In recent years, microRNAs (miRs) have caused a true revolution in the cardiovascular research field. miRs are a class of highly conserved, small noncoding RNAs. They are transcribed from "normal" genes, and their precursor transcripts are enzymatically processed to a mature and active form by Drosha/Dgcr8 and Dicer enzyme complexes. miRs fine tune the expression of 30% to 50% of the protein-coding genes by binding to partly complementary base pairs in 3′ untranslated regions (UTRs) of mRNAs and thereby interfering with translation; targeted mRNAs are either degraded or untranslated. In this way, miRs add another level of complexity to the highly regulated eukaryotic interactome, and their actions (partly) explain why mRNA expression so often does not agree with protein expression levels. So far, >700 human and 500 mouse miR genes have been included in the miRBase (www.microrna.sanger.ac.uk), the primary source of miR data, and computational analyses predict that these numbers will increase.

The complexity of miR regulation of protein expression is illustrated by the fact that several miRs can target 1 gene, whereas several genes can be targeted by 1 miR. Bioinformatical tools to predict gene targets of a given miR exist, and their accuracy increases. Identifying the relevant miR-targeted genes and building new miR-gene networks is a challenge that lies ahead of us.

The expression of miRs is tightly controlled and highly tissue, developmental stage, and disease specific. The heart expresses 2 unique miR families under the control of cardiac transcription factors like the serum response factor and myocyte enhancer factor 2: miR-1 and miR-133a (Figure 1 and please see the online Data Supplement at http://hyper.ahajournals.org for Table S1). miRs -1-1 and -1-2 represent 40% of all of the expressed miRs in the heart and are encoded from bicistronic units together with the 2 members of the miR-133a subfamily. Another family unique to the heart is composed of miRs −208a and −208b, which lie within and are encoded together with the cardiac-restricted α- and β-myosin heavy chain (MHC) genes, respectively.

miRs are of crucial importance to the heart to develop and function properly. In mice, deletion of all of the cardiac miRs by cardiomyocyte Dgcr8 or Dicer knockout is not tolerated, and also the specific deletion of cardiac miRs −1 or −133 leads to (partial) embryonic lethality and heart failure (please see Table S1).

From 2001 until now, several studies have investigated miR expression in the healthy heart, during pressure overload in mice and rats and in different etiologies of human heart failure, as reviewed previously and now updated with the latest studies (please see Figure S1). miRs that consistently come to attention are let-7b and miR-15b, −21, −23a, −27b, −103, −125b, −140*, −195, −199a, and −214, which are upregulated in all of the cardiac pathologies studied, as well as miR-30c, −150, −185, and −422b, which are all downregulated during hypertensive heart diseases. Still, the identification of miRs involved in cardiac development and pathology and knowledge on their biological function is exceedingly incomplete, offering an exciting challenge to cardiovascular researchers. Therefore, miRs currently seem to be the most popular kid in the cardiovascular research school.

Role for miRs in Hypertensive Heart Disease

The number of studies on the involvement of miRs in hypertension-related cardiac pathologies, like cardiac hypertrophy, fibrosis, arrhythmias, and ischemia/reperfusion injury, increases rapidly. Most groups tackle miRs in their favorite cardiac disease model by first performing large-scale expression analyses, followed by in-depth analysis of the function of 1 differentially regulated miR using transgenic mice (Tables S1 and S2). Figure 2 depicts the miRs currently related to cardiac pathologies.

Cardiac Hypertrophy and Heart Failure

Dicer

To overcome embryonic lethality of cardiac Dicer deficiency in mice, cardiac Dicer expression was abrogated in the adult mouse using an inducible system. Dicer deletion in 3-week-old mice resulted in sudden cardiac death within 1 to 2 weeks, with upregulation of the potassium channel–repressing transcription factor Irx5, suggestive of conductance defects. Interestingly, Irx5 is an miR-1 target. Abrogation of Dicer...
expression in 8-week–old mice evoked spontaneous cardiac remodeling and heart failure accompanied by strong induction of fetal genes. The expression of Dicer, the enzyme essential for miR synthesis, is decreased in human end-stage failing hearts, and its restoration is, therefore, an interesting therapeutic target to improve cardiac hypertrophy.

miR-1 and miR-133 Modulate Cardiomyocyte Growth
The cotranscribed miR-1 and -133 regulate cardiac growth in 2 ways: they influence cardiomyocyte proliferation as well as hypertrophy. Increased cardiomyocyte proliferation was found in adult miR-1, as well as miR-133, knockout mice and was linked to cell-cycle regulators like cyclin D2. During cardiac hypertrophy, downregulated miR-1 facilitates cardiomyocyte growth by relieving the repression from growth-related target genes like RasGAP, Cdk9, fibronectin, and Rheb, as well as calmodulin and myocyte enhancer factor 2a. Similarly, decreased miR-133 expression during cardiac hypertrophy enables its targets RhoA, Cdc42, and Nelf-A/WHSC2 to exert their prohypertrophic functions.

In addition, miR-133 controls the fetal gene program by modulating β-adrenergic receptor signaling and thereby regulates cardiomyocyte hypertrophy. Thus, cotranscription of miR-1 and miR-133 seems to ensure hypertrophy by using different mechanisms.

miR-208 Fulfills a Special Role During Mouse Pressure Overload
Some miRs (∼25%) reside in introns of coding genes and are thought to share regulatory elements. Indeed, both miR-208a and -208b expressions correlate with their host gene expressions, the α- and β-MHC genes, respectively. In the adult mouse heart, α-MHC/miR-208a dominates, whereas miR-208b is exclusive for the healthy human heart (Figure S1). In mice, pressure overload induces an MHC isoform switch (from α to β) enabling the heart to adapt to overload by slowing down contraction. α-MHC–encoded miR-208 fits this picture: during pressure overload in mice, it functions in a negative feedback loop to suppress its own expression and that of α-MHC, whereas enabling the upregulation of β-MHC. In this way, it is required for cardiomyocyte hypertrophy and fibrosis. Exactly how the cotranscribed miR-208b fits in this picture remains to be investigated. Also, the role of this mechanism in human hypertrophy needs to be elucidated, because humans are unable to switch isoforms and already predominantly use the slow β-MHC isoform.

Essential Roles for Other miRs Regulated During Cardiac Pathology
Although miR-1, -133, and -208 have obvious roles in the heart because of their cardiac-restricted expression, numerous other “cardiac-independent” miRs have been identified to play a role in cardiac hypertrophy and failure. miR-23a, -195, and -214 are all consistently upregulated during cardiac pathology (Figure S1). Cardiac-specific overexpression of miR-195 in mice resulted in early heart failure, but cardiac-specific miR-214 transgenic mice had no spontaneous phenotype. The ability of the latter to cope with hypertension is still required to be addressed.

AntagomiR-mediated knockdown of miR-23a in mice prevented isoproterenol-induced cardiac hypertrophy. miR-23a is a member of a novel prohypertrophic pathway composed of the transcription factor NFATc3 by which it is activated and the antihypertrophic miR-23a target musclespecific ring finger protein 1.

Cardiac Fibrosis
Downregulation of miR-30, miR-133b, and miR-29 During Pressure Overload Relieves the Repression of Profibrotic Genes
Downregulation of miR-30 and -133b during pressure overload in rat and human hearts allowed levels of connective tissue growth factor to increase in cardiomyocytes, as well as fibroblasts, contributing to collagen synthesis. Profibrotic expression was also allowed by downregulation of the miR-29 family in the infarct border zone, which enabled the heart to increase expression of collagens I and III, fibrillin-1, and elastin-1. In fact, miR-29 downregulates a scala of profibrotic targets and may thereby decrease fibrosis.

Upregulation of miR-21 During Pressure Overload Acts Through Several Mechanisms to Increase Matrix Deposition
Two studies simultaneously report on miR-21 upregulation in mouse pressure-overloaded hearts. One of these finds...
miR-21 to be essential for in vitro cardiomyocyte hypertrophy, whereas the other reports an inhibitory effect of miR-21 on in vitro cardiomyocyte hypertrophy. However, Thum et al suggest that the effects of miR-21 alone on cardiomyocyte hypertrophy are minor. Interestingly, abrogation of miRs specifically in the cardiomyocytes of the adult mouse heart resulted in heart failure and a paradoxical upregulation of miR-21, suggesting a noncardiomyocyte origin for this miR. Indeed, in the hypertrophied and failing heart, miR-21 expression derives from cardiac fibroblasts and functions through sprouty homolog 1 to augment extracellular signal–regulated kinase-mitogen-activated protein kinase activity and interstitial fibrosis. In addition, miR-21 induction in infarcted hearts ensures matrix deposition by the targeting of matrix metalloproteinase 2. In conclusion, although miR-21 could have a role in cardiomyocytes, its predominant function seems to be the control of fibroblast matrix turnover.

Cardiac Arrhythmias: miR-1 and miR-133 Function Individually and in Concert to Induce Arrhythmias

Ventricular arrhythmias are an important cause of sudden death in patients with hypertensive heart disease. Both miR-1 and -133 are proarrhythmic and act on multiple channel messages. Adult miR-1 knockout mice have conductance abnormalities because of misregulation of its target Irx5. miR-1 regulation seems to be etiology dependent; in contrast to its downregulation during mouse and rat pressure overload, expression is elevated in human coronary artery disease and in infarcted rat hearts. miR-1 overexpression in normal or infarcted rat hearts exacerbated arrhythmogenesis, whereas inhibiting miR-1 in infarcted rat hearts relieved arrhythmogenesis. miR-1 is thought to exert its proarrhythmic effects via direct repression of the potassium channel gene KCNJ2 and of connexin 43, and via the protein phosphatase PP2A, which increased the activities of the L-type calcium and ryanodine receptor channels, promoting arrhythmias. On the other hand, downregulation of miR-1 and -133 in hypertrophied rat hearts was associated with arrhythmias via the pacemaker channel genes HCN2, an miR-1 and -133 target, and HCN4, an miR-1 target.

Interestingly, 2 major potassium channels in the heart, KCNQ1 and KCNE1, show regional expression differences, which have now been linked to spatial heterogeneity of miR-1/-133 and the transcription factor Sp1. Although Sp1 transcriptionally activates both proteins, KCNQ1 protein expression is directly repressed by miR-133 and KCNE1 by miR-1.

Taken together, these studies show that 1 miR family can secure its final effect by targeting multiple effectors. miR-1 and -133 are native arrhythmogenic molecules, and their targeted modification could provide a powerful antiarrhythmic therapy.

How to Identify Relevant Targets for miRs

The identification of relevant miR/mRNA pathways is a major challenge, for the following reasons: (1) the identification of miR target genes is time consuming; (2) miR and mRNA need to be coexpressed and both linked to pathology; and (3) multiple delicately balanced pathways eventually contribute altogether to pathology.

Studying mRNA expression to identify miR targets is valid, because miRs seem to have potent effects on mRNA stability. Large-scale mRNA expression studies by microarray are mostly used, but a more direct way to identify degraded mRNA targets is “degradome sequencing,” in which miRNA-cleaved mRNA targets are discerned from other degraded messengers.

With growing consensus about the crucial characteristics of miR/mRNA interactions, in silico prediction programs improve. For example, Selbach et al elegantly show that miRs predominantly affect target gene expression through 3'UTR seed binding. However, it is becoming increasingly clear that 3' UTRs vary among cell types and under different conditions, enabling cells to “play” with their miRNA sensitivity to miRs. Therefore, well-annotated 3'UTRs, preferably cell-type and pathology specific, are indispensable.

Evidence accumulates that miRs also target 5'UTRs and coding regions of mRNAs, also resulting in mRNA destabilization although to a lesser extent than 3'UTR-binding miRs. In addition, small RNAs bind to promoter sites in the cell nucleus and regulate gene transcription; many known miRs appear to have substantial complementarity to sequences within gene promoters. Whether binding of miRs to genetic regions outside the 3'UTR indeed contributes to pathologies like hypertensive heart disease remains to be determined.

In conclusion, miRs generally target 3'UTRs of mRNAs and cause mRNA degradation. The relevance of other miR-binding sites needs further investigation.

Genetics of miRs

Genetic studies could be of help in our search for relevant miR mechanisms contributing to cardiovascular disease. Three variants associated with cardiovascular disease, of which the phenotypic relevance was previously not understood because they lie within nontranslated regions of the transcripts, now get an exciting function and are accepted to actively contribute to disease. A variant associated with hypertension lies within the SLC7a1 gene and results in increased binding of miR-122, lowering SLC7a1 levels and presumably contributing to the endothelial dysfunction seen in hypertensive subjects. Another variant, in the 3'UTR of the angiotensin II type 1 receptor gene and associated with cardiovascular disease, was found in 2 independent studies to decrease miR-155 binding, resulting in increased angiotensin II type 1 receptor levels and, presumably, increased angiotensin signaling. Finally, a variant in the KCNJ1 gene, strongly associated with monogenic hypertension, maps to an evolutionary conserved binding site for miR-155.

These findings have major implications for our way of interpreting genetic data. Now that the understanding increases regarding how UTRs, which were in the past often not included in sequence analyses, exert major impact on expression regulation, one can include them retrospectively and prospectively in genetic analyses.
What Is In It For the Patient?

Diagnostic Potential of miRs
In the cancer domain, miR expression profiles of excised tumors are already recognized as highly accurate to predict outcome, and also the recently identified serum miRs were found to make good diagnostic markers for cancer.\textsuperscript{70–73} The huge potential of serum miRs to diagnose cardiac diseases, in particular, presymptomatic screening of complications of hypertensive heart disease and heart failure, is obvious. Indeed, the cardiac-specific miR-208 was released in the blood after isoproterenol-induced cardiac injury in rats.\textsuperscript{74} Its plasma levels followed those of the clinical marker cardiac troponin I. However, miR-208 was not detected in hypertension-induced hypertrophy in rats, indicating that hypertrophy is not sufficiently damaging cardiomyocytes for miRs to leak out. It will be interesting to learn what happens to the plasma presence of other cardiac miRs during cardiac pathology.

Therapeutic Potential of miRs
The therapeutic possibilities of miRs were very quickly recognized on their identification. Methods to manipulate in vivo miR and/or target gene levels include miR mimics and miR inhibitors, like antagomiRs and sponges. A major obstacle for these small RNA molecules is the difficulty to deliver them to the required site, such as the heart.

AntagomiRs bind to a specific miR and prevent cleavage of its mRNA targets. Several miRs were efficiently targeted in the mouse heart after administration of antagomiRs, with specific and long-lasting effects.\textsuperscript{31,40,75} The clinical value of antagomiRs remains to be established per miR. Although anti-miR-122 treatment was effective and without adverse effects in nonhuman primates to treat hepatitis C,\textsuperscript{76,77} several clinical trials for cancer had variable success.\textsuperscript{78}

miR sponges also inhibit miR function by binding to a specific miR, and their properties prevent cleavage of the sponge with release and consequent recycling of the miR.\textsuperscript{79} They mostly contain multiple miR-binding sites and are delivered to target organs by adeno-associated viral vectors (AAVs), which can contain cell type–specific promoters. In this way, the problem of unwanted modification of miR function outside the target organ/cell type is overcome. An additional advantage for the heart is that AAVs preferably infect nondividing cells, such as cardiomyocytes.\textsuperscript{80} Although many preclinical and phase I clinical studies have provided encouraging results regarding the safe use of AAVs in clinical settings,\textsuperscript{81} the clinical use of AAVs is still a challenge. First, the host immune response remains of concern.\textsuperscript{82} Second, although random integration of AAV DNA into the host genome is low, it is detectable and was reported to often occur in or near genes.\textsuperscript{83}

The presence of some miRs is beneficial, and mimicking their expression may be useful. miR mimics can exactly mimic the miR of interest but can also be designed in a gene-specific manner. Pacemaker channel gene–specific mimics for miR-1 and -133 only affected the regulation of the intended target genes HCN2 and HCN4, preventing unwanted adverse effects.\textsuperscript{84}

Future Perspectives and Open Questions
Our knowledge on the function of miRs in general and on roles of individual miRs in development and disease increases rapidly. Some priming questions on the function of miRs emerge. Is miR function dependent on cell/organ function, developmental state, or stress?

Which mechanisms control the pool of mature miRs, other than transcriptional regulation? Are there microRNases in mammals? This latter question is partly addressed by findings that a substantial regulation of mature miR accumulation after transcription exists.\textsuperscript{85} In plants and in Drosophila, microRNases have been identified, but it is not yet known whether these are operative in mammals.\textsuperscript{85}

Can mature miRs shuttle between cells? Can they even be transported to other locations in blood/serum? Exosomes, which mediate communication between cells, have been shown to contain functionally active mRNA and miRs.\textsuperscript{86} The answers to these questions will have an intriguing impact on our dealing with cardiovascular disease.

In conclusion, miRs represent an exciting and challenging new domain of cardiovascular research. We are currently only entering the field of noncoding RNAs and touching the tip of the iceberg. The Encyclopedia of DNA Elements pilot project has come to the conclusion (on the basis of detailed analyses of 1% of the human genome) that >90% of the human genome is actively transcribed, generating an enormous number of noncoding RNAs with yet-unknown regulatory functions.\textsuperscript{87} To all researchers in the cardiovascular field, it is important to keep an eye on these advances and to work on the relevance of newly identified (noncoding) genes for cardiovascular development and diseases such as hypertension.

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None.

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MicroRNAs in Hypertensive Heart Disease


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MicroRNAs and Beyond: The Heart Reveals Its Treasures
Blanche Schroen and Stephane Heymans

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MICRORNAS AND BEYOND: THE HEART REVEALS ITS TREASURES

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Center for Heart Failure Research, Cardiovascular Research Institute Maastricht CARIM, University of Maastricht, Maastricht, The Netherlands

Short title: MicroRNAs in hypertensive heart disease
References


**Supplementary Table S1. Cardiac miRs, their functions and validated targets**

<table>
<thead>
<tr>
<th>MiR family</th>
<th>Function</th>
<th>Validated cardiac targets</th>
</tr>
</thead>
</table>
| All (Dicer) | -Regulation of cardiogenesis  
-Cardiomyocyte-specific deletion in mice is embryonically\(^1\) or neonatally\(^2\) lethal (depending on promotor)  
| | Not applicable |
| 1 | Embryonic:  
-Modulates cardiogenesis\(^1, 3-5\)  
-Essential to maintain muscle gene expression\(^3\)  
-Deletion in mice is partially embryonically lethal (ventricular-septal defect)\(^1\)  
-Regulation of cardiomyocyte cell cycle\(^1\)  | -Delta, the Notch ligand, involved in cardiac cell differentiation\(^3\); Hand2, a cardiac transcription factor involved in cardiomyocyte expansion\(^1, 4\); and HDAC4, a transcriptional repressor of muscle gene expression\(^5\) |
| | Adult:  
-Conduction\(^1\); pro-arrhythmic\(^6-9\)  | -Irx5, a cardiac TF that represses the potassium channel Kcnq1; potassium channels KCNJ2\(^6\) and KCNE1\(^8\); pacemaker channels HCN2 and -4\(^8\); Connexin 43\(^5\); and B56α subunit of protein phosphatase 2A\(^7\) |
<p>| | -Regulation of cardiomyocyte growth(^10, 11)  | -Pro-hypertrophic genes calmodulin and Mef2a(^10); cell cycle regulators RasGAP and Cdk9 and Rheb(^11); and fibronectin(^11) |
| | -Pro-apoptotic(^12)  | -HSP60 and HSP70(^12) |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Function</th>
<th>Protein/Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic</td>
<td>- Modulates cardiogenesis&lt;sup&gt;5, 13&lt;/sup&gt;</td>
<td>- SRF&lt;sup&gt;5, 13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Deletion in mice is partially embryonically lethal (ventricular-septal defect)&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Regulation of cardiomyocyte cell cycle&lt;sup&gt;13&lt;/sup&gt;</td>
<td>- Cyclin D2&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adult</td>
<td>- Regulation of collagen synthesis&lt;sup&gt;13, 14&lt;/sup&gt;</td>
<td>- CTGF&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Conduction&lt;sup&gt;13&lt;/sup&gt;; pro-arrhythmic&lt;sup&gt;8, 15&lt;/sup&gt;</td>
<td>- Potassium channels KCNQ1&lt;sup&gt;9&lt;/sup&gt; and HERG&lt;sup&gt;15&lt;/sup&gt; and pacemaker channel HCN2&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Regulation of cardiomyocyte growth&lt;sup&gt;16, 17&lt;/sup&gt;</td>
<td>- RhoA, a GDP-GTP exchange protein regulating cardiac hypertrophy&lt;sup&gt;17&lt;/sup&gt;; Cdc42, a signal transduction kinase implicated in hypertrophy&lt;sup&gt;17&lt;/sup&gt;; and Nelf-A/WHSC2, a nuclear factor involved in cardiogenesis&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Anti-apoptotic&lt;sup&gt;12, 13&lt;/sup&gt;</td>
<td>- Caspase-9&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adult</td>
<td>- Regulates cardiomyocyte hypertrophy and fibrosis in response to pressure overload</td>
<td>- THRAP1, a thyroid hormone transcription factor&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

TF, transcription factor
### Supplementary table S2. Role of miRs in hypertensive heart disease

<table>
<thead>
<tr>
<th>miR</th>
<th>Model organism</th>
<th>Phenotype/function</th>
<th>Validated targets</th>
</tr>
</thead>
</table>
| All (Dicer) | Inducible cardiomyocyte-specific KO mice, 3 weeks old (αMHC promotor)<sup>19</sup> | -Sudden cardiac death  
Atrial enlargement | - |
|  | Inducible cardiomyocyte-specific KO mice, 8 weeks old (αMHC promotor)<sup>19</sup> | -Heart failure | - |
| All (Dgcr8) | Muscle-specific KO mice (muscle creatine kinase promotor)<sup>20</sup> | -Premature death between age 2-8 weeks due to DCM and heart failure with conduction defect, thin-walled ventricles and fibrosis | - |
| 1 | AMO-mediated knockdown in rats + MI<sup>6</sup> | Suppression of arrhythmias (Langendorf) | |
|  | miR-1 injection into healthy rat hearts<sup>6</sup> | Arrhythmogenic | |
|  | miR-1 injection into infarcted rat hearts<sup>6</sup> | Promotion of ischemic arrhythmias | Connexin 43 and KCNJ2<sup>6</sup> |
| 23a | AntagomiR-mediated knockdown in mice + pressure overload by isoproterenol<sup>21</sup> | Attenuation of cardiac hypertrophy | MuRF1, Muscle specific ring finger protein 1<sup>21</sup> |
| 133 | AntagomiR-mediated knockdown in mice<sup>17</sup> | Spontaneous induction of left ventricular hypertrophy and fetal gene program activation | RhoA<sup>17</sup>  
Cdc42<sup>17</sup>  
Nelf-A/WHSC2<sup>17</sup> |
|  | Adenoviral overexpression in Akt transgenic mice<sup>17</sup> | Reduced myocyte size | |
| 195 | Cardiomyocyte-specific transgenic mice (αMHC promotor)<sup>22</sup> | Spontaneous heart failure with enlarged myocytes and thinned dilated left ventricular walls | - |
| KO mice + pressure overload by TAC$^{18}$ | Protected against left ventricular hypertrophy and fibrosis | THRAP1, thyroid hormone receptor associated protein 1, involved in thyroid hormone signaling$^{18}$ |
Supplementary Figure S1.
Legend. Compilation of miR expression data from large-scale gene expression studies in the heart of humans, rats and mice, at baseline or during cardiac pathology. Remarkably, miR-26a/b’s expression seems etiology-dependent; it is down-regulated in mouse, rat and human LVH, while up-regulated in the mouse and human ischemic heart. In addition, miR-221 shows a remarkable species-specific expression pattern that seems to be independent of disease-etiology: it is up-regulated in mouse cardiac pathologies while down-regulated in human cardiac disease.