinicaltrials.org).
3. miRNAs have been shown to be stable in plasma and other body fluids and have been shown to be potentially *interesting biomarkers* of diseases, especially for diagnostic and prognostic evaluations. A potential future strength is the combination of miRNA panels as powerful predictors of outcome and/or therapy effectiveness in multiple diseases.

miRNA research is still relatively young, but has opened new avenues in the mechanistic understanding of physiology and pathophysiology, in drug

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therapy, and in diagnostic/prognostic patient evaluation. Following the improved development of miRNA-based diagnostic and therapeutic interventions, other RNA species such as long noncoding RNAs have emerged as interesting, either as targets and/or biomarkers. ■

The author has filed and licensed microRNA-related patents.

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