Mycardin-Related Transcription Factor-A  
Mending a Broken Heart  
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Ventricular remodeling following myocardial infarction (MI) is a complex process driven by the response of both the myocytic and the nonmyocytic components of the heart to dynamic mechanical and neurohumoral stimuli. Despite the advent of reperfusion therapy and the administration of drugs slowing the progression of heart failure, many patients experiencing a MI undergo a progressive decline in ventricular function and deteriorating clinical course.1 Better understanding of the molecular and cellular pathways that influence ventricular remodeling following MI is needed to alter this commonly observed clinical scenario. Although a great deal is understood about the response of the cardiomyocyte to biomechanical stress, much less is understood about the response of the nonmyocytic component of the heart following MI (reviewed elsewhere2). In the acute post-MI setting, collagen accumulation develops in response to cardiomyocyte loss, a process referred to as “replacement fibrosis.” This process is believed to be critical to preserving the structural integrity of the heart. However, clinical studies have revealed that over time the accumulation of collagen and extracellular matrix (ECM) in the heart also contributes to the pathogenesis of ischemic cardiomyopathy and post-MI heart failure.3 As such, elucidation of the molecular and cellular mechanisms regulating fibrosis and scar formation following MI is critical to understanding the molecular and cellular pathways that influence ventricular remodeling in patients with ischemic heart disease.

The cardiac fibroblast comprises the majority (>90%) of the nonmyocytic component of the heart.4 Under homeostatic conditions, cardiac fibroblasts synthesize and secrete ECM components including collagens I, III, and IV, fibronectin, laminin, and elastin influencing the systolic and diastolic properties of the heart.2 Following an MI, in response to mechanical and stress-related signals, a subset of cardiac fibroblasts modulate their phenotype and become myofibroblasts, which are distinguished by their spindle-like morphology, high concentration of smooth muscle α-actin (SMA), and enhanced secretion of ECM (reviewed elsewhere2). Cardiac myofibroblasts migrate to the infarct zone where they secrete abundant ECM and organize and align collagen fibers, leading to myocardial scar formation. Cardiac myofibroblast conversion and activation occurs in response to biomechanical forces, neurohormones, cytokines, and growth factors, most notably transforming growth factor (TGF)-β.6 In animal models, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists have been shown to decrease myocardial fibrosis in the postinfarct setting.3 This has led some to suggest that the development of therapeutic compounds that block myocardial fibrosis may prevent and/or reverse heart failure in patients with ischemic (and nonischemic) cardiomyopathy.

In this issue of Circulation Research, Small et al present exciting new data showing that the transcriptional coactivator myocardin-related transcription factor (MRTF)-A plays a critical role in promoting the conversion of cardiac fibroblasts to myofibroblasts activating a fibrotic gene program.7 MRTF-A is a member of the MRTF family of transcriptional coactivators, which also includes myocardin and MRTF-B (reviewed elsewhere8). The human MRTF-A gene, which had previously been designated as MAL and MKL-1, is located on chromosome 22q13.2.9 MRTF-A is expressed in multiple cell lineages including undifferentiated embryonic stem cells and fibroblasts.10,11 MRTF-A is a remarkably potent transcriptional coactivator that physically associates with the MADS box transcription factor serum response factor (SRF) to synergistically activate transcription of a subset of CArG box-containing genes.9–11 MRTF-A and -B share multiple conserved domains including an N-terminal RPEL domain that facilitates binding to actin.8,12 Despite overlapping patterns of expression and conserved domains and structure, MRTF-A- and MRTF-B–null mutant mice display distinct phenotypes.13,14 Although there are many possible explanations for this surprising finding, it is most likely attributable to subtle differences in protein structure and/or differences in patterns of expression.10,11

The association of inducible transcriptional coactivators with transcription factors provides an efficient mechanism to expand and modulate information encoded within the genome. Transcriptional coactivators transduce signals regulating genes involved in cellular differentiation, migration, and proliferation. Because MRTF-A is able to transduce both biomechanical and humoral signals, it is particularly well suited to coordinate the response of the heart following an acute MI. MI and cardiac ischemia profoundly alter the biomechanical properties of the heart. As schematically depicted in the Figure, mechanical forces are transduced via Rho GTPases to the cytoskeleton.9 Activation of Rho induces actin polymerization via the Rho kinase (ROCK)/LIM kinase (LIMK)/cofilin pathway, stabilizing F-actin and promoting the assembly of G-actin monomers into F-actin filaments. In response to falling concentrations of G-actin, MRTF-A local-
izes to the nucleus, where it associates with SRF, enhancing
the binding of SRF to CArG box motifs.9,15 An MRTF-SRF
protein complex directly activates transcription of a subset of
CArG box–dependent genes including genes encoding com-
ponents of the cytoskeleton.16 As such, the Rho/actin/MRTF/
SRF signaling circuit represents a regulatory axis within the
cell that governs cell structure, adhesion, and motility.

As depicted in the Figure, MRTF-A also transduces TGF-β
signals to the nucleus via its capacity to physically associate
with receptor-activated Smads and/or directly activating
ROCK.16 This is particularly relevant in the setting of an MI,
because TGF-β is induced and rapidly activated in infarcted
myocardium.6 Latent TGF-β residing within the interstitial
space is activated by proteolytic cleavage and binds to cell
surface transmembrane receptors to activate Smad-mediated
transcription. In the days following infarction, activated
TGF-β stimulates the recruitment of monocytes to the infarct
zone, promoting the formation of granulation tissue.6 Subse-
sequently, TGF-β signaling is a major contributor to postinfarct
remodeling, acting via its capacity to activate cardiac fibro-
blasts and stimulate the secretion of ECM.2,5 Consistent with
this observation, Smad3-null mice display reduced myocar-
dial fibrosis following experimentally induced MI.17 From a
translational perspective, it is noteworthy that TGF-β expres-
sion in the infarcted heart is markedly attenuated by ACE
inhibitors and angiotensin receptor blockers.18

Small et al observed a discrete block in the conversion of
cardiac fibroblasts to myofibroblasts with a concomitant
reduction in expression of the smooth muscle cell (SMC)-
restricted contractile genes in MRTF-A–null mice.7 A hall-
mark of myofibroblast conversion is the induction of smooth
muscle α-actin (SMA) expression, as well as the expression
of other SMC lineage–restricted proteins.5 This reinforces the
cytoskeleton altering cell contractility and motility.2,5 Myofi-
broblasts in the perinfarct region closely resemble contractile
SMCs with a distinct spindle-like morphology and abundant,
highly organized stress fibers. As such, activation of the
contractile SMC gene program is a conserved function that
MRTF-A shares with other members of the MRTF gene
family.9 From an evolutionary standpoint, it is intriguing that
myocardin and MRTF-B loss-of-function mutant embryos
develop a spectrum of defects attributable to a block in SMC
differentiation, resulting in defective angiogenesis and vas-
cular patterning.13,19,20 By contrast, cardiovascular develop-
ment of MRTF-A–null mice is unperturbed.14 However,
MRTF-A–null mice have delayed development of mammary
myoepithelial cells, which is accompanied by decreased
expression of genes encoding SMC contractile proteins
including SMA, SM22, and SM-myosin heavy
chain.14 Mammary myoepithelial cells, although ectoder-
mally derived, also bear a striking resemblance to contractile
SMCs. They contain fine muscle filaments in their cytoplasm
required for oxytocin-stimulated contraction and release of
milk. Taken together, these data suggest that MRTF-A has
retained those aspects the SMC contractile gene program
required to enhance cell contractility and motility in non-
muscle cell lineages including the cardiac myofibroblast.

Small et al also identified an MRTF-A–regulated cardiac
fibroblastic gene program that is activated following MI.7
MRTF-A is a critical component of this pathway linking
biomechanical and stress-related signals to SRF-dependent
transcription of genes encoding ECM (Figure). Consistent
with this model, MRTF-A–null mice display a dramatic
reduction in the size of the fibrotic scar following experi-
mental MI. Similarly, myocardial fibrosis and scarring are mark-

Non-standard Abbreviations and Acronyms

- ACE: angiotensin-converting enzyme
- ECM: extracellular matrix
- MI: myocardial infarction
- MRTF: myocardin-related transcription factor
- ROCK: Rho kinase
- SMA: smooth muscle α-actin
- SMC: smooth muscle cell
- TGF: transforming growth factor

Cardiac Myofibroblast Activation

Figure. MRTF-A–regulated cardiac myofibroblast activation.

In response to TGF-β signaling, biomechanical forces and other
cytokines and growth factors, RhoGTPase is activated promot-
ing the assembly of F-actin filaments from monomeric G-actin
via the Rho effectors ROCK-LIMK and mDia. In response to fall-
ing concentrations of G-actin, MRTF-A associates with SRF in
the nucleus, facilitating the binding of an MRTF/CArG complex
to CArG boxes. This, in turn, activates transcription of genes
encoding a subset of contractile SMC proteins and fibrosis-
associated proteins including collagen Ia2. In addition, TGF-β
signaling induces the phosphorylation of receptor-activated
Smads, which form a complex with the common Smad4 and
translocate to the nucleus. In the nucleus, Smads associate with
MRTF-A, facilitating the binding of an MRTF-A/Smad complex
to transcriptional regulatory elements controlling transcription of
a subset of genes encoding contractile SMC proteins and fibrosis-associated proteins.
edly attenuated in MRTF-A–null mice following infusion of angiotensin II, demonstrating that activation of the fibrotic gene program is not restricted to the post-MI setting. As predicted by analyses of MRTF-A–null mutant mice, forced expression of MRTF-A in isolated cardiac fibroblasts stimulates collagen synthesis, which is further enhanced by TGF-β1 exposure and decreased by pharmacological blockade of ROCK. These data support the conclusion that MRTF-A sits at a nodal point in the fibrotic gene program, which is influenced by biomechanical and stress-related signals promoting the conversion of cardiac fibroblasts to myofibroblasts. Moreover, Small et al demonstrated that MRTF-A–induced activation of at least some ECM genes, including collagen type Iα2 (Col1a2), occurs via the direct binding of an MRTF-SRF complex to CArG boxes embedded within the promoter controlling transcriptional activity. Of note, the Col1a2 promoter contains both a nonconsensus CArG box and a consensus SMAD motif, suggesting that the combination of these 2 cis-acting elements may serve as a genetic signature for a cardiac fibrotic gene program.

Although the discovery of an MRTF-A–regulated molecular pathway driving cardiac myofibroblast conversion and activation represents an important advance, these findings also highlight gaps in our understanding of the molecular and cellular mechanisms regulating cardiac remodeling. Further studies examining the biology of the cardiac fibroblast are necessary to increase understanding of common pathologies associated with cardiac fibrosis including ischemic and nonischemic cardiomyopathy. Remarkably, we still do not know when, and under what circumstances, cardiac fibrosis is adaptive and beneficial and when it may be deleterious. The answer to this basic question is likely to be complex and dependent on specific temporal windows and pathological circumstances. Might blockade of myocardial fibrosis be therapeutically efficacious in certain forms of cardiomyopathy? Although the answer to this question remains to be determined, it is tempting to speculate that at least some of the benefit of ACE inhibitors, β-blockers, and aldosterone antagonists in the treatment of heart failure could arise from the blockade of myocardial fibrosis and the MRTF-A–regulated fibrotic gene program. In any case, the discovery of the MRTF-A–regulated fibrotic gene program opens up new avenues of investigation that are both fundamentally important and clinically relevant to understanding the pathogenesis of cardiac remodeling, cardiomyopathy, and heart failure.

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References


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