**MITF SWITCHES FROM ACTIVATOR TO REPRESSOR OF ERBIN EXPRESSION DURING CARDIAC HYPERTROPHY**

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*Background*: Changes in cardiac gene expression contribute to the progression of heart failure by affecting cardiomyocyte growth, function, and survival. Microphthalmia-associated transcription factor (MITF) is highly expressed in cardiomyocytes. We have previously reported that MITF-mutated mice have diminished cardiac hypertrophy in response to beta-adrenergic stimulation resulting in decreased cardiac function, and that cardiac size and function are decreased in middle aged MITF-mutated mice. Thus, MITF is required for cardiac hypertrophy but the molecular mechanisms involved are unknown.

*Objective*: To elucidate the molecular mechanism by which MITF regulates cardiac hypertrophy.

*Methods and Results*: Gene array analysis of hearts from MITF-mutated mice indicated that ErbB2 interacting protein (Erbin), which we have recently shown to be a negative modulator of pathological cardiac hypertrophy, is a candidate target gene for MITF. Here we show that Erbin expression is regulated by MITF. Under basal conditions MITF activates Erbin expression by direct binding to its promoter. However, under beta-adrenergic stimulation Erbin expression is decreased only in wild type mice, but not in MITF-mutated mice. Yeast two-hybrid screening, using MITF as bait, identified interaction with the cardiac-predominant four-and-a-half LIM domain protein 2 (FHL2), which was confirmed by co-immunoprecipitation in both mouse and human hearts. Upon beta-adrenergic stimulation, FHL2 and MITF bind Erbin promoter as a complex, and repress MITF-directed Erbin expression. Overexpression of FHL2 alone had no effect on Erbin expression, but in the presence of MITF, Erbin expression was decreased. FHL2-MITF association was also increased in biopsies from heart failure patients.

*Conclusion*: Our results suggest that MITF-FHL2 interaction acts as signal responsive activator/repressor of Erbin expression during cardiac hypertrophy, and this fine tuning mechanism could be an important regulator of cardiac hypertrophy.