ATVB in Focus
MicroRNAs: From Basic Mechanisms to Clinical Application in Cardiovascular Medicine

Series Editor: Christian Weber

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MicroRNAs

From Basic Mechanisms to Clinical Application in Cardiovascular Medicine

Christian Weber

MicroRNAs (miRs) are small noncoding RNAs (≈23 nucleotides) that regulate gene expression at a post-transcriptional level by degradation or translational inhibition of target mRNAs. Initially discovered as regulators of development in plants, worms, and fruitflies, miRs are emerging as pivotal modulators of cardiovascular biology and disease in mice and men.[1] Besides a cell-specific transcription factor profile, cell-specific miR-regulated gene expression is integral to cell fate and activation decisions. Thus, the cell types involved in atherosclerosis, vascular disease, and its myocardial sequelae may be differentially regulated by distinct miRs, thereby controlling highly complex processes, for example, smooth muscle cell phenotype and inflammatory responses of endothelial cells or macrophages.[2]

The generation of mature miR strands requires several steps of processing of the primary miR gene transcript, including cleavage of the terminal loop of miR-precursors by the RNase III enzyme, Dicer, to produce miR duplexes. Although either strand of the miR duplex can be stably associated with an Argonaute (Ago) family protein, preferential loading of a specific strand (ie, the guide strand) onto the miR-induced silencing complex (RISC) is common. The strand that is not loaded into the RISC (ie, the passenger strand or miR*) is typically degraded.[3] Strand selection may be tissue-specific, and an accumulation observed for both strands implies that each strand can separately enter the silencing complex.[4] Because of the often imperfect complementary binding of the miR seed sequence to the mRNA recognition element, an individual miR can affect the expression of hundreds of target mRNAs. However, the degree of repression seems to be rather modest for most targets, with only a minority of targets being repressed by >50%. This gives rise to an enormous complexity of miR expression and function in the cardiovascular system. This review series attempts to provide comprehensive overviews summarizing the most important features and recent developments in an evolving and maturing field.

A review by Abraham et al dedicated to inflammation highlights the roles of miRs in innate and adaptive immune responses characterized, for example, after microbial challenge, and the deregulation of miRs during diseases associated with excessive or uncontrolled inflammation. The discussion of the functions of miRs in macrophage polarization is not only of relevance to inflammation in general but also to atherosclerosis, which is considered as a lipid-induced inflammation of the vessel wall orchestrated by a complex interplay of various cell types, namely endothelial cells, smooth muscle cells, and macrophages. A review by Schober et al[5] consequently surveys the differential roles of distinct miRs during the pathogenesis of atherosclerosis, which encompass downregulation of miR-145 controlling smooth muscle cell differentiation, delivery of miR-126 in endothelial cell-derived microparticles to signal the need for endothelial repair,[6] or an upregulation of miR-155 relevant in proinflammatory macrophage polarization. The identification of this miR triad sheds light on the current concepts of atherogenesis and establishes novel treatment options. An important contribution of miRs to the regulation or alteration of lipid metabolism and glucose homeostasis may determine the predisposition to cardiometabolic disease and

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(*Arterioscler Thromb Vasc Biol*. 2013;33:168-169.)

***Arterioscler Thromb Vasc Biol* is available at http://atvb.ahajournals.org**
DOI: 10.1161/ATVBAHA.112.300920

atherosclerosis. For instance, miR-33 controls cellular cholesterol export and fatty acid degradation, which are stimulated by its host genes, whereas miR-122 can limit cholesterol synthesis and lipoprotein secretion in the liver. Underlying mechanisms are detailed by Fernandez–Hernando et al,[7] in a review, which also discusses the modulation of miRs as a strategy to treat metabolic diseases.

Membrane-derived vesicles and lipoproteins can serve to carry and transport miRs between cells with distinct signatures altered by cardiovascular pathologies. A review by Boon and Vickers[8] is focused on the complexities and multitude of open questions remaining about the roles of miRs intercellular communication and their applicability to cardiovascular disease. A review by Fish et al[9] highlights how miRs regulate multiple aspects and functions of the vascular endothelial growth factor signaling pathway in vasculogenesis and angiogenesis, in particular providing insights into the role of miRs and downstream effectors in modulating vascular endothelial growth factor output during development. This knowledge may be relevant to therapeutic targeting of pathological blood vessel growth and identifying clinical applications for miR manipulation. Myocardial infarction as a common and severe manifestation of advanced atheroscleoris is characterized by altered gene expression and dysregulation of underlying signaling pathways, which may involve an induction or repression of miRs affecting cell-specific downstream effects on cardiac function. A review by Fiedler and Thum[10] summarizes the current knowledge about the mechanistic importance of several miRs and novel miR-based therapeutic approaches to counteract maladaptive remodeling after myocardial infarction. Postgenomic technologies enable an interrogation of complex pathophysiological perturbations of gene regulatory networks by introducing a systems context to biomarker discovery. As cardiovascular diseases develop over decades, a multi-biomarker panel including miRs may be required to detect and monitor different stages of disease, example, vulnerable atherosclerotic plaques. A review by Mayr et al[11] discusses strategies for biomarker discovery using postgenomic technologies with a particular focus on circulating miRs. This may eventually serve and reveal distinctive cardiovascular phenotypes and identify biomarker signatures that complement the traditional scores in clinical risk prediction.

A key regulatory event in miR pathways is Ago loading, when Ago proteins undergo conformational opening to bind double-stranded small RNA duplexes forming a pre-RISC, and subsequently mediate unwinding to finally leave a single strand stably incorporated in a mature RISC. The N domain of Ago2 has been required for active wedging and unwinding of the duplex during RISC assembly but not for precedent duplex loading or subsequent target cleavage.[12] Moreover, the evolutionarily conserved PAZ domain is dispensable for Ago loading of slicing-competent RISC but in the absence of slicer activity or slicer-substrate, duplex miRs is required for ejecting the passenger strand and forming functional RISC complexes.[13] Although it was thought that, depending on the thermodynamic stability of the strands in a precursor miR, cells preferentially select the less stable one (guide strand) and degrade the other (passenger strand), expression profiling analyses indicate that both strands can accumulate as miR pairs in some tissues but are subject to strand selection in others.[4] Furthermore, target prediction and validation assays demonstrated that both strands of a miR pair can target equal numbers of genes to suppress their expression. Because the number of context- and tissue-specific targets may therefore vary, likely being higher and more versatile than expected, it will be important to determine the mechanisms involved in tissue-dependent miR biogenesis, expression, and degradation, as well as those contributing to context-dependent strand and target selection. It may be envisioned that a specific regulation of the N and PAZ domains of Ago within the RISC may give rise to such selectivity, depending on the duplex pair and the target cell. Given the abundant involvement of miRs in posttranscriptional regulation that has been revealed in various models, the elucidation of the tissue-specific strand selectivity seems to be of particular relevance for future studies in the cardiovascular system, both to unravel the basic mechanisms and to improve the options for therapeutic applicability in clinical cardiovascular medicine.

References

1. Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. *Nature*. 2011;469:336–342.
2. Nazari-Jahantigh M, Wei Y, Schober A. The role of microRNAs in arterial remodelling. *Thromb Haemost*. 2012;107:611–618.
3. Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet*. 2010;11:597–610.
4. Ro S, Park C, Young D, Sanders KM, Yan W. Tissue-dependent paired expression of miRNAs. *Nucleic Acids Res*. 2007;35:5944–5953.
5. Schober A, Wei Y, Nazari-Yahantigh M, Neth P, Weber C. MicroRNA-126, miR-145, and miR-155: a therapeutic triad in atherosclerosis? *Arterioscler. Thromb. Vasc. Biol*. 2013; in press.
6. Zernecke A, Bidzhekov K, Noels H, Shagdarsuren E, Gan L, Denecke B, Hristov M, Köppel T, Jahantigh MN, Lutgens E, Wang S, Olson EN, Schober A, Weber C. Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection. *Sci Signal*. 2009;2:ra81.
7. Fernandez-Hernando C, Ramirez CM, Goedeke L, Suarez Y. MicroRNAs in metabolic disease. *Arterioscler Thromb Vasc Biol*. 2013;33:178–185.
8. Boon RA, Vickers KC. Intercellular transport of microRNAs. *Arterioscler Thromb Vasc Biol*. 2013;33:186–192.
9. Dang LTH, Lawson ND, Fish JE. MicroRNA control of vascular endothelial growth factor signaling output during vascular development. *Arterioscler Thromb Vasc Biol*. 2013;33:193–200.
10. Fiedler J, Thum T. MicroRNAs in myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2013;33:201–205.
11. Mayr M, Zampetaki A, Willeit P, Willeit J, Kiechl S. MicroRNAs within the continuum of postgenomics biomarker discovery. *Arterioscler Thromb Vasc Biol*. 2013;33:206–214.
12. Kwak PB, Tomari Y. The N domain of Argonaute drives duplex unwinding during RISC assembly. *Nat Struct Mol Biol*. 2012;19:145–151.
13. Gu S, Jin L, Huang Y, Zhang F, Kay MA. Slicing-independent RISC activation requires the argonaute PAZ domain. *Curr Biol*. 2012;22:1536–1542.

KEY WORDS: argonaute ■ editorial ■ microRNA ■ miR-induced silencing complex

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2013;33:168-169
doi: 10.1161/ATVBAHA.112.300920
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636