This Review is in a thematic series on MicroRNA in the Cardiovascular System, which includes the following articles:

- Introduction to the Series on MicroRNAs in the Cardiovascular System
- Circulating MicroRNAs: Novel Biomarkers and Extracellular Communicators in Cardiovascular Disease?
- Developing Microrna Therapeutics
- MicroRNAs in Vascular and Metabolic Disease
- Differential Expression of MicroRNAs in Different Disease States
- MicroRNAs in Cardiovascular Development
- Methods for MicroRNA Target Determination & Target Regulation

Eva van Rooij, Guest Editor

**Introduction to the Series on MicroRNAs in the Cardiovascular System**

Eva van Rooij

**Abstract:** Until recently, microRNAs (miRNAs) were considered to be relatively small players in biological systems by having a balancing function through moderate effects on gene expression levels. However, it has become appreciated that miRNAs are actually much more relevant during both development and disease, which is underscored by the attention they have been receiving. The goal of this thematic review series is to highlight current knowledge of miRNA function during cardiovascular development, their dysregulation under disease conditions and the disease modifying functions they have been shown to exert in the cardiovascular system. These reviews, in addition to discussing the recent advancements in using miRNAs as circulating biomarkers or therapeutic modalities, will hopefully be able to provide a strong basis for future research to further expand our insights into miRNA function in cardiovascular biology. (Circ Res. 2012;110:481-482.)

**Key Words:** microRNA ■ molecular biology cardiovascular research ■ signal transduction

The initial concept of microRNAs (miRNAs) regulating gene expression in part through Watson-Crick base pairing was developed almost 20 years ago in the labs of Ambros and Ruvkun. While the Ambros laboratory discovered that the lin-4 gene does not encode a protein product, but instead gives rise to a 61-nucleotide precursor gene that matured to a more abundant 22 nucleotide transcript,1 the Ruvkun laboratory found that LIN-14 protein synthesis is regulated post-transcriptionally, and that LIN-14 levels are inversely proportional to those of lin-4 RNA. Sequence analysis indicated complementarity between the lin-4 RNA and the 3’ untranslated region of the lin-14 gene, revealing the first miRNA and mRNA target interaction.2 It took another 7 years before the second miRNA, let-7, was discovered,3 of which homologs were quickly identified in many vertebrate species including humans.4 Several follow-up studies have now demonstrated there to be roughly 1000 human miRNAs, which are evolutionarily conserved across species and are often ubiquitously expressed.5–7

The first genetic evidence for functional relevance of miRNAs in mammals came from a study showing that homozygous deletion of Dicer, a key miRNA processing gene, disrupted prenatal development of the murine embryo through its role in miRNA biogenesis.8 The conditional Dicer allele, in addition to genetic gain-and-loss of function studies for individual miRNAs, have now shown the importance of...
individual miRNAs in the development of the cardiovascular system. Both genetic and oligonucleotide-based studies, as well as profiling studies showing the dysregulation of miRNA levels during disease, have indicated that these overall moderate gene regulators appear to have dominant functions under stress conditions leading to a diversity of cardiovascular indications. The current status of studies on miRNA function in cardiac development and disease will be summarized in this series.

In the last few years several groundbreaking studies have indicated that in addition to being relevant in cardiac remodelling and function, miRNAs exert dominant functions in vascular and metabolic disease as well. In 2009 Stefanie Dimmer’s group showed that therapeutic inhibition of miR-92a in vivo enhances blood vessel growth as well as functional improvement of damaged tissue in models of hind limb ischemia and myocardial infarction. Although by now many additional miRNAs have been implicated in different aspects of vascular disease, a particular miRNA family that has recently gained a lot of attention is the miR-33 family. In vivo efficacy studies in rodents and nonhuman primates indicate that raising HDL levels by anti-miR mediated inhibition of miR-33 through its effects on cholesterol transport and atherosclerosis regression may be a promising therapeutic approach to treat vascular disease. Present understanding of miRNA function in vascular disease will be reviewed.

Another discovery in miRNA biology that is developing with remarkable pace is the revelation that miRNAs are detectable and highly stable in plasma or serum. Circulating miRNAs appear to correlate with disease, opening up the possibility to use them as novel diagnostic biomarkers. For cardiovascular disease, circulating miRNAs so far have been shown to be potential biomarkers for acute myocardial infarction, heart failure, coronary artery disease, stroke, and type II diabetes. Although it remains to be evaluated how circulating miRNAs compare to current biomarkers for cardiovascular indications, the first hints toward functionality of these circulating miRNAs are starting to appear. Although our understanding of the underlying biology is still in its infancy, it is intriguing to consider that tissues can secrete miRNAs to exert an effect in other tissue or cell types.

Potentially one of the main reasons why miRNAs have received so much attention is the wealth of recent animal and even human efficacy data indicating the therapeutic efficacy of miRNA modulation. Based on lessons learned from antisense technologies, the opportunity to potently regulate miRNAs in vivo opened up the potential for miRNAs to become a new class of drugs. The advantages of therapeutically targeting miRNAs are that they are small and comprise a known sequence that is often completely conserved among species, which are attractive features from a drug development standpoint. However, compared to classical drug approaches, the development path for such oligonucleotide chemistries into a therapeutically useful modality requires some adaptation. As part of this series we will try to provide some general insight into developing miRNAs as a therapeutically useful modality and will summarize the current patent landscape and the companies that have started to explore microRNAs as the next class of drugs.

It is in light of all these recent findings and reports that I am excited to introduce this review series on miRNAs in the cardiovascular system. The overall goal is to highlight what is currently known, provide food for thought on current drawbacks and issues in this relatively new field of research and provide some insight as to where we currently stand in advancing miRNA related diagnostic and therapeutic strategies. I hope you find these articles to be both informative and thought provoking.

Disclosures

Eva van Rooij is an employee of miRagen Therapeutics.

References

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