Molecular Therapy
Nucleic Acids
Commentary

miRNAs to the rescue: Reversing heart failure by targeting miR-29

Xinghua Wang,[1] Iqra Anwar,[1] and Conrad P. Hodgkinson[1]

https://doi.org/10.1016/j.omtn.2023.102105

Heart failure is a condition whereby the heart is unable to pump enough blood to meet the body's needs. Commonly, heart failure arises from damage to the heart muscle. Heart muscle damage can occur from myocardial infarction (heart attack), coronary heart disease, inflammation, elevated blood pressure, cardiomyopathies, or an irregular heartbeat. The incidence of heart failure is high and is projected to markedly increase over the coming decades. While therapies can manage the condition with respect to quality of life, there are no cures, and heart failure remains irreversible. In that light, it is with interest that Zhang and colleagues were able to prevent heart failure in mice by targeting miR-29.[1]

In their report, Zhang and colleagues build on previous evidence that miR-29 is a potentially attractive target for reversing heart failure (Figure 1).[2] Through the expression of a novel transgene inhibitor, the authors demonstrated that reducing miR-29 expression prevented many of the cardiac problems that come with pressure-overload-induced heart failure.[1] Where the study is particularly notable is its focus on mechanism and therapy. With respect to mechanism, the authors identified novel targets for miR-29 including genes associated with calcium handling, cell stress and hypertrophy, metabolism, ion transport, and extracellular matrix remodeling. The therapeutic direction the authors adopted was particularly innovative and is called "tough-decoy." With "tough-decoy," an RNA molecule is expressed with two microRNA (miR) binding sites. Essentially, these "tough-decoy" RNA molecules act as miR sponges and sequester the miR from binding to target molecules.[3] In their iteration of the technique, the authors generated a U6-driven "tough-decoy" RNA that comprised a stem-loop structure capable of sequestering two miR-29 molecules. Through the "tough-decoy" approach, the authors observed significant increases in the expression of the miR-29 targets Ryr2, Serca2, and Bdh1 *in vivo*. Refining the approach further, the authors expressed their "tough-decoy" miR-29 inhibitor via the cardiomyocyte tropic virus adeno-associated virus serotype 9 (AAV9), thus targeting the cells that express the majority of miR-29 in the failing heart.[1] The approach is an elegant one, and it will be interesting to see how the group furthers their technology in large-animal models. On that point, it is perhaps important to note that the miR-29 sequence and miR-29 targets are apparently conserved in mammals. This is a common feature of miRs and would be expected to facilitate their progression from small-animal models to large animals and ultimately humans. However, it is likely that the approach will need modification. Many people naturally have AAV-neutralizing antibodies. Moreover, AAV9 targets other organs besides the heart. Thus, it would be necessary to more precisely target the miR-29 inhibitor to the cardiomyocyte via injection of the virus into the heart, express the miR-29 inhibitor with a cardiomyocyte-specific promoter, or find an alternative to AAV delivery. Similarly, it will be important to ascertain the target populations for which this approach would be useful. It is clear that the authors' approach could be used in a preventative manner, targeting populations that are susceptible to developing heart failure. It is less clear if the approach could be applied to reversing established heart failure. Preventing damage versus reversing the effects of damage often employ distinct mechanisms.

The study of Zhang and colleagues is another elegant example of the power of miRs. In the literature, miRs are commonly referred to as master regulators. Since miRs do not require perfect pairing to their mRNA targets, a single miR typically binds to multiple targets.[4] This is especially important in complex diseases such as heart failure, where multiple pathways are involved. Despite this, the utility of miRs to target multiple pathways has not been harnessed to any great degree by the medical community, and clinical trials involving miRs are rare. Generally, the emphasis remains on single-target methodologies. However, this may not be the best tactic. One example of why is provided by hypertension management. A small fraction of hypertensive patients can be classified as monogenic or primary. Monogenic hypertension, which is rare, results from a gain- or loss-of-function mutation in a single gene. As such, monogenic hypertension is relatively easy to treat with a single pharmacological agent. However, primary hypertension, by far the most dominant form, results from environmental factors combining with small effects arising from mutations in multiple genes. This is harder to treat with a single agent, and indeed, primary hypertension is often poorly controlled in a large number of people.[5] It would seem that complex diseases, such as hypertension, are ideal candidates for a miR-based therapy.

Similarly, the study of Zhang and colleagues highlights the impact of aging on cardiac disease. General wear and tear increases the risk of heart failure, and the authors referred to previous work identifying increases in miR-29 expression as the heart ages. Moreover, the authors found in their sequencing datasets of miR-29 targets that a number of aging-related genes were among the top hits. Of note, the authors demonstrated that reversing an aging process was beneficial.

[1]Mandel Center for Heart and Vascular Research, and the Duke Cardiovascular Research Center, Duke University Medical Center, Durham, NC 27710, USA

Correspondence: Conrad P. Hodgkinson, Mandel Center for Heart and Vascular Research, and the Duke Cardiovascular Research Center, Duke University Medical Center, Durham, NC 27710, USA.
E-mail: conrad.hodgkinson@duke.edu

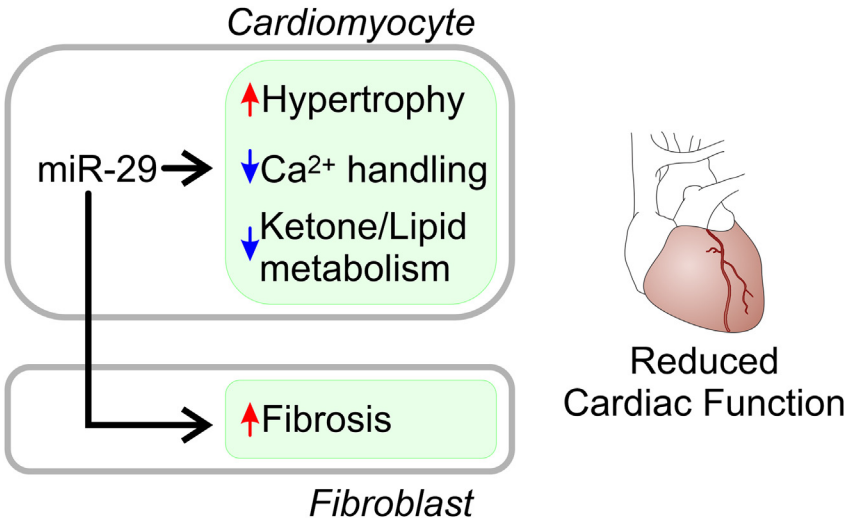

Figure 1. The roles of miR-29 in the failing heart

The study of Zhang et al. indicates that increased miR-29 expression in cardiomyocytes reduces cardiac function via several mechanisms. Cardiomyocytes become hypertrophic, with corresponding deleterious changes in metabolism and calcium handling. Moreover, cardiomyocytes secrete factors that induce fibroblasts to produce fibrotic proteins. Importantly, the authors demonstrated that these effects can be prevented by sequestering miR-29.

In the absence of any injury, reversing age-related increases in miR-29 expression via their miR-29 inhibitor increased end-diastolic volume, stroke volume, and cardiac output by ~20%.[1] In a broader context, other studies have also shown that there is a therapeutic benefit in reversing aging-related effects. In mammals, cardiac muscle cells (cardiomyocytes) quickly exit the cell cycle and remain quiescent for the remainder of life. Similarly, cardiac fibroblasts slowly transition from producing certain collagens to expressing inflammatory proteins. Both events are deleterious, as cardiomyocyte quiescence prevents the heart from making new muscle following injury and inflammatory proteins provided by fibroblasts worsen outcomes. Reversing the respective aging processes, whether by forcing cardiomyocytes to re-enter the cell cycle or by manipulating genes involved in fibroblast aging, improves cardiac function in myocardial infarction models of cardiac injury.[6] As highlighted by these studies by Zhang and colleagues, understanding and manipulating the mechanisms of cardiac aging appear to be fruitful avenues for the development of future therapeutics.

In summary, Zhang and colleagues provide an interesting study highlighting the importance of miR-29 in heart failure and describe an innovative method for targeting the miR *in vivo*. Moreover, in a wider context, the study provides another important example of the strengths of miRs as therapeutic agents.

ACKNOWLEDGMENTS

The authors are funded by the Edna and Fred L. Mandel, Jr. Foundation.

AUTHOR CONTRIBUTIONS

I.A., X.W., and C.P.H. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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