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Administration of miR-665 modulates cardiomyocyte mechanotransduction and prevents pathological cardiac remodelling after pressure overload

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Background/Purpose: The adult heart undergoes remodelling in response to different pathological stimuli; in most cases, a phase of compensated hypertrophy evolves into frank dysfunction and heart failure. To identify microRNAs able to prevent cardiac hypertrophy and preserve cardiac function, we performed a high-content microscopy, high-throughput functional screening for human miRNAs able to reduce neonatal cardiomyocyte (CM) cell size using a whole-genome miRNA library.

Methods: RNAi High Content Screening (HCS), RNAseq, qRTPCR, in vivo mouse model of cardiac hypertrophy (TAC) and HFpEF, echocardiography, pressure/volume conductance, histology.

Results: The most effective anti-hypertrophic miRNAs in the screening was hsa-miR-665. In a model of transverse abdominal aortic constriction (TAC) in 8 weeks old CD1 mice (n=14 per group), AAV9-mediated delivery of hsa-miR-665 protected against pathological cardiac hypertrophy, preserved ejection fraction, avoided LV-dilation and prevented development of heart failure. This effect was observed both when the vectors were delivered before (LVEF at 60 day after TAC: 51.3±5.8% in treated vs. 34.8±0.77% in controls; P<0.01) or after hypertrophy onset (LVEF at 60 days after TAC: 57.5±5.60% in treated vs. 28.4±15% in controls; P<0.01). Global mRNAs changes in hearts treated with miR-665 were evaluated by mRNA deep sequencing. All the 67 genes that were found to be expressed ≥2 fold over control were individually downregulated by specific siRNAs and tested for being direct miR-665 targets. This approach identified three sarcomeric proteins as direct mediators of miR-665 activity, namely Enah, Fhl1 and Xirp2, which are known to be involved in mechanotransduction, cardiomyocyte passive stiffness regulation and myofibrillar remodelling. In addition, AAV9-mediated delivery of hsa-miR-665 in an AngII-mediated mouse model of diastolic dysfunction (HFpEF) ameliorated LV passive stiffness, supporting the conclusion that hsa-miR-665 acts not only by reducing cardiac hypertrophy but also by modulating cardiomyocyte compliance to stretch.

Conclusions: hsa-miR-665 represents a novel tool to decipher the molecular mechanisms of cardiac pathological remodelling and heart failure and a potential lead for the development of new RNA-based therapeutics.