microRNA-22 promotes heart failure through coordinate suppression of PPAR/ERR-nuclear hormone receptor transcription.

Abstract: Increasing evidence suggests that microRNAs are intimately involved in the pathophysiology of heart failure. MicroRNA-22 (miR-22) is a muscle-enriched miRNA required for optimum cardiac gene transcription and adaptation to hemodynamic stress by pressure overload in mice. Recent evidence also suggests that miR-22 induces hypertrophic growth and it is oftentimes upregulated in end stage heart failure. However the scope of mRNA targets and networks of miR-22 in the heart failure remained unclear. We analyzed transgenic mice with enhanced levels of miR-22 expression in adult cardiomyocytes to identify important pathophysiologic targets of miR-22. Our data shows that forced expression of miR-22 induces a pro-hypertrophic gene expression program, and it elicits contractile dysfunction leading to cardiac dilation and heart failure. Increased expression of miR-22 impairs the Ca(2+) transient, Ca(2+) loading into the sarcoplasmic reticulum plus it interferes with transcription of estrogen related receptor (ERR) and PPAR downstream genes. Mechanistically, miR-22 postranscriptionally inhibits peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1?), PPAR? and sirtuin 1
(SIRT1) expression via a synergistic circuit, which may account for deleterious actions of unchecked miR-22 expression on the heart.