A s deaths from acute myocardial infarction have declined dramatically over the past several decades, more and more patients survive with chronic myocardial ischemia.1,2 Hearts of most patients who survive acute myocardial infarction undergo remodeling. Hearts of most patients with sustained hypertension, another common cardiovascular disease, also show some degree of remodeling.

The heart consists of 3 primary cell types: cardiomyocytes, fibroblasts, and endothelial cells. Myocytes occupy 75% of cardiac mass, generate the electric impulses, and induce cardiac contraction. Fibroblasts are primarily responsible for the maintenance of extracellular matrix (ECM) that is composed of collagens, fibronectins, elastins, fibrillins, and several other proteins. The capillary microcirculation network composed primarily of endothelial cells that serves the contractile assembly.3 In state of health, renin–angiotensin–aldosterone system is thought to be responsible for sustenance of cardiomyocyte, fibroblast, and endothelial cell biology. However, renin–angiotensin–aldosterone system activation leads to profound changes in cell biology during sustained hypoxia. Cardiomyocytes in the regions adjacent to ischemic area become large to maintain cardiac contraction. Fibroblasts around the cardiomyocytes begin to grow and differentiate into myofibroblasts to compensate for low-cardiac output. This process of cardiomyocyte hypertrophy and cardiac fibroblast growth is commonly known as cardiac remodeling.4–6 Release of large amounts of reactive oxygen species in the ischemic myocardium and the associated inflammatory response are thought to be mechanistic contributors to cardiac remodeling. Local activation of renin–angiotensin–aldosterone system contributes to further reactive oxygen species generation and release of transforming growth factor-β (TGF-β); the latter plays a central role in fibroblast transformation into myofibroblasts and subsequent activation of matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), and synthesis of collagens.7 MMPs and TIMPs mediate the balance between formation of collagens and their degradation, and their abnormal expression promotes secretion of large amounts of collagens by rapidly growing fibroblasts. These processes, along with inappropriate release of proinflammatory cytokines from endothelial cells, inflammatory cells, and cardiomyocytes,8 lead to a state of cardiac dysfunction resulting in the clinical syndrome of heart failure.

Fibrosis during chronic ischemia and sustained hypertension occurs not only in the heart but also in distant organs, such as lung, liver, kidney, pancreas, spleen, nervous system, and bone marrow.9 Precise steps in the pathogenesis of fibrosis during chronic ischemia are not fully elucidated, but a state of oxidative stress and inflammation, as discussed above, is thought to be largely responsible for the development of a fibrotic phenotype.

At present, there are few effective options for the treatment of cardiac fibrosis, except targeting renin–angiotensin–aldosterone system.10–12 A host of novel therapies targeting inflammatory mediators are being considered.10 Recently, there has been an emphasis on the involvement of a host of miRs, which may lead to new therapies for postischemic fibrosis.13–17

**Function of miRs in Postischemic Fibrosis**

miRs are small endogenous noncoding RNAs. Many of them are significantly conserved and expressed in eukaryotes.18 They inhibit the transcription of several mRNAs through base-pairing with the coding or 3′-untranslated regions of mRNAs. This results in altered degradation of mRNAs and translation into proteins, resulting in diverse biological processes.19

miRs regulate cardiovascular system and have critical roles in cardiovascular physiology and disease development. They participate in the pathogenesis of many disease states, such as atherosclerosis, coronary artery disease, and heart failure.20 Several reviews have appeared on the role of miRs in atherosclerosis and heart failure, resulting from hypertension and myocardial infarction, but few have addressed the function and signaling pathways of miRs involved specifically in cardiac fibrosis. This review specifically addresses miRs specific to fibrosis that develops in the chronically ischemic heart.

As mentioned above, fibrosis is related to ECM dysfunction and fibroblast proliferation and migration. Here, we focus on those miRs that target ECM proteins or play a key role in this process. Different miRs to be discussed in this article, whether they are upregulated after myocardial infarction, their target
genes, and their ultimate effect on postischemic fibrosis are summarized in the Table.

**miR-21**

The involvement of miR-21 has been demonstrated in several pathological processes, including cancers, cardiac hypertrophy, and development of fibrosis. Tatsuguchi et al\(^2\) transfected miR-21 duplexes (a mimic of miR-21) and locked nucleic acid (a modified RNA nucleotide)-modified antisense oligonucleotides (inhibitors of miR-21) into rat cardiomyocytes and showed that miR-21-inhibited neonatal rat cardiomyocyte hypertrophy. However, in mouse 3T3 fibroblasts, miR-21 acted as a promoter of collagen generation and development of fibrosis. In a subsequent study in a \(\beta_1\)-adrenergic receptor transgenic mouse model of cardiac dysfunction, Thum et al\(^2\) showed that miR-21 inhibition with antimiR-21 attenuated interstitial fibrosis and upregulated the expression of protein sprouty homolog 1 (Spry1), an important inhibitor of mitogen-activated protein kinase pathway. Spry1 negatively regulated mitogen-activated protein kinase signaling that enhances cardiac fibroblast secretion of fibroblast growth factor 2. These observations gained support from the work of Adam et al\(^2\), who showed that direct inhibition of miR-21 prevented cardiac fibrosis through augmentation of Spry1 in a mouse myocardial infarction model, as well as in patients with atrial fibrillation. In further support of this work, Roy et al\(^2\) demonstrated that upregulation of miR-21 induced cardiac fibrosis in mice subjected to myocardial ischemia. They also found that miR-21 inhibited phosphatase and tensin homolog, a tumor suppressor gene, that inactivates the phosphatidylinositol 3-kinase-protein kinase B pathway activates MMP-2 as well as TIMPs sequences for miR-29. After transfection of fibroblasts with a pCMV6-ligated miR-29 coding region in vitro, they observed that miRNA for all collagens decreased. In keeping with this concept, their study in a murine model of myocardial infarction revealed that knockdown of miR-29b increased the expression of collagens and resulted in an increase in ECM in the border zone 2 weeks after myocardial infarction. Additionally, the number of myofibroblasts, which are partially transformed from fibroblasts and are the real effectors of ECM, including elastin (ELN), fibrillin-1 (FBN1), collagen type I, \(\alpha_1\) and \(\alpha_2\) (COL1A1, COL1A2), and collagen type III \(\alpha_1\) (COL3A1), showed 1 or more potential seed binding sequences for miR-29.

Collectively, these studies indicate that miR-21 plays a significant role in regulating postischemic cardiac fibrosis. Although inhibition of miR-21 has generally been shown to reduce fibrosis, it (miR-21 inhibition) may enhance cardiomyocyte hypertrophy. Cardiac remodeling is a result of both fibrosis and cardiomyocyte hypertrophy, and inhibition of miR-21 may have opposite effects on the 2 processes. Therefore, further studies need to be performed before anti-miR-21 can be viewed as a useful therapy for prevention of fibrosis.

**miR-29**

The miR-29 family contains 3 members: miR-29a, miR-29b, and miR-29c. van Rooij et al\(^2\) demonstrated that upregulation of the entire miR-29 family can prevent cardiac fibrosis by reducing ECM formation. Their analysis of 3′-untranslated regions of several genes coding for the components of ECM, including elastin (ELN), fibrillin-1 (FBN1), collagen type I, \(\alpha_1\) and \(\alpha_2\) (COL1A1, COL1A2), and collagen type III \(\alpha_1\) (COL3A1), showed 1 or more potential seed binding sequences for miR-29. After transfection of fibroblasts with a pCMV6-ligated miR-29 coding region in vitro, they observed that miRNA for all collagens decreased. In keeping with this concept, their study in a murine model of myocardial infarction revealed that knockdown of miR-29b increased the expression of collagens and resulted in an increase in ECM in the border zone 2 weeks after myocardial infarction. Additionally, the number of myofibroblasts, which are partially transformed from fibroblasts and are the real effectors of ECM, including elastin (ELN), fibrillin-1 (FBN1), collagen type I, \(\alpha_1\) and \(\alpha_2\) (COL1A1, COL1A2), and collagen type III \(\alpha_1\) (COL3A1), showed 1 or more potential seed binding sequences for miR-29.

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**Table. Summary of miRNAs and Their Impact on Genes Involved in Postischemic Myocardial Fibrosis**

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>miR-21</th>
<th>miR-23*</th>
<th>miR-24</th>
<th>miR-29</th>
<th>miR-101</th>
<th>miR-132</th>
<th>miR-206</th>
<th>miR-214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental conditions</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
<td>In vivo</td>
</tr>
<tr>
<td>Expression after MI</td>
<td>Increase</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Target genes</td>
<td>PTEN, TGF-β RIII, Spry1</td>
<td>TGF-β1</td>
<td>Furin</td>
<td>Elastin, fibrillin-1, collagens</td>
<td>FOS</td>
<td>MeCP2</td>
<td>TIMP3</td>
<td>NCX1</td>
</tr>
<tr>
<td>Function of miR on post-MI fibrosis</td>
<td>Induces post-MI fibrosis</td>
<td>Inhibits post-MI fibrosis</td>
<td>Inhibits post-MI fibrosis</td>
<td>Inhibits post-MI fibrosis</td>
<td>Inhibits post-MI fibrosis</td>
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<td>Inhibits post-MI fibrosis</td>
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</tr>
</tbody>
</table>

C indicates cardiomyocyte; E, endothelial cell; F, fibroblast; FOS, FBG Osteosarcoma Oncogene; MeCP2, methyl-Cpg-binding protein 2; MI, myocardial infarction; NCX1, sodium–calcium exchanger 1; PTEN, phosphatase and tensin homolog; Spry1, sprouty homolog 1; TGF-β RIII, transforming growth factor-β receptor III; TGF-β1, transforming growth factor-β1; and TIMP3, tissue inhibitors of metalloproteinase 3.

The extreme left row refers to the condition of each miRNA experiment, cell types which refer to miRs expression of what kind of cell in the heart and their expression, target genes, signaling pathway, and the direct function on post-MI fibrosis. The asterisk (*) means that this miRNA probably regulates post-MI fibrosis.
of fibrosis, increased significantly after tail vein injection of anti–miR-29b. Zhou et al. provided further evidence for a role of miR-29 in the development of fibrosis after myocardial infarction. Their study showed downregulation of miR-29 in response to overexpression of TGF-β via activation of Smad2 and Smad3, transcription factors that transduce extracellular TGF-β from cell membrane to cytoplasm. Another interesting study by Soci et al. showed that aerobic training decreased collagen expression in the heart via increasing miR-29. These observations provide further evidence for a role for miR-29 in preventing cardiac fibrosis.

However, some other studies have shown that miR-29 can promote cardiomyocyte apoptosis via negative regulation of antiapoptosis genes, such as B-cell lymphoma 2 (Bcl-2), cell division cycle 42 (CDC42), and T-cell leukemia/lymphoma 1 (Tcl-1). This suggests that miR-29-based therapy may exert opposite effects on cardiomyocyte and fibroblast biology, the 2 main components of the heart.

Collectively, these observations suggest double-edged functions of miR-29 family members; some improve postischemic remodeling by blocking expression of collagens, whereas others induce cardiomyocyte apoptosis and may contribute to cardiac failure. The overall effect of miR-29 activation may depend on the timing of miR-29-based therapy after myocardial infarction. In early stages, inhibition of miR-29 may protect against heart failure by repressing cardiomyocyte apoptosis, whereas in later stages (2 weeks after myocardial infarction), stimulation of miR-29 may protect the heart from fibrosis.

miR-24 Family

miR-24 is clustered with miR-23 and miR-27. miR-23 and miR-27 are highly expressed in the heart after myocardial infarction and influence capillary formation and fibrosis. miR-23a regulates cardiomyocyte growth, whereas miR-23b targets E2F1, a transcription factor in eukaryotes and plays a proangiogenic role.36 Additionally, miR-23 is reported to repress TGF-β-induced endothelial-to-mesenchymal transition, a process that regulates the origin of fibroblasts from endothelial cells, which indicates its potential as an antifibrotic mediator. miR-27a/b regulates myocardial neovascularization after ischemia by targeting the 3’-untranslated regions of semaphorin 6A (SEMA6A), which has been found to inhibit growth factor– and tumor cell line–induced neovascularization.38,39 It is of note that angiogenesis in the ischemic myocardium has been linked to scar formation.40 However, any direct effect of miR-23 and miR-27 to reduce fibrosis needs to be determined.

In addition to the indirect link, miR-24 seems to have a direct relationship with cardiac fibrosis. Wang et al. showed that the overexpression of miR-24 inhibits fibrosis after myocardial infarction. They demonstrated that miR-24 expression peaked 1 week after myocardial infarction in a mouse model followed by a gradual decrease in collagen-I and TGF-β and then reverted to normal levels at 4 weeks. To further ascertain the function miR-24 in this process, they injected lentivirus–vector-miR-24 into the infarcted mouse heart and found that miR-24 not only improved cardiac function but also diminished fibrosis in the border zone (36.9% reduction in scar size versus control). In vitro work by these authors showed that transflecting synthetic miR-24 precursors in cardiac fibroblasts decreased the migration and differentiation of cells via downregulation of profibrotic cytokines. Furthermore, based on bioinformatics prediction and siRNA technology, they established that furin, a protease that controls latent TGF-β activation processing, is a direct target in this process. These observations collectively suggest that miR-24 plays an important role in the regulation of postischemic fibrosis.

miR-101

miR-101 has been shown to inhibit tissue invasion by cancer cells. It is also known to mediate the suppressive effect of laminar shear stress in vascular endothelial cells. The regulation of cardiac fibrosis by miR-101 was shown recently by Pan et al. They found that the expression of miR-101a and miR-101b (miR-101a/b) was decreased in the peri-infarct area 4 weeks after coronary artery ligation in rats. The critical role of miR-101 became evident from the observation that overexpression of premiR-101a in the left ventricle significantly improved cardiac contractile function after coronary artery ligation. Furthermore, they showed that forced expression of miR-101a/b suppressed proliferation and collagen production in rat neonatal cardiac fibroblasts, and this effect was abrogated by cotransfection with AMO-101a/b, antisense inhibitors of miR-101a/b. The authors attributed this beneficial effect to the repression of FBJ osteosarcoma oncogene (FOS), an oncogene that is expressed in fibroblasts and may be a direct target of miR-101. To prove this concept, they transfected FOS siRNA into fibroblasts and showed a decrease in cell proliferation and TGF-β1 expression. The decrease of TGF-β1, both at transcriptional and translational levels, prevented postischemic fibrosis.

miR-206

High mobility group box-1 protein (HMGB1) is a nuclear protein that regulates regenerative processes. Bianchi et al. have implicated HMGB1 in tissue repair. This notion was confirmed in a recent study. Limana et al. demonstrated that a direct injection of HMGB1 into infarcted mouse heart resulted in enhanced MMP2 and MMP9 activity and reduced TIMP-3 levels and collagen deposition. Compared with controls, the hearts of animals with overexpression of HMGB1 exhibited 4- to 5-fold higher expression of miR-206, 3 days after HMGB1 treatment. Additionally, an improvement in cardiac function was found 3 weeks after coronary ligation. In a luciferase reporter assay on cardiac fibroblasts, miR-206 was shown to target the TIMP-3 3’-untranslated regions. Interestingly, Winbanks et al. showed that TGF-β suppresses miR-206 via upregulation of Smad2, which again suggests that miRs interact with each other in regulating TGF-β expression or are themselves regulated by TGF-β expression.

miR-132

Pericytes are key regulators of vascular maturation. A recent study by Katare et al. showed that saphenous vein–derived pericyte progenitor cells (SVPs) regulate cardiac repair through upregulating miR-132. In this study, these investigators showed that SVPs can upregulate miR-132 expression which, in turn,
significantly reduces interstitial fibrosis after myocardial infarction. In SVPs-treated mouse hearts subjected to coronary occlusion, scar area was 25.4% (compared with 32.3% in the control group), and this effect was blocked by treatment with anti-miR-132. In subsequent in vitro experiments, they showed that SVP conditioned medium-stimulated endothelial tube formation and reduced myofibroblast differentiation. This effect was attributed to a reduction of methyl-CpG-binding protein 2 (MeCP2), a protein which controls an epigenetic pathway that promotes myofibroblast differentiation and fibrogenesis. Importantly, these effects were canceled by exposure of fibroblasts to anti-miR-132-transfected SVPs, suggesting MeCP2 as a direct target of miR-132.

miR-214

Some studies show that miR-214 impacts postmyocardial infarction fibrosis. Aurora et al showed that compared with wild-type animals, the hearts of mice lacking miR-214 were prone to the development of extensive myocardial fibrosis on day 7 after ischemia–reperfusion injury. This effect was attributed to increased expression of a miR-214 target gene, sodium–calcium exchanger III (NCX1), a sodium–calcium exchanger which normally extrudes Ca$^{2+}$ out of the cell but may cause Ca$^{2+}$ influx into the myocyte during ischemia–reperfusion, resulting in Ca$^{2+}$ overload, and induction of myocyte death, extensive fibrosis, and subsequently heart failure. However, the mechanism of miR-214–induced fibrosis was not elucidated in this study. Also, different from other antifibrotic miRs, miR-214 seems to be upregulated during ischemic injury, probably as a compensatory mechanism. Although there is only limited evidence that miR-214 mimic improves postischemic fibrosis, its overexpression may be regarded as an indicator of fibrotic events during sustained ischemia.

Summary of Effects of Individual miRs on Cardiac Fibrosis

The Table lists the miRs that are upregulated after myocardial infarction, their target genes, and their effect on postischemic cardiac fibrosis. The Figure summarizes the salient points made in this review and provides additional details as to which individual genes are up- or downregulated during ischemia and by the changes induced by different miRs. The Figure also delineates how changes in gene expression lead to fibrosis, whether through altering fibroblast survival (miR-21 and miR-23), fibroblast growth and differentiation (miR-132 and miR-214), or dysfunction of the ECM (miR-21, miR-23, miR-24, miR-29, miR-101, and miR-206).

Combination of Different miRs

A recent study showed that miRs-1-133, -208, and -499 in combination can reprogram fibroblasts directly to cardiomyocyte-like cells in vitro. This is completely different from traditional induced pluripotent stem cells. Fibroblast conversion in this study was documented by expression of mature cardiomyocyte markers, including GATA-binding factor 4 (GATA4), myocyte-specific enhancer factor 2C (Mef2c), and T-box transcription factor 5 (Tbx5), as well as later stage cardiomyocyte markers, such as troponin I, cardiac muscle 3 (Tnni3), sarcomeric organization, and exhibition of spontaneous calcium flux, all features of a cardiomyocyte phenotype. The authors of this study also showed that administration of miRs in combination with the ischemic myocardium of mice resulted in the direct conversion of cardiac fibroblasts into cardiomyocytes in situ. Although the authors did not provide information on the development of fibrosis, it is possible that collagen deposition in the infract and peri-infract regions was diminished because the fibroblasts were transformed into cardiomyocytes under the influence of miRs. These innovative studies provide the first evidence that miRs in combination can be used to redirect growing fibroblasts in the ischemic heart into a cardiomyocyte phenotype without the concerns associated with pluripotent stem cells (ie, functional heterogeneity, low survival and retention of delivered cells, and potential tumorigenicity).

Additionally, miRNAs are regulated by environmental perturbations, many of which are common to the triggers present in ischemia. Parikh et al have shown that hypoxia, which is present in the ischemic tissues, activates the hypoxia-inducible factor pathway, which in turn regulates the expression of around 200 miRs. Using a bioinformatics approach, they suggested that in pulmonary hypertension, TGF-β is regulated by a number of fibrotic miRs, including those mentioned above. These findings suggest a potent network of miRs controlling tissue fibrosis and potential benefit of miR-based therapy for disease states characterized by fibrosis.

Conclusion

Cardiac fibrosis after myocardial infarction or sustained hypertension remains a major clinical problem. As reviewed here, several fibrotic miRs seem to regulate cardiac fibrosis by targeting multiple genes, including phosphatase and tensin homolog, furin, collagens, MeCP2, and NCX1. In particular, TGF-β, a profibrotic mediator, seems to be a focal point of miR-based modulation of cardiac remodeling, as it not only stimulates fibrosis by inhibiting miR-29 and miR-206 but also is upregulated by the miR-24 target gene furin as well as the miR-101 target FOS. It also seems that some fibrosis-related miRs (eg, miR-21) act through stimulation of prosurvival signaling pathways and increase of cell resistance to apoptosis.

We believe that an improved understanding of the role of multiple miRs targeting several different signaling pathways will provide novel and exciting therapeutic modalities. Furthermore, the use of specific miR mimics and inhibitors may become a main therapeutic method to treat or attenuate postischemic cardiac fibrosis and heart failure in the future. However, this potential therapy is currently inhibited by several concerns as follow:

1. Lack of complete understanding of the biology of miRs.
2. Besides one-to-one relationship between a miR and its target, it is likely that a single miR could regulate several target genes and vice versa. This implies that the specific miR therapy may have unknown side-effects.
3. miRs regulate each other, which makes the miR-based therapeutic approach more complex. Therefore, an appropriate understanding of the networks of miRs, their relationships with the fibrotic process, and their target genes are necessary before miRNA-based therapy can be developed to prevent cardiac fibrosis.
Figure. Pathways of regulation of fibrosis postinfarct by different microRNAs (miRNAs). Arrows depicting activation or inhibition between the indicators means that the upper indicator normally activates or inhibits the one below. Red or blue font color indicates that this indicator is upregulated or downregulated after myocardial infarction. Dotted line between miR-23 and transforming growth factor (TGF)-β1 means that miR-23 probably plays an antifibrosis role by inhibiting TGF-β1. *miR-214 inhibit sodium-calcium exchanger 1 (NCX1) but its upregulation after myocardial infarction is not enough to modulate fibrosis. Orange boxes refer to miRs and light green boxes refer to their target genes. ECM indicates extracellular matrix; FGF2, fibroblast growth factor 2; FOS, FBJ Osteosarcoma Oncogene; HMGB1, high mobility group box-1 protein; MAPK, mitogen-activated protein kinase; MeCP2, methyl-CpG-binding protein 2; MMP-2, matrix metalloproteinase 2; PI3K-Akt, phosphatidylinositol 3-kinase-protein kinase B; PTEN, phosphatase and tensin homolog; SMad2,3, Caenorhabditis elegans protein SMA and homologs of both the drosophila protein and mothers against decapentaplegic (MAD); Spry1, sprouty homolog 1; and TIMP-3, tissue inhibitors of metalloproteinase 3.

Disclosures

None.

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