Cardiac hypertrophy is a pathological manifestation in the chronically stressed heart and a significant factor in the pathogenesis of heart failure. In the past decade, numerous intracellular signaling pathways and molecular mechanisms have been discovered in pathological hypertrophy, from transcriptional regulation to signaling cascades and from epigenomic modulation to redox homeostasis. It is clear that the regulatory network contributing to cardiac hypertrophy involves complex interactions between positive and negative regulators with different molecular and mechanistic characteristics.

Earlier studies, particularly Sadoshima and colleagues, have revealed the importance of thioredoxin (Trx)-mediated regulation of oxidative stress in cardiac hypertrophy, particularly through targeted modification of histone deacetylase (HDAC) class II and apoptosis signal-regulating kinase.1–7 These studies have contributed to the present understanding that oxidative injury is a major underlying mechanism and contributor of pathological hypertrophy in the diseased heart and established the mechanistic basis for antihypertrophic function of Trx-1. In this issue of Circulation Research, Yang et al from the Sadoshima group now report identification and functional characterization a microRNA, miR-98, as one potentially important downstream effector of Trx-1 in suppressing cardiac hypertrophy,8 representing another excellent showcase for intricate molecular networking in cardiac hypertrophy regulation that spans from redox regulation and epigenomic modulation to gene regulation.

Since establishing regulation of genes by small noncoding RNAs (miRNAs), the impact on cardiac biology has been anything but small. An explosion of reports on the discovery and characterization of different miRNA species and their involvement in almost every aspect of cardiac biology and diseases has established an exciting new dimension in gene regulation networks for cardiac development and pathogenesis.9,10 Early profiling studies identified scores of miRNA species that were up- and downregulated during cardiac hypertrophy.11–14 Subsequent characterizations established that some miRNAs induce or suppress cardiomyocyte hypertrophy. For example, in addition to critical roles in cardio-myocyte differentiation and normal development,15 miR-1 also negatively regulates myocyte size and endothelin-1– or isoproterenol-induced hypertrophy.16 A similar negative regulatory effect on hypertrophy was also demonstrated for miR-133.17 On the other hand, miR-23, miR-195, and miR-208 promote cardiac hypertrophy. Numerous downstream targets have been established for these miRNAs. Not surprisingly, some of the targets include well-established key transcription factors for cardiac hypertrophy, such as Gata4, Mef-2a, and NFATc4.16,18 In addition, other hypertrophy-related genes have been targeted by miRNAs as well, including MuRF1 (muscle-specific ring finger protein 1), RasGAP (GTPase-activating protein), Cdk9 (cyclin-dependent kinase 9), fibronectin, and Rheb (Ras homolog enriched in brain), RhoA, Cdc42, thyroid hormone receptor–associated protein 1, and myostatin, just to name a few.13,19–21

MiR-98 is a member of the let-7 family. Let7 family members are expressed in many tissues and at high levels in the heart.22,23 It has been shown that the expression of let-7 family members were upregulated by ischemia/reperfusion in mouse heart24 and in human failing heart.25–27 However, their function in hypertrophy regulation was never reported. In the present study,8 Yang et al found that miR-98 was also upregulated in pressure-overloaded or angiotensin II (Ang II)–treated hearts and isolated cardiomyocytes. One of the most intriguing findings from this report, though, is that miR98/let-7 appears to be a downstream effector of Trx1. First, they found that Trx1 overexpression was sufficient to induce the expression of several members of let-7 miRNA family, including miR-98 in cardiomyocytes. Furthermore, they demonstrated that Trx-1 expression was required for Ang II–induced miR-98 expression. More importantly, without miR98, Trx1 failed to suppress Ang II–induced hypertrophy, suggesting that miR98 is indispensable for the antihypertrophic function of Trx1. These experiments provide a compelling argument that miR-98 is a downstream effector of Trx1 and critical to Trx1-mediated antihypertrophy function in cardiac hypertrophy. Therefore, in addition to modulating the oxidative activation of stress kinases, class II HDACs, and transcription factor, a nonprotein player at epigenomic level was added into this complex negative feedback scheme of hypertrophy regulation (Figure).

Yang et al went further to characterize cyclin D2 as a functional target of miR98.8 They showed that miR-98–regulated Ang II–induced cyclin D2 expression via a specific binding motif in the cyclin D2 3′ untranslated region, and Trx1 overexpression decreased the level of cyclin D2 in a miR-98–dependent manner. They also showed that knockdown of cyclin D2 attenuated Ang II–induced hypertrophy and miR98-mediated suppression of hypertrophy was attenuated by overexpression of cyclin D2. This is consistent with the conclusion that miR98 functions as a key player in an
intricate negative-feedback loop for hypertrophy regulation. However, a major caveat in this conclusion is that most of the experimental data are established in cultured myocytes or acutely treated hearts via adenovirus vectors; thus, the exact role of miR98/cyclin-D2 axis in cardiac hypertrophy needs further examination with better genetic tools. In fact, miR-133 was shown to suppress cardiac hypertrophy in vitro and in vivo using acute knockdown approaches but had no significant impact on cardiac hypertrophy in genetic knockout model.28 Therefore, possibility of off-target effects and compensatory changes may complicate the observation and conclusions.

Comprehensive as a single report, this study also opens many more questions that need to be addressed. The underlying mechanisms of Trx1-mediated miR98 induction are unclear. Is this a general response to the antioxidative effect of Trx1 or through another Trx1-dependent pathway? Because several members of the let-7 family other than miR-98 are also upregulated by Trx1, do they share similar function in hypertrophy regulation? In addition to cyclin D2, other downstream targets of miR98 might also contribute to its antihypertrophic effect. The authors of the present report noted that miR-98 inhibits NFAT signaling pathway in cardiomyocytes, but limited information was provided.8 More importantly, this report focuses mostly on the effect of hyper trophy in terms of myocyte size, whereas other associated pathological changes from contractility and metabolism to electrophysiology are not fully addressed. It needs to be established whether miR98 is involved solely in reducing myocyte hypertrophy or also directly or indirectly attenuates other aspects of cardiac pathologies. Finally, the expression pattern and the potential role of miR98 in human hypertrophic cardiomyopathy is unknown.

Nevertheless, this study offers a real opportunity for translation into a targeted therapy for hypertrophy. The functional relevance of miR98 in hypertrophy, as demonstrated from this study by both loss-of-function and gain-of-function approaches in intact hearts, provides a proof of concept that targeted expression of miR98 may attenuate pathological hypertrophy and improve the clinical outcome. Although Trx1 is a potent suppressor of pathological hypertrophy, it would be a major challenge to manipulate the Trx1 gene expression or protein function in intact hearts via gene or protein therapy.1 In contrast, long-term administration of miRNAs or antagoners can now be achieved via systemic delivery.29,30 The discovery of miR-98 as a downstream mediator of Trx1 should provide another valuable target of intervention for cardiac hypertrophy. The study is yet another piece of evidence that the impact of small RNA in cardiac biology and therapy is only getting bigger.

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References


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