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ERK1/2 Regulate the Balance between Eccentric and Concentric Growth of the Heart

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Introduction: The myocardium undergoes cellular and chamber remodeling as a means of maintaining cardiac output in response to increased workload. An increase in cardiac afterload typically produces concentric hypertrophy characterized by an increase in cardiomyocyte width, while volume overload results in eccentric growth, characterized by cellular elongation and addition of sarcomeres in series. Concentric and eccentric growth likely result from orchestrated activation of specific intracellular signaling pathways.
Material and Methods: To determine the role of extracellular signal-regulated kinases 1/2 (ERK1/2) in regulating the cardiac hypertrophic response we used mice lacking all ERK1/2 protein in the heart by crossing Erk1-/- mice with Erk2fl/fl targeted mice and a cardiac Cre-recombinase expressing line. We also studied mice expressing activated MEK1 in the heart to induce ERK1/2 signaling and used mechanistic experiments in cultured myocytes to assess cellular growth characteristics associated with this signaling pathway.
Results: While loss of all ERK1/2 from the heart did not block the cardiac hypertrophic response per se, it did dramatically alter how the heart grew. For example, adult myocytes from hearts of Erk1-/-;Erk2fl/fl-Cre mice showed preferential eccentric growth (lengthening) while myocytes from MEK1 transgenic hearts showed concentric growth (width increase). Isolated adult myocytes acutely inhibited for ERK1/2 signaling by adenoviral gene transfer showed spontaneous lengthening while infection with an activated MEK1 adenovirus promoted constitutive ERK1/2 signaling and increased myocyte thickness.
Conclusions: Taken together these data demonstrate that the ERK1/2 signaling pathway uniquely regulates the balance between eccentric and concentric growth of the heart. Thus, the MEK1-ERK1/2 pathway may be the first identified signaling pathway capable of specifically directing the mode of cardiomyocyte hypertrophy.