Plasma MicroRNA Clusters in Human Left Ventricular Remodeling

A Biomarker and Discovery Platform

See Article by Shah et al

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Impaired cardiac function results in increased neurohormonal activity, a stress response initially mounted to augment cardiac output. However, chronic or excessive activity of the neurohormonal response contributes to progressive myocardial damage and the clinical manifestations of the heart failure (HF) syndrome.[1] This myocardial injury leads to a vicious cycle of organ remodeling, wherein the shape, thickness, volume of the ventricular cavity, and the functional state of the cells populating the stressed heart are adversely altered in a manner that further compromises cardiac performance.[1,2] Early work in animal models of myocardial infarction demonstrated the pathophysiologic significance of cardiac remodeling and a role for neurohormonal blockade in its prevention and reversal.[2] These findings were subsequently extended to humans with myocardial infarction–associated HF and cardiac dilation in the absence of HF, with the severity of remodeling serving as a poor prognostic indicator.[3,4] Current guideline-directed medical therapy for HF is associated with regression of ventricular dilation and improvement of ejection fraction in a subset of patients, a process called left ventricular reverse remodeling (LVRR). As LVRR has emerged as a strong predictor of improved outcomes in HF patients,[5,6] understanding the molecular determinants of LVRR in humans and developing improved molecular biomarkers that predict LVRR are of great clinical interest. In this issue of *Circulation: Heart Failure*, Shah et al[7] implicate a panel of plasma microRNAs (miRNAs) as predictors of LVRR in a cohort of patients with HF with reduced ejection fraction, findings which may point to novel mechanisms of human HF pathogenesis.

miRNAs are a class of 19 to 25 nucleotide endogenous single-stranded noncoding RNA molecules that regulate gene expression post-transcriptionally through limited complementary base-pair sequence interactions with their target mRNA transcripts.[8] By virtue of the limited nature of this base-pairing interaction, individual miRNAs have multiple target mRNAs and thereby orchestrate regulation of multiple biological pathways and coordinated cellular processes.[9] Several individual miRNAs have been implicated in cardiovascular disease and development,[10] and strategies to modulate the function of specific miRNA molecules are being considered as novel therapeutics for HF.[11] Although many studies have profiled miRNA expression from human cardiac tissue,[12,13] this approach is not readily adapted for the discovery of prospective biomarkers of LVRR. The existence of extracellular circulating plasma miRNAs that are both stable and easily detectable has made this class of molecules attractive candidates as clinically useful biomarkers for a host of human diseases.[14] In contrast to studies of individual miRNA species in model organisms or the miRNA expression patterns from human LV samples, there is far less known about the profile and significance of plasma miRNAs in HF patients.

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Shah et al[7] hypothesized that a panel of plasma miRNA species assayed from patients with chronic HF with reduced ejection fraction could prospectively discriminate the subset of patients who went on to have favorable LVRR. They leverage a novel platform for plasma miRNA quantification to prospectively interrogate a cohort of carefully phenotyped HF patients in whom serial, high-quality 2-dimensional echocardiograms were performed at defined intervals. They coupled their human observations with network bioinformatics approaches and miRNA profiles in animal models of HF to identify miRNAs associated with LVRR. The investigators studied a subset of 64 patients with both ischemic and nonischemic HF with reduced ejection fraction from the PROTECT trial (Pro-BNP Outpatient Tailored Chronic HF Therapy),[15] a single-center, prospective, randomized controlled trial of 151 patients with left ventricular ejection fraction <40% whose goal was to evaluate whether NT-proBNP (N-terminal pro-B-type natriuretic peptide) biomarker-directed medical therapy was superior to standard medical therapy alone. In 64 patients from PROTECT, they prospectively measured serum concentration of 51 miRNAs and identified 11 that were associated with echocardiographic evidence of LVRR after an average of 10 months of guideline-based medical therapy. In this study, LVRR was defined as a 15% reduction in LV end-systolic volume index. Importantly, the miRNA-based prediction model provided improved risk discrimination for LVRR over a standard clinical criteria-based model. The investigators then used bioinformatics approaches to identify the predicted target genes of these miRNAs, analyses which suggested a significant degree of target gene overlap between these candidate miRNAs. To support the contention that these plasma miRNAs could originate from the stressed myocardium, the investigators demonstrated that several of the plasma miRNAs they identified as being associated with LVRR in human HF are also dysregulated in heart tissue of mice subject to LV pressure overload and in cultured neonatal rat cardiomyocytes stimulated with the adrenergic agonist phenylephrine. Of note, they found that many of these miRNAs were expressed in multiple cell types that populate the heart, including cardiomyocytes, fibroblasts, and endothelial cells.

This study takes a unique translational approach to biomarker discovery in the context of HF that identifies novel clusters of miRNAs that prospectively discriminate patients who develop LVRR on medical therapy. In addition, the prediction of putative miRNA-regulated gene products simultaneously serves as a discovery platform for identification of novel HF-associated molecular pathways in humans. As the authors discuss, future studies using a larger sample size and subsequent validation in an external cohort are essential to bolster the generalizability of their findings. Gain- and loss-of-function analyses of some of these individually identified miRNAs have been previously performed in animal models,[16–18] supporting that dysregulation of these miRNAs plays a causal role in cardiovascular pathophysiology. Importantly, the authors find that several of the plasma miRNAs that are associated with human LVRR have overlap in their predicted targets genes, including several targets which have not previously been implicated in HF pathogenesis. Therefore, the findings in this human translational study should catalyze further experiments to more precisely elaborate the role of these miRNAs and their putative target genes in models of HF and suggest that this plasma miRNA profiling approach can serve as a discovery tool that is relevant to a broad array of cardiovascular diseases. A critical aspect of this work that will certainly require further investigation is the precise identification of the cell types of origin for these human plasma miRNAs. As HF is a systemic syndrome in which dysfunction of multiple organs contributes to disease progression, it remains possible that these miRNAs may have extracardiac sources that are relevant to the mechanisms of HF pathogenesis and the use of these miRNAs as biomarkers. For example, miRNA-193b-5p is expressed not only in the heart but also in kidney, bladder, breast, pancreas, and testis,[19,20] suggesting that it may be released by several other tissues in the setting of cardiac stress. Ultimately, direct experimental evidence in model systems will be required to confirm the dominant tissues of origin and relevant downstream targets for these plasma miRNA species in the setting of cardiac remodeling.

This report by Shah et al[7] highlights the strength of leveraging a well-characterized human HF cohort with molecular interrogation of human plasma and animal models to gain novel insights into the mechanisms underlying reverse myocardial remodeling. In addition to its worthy goal of developing better clinical biomarkers for predicting outcomes in HF patients, studies such as this highlight the value of well-designed clinical trials as a molecular discovery platform. When interwoven with rigorously controlled and mechanistically based experiments in model systems aimed at precisely defining the function of these miRNAs, human studies like this lay the foundation for the development of novel HF therapeutics that can be tailored for patient subsets with the greatest likelihood of benefit.

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DISCLOSURES

Dr Haldar is a shareholder and consultant for Tenaya Therapeutics. The other author reports no conflicts.

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FOOTNOTES

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