Correspondence

Response to Letter Regarding Article, “Circulating MicroRNA-30d Is Associated With Response to Cardiac Resynchronization Therapy in Heart Failure and Regulates Cardiomyocyte Apoptosis: A Translational Pilot Study”

We thank Sardu and colleagues for their comments. Our report demonstrates that baseline levels of microRNA-30d (miR-30d) are correlated with response to cardiac resynchronization therapy and that miR-30d was dynamically regulated by mechanical stress. Moreover, miR-30d appeared to be an adaptive response and was cardioprotective against tumor necrosis factor-α–mediated apoptosis. Similar to our study, Marfella et al noted differential expression of several plasma miRNAs in cardiac resynchronization therapy responders versus nonresponders 1 year after cardiac resynchronization therapy. The lack of significant overlap between the sets of extracellular miRNAs reflects some of the ongoing issues in extracellular RNA research. The first issue is differences in patient populations and small sample sizes. The second is variances in methodology. Several groups, including ours, have noted that differences in the manner of acquisition/storage of archived biofluid specimens, RNA isolation methods, and platforms for measuring extracellular RNAs can have significant effects. The third issue is a lack of adequate normalization strategies for extracellular RNAs, leading to the use of spike-ins for normalization (does not normalize for sample quality).

Nonetheless, several intriguing themes emerge when the 2 studies are compared. Most notably, the candidate miRNAs appear to play a functional role in cellular processes relevant to cardiac remodeling. Second, although miR-30d was downregulated in our study after cardiac resynchronization therapy in responders, levels of miR-30d were higher in responders compared with nonresponders (much like the candidates in the work by Marfella and colleagues). We focused on miR-30d in our article, given that it was the leading candidate from our clinical cohort. Nevertheless, we agree with Sardu et al that other members of the miR-30 family—and other extracellular miRNAs that are differentially present in responders versus nonresponders—may indeed play complementary roles in cardiac remodeling. Specifically, the miR-30 family is particularly interesting in that it is altered in several models of cardiovascular diseases and appears to modulate central molecular pathways in cardiac remodeling, including inflammation, apoptosis, autophagy, and the cellular response to adverse neurohormonal signaling (eg, angiotensin II). In our study, we not only demonstrated the antiapoptotic role for miR-30d but also showed that it blocked tumor necrosis factor-α–induced markers of pathological hypertrophy. Ultimately, the proof of the adaptive role for miR-30 family members in cardiac diseases will have to come from in vivo gain-of-function/loss-of-function experiments. Such experiments would ultimately strengthen the notion that extracellular RNA biomarkers may play a functional role in disease pathogenesis, a new frontier of molecular biomarkers of disease and personalized medicine.

Disclosures

None.

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