4. Park K, Youn TJ, Park KW, et al. Physiologic evaluation of myocardial bridging: a new analysis for an old disease. Can J Cardiol 2011;27:596–600.

5. Samady H, Eshtehardi P, McDaniel MC, et al. Coronary artery wall shear stress is associated with progression and transformation of atherosclerotic plaque and arterial remodeling in patients with coronary artery disease. Circulation 2011;124:779–88.

MicroRNA-29, a Mysterious Regulator in Myocardial Fibrosis and Circulating miR-29a as a Biomarker

Myocardial fibrosis is characterized by pathological modification of myocardium, in which cardiomyocytes undergo apoptosis and the heart tissue is replaced by fibroblasts; this phenomenon is usually referred to as cardiac remodeling. However, the pathogenesis of myocardial fibrosis is still unclear despite advances in our understanding of the ischemic process.

MicroRNAs (miRs), small endogenous noncoding RNAs, have a well-documented role in the regulation of the cardiovascular system. miRs such as miR-29 and miR-21 have been shown to have a role in the genesis of myocardial fibrosis.

Roncarati et al. (1) measured a set of miRs in the plasma of patients with hypertrophic cardiomyopathy to understand which miRs can be regarded as biomarkers of this disease. Only miR-29a levels were found to correlate with cardiac fibrosis, along with several miRs related to cardiac hypertrophy. This discovery is significant in that it may help define patients who may develop fibrosis. However, it is important to know where miR-29a comes from and what types of cells, cardiomyocytes or fibroblasts, secrete it. Previous studies have shown the opposite effect of miR-29 in different types of cells (2–5). On one hand, miR-29 can promote cardiomyocyte apoptosis via down-regulation of antiapoptosis genes, such as Bcl-2, CDC42, and Tcl-1 (2–4); on the other hand, miR-29 can protect against fibrosis through inhibition of collagens released from extracellular matrix (5). Because the majority of cell types change from cardiomyocyte to myofibroblast phenotype during progression of cardiac remodeling, it is reasonable to hypothesize that up-regulation of miR-29a in the plasma of these patients is mainly due to cardiomyocyte apoptosis and not secretion from fibroblasts. It is also possible that the up-regulation of miR-29a in plasma reflects the body's attempt to express more fibrosis-protective mediators to prevent adverse cardiac remodeling.

Cardiac remodeling is a complicated process that involves a number of molecular and pathological alterations (5). A simple measurement of miRs at one time point may not be enough to define molecular changes. Identification of miR-29a (and other miRs) in different cell types and at different time points is necessary before recognizing it as a biomarker for cardiac remodeling.

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REFERENCES

1. Roncarati R, Viviani Anselmi C, Losi MA, et al. Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2014;63:920–7.

2. Pekarsky Y, Santanam U, Cimmino A, et al. Tcl1 expression in chronic lymphocytic leukemia is regulated by miR-29 and miR-181. Cancer Res 2006;66:11590–3.

3. Mott JL, Kobayashi S, Bronk SF, Gores GJ. Mir-29 regulates Mcl-1 protein expression and apoptosis. Oncogene 2007;26:6133–40.

4. Wang H, Garzon R, Sun H, et al. NF-kappaBYY1-miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma. Cancer Cell 2008;14:369–81.

5. van Rooij E, Sutherland LB, Thatcher JE, et al. Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. Proc Natl Acad Sci U S A 2008;105:13027–32.

REPLY: MicroRNA-29, a Mysterious Regulator in Myocardial Fibrosis and Circulating miR-29a as a Biomarker

We thank Dr. Dai and colleagues for their interest in our paper (1). As their letter suggests, it is possible that microRNA (miR)-29 is secreted by more than one cell type. However, our intention was not to address this question, which has been partly done and should be tackled further in other settings and with appropriate technologies (tissue-specific knockout mice, transgenic mice, and so on); we simply found a significant correlation between a few circulating miRs, in particular miR-29a, and the degree of cardiac fibrosis in patients with hypertrophic cardiomyopathy.

We therefore agree with the concept expressed in the letter by Dr. Dai and colleagues that miR-29s are expressed in many cell types, where it probably plays

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a critical regulatory role. As stated in the letter, this miR family has been found to be an important player not only in fibroblasts and fibrosis but also in regulating the functions of macrophages and other inflammatory and immune cell types. It is worth noting that inflammation precedes or accompanies fibrosis. Fibrosis and inflammation are therefore 2 highly correlated phenomena. It is also possible, even though not yet proven, that miR-29s play a role in cardiomyocytes. As previously noted, more experimental studies need to address these important questions. The published data today show that a nonselective, ubiquitous knockout of miR-29s affects cardiac fibrosis in mice. To determine which cell type is responsible for this phenomenon, miR-29 cell-specific knockout approaches are needed.

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REFERENCE

1. Roncarati R, Viviani Anselmi C, Losi MA, et al. Circulating miR-29a, among other up-regulated microRNAs, is the only biomarker for both hypertrophy and fibrosis in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2014;63:920–7.