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REPLY: The Complex miRNAs-p53 Signaling Network in Cardiovascular Disease

We appreciate the comments by Dr. Patanè on our review on microribonucleic acids (miRNAs) in cardiovascular disease. To concisely summarize the current knowledge and give our opinion on the way ahead, we have selected key publications that illustrate the great potential of this type of noncoding RNA. The vast number of studies that have been published in the past decade in this field require a balance between addressing the full breadth of cardiovascular disease, and a thorough critical appraisal of these fields.

With this in mind, we briefly touch on miRNA effects on cardiomyocyte apoptosis and regeneration. We highlight the study by Boon et al. (1), reporting a regulatory function of miR-34a on cardiomyocyte survival. These results build on previous studies with an oncological focus, reporting this miRNA to be induced by p53 and acting as a proapoptotic signal (2). On the other hand, miRNAs such as miR-590 and miR-199a were shown to promote cardiomyocyte proliferation through cell cycle re-entry (3). miR-199a has also been shown to reduce p53-mediated apoptosis in hypoxic cardiomyocytes (4). These studies illustrate the role that miRNAs seemingly play in apoptosis and proliferation, including the p53 pathway.

Steering cardiomyocytes toward regeneration can certainly be seen as a "Holy Grail" for heart failure therapy, and we applaud all efforts to further elucidate the mechanisms that are at play. On the other hand, there are profound differences in both miRNA expression and structural protein regulation between the (regenerative) zebrafish heart and the (proliferative) neonatal mouse heart compared with the adult mouse heart and human cardiomyocytes that lack these endogenous repair mechanisms (5). In our review, we aim to emphasize the systemic effects of miRNAs that come as a consequence of their expression across tissues and cell types. This is just as true for p53-related actions of miRNAs as it is for any others, on one hand protecting against dysplasia and on the other hand restricting repair of dysfunctional tissue in the failing heart. The lack of techniques that selectively target miRNAs in the heart remains a major impediment to clinical utility. Therefore, we argue for comprehensive evaluation of miRNA effects that takes into account their ubiquitous expression.

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Deep Learning With Unsupervised Feature in Echocardiographic Imaging

We read with interest the paper by Narula et al. (1) in which supervised machine learning (ML) was applied to speckle tracking echocardiography (STE) to differentiate hypertrophic cardiomyopathy from athlete's heart. The authors demonstrated the potential of ML in echocardiographic imaging by performing 3 ML algorithms included artificial neural networks, support vector machines, and random forests using 9 subsets for training and then 1 subset for prediction. In the realm of Big Data, ML is revolutionizing the echocardiographic imaging. Recently, preliminary data showed that ML algorithms using STE data might be useful for assessment of left ventricular filling pressures (2). In addition, Sengupta et al. (3)