Review

Nandini Nair* and Enrique Gongora

MicroRNAs as therapeutic targets in cardiomyopathies: myth or reality?

Abstract: The identification of biomarkers for cardiomyopathy presents a distinct challenge as the etiologies are widely varied. The discovery of small non-coding miRNAs with gene regulatory function has opened new avenues of investigation in basic and clinical sciences. The search for regulatory nucleotide sequences that have specific gene targets have put miRNAs at the forefront of development of therapeutics, and may serve as valuable diagnostic and/or therapeutic targets. MiRNAs appear to influence both positive and negative remodeling. As cardiac remodeling is a complex process, global molecular networks and miRNA profiles may be required to fulfill the roles of macroregulators. The type of cardiomyopathy leading to heart failure in the long run appears to have a distinct molecular pattern underlying the pathophysiology. This review discusses in brief the existing literature on the molecular signatures in dilated, ischemic, hypertrophic, stress, and peripartum cardiomyopathies that may be used to target therapies for specific etiologies once diagnosed, therefore exploring the utility of specific miRNAs in tailoring therapy for heart failure based on etiology.

Keywords: cardiomyopathy; microRNA; molecular signatures; therapeutic targets.

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Introduction

The discovery of microRNAs (miRNAs) has opened a whole new area of investigation in diagnostics and therapeutics for cardiovascular diseases. MiRNAs are approximately 22-nucleotide non-coding RNA sequences that regulate gene expression at the post-transcriptional level by targeting the 3′-untranslated region of mRNA sequences. Gene expression studies and research on loss of function in animal models have established the role of miRNAs in the regulation of growth and development. The existence and regulatory function of small non-coding miRNAs were first identified in *Caenorhabditis elegans* in 1993 (1–3), and since then their importance has grown in logarithmic proportions in the basic and clinical sciences. The search for regulatory nucleotide sequences through advances in bioinformatics and sequencing, which enhance the prediction of specific gene targets, have put miRNAs at the forefront of development in therapeutics.

MiRNAs have proven to be attractive candidates as biomarkers, as they circulate packaged either in microvesicles, exosomes, or apoptotic bodies, which makes them resistant to temperatures >100°F and be conveniently stored at room temperature for long periods. These small non-coding nucleotides are also tolerant to acidic and alkaline conditions (4). Binding of miRNAs to RNA-binding proteins such as argonaute 2 and nucleophosmin 1, or by linkage to high-density lipoprotein (HDL), confers protection from circulating RNases (5–8).

Primary RNAs give rise to miRNAs in a two-stage process catalyzed by ‘drosha’ in the nucleus and ‘dicer’ in the cytoplasm. The freshly synthesized miRNAs bind to the argonaute protein to produce the RISC complex (effector RNA-induced silencing complex), which, in turn, binds to target mRNAs, resulting in the inhibition of translation and or degradation of the target RNA.

Many properties of miRNas have set them apart as candidates not only for diagnostic but also for therapeutic purposes. Their remarkable stability in circulation is an important aspect that enables their easy and sensitive detection. This property also makes them good targets for therapeutic interventions as they can be silenced by antisense oligonucleotides. Some of the major strategies to target miRNas are to either construct molecules that mimic the functions of the miRNAs and thereby make them dysfunctional, or overexpress the miRNA of interest

***Corresponding author: Nandini Nair,** Sacred Heart Medical Center, Providence Spokane Heart Institute, 122 West 7th Avenue, Suite 450, Spokane, WA 99204, USA, e-mail: nandini.nair@gmail.com
Enrique Gongora: Memorial Cardiac and Vascular Institute, Hollywood, FL 33021, USA

in diseases where it is downregulated, or to construct directly inhibiting antisense oligonucleotides that are specific and can be target delivered.

The anti-miRNA concept is currently much used; however, the problems of specificity and stability are still in the process of being resolved. Chemically modified mRNAs ensure stability. 2-*O*-methyl-group (OMe)-modified oligonucleotides and locked nucleic acid (LNA)-modified oligonucleotides are some of the current modifications in use. Additionally, oligonucleotides with increased phosphorothioate versus phosphodiester linkages between nucleotides confer more stability and increased resistance to nucleases.

Present-day medical management consists of neurohormonal blockade with β-blockers/angiotensin inhibitors/angiotensin receptor blockers and aldosterone receptor blockers. The current optimal medical management is a generalized strategy that targets all types of cardiomyopathies by blockade of the sympathetic and renin-angiotensin and aldosterone systems, which helps alleviate symptoms and prevents remodeling but cannot be tailored for specific etiologies. The concept of molecular medicine, which can be used to target specific etiologies, drives home an important point in the practice of personalized medicine.

The identification of biomarkers can lead to the development of diagnostics and therapeutics. However, there are many challenges in developing robust biomarkers that would be useful in the development of therapeutic targets. This review attempts to explore the existing literature on different types of cardiomyopathies and the utility of specific miRNAs in tailoring therapy for heart failure depending on the etiology.

MiRNAs are versatile molecules of regulation. They can either inhibit translation or degrade their target mRNAs, depending on the extent of complementarity and number of binding sites. It is also dependent on the accessibility of these sites, which is largely dependent on free energy states. Greater complementarity of the accessible binding sites results in target mRNA degradation. Imperfect sequence complementarities with target mRNAs primarily result in inhibition of translation. MiRNAs constitute >2% of the predicted human genes that regulate ~30% of protein-coding genes and are in some cases expressed at >1000 copies per cell (9–12).

The transport of miRNAs to target genes is a complex process in which they are enclosed in protective vesicles during intercellular transport. Exosomes, microparticles, and high- and low-density lipoproteins (LDLs) have been implicated in the process. MiRNas carried in exosomes are released into the extracellular compartment on fusion with the plasma membrane. Microparticles form by outward budding and blebbing of the plasma membrane. During the process of apoptosis or programmed cell death, cells release microparticles and apoptotic bodies containing miRNAs, which then constitute the intercellular transport (13–15).

The type of cardiomyopathy leading to heart failure in the long run appears to have a distinct molecular pattern influencing the pathophysiology. This review discusses in brief the existing literature on the molecular signatures in dilated, ischemic, hypertrophic, stress, and peripartum cardiomyopathies, which may be used to target therapies for specific etiologies once diagnosed. MiRNAs have been shown to be involved actively in cardiac development, hypertrophy, and failure. They appear to play a role in positive and negative remodeling. However, cardiac remodeling and heart failure is a complex phenotype and may require global molecular networks and miRNA profiles suggesting that miRNAs could be the macroregulators. Therefore, it is yet to be proven if miRNA signatures or single miRNAs would be suitable as therapeutic targets. It is possible that both miRNA signatures and individual miRNAs may serve as therapeutic targets for different cardiomyopathies as more specific mRNAs are discovered for each disease process. Figure 1 shows the existing miRNA patterns in cardiomyopathies of different etiologies from the current literature.

Dilated cardiomyopathy

Dilated cardiomyopathy is essentially the end product of a number of pathological processes involving hypertrophy and disarray of myocytes as well as changes involving the extracellular matrix proteins. β-Adrenergic receptor signaling plays an important role in the progression of cardiac failure. In cardiac explants from patients with dilated cardiomyopathy, inhibition of miR-100, an miRNA upregulated in heart failure, typically prevents β-adrenergic-mediated downregulation of the adult component of the fetal gene program. In the murine system, overexpression of miR-195 leads to hypertrophic growth and myocyte disarray, leading to dilated cardiomyopathy and finally heart failure (16–18). In a small study of dilated cardiomyopathy patients compared with age- and sex-matched controls, elevated plasma miR-423-5p levels were noted, which correlated positively with the level of NT-proBNP (19).

Deep sequencing experiments in a loss-of-function mouse model showed that miR-1 and miR-133a were responsible for the dramatic loss of function seen in Dgcr8-deficient cardiomyocytes derived from these knockout mice (20). Analysis of data from a small study of 82 dilated cardiomyopathy patients compared with 21 normal subjects

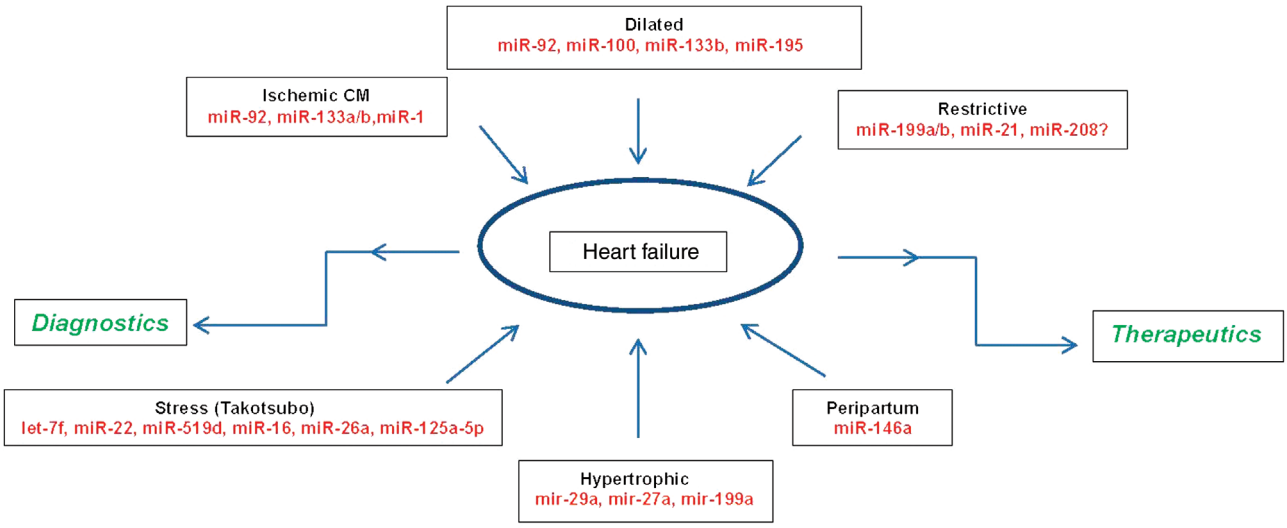

Figure 1 MicroRNAs in cardiomyopathies with different etiologies.

showed involvement of mir-208a. Mir-208a was found to correlate with myosin heavy chain mRNA expression, with increase in miR-208 levels being a strong predictor of clinical outcomes in dilated cardiomyopathy (21).

Although a number of miRNAs have been shown to be involved in dilated cardiomyopathy, few have been directly implicated as therapeutic targets. Interestingly, in a mouse model, *Sgcb*-null mice, which are genetically engineered to produce sarcoglycanopathy, necrotic foci appear at 9 weeks of age and dilated cardiomyopathy from 20 weeks. Intraventricular delivery of adeno-associated viral-mediated miRNA therapy in this transgenic model of severe, chronic myotonic dystrophy-associated dilated cardiomyopathy shows a long-term benefit. Overexpression of mir-699a improved survival and decreased cardiac remodeling fibrosis and apoptosis. Sarcomere organization improved with reduced ventricular atrial natriuretic peptide and improved molecular markers of dilated cardiomyopathy. Increases in fractional shortening were also observed on long-term treatment of these mice (22). Such direct implication of miRNA-targeted therapeutic benefit brings hope to this area of investigation. More precise studies in patient populations are needed to advance these findings toward the development of therapeutics.

Ischemic cardiomyopathy

Reduced contractility and negative remodeling after an acute myocardial infarction usually results from increased fibrosis of the extracellular matrix (ECM). The pathophysiology underlying this process involves transformation of myocardial fibroblasts into myofibroblasts secreting ECM molecules. Such changes cause disturbances in conduction of electrical impulses in addition to deterioration of pump function.

Several miRNAs have been shown to be involved in the regulation of fibrotic reactions. MiR-29 appears to play a role after myocardial infarction, while miR-21 may exert a fundamental role in post-angioplasty restenosis. MiR-208 is involved in the shift toward a fetal gene expression pattern in contractile proteins in heart failure. MiR-1 influences susceptibility to cardiac arrhythmias after myocardial infarction. Shear stress induces expression of miR-21 in endothelial cells, which leads to decreased apoptosis and activation of the nitric oxide pathway (23). This is important, as apoptosis is also reported to play an important role in the progression of left ventricular (LV) remodeling in ischemic hearts.

It is interesting to note that a number of miRNAs have been implicated in plaque formation and pathogenesis of atherosclerosis, in a variety of roles such as monocyte and macrophage activation, LDL and HDL level modulation, as well as plaque angiogenesis and fibrous cap stabilization. Mir-221and mir-222 have been shown to induce vascular smooth muscle cell proliferation, whereas mir-195 was noted to reduce proliferation of this cell type (24–34). Such miRNAs may serve as therapeutic targets if delivered appropriately and can be modulated.

Cardiac fibrosis and hypertrophy

Two miRNAs appear to play key roles in cardiac fibrosis and hypertrophy. MiR-1 and miR-133 are specific to skeletal muscle and cardiac myocytes. Overexpression of

miR-1 *in vivo* results in thinning of the ventricular walls. On the contrary, miR-1 knockout mice have thickened ventricles. MiR-1 is downregulated at the onset of pressure overload, possibly leading to the initiation and progression of cardiac hypertrophy. At the molecular level, miR-1 downregulates calcium-calmodulin signaling through the calcineurin/NFAT pathway and negatively regulates the expression of Mef2a and Gata-4 to inhibit cardiomyocyte growth. The cytoskeleton regulatory protein twinfilin-1 is a novel target of miR-1, and reduction of miR-1 by hypertrophic stimuli upregulates twinfilin-1, which, in turn, leads to hypertrophy (35–40).

MiR-133 also has been shown to influence cardiomyocyte hypertrophy. Expression of mir-133 was downregulated in both *in vivo* and *in vitro* cardiac models of hypertrophy. In these systems, calcineurin activity was enhanced. When cyclosporine was used to inhibit calcineurin, the downregulation of mir-133 was suppressed, suggestive of a reciprocal association. Such effects of downregulation of mir-133a were also noted in diabetes-induced cardiac hypertrophy through SGK1 and IGFR1 (18, 41–44).

The miR-29 family targets a series of mRNAs that encode proteins involved in fibrosis, including collagens, fibrillins, and elastin. In a recent study by Roncarati et al. (45), about a dozen miRNAs were found to be elevated in plasma from hypertrophic cardiomyopathy subjects. These include miR-27a, miR-199a-5p, miR-26a, miR-145, miR-133a, miR-143, miR-199a-3p, miR-126-3p, miR-29a, miR-155, miR-30a, and miR-21. Interestingly, in this study, the miRNA signature obtained was different from those seen in hypertrophy resulting from aortic stenosis. MiR-199a-5p, miR-27a, and miR-29a were shown to correlate with LV hypertrophy. Of these, miR-29a is the only molecule that was significantly associated with both hypertrophy and fibrosis, making it an attractive candidate as a specific biomarker for hypertrophic cardiomyopathy.

Restrictive cardiomyopathy

Restrictive cardiomyopathy can be of multiple etiologies, with a common tenet that it is always a consequence of fibrosis. Several miRNAs are upregulated in fibrosis; however, only a few have been thus far shown to affect the pathophysiology. Cardiac fibrosis results from a combination of an exaggerated fibroblast proliferation accompanied by ECM deposition. Upregulation of miR-21 and downregulation of miR-29 and miR-30 in cardiac fibroblasts, as well as downregulation of miR-30 and miR-133 in cardiomyocytes, have been characteristically noted in stress. Spry1 is a negative regulator of ERK-MAP kinase, which is repressed by miR-21, resulting in extensive fibroblast proliferation contributing to fibrosis (46). Other miRNAs that are known to be involved in actively repressing downstream signaling pathways are miR-29, mir-30, and mir-133. Mir-29 represses expression of collagens, targets TGFβ/SMAD, and disrupts regulation of cell differentiation/proliferation/apoptosis/generation of ECM (47–49). MiR-30 and miR-133 repress the expression of CTGF, a positive regulator of fibrosis. MiR-199 upregulation augments fibrosis through the calcineurin/NFAT pathway, thus illustrating the importance of calcineurin signaling in this process (50, 51). Hence, it would be interesting to determine the miRNA signature for cardiac fibrosis and then use it to decipher how it compares and varies with the different etiologies for restrictive cardiomyopathy.

Stress cardiomyopathy

Stress cardiomyopathy or takotsubo cardiomyopathy is usually triggered by emotional or physical stress leading to reversible wall motion abnormalities involving apical, midventricular, basal, or focal segments of the LV (52–55). Typically, wall motion abnormalities resolve within a few days to weeks, and the overall prognosis is generally good. However, stress cardiomyopathy can be life-threatening in the acute phase, with 10% of the patients developing malignant arrhythmia, cardiogenic shock, or ventricular wall rupture resulting in up to 8% mortality. In the acute phase, it is indistinguishable from an acute myocardial injury with respect to clinical symptoms, electrocardiographic changes, and cardiac biomarkers (56–60). Although the peak ratio of NTproBNP/troponin has been used to distinguish these patients with those with acute myocardial infarctions, rapid diagnosis on admission still remains a problem and requires coronary angiography for confirmation (61, 62).

The first report on a specific miRNA signature for takotsubo cardiomyopathy consisting of miR-1, miR-16, miR-26a, and miR-133a has been recently published (63). This panel has a diagnostic accuracy of 0.835, sensitivity of 74.2%, and specificity of 78.6% when patients were compared with healthy subjects. The panel can also be used to differentiate takotsubo cardiomyopathy from an ST elevation myocardial infarction, which makes it a fairly robust test. What makes this panel interesting is that in addition to mir-1 and mir-133a, which are upregulated in myocardial ischemia/infarction, two other miRNAs upregulated

in psychological stress, mir-16 and mir-26a, are also elevated in stress cardiomyopathy. Three other miRNAs that are elevated in stress cardiomyopathy (mir-22, mir-519d, and let-7f) are not statistically significant (63). However, mir1-25a-5p has been shown to regulate the expression of endothelin-1. Downregulation of mir-125a-5p in takotsubo cardiomyopathy is accompanied by upregulation of ET-1 (63). Although it is a small study of 91 subjects (63), this paves the way for the development of diagnostic and therapeutic targets for takotsubo cardiomyopathy.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a devastating disease of unknown etiology causing considerable morbidity and mortality in the peripartum period and beyond. Insight into the pathophysiology of the disease was first elucidated in elegant experiments in mice with stat3 deletion (64). These mice showed increased expression/activity of cathepsin D associated with the generation of a cleaved antiangiogenic and proapoptotic 16-kDa form of prolactin. Bromocriptine, an inhibitor of prolactin secretion, prevented PPCM in the STAT3-deletion-carrying mice. Production of the 16-kDa form of prolactin impaired the cardiac capillary network and function in the myocardium, resulting in the cardiac phenotype of PPCM. Analysis of myocardial STAT3 protein levels showed reduction in serum levels of activated cathepsin D and parallel elevations of the 16-kDa prolactin (64, 65). At the molecular level, mir-146a has been implicated in the regulation of the prolactin signaling pathway (66). Studies in mouse models suggest a major role for a systemically damaged vasculature in PPCM. The truncated 16K PRL fragment exerts negative effects on endothelial cells by upregulating miR-146a, which, in turn, impairs their proliferation and survival (67). MiR-146a is also known for its role in innate immunity where it targets TRAF6 and IRAK1 and prevents constitutive activation of NF-κB inflammation (27).

Elegant *in vitro* experiments have shown that mir-146a has a significant role in antiangiogenesis. Levels of miR-146a increased when pre-miR-146a was transfected into human umbilical vein endothelial cells (HUVECs), and this, in turn, reduced their proliferation. Alternately, inhibition of mir-146a by anti-miR-146a enhanced the proliferation of these cells. This effect has been demonstrated in other proliferation assays such as *ex vivo* aortic ring assay and in an *in vitro* model of choroidal neovascularization.

A new target for mir-146a was identified as NRAS, which was found to be downregulated in HUVECs treated with the 16K prolactin fragment. This effect was reversed when HUVECs were transfected with anti-miR-146a antisense oligonucleotide (66). Interestingly, delivery of mir-146a through transfection or fusion of mir-146a-laden exosomes to neonatal rat cardiomyocytes showed a downregulation of target genes *Erbb4*, *Notch1*, and *Irak1*. *In vivo* cardiac tissue from cardiomyocyte-specific Stat3 knockout mice with post-partum cardiomyopathy phenotype showed increase in mir-146a levels and an associated decrease in mRNA levels of NRAS, Erbb4, Notch1, and Irak1. Additionally, mir-146a levels were increased in patients with PPCM acutely, and this was resolved after treatment with heart failure regimen and bromocriptine defining the role of prolactin (66).

Functional targets of miRNAs

The complexity of molecular basis of disease has always been very intriguing. Table 1 summarizes the functional targets known in the literature for a wide variety of miRNAs. It helps illustrate the fact that miRNAs can target numerous genes and biochemical pathways so upregulating or downregulating these molecules can have a multitude of effects, some of which may be unwanted. However, if specific miRNA signatures are identified, it may better suit therapeutic strategies as adverse effects could be minimized if not eliminated. This is well illustrated in the discussions on peripartum and takotsubo cardiomyopathies where specific miRNAs have been found to play a major role in the pathophysiology of both diseases. The targeted delivery of antisense nucleotides to regulate specific genes remains the greatest challenge.

Therapeutic potential of miRNAs

Antisense oligonucleotides and their modified counterparts can be used in gain-of-function or loss-of-function approaches by specific targeting of mRNAs. Antisense miR oligonucleotides are usually complementary to target miRs, and abolish miR action. Antisense oligonucleotides when chemically modified to produce antagomirs have been noted to be more effective in suppressing target genes than the unmodified oligonucleotides. An antagomir is a tagged oligonucleotide that has a cholesterol base at its 3′ end. The difference in effectiveness can be attributed to the lipid modification, which allows binding to apolipoproteins, facilitating systemic delivery and also allows easier cellular uptake through the LDL scavenger

Table 1 Selected miRNAs and possible functional correlations.

miRNA	Functional target	Possible role in pathophysiology	References
mir423-5p	Unclear (specifically expressed in heart failure)	Possible role in atherosclerosis	(19, 83)
miR-100	α-Myosin heavy chain, SERCA-2a	Fetal gene reprogramming	(16, 18)
miR-133b	β-Adrenergic receptor stimulation	Fetal gene reprogramming	(18)
miR-1	Sorcin	Modulation of calcium signaling in EC coupling	(38, 40)
miR-19a	CTGF, TSP	Modulation of ECM	(84, 85)
miR-19b	CTGF, TSP	Modulation of ECM	(85)
miR-18	CTGF, TSP	Modulation of ECM	(85)
miR-214	Ubiquitin E2 ligases	Regulation of the ubiquitin-proteasome system (UPS)	(84)
miR17-92 cluster	Pten, connexin-43	Dysregulation of cardiovascular morphogenesis	(86)
miR-22	p21 (Cyclin-dependent kinase inhibitor)	Induction of cell cycle arrest	(63, 87)
miR-519d	TGFβ	Regulation of cell proliferation	(88)
miR16	MAP7, PRDM4, CDS2	Regulation of cell proliferation	(89)
miR-26a	Bone morphogenetic protein/SMAD1	Endothelial cell-mediated angiogenic response	(90)
miR-125a-5p	Endothelin -1	Neurohormal upregulation	(63)
mir-29a	TGFβ/SMAD	Regulation of cell differentiation/proliferation/apoptosis/ECM	(30, 45, 47, 48)
mir-146a	NF-κB	Prolactin dysregulation	(66)
mir-208a	Thyroid receptor-associated protein-1	Fetal gene reprogramming	(21, 91)
mir-21	PTEN, Bcl-2	Proapoptosis	(91)
mir-29	Collagens type 1 α1, type 1 α2, type 3 α1, fibrillin, elastin	Profibrosis in the post-myocardial infarction state	(91)

receptor. Once inside the cell, they bind to mature miRs, interfere with RNA-induced silencing complex loading, and therefore initiate miR degradation. Specific silencing has been demonstrated in murine models (44, 46, 68). Another intelligent design has been to target all members of an miR seed family through a series of tandem-binding sites for a seed into the 3′-untranslated region of a reporter gene. Such 'sponges' are spatially designed so that miR-binding sites have a bulge at the argonaute 2 cleavage site. This design allows targeting of miRs while protecting the sponges themselves from being degraded. When miR sponges are transfected into cells, the level of targeted miRs is more strongly suppressed than when using separate inhibitors because an entire miR family is affected. Mir sponges have been shown to more effectively repress (68, 69).

Current challenges

Although challenges exist, successful therapeutic developments have emerged in other disease states. In prostate cancer cells, mir-34a was found to be downregulated. Hence, transfection of mir-34a showed inhibition of tumorigenesis, whereas expression of antagomirs to mir-34a promoted tumorigenesis in a murine model (70). Another area that has shown success is antiviral therapy against hepatitis C. In chronically infected chimpanzees, hepatitis C viremia was abolished with no essential adverse effects by an LNA-modified oligonucleotide (SPC3649) complementary to miR-122. This is relevant because mir-122 binds to two closely spaced target sites in the 5′ non-coding region of the hepatitis C viral genome, resulting in its upregulation and leading to pathological consequences of the disease process (71).

Nucleic-acid-based therapies are challenging because of the difficulties in targeting therapies. With ongoing investigations showing that miRNAs play a substantial role as extracellular messengers, new avenues for efficient systemic delivery of therapeutic miRNAs may open. Non-viral basic strategies currently being explored for delivery of therapeutic oligonucleotides are lipid-based delivery systems and polymer-based carriers for oligonucleotide delivery. Carrier-encapsulating oligonucleotides based on ionizable lipids as stabilized antisense lipid particles or stable nucleic acid lipid particles have provided an important advancement in the field. Polymeric micro- and nanostructured platforms are another area of investigation (72).

A recent review by van Rooij and Kauppinen (73) highlights the specific successes in the treatment of hepatitis C,

atherosclerosis, diabetes, and heart failure. However, challenges remain in the safe delivery and targeting of these molecules. Restoring miRNA in diseases where it is depleted is very much possible through double-stranded mimics as evidenced in cancer therapeutics (74–76). However, the challenges are to avoid reaching suprath-erapeutic levels and to target these molecules in a guided fashion to avoid adverse effects. Inhibition of miRNA can be done using either miRNA sponges or antisense oligo-nucleotides (antimirs). Antimirs have been considered more effective, especially when they are modified to have better binding affinity, biostability, and pharmacokinetic properties. One of the important chemical modifica-tions is to increase nuclease resistance by substituting the phosphodiester backbone with a phosphorothioate linkage (77). In addition, phosphothiorate linkages confer enhanced binding to plasma proteins, leading to reduced clearance by glomerular filtration and urinary excretion. Another modification is the PNA (peptide nucleic acid) or morpholino linkage studied *in vitro* and in animal models (78–80).

Delivery of miRNA modulators has always been an extraordinary challenge. It has been shown that *in vivo* delivery of anti-miR oligonucleotides through choles-terol conjugation or by modification of the phosphate backbone with phosphothiorate linkages could be effec-tive. Intravenous administration of antagomers has been shown to be effective in a mouse pancreatic cancer model (81). However, local delivery appears to be more effective than systemic. Regional LNA-92a delivery reduced miR-92a levels and infarct size in a porcine model (82). The exact mechanisms underlying cellular uptake and distribution are still not well understood. Generating tissue specific-ity is an ongoing area of investigation. Targeted delivery to specific cell types using conjugation or encapsulation strategies appear to have success (73).

In the last decade, there has been an explosion of studies on the role of miRNAs in regulating gene expres-sion. MiRNAs have definitely evolved as major players in the development of molecular therapeutics; however, challenges still remain. Further investigations are needed to tailor specificity and determine the extent of reversibil-ity and potential toxicity of these molecules in different microenvironments.

This review highlights the current literature on some of the successes achieved, especially in PPCM, there-fore rendering hope to the concept of using miRNAs as therapeutics. However, more studies are needed before it evolves into a true reality in routine medical practice to tailor heart failure therapy depending on molecular etiology.

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Bionotes

Nandini Nair
Sacred Heart Medical Center, Providence Spokane Heart Institute, 122 West 7th Avenue, Suite 450, Spokane, WA 99204, USA
nandini.nair@gmail.com

Nandini Nair received her PhD from the Department of Biochemistry, Indian Institute of Science, Bangalore, India and her MD from St George's University School of Medicine, Grenada, W.I. She then completed a basic science postdoctoral fellowship at the University of Massachusetts Medical School, Worcester, MA in Molecular Virology. She also completed her clinical training fellowships in Internal Medicine and Cardiovascular Diseases at Drexel University College of Medicine, Philadelphia, PA and advanced fellowships in Vascular Medicine, Advanced Heart Failure and Cardiac Transplantation at Stanford University School of Medicine, CA. Dr. Nair is board certified in Internal Medicine – Cardiovascular Diseases and Vascular Medicine. Dr. Nair is currently a Clinical Associate Professor at the University of Washington and the Medical Director for Advanced Heart Failure, Mechanical Circulatory Support and Cardiac Transplantation at Sacred Heart Medical Center, Spokane, WA. Her research interests are in understanding molecular mechanisms underlying systolic and diastolic heart failure and development of molecular diagnostics and therapeutics.

Enrique Gongora
Memorial Cardiac and Vascular Institute, Hollywood, FL 33021, USA

Enrique Gongora is a cardiac surgeon by training. He earned his Medical degree from the Universidad del Rosario in Bogota, Columbia. Dr. Gongora completed his residency training in General Surgery and a fellowship in Surgical Critical Care at Washington Hospital Center in Washington, DC. He then completed a residency in Cardiothoracic Surgery at the Mayo Clinic, Rochester and further fellowship training in Adult Cardiac Surgery and Thoracic Transplantation/Mechanical Circulatory Support at the University of Pittsburgh Medical Center, PA. Dr. Gongora currently serves as the Medical Director, Adult Cardiac Surgical Transplant Program, Memorial Heart and Vascular Institute, Hollywood, FL. Dr. Gongora is board certified in General Surgery and Cardio Thoracic Surgery. Dr. Gongora's research includes the molecular basis of cardiac failure inaddition to developing novel surgical stratigies for advanced heart failure.