Published in final edited form as:

J Heart Lung Transplant. 2014 March ; 33(3): 233–234. doi:10.1016/j.healun.2013.12.020.

One Generation's "Junk" is Another's Treasure: the emerging role of miRNAs as therapeutic targets

Evan L. Brittain, MD^a and Anna R. Hemnes, MD^b

^aDivision of Cardiovascular Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

^bDivision of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

Heart failure is the leading cause of death in the Western world and the incidence and prevalence are expected to rise in aging populations.¹ Advances in revascularization strategies and medical therapies targeting neurohormonal blockade have dramatically improved HF survival over the last two decades resulting in an increase in the prevalent HF population. However, the rate of HF survival may be plateauing due to lack of new therapeutic targets that are not redundant with available medication classes. Indeed recent trials of new medications in heart failure have shown only incremental if any improvements in mortality. Therefore, the development of novel therapeutic strategies is a critical area of focus for cardiovascular researchers.

Since their discovery in *C. elegans* in 1993, small non-coding RNAs or microRNAs (miRNAs) have emerged as an area of intense investigation across nearly all biomedical fields (Figure 1).² miRNAs are small (21–23 nucleotides) single strands of RNA transcribed from miRNA genes, most often intronic. After post-transcriptional processing, miRNAs targets complementary sequences on messenger RNAs (mRNAs) usually resulting in mRNA degradation. To date, over 25,000 miRNAs have been described in 193 species including 2000 distinct miRNAs in humans.^{3,4} The biologic function and clinical implications of the vast majority of the human miRNA have yet to be fully elucidated.

The first discovery of a role of miRNA in human heart failure came in 2006 with the demonstration of differential miRNA expression patterns in normal vs. failing hearts.⁵ miRNAs have subsequently been shown to play a role in the regulation of cardiac development and regeneration, cardiac hypertrophy, development of fibrosis, and electrophysiological remodeling among other functions.

In this issue of *The Journal of Heart and Lung Transplantation*, Kreth et al provide evidence for a role of miRNAs in the regulation of the insulin-sensitizer adiponectin in human and experimental heart failure. (Ref when available) Adiponectin has numerous salutary effects on the cardiovascular system including improvement in endothelial cell function and anti-hypertrophic and anti-atherogenic properties. These findings have translated to important clinical observations including increased risk of myocardial infarction and systemic hypertension in patients with low adiponectin levels. Conversely, elevated levels of adiponectin have been observed in patients with heart failure leading to the "adiponectin

resistance” hypothesis whereby the failing heart is resistant to the beneficial effects of adiponectin. The authors sought to evaluate the function of adiponectin receptors on cardiomyocytes and possible regulation by miRNAs.

Consistent with prior reports, the authors found elevated serum levels of adiponectin in patients with HF compared to controls. By then measuring mRNA and protein in the myocardium from HF patients and non-HF controls, the authors determined that elevated adiponectin was not due to excess production from the myocardium. In contrast, the authors found increased expression of Adiponectin 1 and 2 (ADIPOR1, ADIPOR2) as well as downstream mediators APPL1 and AMPK in atrial and ventricular tissue in HF compared to controls. Using small interfering RNA, the authors knocked-down DICER, a key miRNA processing protein, in human cultured cardiomyocytes and found a preferential increase of ADIPOR2 with no effect on ADIPOR1 indicating likely regulation of ADIPOR2 by miRNA. Based on an *in silico* analysis of the 3'UTR sequence analysis, the authors identified miR-150 as a likely target of ADIPOR2. Premir-150 overexpression in cultured cardiomyocytes led to a 60% decrease in ADIPOR2 mRNA and protein expression.

In human myocardium, the authors found increased expression of mir-150 in both CHF and control samples with a 1.7 fold increase in CHF. The correlation between miR-150 and ADIPOR2 expression in individual CHF patients was borderline significant. To test the functional significance of ADIPOR2 in the setting of myocardial stress, the authors showed that knock-down of ADIPOR2 with siRNA resulted in increased apoptosis and decreased cell proliferation in cells exposed to hypoxia and serum starvation. The addition of miR-150 to the stress model reduced downstream mediators of ADIPOR2 similar to ADIPOR2 knock-down with siRNA.

This report by Kreth et al confirms previous findings of elevated adiponectin and up-regulation of adiponectin receptors in HF and provides important new evidence of ADIPOR2 down-regulation by miR-150 in human heart failure. Because adiponectin has numerous beneficial cellular effects, the authors hypothesize that the failing heart is in a state of “adiponectin resistance.” The implication of the present findings is that increased myocardial expression of miR-150 in HF prevents an adequate increase in ADIPOR2 and the myocardium suffers as a consequence. Several limitations of the study deserve comment. First, the mechanism of increased miR-150 in heart failure is unexplored. miR-150 is not cardiac specific, therefore measurement of miR-150 in the serum of HF patients would have assisted in determining whether the site of regulation is peripheral or cardiac. Second, use of an animal heart failure model to test the effect of antagonizing miR-150 would have provided stronger evidence for the role of this miR and adiponectin resistance in the pathogenesis of heart failure. Nonetheless, this report provides the basis for future human and animal studies testing the role for miR-150 and adiponectin in heart failure development and propagation.

Therapeutic potential of miRNAs

While miRNAs show great promise as a novel class of therapeutics for HF, several practical concerns surrounding clinical implementation deserve comment. First, a single miRNA can

target several mRNAs, often coding for functionally similar proteins. This is a potential advantage in that complete pathways may be targeted with a single therapy; however, mRNAs in unrelated pathways may result in unwanted or even detrimental off-target effects. Second, the optimal delivery method of miRNAs or miRNA scavengers remains to be determined but several innovative techniques are presently being tested in pre-clinical models. Existing methods include cholesterol conjugation of miRNA antagonists (antagomirs) to allow cellular entry, adeno-associated virus vectors, nanoparticle delivery, and miRNA sponges that bind the miRNA of interest within a cell.

New technologies now allow rapid detection and quantification of thousands of miRNAs permitting researchers to elucidate the specificity of miRNAs for tissues, cells, and biologic pathways. This technology also allows exploration of miRNA as biomarkers of disease presence and severity. Previously thought to be functionally inconsequential “junk” DNA, non-coding portions of the genome now hold potential to be the next great therapeutic advance in heart failure.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013; 127(1):e6–e245.10.1161/CIR.0b013e31828124ad [PubMed: 23239837]
2. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in *C. elegans*. *Cell*. 1993; 75(5):855–862. [PubMed: 8252622]
3. Kumarswamy R, Thum T. Non-coding RNAs in cardiac remodeling and heart failure. *Circulation Research*. 2013; 113(6):676–689.10.1161/CIRCRESAHA.113.300226 [PubMed: 23989712]
4. Elzenaar I, Pinto YM, van Oort RJ. MicroRNAs in heart failure: new targets in disease management. *Clin Pharmacol Ther*. 2013; 94(4):480–489.10.1038/clpt.2013.138 [PubMed: 23852395]
5. van Rooij E, Sutherland LB, Liu N, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci USA*. 2006; 103(48):18255–18260.10.1073/pnas.0608791103 [PubMed: 17108080]

Figure 1.