Activation of FGFR1 in Adult Murine Cardiomyocytes Leads to Development of a Hypertrophic Cardiomyopathy

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In both humans and mice, Fibroblast Growth Factor (FGF) is upregulated following injury to the heart, and published studies have shown that FGF2 serves as a mediator in cardioprotection following cardiac stress or injury. It is currently unknown how FGF signaling is regulated in the adult heart and why the effects are only observed following injury. We hypothesized that FGF signaling may be repressed in the adult heart under homeostatic conditions and becomes reactivated following injury. A doxycycline-inducible, cardiomyocyte specific, constitutively-active FGF receptor mouse model (αMHC-rtTA, TRE-caFGFR1-myc) was utilized to test whether the cardiomyocyte has the capacity to respond to a cell autonomous FGF signal. Twelve- to 14-week old mice were fed doxycycline-containing (DOX) chow to induce caFGFR1 in cardiomyocytes. Histologic analysis showed significantly increased cardiomyocyte-cross sectional area in caFGFR1 hearts by one week following induction. Trichrome and H&E staining indicated an increase in fibrosis and myocyte disarray in caFGFR1 hearts. Gene expression analysis confirmed the presence of hypertrophy and fibrosis by one week and demonstrated that pathologic remodeling was underway by 24 hours. Western analysis to elucidate the in vivo mechanisms by which FGF signaling affects cardiomyocyte hypertrophy is currently under investigation. Experiments investigating the effects of administering targeted pathway inhibitors to prevent the development of the hypertrophy phenotype are also underway. The findings demonstrate involvement of FGF signaling in the development of a hypertrophic cardiomyopathy (HCM), a pathological condition characterized by preserved or enhanced systolic function, myocyte hypertrophy and disarray, and interstitial fibrosis. The mechanisms that result in hypertrophy are still poorly understood, but this new model of HCM could potentially provide valuable insight into specific mechanisms that regulate cardiomyocyte growth and remodeling in the adult heart.