MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts.

Abstract:
MicroRNAs comprise a broad class of small non-coding RNAs that control expression of complementary target messenger RNAs. Dysregulation of microRNAs by several mechanisms has been described in various disease states including cardiac disease. Whereas previous studies of cardiac disease have focused on microRNAs that are primarily expressed in cardiomyocytes, the role of microRNAs expressed in other cell types of the heart is unclear. Here we show that microRNA-21 (miR-21, also known as Mirn21) regulates the ERK-MAP kinase signalling pathway in cardiac fibroblasts, which has impacts on global cardiac structure and function. miR-21 levels are increased selectively in fibroblasts of the failing heart, augmenting ERK-MAP kinase activity through inhibition of sprouty homologue 1 (Spry1). This mechanism regulates fibroblast survival and growth factor secretion, apparently controlling the extent of interstitial fibrosis and cardiac hypertrophy. In vivo silencing of miR-21 by a specific antagonir in a mouse pressure-overload-induced disease model reduces cardiac ERK-MAP kinase activity, inhibits interstitial fibrosis and attenuates cardiac dysfunction. These findings
reveal that microRNAs can contribute to myocardial disease by an effect in cardiac fibroblasts. Our results validate miR-21 as a disease target in heart failure and establish the therapeutic efficacy of microRNA therapeutic intervention in a cardiovascular disease setting.