MicroRNAs Put their Signatures on the Heart

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The authors are cofounders of Miragen Therapeutics, a company based on the therapeutic application of miRNAs in heart disease.
Few would disagree that there is a major need for innovative therapies for heart disease. Traditional drug targets, such as cell surface receptors, enzymes and ion channels, have posed significant challenges to the development of new therapeutics for restoring function to the failing heart. Consequently, many major pharmaceutical companies have abandoned their heart failure programs, feeling the disease is simply too complex, despite being a major cause of human morbidity and mortality with a staggering impact on the health care system (estimated to exceed $30 B/year). Thus, it seems an opportune time to think “outside the box” about unconventional disease mechanisms and therapeutic approaches for heart failure. Rarely has such an opportunity existed to unveil and exploit an entirely new biology of disease, as has been provided by the recent discovery of microRNAs as markers and modulators of heart failure and pathological cardiac remodeling (9).

MicroRNAs are ~22-nucleotides long and act as negative regulators of gene expression by inhibiting mRNA translation or promoting mRNA degradation. There are estimated to be over 1000 microRNAs encoded by the human genome, each of which acts on many mRNAs. Conversely, individual mRNAs are commonly targeted by multiple microRNAs, allowing for enormous combinatorial complexity and regulatory potential. An especially powerful aspect of miRNA function is the ability of individual miRNAs to coordinately regulate target genes encoding proteins with related functions (e.g. cell growth or metabolism). Therein lies the power of single microRNAs to modulate complex physiological or disease phenotypes by regulating entire functional networks, in contrast to classical drugs, which act on specific cellular targets.

Numerous recent studies point to the involvement of microRNAs in the regulation of cellular responses to stress. MicroRNAs have been identified, for example, that are up-regulated in response to stresses, such as hypoxia, nutrient deprivation and DNA damage (5). The possibility that microRNAs might participate in heart disease was first suggested by the discovery of distinctive patterns of microRNA expression in the hearts of normal mice and mice that suffered from heart disease (10). Specific microRNAs were up- or down-regulated in mice that were subjected to thoracic aortic banding (TAB), a potent stimulus for pathological hypertrophy, or in response to constitutive activation of calcineurin, a stress-inducible mediator of the hypertrophic response. Importantly, many of these microRNAs were also dysregulated in failing human hearts, suggesting they established a diagnostic molecular signature for cardiac pathogenesis (10). Based on a hand full of genetic studies in mice, it is becoming increasingly clear that miRNAs are indeed actively involved in cardiac remodeling, growth, conductance and contractility (1, 10, 11, 13-15).

A study by Pu and coworkers in this issue of Physiological Genomics adds to a series of papers describing signature patterns of microRNAs in hypertrophic and failing hearts from humans and animal models (2, 6, 7-9). Using a bead-based platform to measure the expression of 428 miRNAs, Pu and colleagues compared miRNA expression in 3 different types of human heart disease (ischemic cardiomyopathy, dilated cardiomyopathy, and aortic stenosis) with normal heart. Among the 87 miRNAs detected in the heart, roughly half were differentially expressed in at least one disease group, while
7 miRNAs were regulated in the same direction in all 3 disease states. Although several studies already indicated miRNA expression to be regulated in human heart disease (1, 8, 10, 13), this study is the first to show commonalities in expression between distinct disease etiologies. These divergent miRNA expression patterns point to miRNAs as biomarkers for subtle phenotypic differences and disease progression, and imply that they are active participants in the disease processes.

The involvement of miRNAs in human heart disease is exciting and promising for future therapeutic applications, but still requires verification and functional validation. The study presented by Pu and colleagues nicely complements the miRNA expression data shown in other studies. Although there is substantial overlap in the expression patterns of the regulated miRNAs in the different studies, there are some discrepancies that require further validation. For example, a previous study by Care et al. showed miR-133 to be down-regulated in patients suffering from hypertrophic cardiomyopathy (1), whereas this microRNA was unchanged in the studies performed by Pu and Thum et al. (8). Given the apparent specificity of miRNA expression for relatively subtle variations in disease state, the disparities between these studies may reflect variations in the progression of disease of the different samples tested or even variations in miRNA expression in different regions of the ventricular wall that were taken for biopsies. Indeed, cardiomyocyte heterogeneity within different regions of the heart has recently been appreciated as an important facet of cardiac function. Since new microRNAs are being discovered almost on a daily basis, and the technology for microRNA microarrays remains to be further optimized, it is also likely that current expression data are still incomplete and many additional microRNAs with roles in heart disease remain to be identified.

Although it is now clear that cardiac disease is accompanied by dramatic changes in miRNA expression, the burning question is whether microRNAs are simply biomarkers for heart disease or whether they actually regulate the disease process. Several recent studies in genetically modified mice argue strongly for the latter. MiR-195, which is up-regulated during hypertrophy, is sufficient when over-expressed in the hearts of transgenic mice to induce pathological cardiac growth culminating in ventricular dilatation, myocyte disarray and cardiac sudden death (10). Thus, this microRNA appears to be sufficient to drive the disease process. Conversely, miR-208, a cardiac-specific microRNA encoded by an intron of the alpha-myosin heavy chain (MHC) gene, is required for pathological cardiac growth, fibrosis and up-regulation of beta-MHC expression in response to TAB, calcineurin activation and hypothyroidism (11). Knockdown of miR-133 expression with anti-sense oligonucleotides has also been shown to cause cardiac hypertrophy, suggesting an essential role for this microRNA in the suppression of myocyte growth (1). Nevertheless, not all microRNAs that are modulated during heart disease are likely to be directly involved in the disease process. In this regard, among the 24 miRNAs that Pu et al. found to be up-regulated in human heart disease, miR-214 was the most highly up-regulated in all three groups. However, cardiac-specific over-expression of miR-214 in transgenic mice failed to induce a cardiac phenotype (10).
The manipulation of microRNAs poses several unique opportunities for therapeutic development. In classical drug discovery, it can take years to identify therapeutic targets, devise and execute high throughput screens, and eventually find small molecules that inhibit those targets, but that’s just the beginning. MicroRNAs offer the possibility of leapfrogging over these preliminary studies, once the microRNA that regulates the disease is known. The use of chemically modified oligonucleotides to target either a specific miRNA or to disrupt the binding between a miRNA and a specific mRNA target in vivo represents a potentially effective means of inactivating pathological miRNAs.

Developing microRNAs into therapeutics will also, undoubtedly, pose significant challenges, such as modes of delivery and duration of action. Methods for local delivery to the heart, through direct injection or via catheters or coated stents will obviate these challenges and should make it possible to avoid off-target effects on non-cardiac tissues. Moreover, given the infatuation of cardiologists with delivery procedures and devices, heart disease seems likely to be among the first therapeutic targets to succumb to microRNA based therapeutics.

There is a sense of standing on the brink of a new revolution in understanding the molecular basis of disease based on the biology of microRNAs. The recent papers on microRNA signatures of the failing heart are harbingers of the future. The discovery of microRNAs that participate in heart disease and the analysis of their targets have the potential to reveal unanticipated disease mechanisms and facilitate novel therapeutic approaches. With a 1000 or more microRNAs encoded by the human genome, only a few of which have been analyzed, all things seem possible. We expect in the near future that microRNA-based diagnostics will be commonplace and that microRNA-based therapeutics will play a major role in the armamentarium for heart failure. Stay tuned!

References