autophagy might be exploited to therapeutic advantage in failing hearts. Augmentation of autophagy might be beneficial when autophagosome clearance is normal. Inhibition of autophagosome formation, on the other hand, might lessen the burden of autophagosome accumulation in patients with defective clearance such as those with the cardiomyopathy of Danon's disease.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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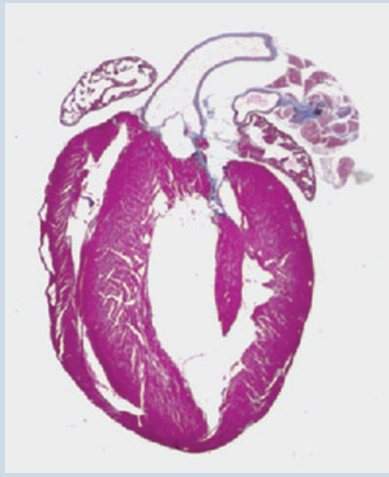
MicroRNAs loom large in the heart

How microRNAs (miRNAs) influence heart development and disease is a topic of growing interest. miRNAs regulate gene expression post-transcriptionally, typically by binding to mRNAs and inhibiting their translation. Three recent papers show that miRNAs are essential for heart development and function, regulating the expression of genes involved in electrical conductance, hypertrophy and contractility.

In mice with deletion of the muscle-specific miRNA *miR-1-2*, Zhao *et al.* observed a range of heart abnormalities (*Cell* **129**, 1–15). Some embryos died from heart structure defects, whereas surviving adults had electrical conduction defects and, unusually, mitotically active cardiomyocytes. The researchers identified several potential *miR-1-2* target mRNAs, including *Irx5*, which they showed is a direct target of *miR-1-2*. Since *Irx5* encodes a homeobox transcription factor known to regulate cardiac repolarization, it may be the culprit for the electrical conduction defect seen in adult mice.

Muscle-specific miRNAs also regulate hypertrophic growth of heart muscle, report Carè *et al.* in this issue of *Nature Medicine* (**13**, 613–618). The researchers showed that expression of *miR-1* and another muscle-specific miRNA, *miR-133*, is decreased in human and mouse hypertrophic heart tissue. In functional studies, the researchers showed that both miRNAs block cardiomyocyte hypertrophy. Most notably, suppression of *miR-133* expression in mice using an oligonucleotide "antagomir" resulted in cardiac hypertrophy. In search of a molecular mechanism for how *miR-133* controls heart size, the researchers showed that the transcripts of *Rhoa*, *Cdc42* and *Whsc2* are direct targets of this miRNA.


Science

Histological section of mouse heart (stained for Masson's trichrome).

In the third study, Van Rooj *et al.* showed that the muscle-specific *miR-208* controls expression of the β-*MHC* gene, a regulator of cardiac contractility (*Science*, doi: 10.1126/science.1139089). Mice with *miR-208* deleted developed slight defects in heart function as they aged. More strikingly, these mice failed to undergo cardiac hypertrophy under inducing conditions, and β-*MHC* expression was not upregulated as expected during the hypertrophic response. Repression of β-*MHC* expression by the thyroid hormone receptor is important for regulating cardiac contractility. The researchers showed that *miR-208* targets THRAP1, a regulator of the thyroid hormone receptor, suggesting a regulatory circuit by which *miR-208* controls β-*MHC* expression.

From these and other recent papers, it seems clear that miRNAs have a pivotal role in regulating gene expression in the heart. Unraveling the regulatory circuits involved may be challenging, given that a single miRNA can regulate the expression of many mRNA targets. As important regulators of heart function, miRNAs may represent attractive targets for treating heart disease. – ***Michael Basson***