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

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MicroRNAs in Myocardial Infarction

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Abstract — The complexity of posttranscriptional regulation by noncoding microRNAs (miRNAs, miRs) is still not completely understood. A large fraction of the genome is under the control of miRs via (partial) complementary base pairing within the corresponding mRNA region. Myocardial infarction is characterized by strongly altered gene expression, deregulation of underlying signaling pathways, and crucial participation of several miRs in this context. Mechanistically, miR induction or repression after myocardial infarction triggers downstream events in a cell-type–specific manner, and interference with endogenous miR expression might regulate overall cardiac function. In this brief review, we (1) summarize the current knowledge about the importance of several miRs after myocardial infarction, (2) report about novel miR-based therapeutic approaches to counteract maladaptive remodeling upon cardiac ischemia, and (3) discuss briefly the use of miRs as biomarkers for cardiac ischemia. **(*Arterioscler Thromb Vasc Biol*. 2013;33:201-205.)**

Key Words: heart failure ■ microRNA ■ myocardial infarction

Myocardial infarction (MI) is a leading cause of death in the industrialized world, and thus development of new therapeutic strategies is an important aim of both clinical and basic cardiovascular research. Despite the available therapeutic approaches, MI is still associated with high rates of acute death and long-term complications, such as heart failure (HF). Acute myocardial damage attributable to ischemia is a result of cellular hypoxia and the subsequent cascade of cellular events, such as an increase in reactive oxygen species during early reperfusion, endothelial cell (EC) activation, and production of proinflammatory chemokines and cytokines in the damaged area, ultimately priming and recruiting neutrophils and other inflammatory cells to the infarcted region.[1,2] The cascade of maladaptive signaling triggers further release of oxidants and proteolytic enzymes,[3] leading to infarct size extension, cardiomyocyte death, and endothelial capillary impairment. Although early reperfusion therapy helps to reduce tissue injury, chronic loss of cardiac muscle entails progressive remodeling of the remaining active myocardium. The remodeling process is initially an adaptive mechanism to maintain adequate cardiac function; however, it eventually leads to fibrosis, left ventricular dilatation, and HF.[4] Insufficient myocardial capillary density after MI has been identified as a critical event in the remodeling process that can be targeted with novel therapeutic strategies.[5] Despite recent advances in our molecular understanding, the underlying signaling events among cardiomyocytes, extracellular matrix, and vascular tissue during the development of HF associated with MI is far from being understood. Endogenously encoded miRs have been described to impact on cardiovascular biology[6,7] in recent times. MiRs are a subclass of noncoding RNA (approximately 22 nucleotides in length) that is capable to control gene expression by sequence interaction with the 3′-untranslated region of target genes. Indeed, a large fraction (≈60%) of the genome is regulated by miRs,[8] and the participation of miRs during cellular signaling has been reported both in physiological and pathophysiological conditions (excellently reviewed in Mendell and Olson[9]). A ground-breaking genetic deletion study in vivo discovered key functions for miR biogenesis, and its role for proper cardiac development and function.[10] Several clues also pointed to a participation of miRs in cardiac disease. In failing hearts, a profibrotic role was attributed for miR-21.[6] Therapeutic miR-21 antagonism was shown to reduce progression of maladaptive fibrosis. Contrary to standard pharmacological agents targeting only single molecular pathways, miRs are capable of regulating multiple downstream mediators in parallel, thus affecting various signaling cascades. Van Rooij et al[11] nicely demonstrated the direct impact of miR-29 expression for fibrotic scar formation in the failing heart. Next to the development of cardiac fibrosis, miR-133 was closely linked to cardiomyocyte function by altering hypertrophic response.[12] MiRs were also shown as therapeutic entry points in several MI-related disease settings (eg, miR-92a, miR-24),[7,13] and its use as biomarkers for heart disease has recently been discovered intensively.[14–16] In this brief review, we aim to highlight the impact of MI-regulated miRs on myocardial function and present novel miR-based therapeutic approaches.

MI-Related miRs

Cardiac remodeling post-MI is crucially dependent on the infarct size determining heart architecture alteration.[17] The ischemic process then triggers inflammatory response, as well

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as global transcriptome changes within the heart.[18,19] Cardiac remodeling over time is finally the leading cause for cardiac malfunction and lower performance (reviewed in Jessup and Brozena[4]). Underlying molecular mechanisms are still not well understood, and miR participation came into focus in recent days. Da Costa Martins et al[10] reported that cardiomyocyte-restricted conditional knockout of miR biogenesis enzyme Dicer induced maladaptive cardiac remodeling and HF. MiR biogenesis pathway is thus of utmost importance for overall cardiac function (reviewed in Bauersachs and Thum[20]). Furthermore, miRNA gene silencing upon a hypoxic stimulus is potentiated by posttranslational modifications toward argonaute 2, a central factor for the miRNA machinery.[21] In addition, several studies indicated a crucial role for miR-dependent regulation of cardiac angiogenesis, fibrosis, and cardiomyocyte hypertrophy upon MI.[7,13,22,23] These observations clearly link cardiac ischemic disease to altered miR expression. However, miR deregulation also offers a new therapeutic entry point to counteract MI-induced cardiac dysfunction. During ischemic preconditioning, for example, a well-known cardioprotective mechanism, deregulated miRs were identified, and a cocktail injection of upregulated miRs before experimental infarction protected the mouse heart from severe damage.[24] Cluster members miR-144/451 were also proven to be essential in this process.[25] In the following, we will summarize novel approaches to decipher single miR function after MI and discuss potential translational aspects for human heart disease.

MicroRNA-1

SERCA2a gene therapy for chronic HF after MI in rats revealed an involvement of miR-1.[26] Besides other miRs also being normalized upon SERCA2a adeno-associated virus–mediated delivery, miR-1 was extensively characterized. Cardiomyocyte-specific miR-1 was found to have antihypertrophic characteristics. Increase in miR-1 expression could support cardiomyocyte function via derepressing sodium–calcium exchanger-1 target gene. This report combines an adeno-associated virus- and miR-based therapeutic approach to counteract cardiac dysfunction, although earlier findings indicated miR-1 may impact on cardiac arrythmogenesis after MI.[27] Another recent study reported miR-1 overexpression in ischemic myocardium.[28] Here, β-blocker propranolol repressed miR-1 expression efficiently and contributed to improved cardiac conduction and function. In agreement with this study, MI in rats also induced miR-1 expression and lowered miR-1 target insulin-like growth factor-1, thereby contributing to enhanced proapoptotic pathways in cardiomyocytes.[29] Collectively, miR-1 seems to be an attractive miR target for HF and might also be relevant in HF patients, at least as a potential biomarker that will be discussed later on.

MicroRNA-15

In a very recent study, Hullinger et al[30] used a murine and porcine MI model to study altered miR expression. Dissection of cardiac tissue toward infarct and border zone revealed upregulation of miR-15 family members. Importantly, endogenous silencing of miR-15 in cardiomyocytes decreased cellular stress. Applying a translational approach, locked-nucleic-acid–based miR therapy was used and sufficiently inhibited miR-15 in vivo. Successful therapy was indicated by a smaller infarct size in animals treated with locked-nucleic-acid antagonist against miR-15, even in larger animal models. Underlying molecular mechanisms are speculative but point to a participation of direct downstream mediators Pdk4 and Sgk1 for mitochondrial function and cardiomyocyte apoptosis.

MicroRNA-21

A functional role was attributed to miR-21 in a murine ischemia-reperfusion model.[31] Elevated levels for miR-21 expression in the infarct zone led to a specific repression of downstream effector phosphatase and tensin homolog. As a direct consequence, fibroblast matrix metalloproteinase-2 expression increased, activated fibroblast survival, and triggered fibrotic infarct remodeling. In line, a recent report indicated beneficial effects upon miR-21 antagonism after permanent MI in rats.[32] Therapeutic inhibition decreased atrial fibrosis and sustained heart function in comparison with controls.[33] Besides the relevance of miR-21 expression for ischemic heart disease, other signaling pathways are affected within HF. The prominent role of enhanced miR-21 expression during HF has been early demonstrated.[6,34] A fibroblast-specific prosurvival action was validated by Thum et al demonstrating increased fibroblast proliferation upon elevated miR-21 levels. Therapeutic miR-21 antagonism decreased the amount of proliferating fibroblasts, and thus overall fibrosis. This initial antagomir-21 intervention paved the way for further antifibrotic miR-21 treatment strategies in lung, skeletal muscle, and kidney fibrosis.[35–37] Despite these convincing findings for antifibrotic action of miR-21 therapy, no genetic evidence was found in a global miR-21 knockout model.[38] Because a global knockout was used, only fibroblast-specific deletion of miR-21 would further help to clarify the role of miR-21 for fibroblast biology. The use of antagomir-21 chemistry has also recently been compared with locked-nucleic-acid–chemistry, proofing the therapeutic value and concept of antagomir-mediated knockdown for miR-21 in fibrotic disease.[39] Translation of these findings into larger animal models (eg, minipig) and proper toxicological testing is clearly needed before initiating clinical trial studies with regard to miR therapeutics' chemistry.

MicroRNA-24

The miR-24 encoded by 2 genomic loci was recently investigated in MI by various groups.[13,22,23] Expression pattern after MI was reported to be downregulated and impacting either on fibroblast or cardiomyocte biology.[22,23] Therapeutic overexpression applying lentivirus triggered myocardial healing by inhibiting fibrosis via repression of fibroblast marker genes Col1a2, Col3, fibronectin, and αSMA.[22] In parallel, Srivastava et al reported that lentiviral miR-24 delivery decreased cardiomyocyte apoptosis.[23] Sustaining miR-24 expression in cardiomyocytes counteracted proapoptotic pathways and diminished loss of cardiac muscle. However, another EC-specific function was investigated by our lab.[13] Hypoxia and cardiac ischemia in mice increased miR-24 expression in ECs. In vitro overexpression revealed a proapoptotic function for miR-24 in ECs. Antiangiogenic features were also observed in vitro and in the developing vasculature of zebrafish. Therapeutic antagonism of

miR-24 in a mouse model of MI improved ischemic remodeling by direct effects on cardiac EC survival. These findings on fibroblast, cardiomyocyte, and endothelial biology highlight the versatile characteristics of miR-24 within the heart.

MicroRNA-29

Microarray-based analysis of miR expression after MI pointed to a role for miR-29 in cardiac remodeling.[11] In accordance with aforementioned miR-21, miR-29 is highly abundant in fibroblasts. Reduced miR-29 expression was correlated to the extent of fibrotic extracellular matrix appearance, and downstream endogenous effectors such as different collagens were identified. Importantly, inhibition of miR-29 induced collagen expression pattern both in cell culture and in mice after experimental infarction. Systemic organ fibrosis was detected, demonstrating the profibrotic properties of miR-29 shutdown. In line, miR-29 overexpressing fibroblasts showed a reduction in collagen gene battery expression, thus giving a clue to a potential therapeutic option. In agreement with this study, Port et al[40] confirmed the direct effects of miR-29 on collagen expression. The synergistic detection of both mRNA and miR expression could validate the fibrogenic relationship for miR-29. Another report studied the effect of miR-29 inhibition during cardiac ischemia-reperfusion injury.[41] Here, pharmacological protection was achieved by miR-29 downregulation and repression of cardiomyocyte apoptosis.

MicroRNA-92a

Endothelial miR-92a is clustered within the miR-17 to miR-92 locus and has been investigated in ischemic models.[7] Hindlimb ischemia or MI specifically altered miR-92a expression. Important angiogenic pathways are subsequently targeted in ECs triggering angiogenic defects (eg, reduced sprouting capacity). Systemic administration of a miR-92a antagonist blocked this deteriorating antiangiogenic route in ECs. In a more recent publication, other miR cluster members were also highlighted with strong antiangiogenic features.[42] Taken together, this specific miR cluster implicates a powerful tool to control neovascularization after ischemic injury.

MicroRNA-101

Very recently, miR-101 comprising isoforms miR-101a and miR-101b were shown to influence cardiac fibrosis after MI in rats.[43] Chronic infarction led to a downregulation of miR-101 expression in the peri-infarct zone. Underlying mechanisms were found to rely on control of collagen expression in cardiac fibroblasts. Therapeutically, adenoviral-mediated delivery of miR-101a to the heart had beneficial effects on cardiac function by reduction of the fibrotic scar. Of note, interference with transforming growth factor-β-signaling counteracted the maladaptive remodeling in the long term.

MicroRNA-126

Endothelial-specific miR-126 is a key player for endothelial function and integrity after MI.[44] Targeted loss of endothelial miR-126 in vivo causes a cascade of reduced angiogenic signaling. Prominent chemokines vascular endothelial growth factor and fibroblast growth factor cannot fulfill their important roles for neovascularization after MI, although miR-126 is absent. In contrast, miR-126 supplementation enhances angiogenic capacity and sustains endothelial properties. Collectively, endothelial miR-126 is of outstanding need for vascular development, as well as ischemia-induced neovascularization. Besides decisive endothelial function, miR-126 has also been described to mediate chemokine (C-X-C) motif ligand-production during atherosclerosis in apoptotic bodies, which is a novel communicatory mechanism between cells.[45]

MicroRNA-214

Another cardioprotective role was recently reported for HF-upregulated miR-214.[46] In knockout mice, ischemia-reperfusion injury was more severe in comparison with the wild-type condition. Fibrosis progression as well as cardiomyocyte apoptosis increased and triggered cardiac imbalance. Similar to miR-1, miR-214 also targets sodium–calcium exchanger-1 and thus influences cardiomyocyte calcium trafficking. Next to the function for cardiomyocyte signaling, miR-214 regulates compensatory angiogenesis that might also attribute to cardiac disease.[47] Taken together, miR-214 also presents an interesting miR target for intervention in HF.

Table. Several MicroRNAs Are Involved in Cardiac Remodeling After MI

Myocardial Infarction Is Controlled by MicroRNA			
MiRNA(s)	Cellular Origin	Downstream Targets	Reference
miR-1	Cardiomyocyte	Ncx-1; KCNJ2, GJA1; IGF-1	(26,27,29)
miR-15	Cardiomyocyte	Pdk4, Sgk1	(30)
miR-21	Fibroblast	Pten; Sprouty-1, collagens	(11, 6, 32)
miR-24	Cardiomyocyte, fibroblast, endothelial cell	Bim; Furin; Gata2, Pak4	(23,22,13)
miR-29	Cardiomyocyte, fibroblast	Mcl-1; Collagens	(11,40,41)
miR-92a	Endothelial cell	Itga5	(7)
miR-101	Fibroblast	Collagens	(43)
miR-126	Endothelial	Spred-1	(44)
miR-214	Cardiomyocyte	Ncx-1	(46)

miR indicates microRNA; MI, myocardial infarction; IGF, insulin-like growth factor; and PTEN, phosphatase and tensin homolog..

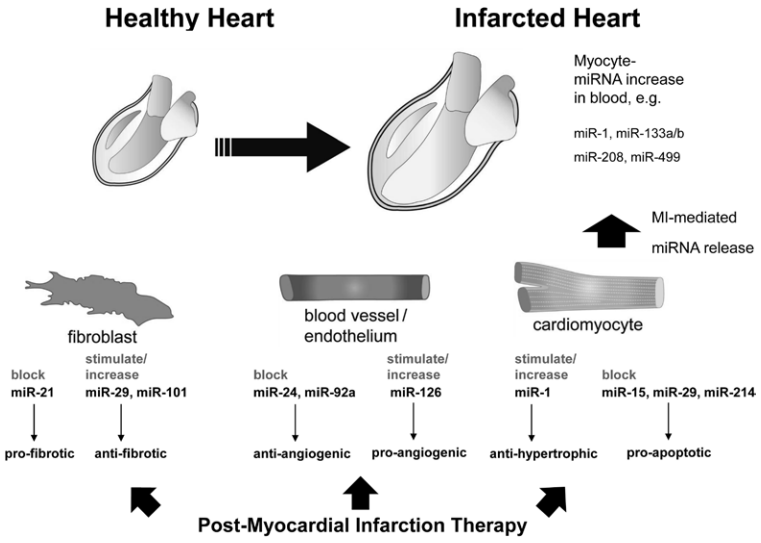

Figure. Cardiac cells undergo phenotypic changes during cardiac ischemia, and specific microRNAs (miRs) participate in regulation of cell fate after myocardial infarction. A regulatory potential is indicated for cardiomyocyte, fibroblast, and endothelial miRs. Further miRs might also be of diagnostic potential and are mentioned as myocyte-miRs that are deliberated after myocardial infarction into the circulation.

MiRs as Biomarkers of Cardiac Ischemia

Prognostic and diagnostic value for circulating miRs in ischemic cardiac disease has been investigated in several up-to-date publications.[14–16] The use of high-sensitive real-time PCR (RT-PCR) or array technique facilitates miR detection in body fluids, even if miRs are present at very low concentration in the circulation. Nevertheless, this is technically different from standard biomarker detection (eg, troponins). D'Alessandra et al[48] conclusively reported the early use of miR-detection (for miR-1, miR-133a, miR-133b, miR-499-5p) in comparison with troponins as biomarkers in a patient cohort with ST-segment elevation MI. Peaking miR abundance proofs the general feasibility of miRs as early biomarkes for cardiac disease, although this has to be validated in larger cohorts. Likewise, urine miRs were also detected after MI and pointed to abundance of miR-1 in transferrable exosomes within the circulation.[49] A study from Corsten et al[50] proofed the availability of miR-208b and miR-499 for different HF settings, for example, MI or diastolic dysfunction. However, prognostic value remains speculative as reported for cardiomoycyte-enriched miRs.[14,16] In a very recent study using 820 participants of the Bruneck study, taking into account prospective values of miR-126, miR-197, and miR-223 led to a reclassification for MI in addition to the Framingham Risk Score.[15] The contribution of an inflammatory biomarker, C-reactive protein, revealed less substantial improvement for risk reclassification. Noteworthy, cellular origin for many detected miRs was attributed to platelets, highlighting a potential new avenue for miR research. Circulating miRs to be enforced as true biomarkers or even mediators for HF is elusive and may be solved by additional studies in future times.

Conclusion and Open Questions

Treatment of MI and its consequences is an enormous task and needs careful consideration. Besides the use of standard pharmacological approaches, miR-based therapies offer new challenging avenues (summarized in Table and Figure). The identification of MI-associated miRs is of great interest to develop miR therapeutics, and herein discussed miRs offer certain therapeutic value. However, some studies remain limited as they apply to permanent MI, which is in contrast to the clinical scenario aiming at immediate intervention and reperfusion. Limitations might be circumvented by appropriate ischemia-reperfusion models better reflecting the clinical setting.[51] Systemic delivery, and thus no organ or even cell-type–specific uptake, additionally puts up certain limits to most works. Here, major improvements are needed to minimize off-target effects. Although knockdown strategies are available with different chemistries, miR overexpression still requires viral approaches currently hindering potential translational studies to humans. In summary, miR therapeutics are entering the stage as novel candidates for treatment of HF, and clinical trials (eg, miR-122 in hepatitis C infection[52]) are underway to prove feasibility, toxicity profile, pharmacokinetics, and pharmacodynamics. Ultimately, this may lead to the development of effective diagnostic and miR-based treatments for ischemic heart disease.

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T.T. and J.F. have filed patents in the field of cardiovascular miRNA diagnostics and therapeutics.

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MicroRNAs in Myocardial Infarction

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