Regulation of physiological cardiac hypertrophy by microRNAs

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MicroRNAs are small, highly conserved non-coding RNAs that target specific complementary sequences in the 3′ untranslated region of target mRNA, leading to mRNA cleavage and/or translational repression. MicroRNAs are involved in a range of biological processes, including proliferation, apoptosis, and differentiation. Among the microRNAs discovered to date (>1000 human microRNAs), both muscle-specific and more ubiquitously expressed microRNAs have been shown to be essential for myogenesis and muscle regeneration following injury, and for cardiac function, pathology and hypertrophy. Moreover, microRNAs are also dysregulated in settings of disease (including muscle-related and cardiac diseases), and have emerged as novel therapeutic targets for numerous pathologies, thus their potential as therapeutic drug targets is being widely explored. As the majority of studies investigate microRNAs that are associated with pathological processes in the heart (*i.e.* pathological cardiac hypertrophy – 'detrimental' heart growth associated with increased risk of heart failure), we set out to identify microRNAs regulated in physiological heart growth (*i.e.* normal/beneficial heart growth that is associated with cardiac protection), as targeting microRNAs differentially regulated in settings of stress and protection could represent a new therapeutic approach for the treatment of heart failure.

We have identified a number of microRNAs as being upregulated in a mouse model of cardiac stress (myocardial infarction, MI) and down-regulated in a mouse model of cardiac protection (physiological cardiac growth). My recent studies assess whether inhibition of microRNAs that are differentially regulated in settings of stress and protection (*i.e.* miR-34 family, miR-34a, miR-652) using locked nucleic acid (LNA)-antimiRs (*i.e.* microRNA inhibitors) can provide therapeutic benefit in mouse models with preexisting pathological cardiac remodeling and dysfunction due to myocardial infarction or pressure overload. I have recently demonstrated that inhibition of the miR-34 family (using seed-targeting LNA-antimiRs that simultaneously inhibit microRNA family members) in a mouse model of pressure overload improved cardiac function, decreased cardiac hypertrophy and attenuated lung congestion and atrial enlargement. This was associated with reduced cardiac fibrosis and decreased cardiac stress gene expression, improved angiogenesis and upregulation of several direct microRNA-34 targets. In addition, in the MI model, LNA-antimiR-34 attenuated cardiac dysfunction, cardiac remodelling and atrial enlargement. In contrast, inhibition of miR-34a alone did not attenuate cardiac dysfunction or cardiac remodelling in a mouse model of pressure overload and MI, thus highlighting the utility of seed-targeting LNA-antimiRs for the pharmacologic inhibition of disease-implicated microRNA seed families.

More recently, I have shown that administration of LNA-antimiR-652 in a mouse model of pressure overload was able to improve cardiac function and attenuate cardiac hypertrophy. This was associated with preserved angiogenesis and decreased fibrosis. Current work is examining the expression of miR-652 predicted targets to elucidate precise mechanisms by which miR-652 may mediate protection in settings of cardiac stress. Collectively, my studies demonstrate the potential of targeting microRNAs that are differentially regulated in settings of stress and protection as a promising therapeutic approach for the treatment of heart failure.