HEART FAILURE

Targeting miRNA pathology in heart disease

Current treatments for heart failure (defined as stiffening and weakening of the heart muscle) are symptomatic and largely fail to address the underlying pathology. Now, reporting in *Nature*, Mercola, Hajjar and colleagues show that the pathological overexpression of the microRNA miR-25 causes impaired calcium handling during heart failure, and that targeting this molecule improves survival rates in animal models.

Calcium has a crucial role in regulating the cardiac cycle, and it has been found that the contractility of heart muscle cells can be improved by enhancing the expression of the sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) in cardiomyocytes. SERCA2a facilitates Ca^{2+} uptake from the cytosol into the sarcoplasmic reticulum during excitation–contraction coupling, and decreased expression or reduced activity of SERCA2a — leading to impaired Ca^{2+} uptake — is a hallmark of heart failure. Gene therapy approaches to boost the expression of SERCA2a have generated promising results in animal models and in early-stage clinical trials of heart failure.


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In a quest for new targets to treat heart failure, the authors focused their attention on microRNAs (miRNAs), which are known to fine-tune complex biological processes by downregulating key proteins in molecular signalling networks. To search for miRNAs that may downregulate SERCA2a expression, they carried out a high-throughput screen of a whole-human-genome collection of miRNAs using a 'target sensor' construct consisting of the *SERCA2A* mRNA 3′ untranslated region fused to enhanced green fluorescent protein (eGFP). A number of miRNAs were identified that were both evolutionarily conserved and had previously been reported to be upregulated in patients with heart failure. Of these, miR-25 showed the most potent effect in *in vitro* experiments: it strongly affected calcium flux in a cardiomyocyte cell line, eliciting a physiological effect comparable to that of small interfering RNA (siRNA) against SERCA2a.

In situ hybridization experiments confirmed that miR-25 is pathologically upregulated in tissue samples from patients with severe heart failure, and showed that it is also specifically upregulated in cardiomyocytes of transaortic constriction (TAC)-induced failing mouse hearts.

Further *in vivo* experiments in TAC mice showed that overexpression of miR-25 using an adenoviral vector led to a reduction in myocardial contractile function. By contrast, intravenous injection of an anti-miR-25 antagomir (an antisense oligonucleotide that pairs with miR-25 and inhibits its function) restored the loss of SERCA2a protein and improved cardiac function and survival in the TAC model. In SERCA2a-knockout mice, the anti-miR-25 antagomir had no effect on cardiac function, indicating that SERCA2a is indeed the critical target of miR-25 in the context of heart failure.

These results identify miR-25 as a powerful suppressor of SERCA2a expression, and suggest that it could be therapeutically targeted for the treatment of heart failure.

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ORIGINAL RESEARCH PAPER Wahlquist, C. *et al.* Inhibition of *miR-25* improves cardiac contractility in the failing heart. *Nature* http://dx.doi.org/10.1038/nature13073 (2014)