MiR-378 controls cardiac hypertrophy by combined repression of mitogen-activated protein kinase pathway factors.

Several microRNAs (miRs) have been shown to regulate gene expression in the heart, and dysregulation of their expression has been linked to cardiac disease. miR-378 is strongly expressed in the mammalian heart but so far has been studied predominantly in cancer, in which it regulates cell survival and tumor growth. Here, we report tight control of cardiomyocyte hypertrophy through miR-378. In isolated primary cardiomyocytes, miR-378 was found to be both necessary and sufficient to repress cardiomyocyte hypertrophy. Bioinformatic prediction suggested that factors of the mitogen-activated protein kinase (MAPK) pathway are enriched among miR-378 targets. Using mRNA and protein expression analysis along with luciferase assays, we validated 4 key components of the MAPK pathway as targets of miR-378: MAPK1 itself, insulin-like growth factor receptor 1, growth factor receptor-bound protein 2, and kinase suppressor of ras 1. RNA interference with these targets prevented the prohypertrophic effect of antimiR-378, suggesting their functional relation with miR-378. Because miR-378 significantly decreases in cardiac disease, we sought to compensate for its loss through adeno-associated virus-mediated,
cardiomyocyte-targeted expression of miR-378 in an in vivo model of cardiac hypertrophy (pressure overload by thoracic aortic constriction). Restoration of miR-378 levels significantly attenuated thoracic aortic constriction-induced cardiac hypertrophy and improved cardiac function. Our data identify miR-378 as a regulator of cardiomyocyte hypertrophy, which exerts its activity by suppressing the MAPK signaling pathway on several distinct levels. Restoration of disease-associated loss of miR-378 through cardiomyocyte-targeted adeno-associated virus-miR-378 may prove to be an effective therapeutic strategy in myocardial disease.