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NOVEL MECHANISMS OF CARDIAC HYPERTROPHY

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In the adult heart, a variety of stresses induce re-expression of a fetal gene program in association with myocyte hypertrophy and heart failure. We have shown that HDAC2 regulates expression of many fetal cardiac isoforms. Loss of HDAC2 and chemical HDAC inhibition prevent re-expression of fetal genes, and attenuate cardiac hypertrophy in adult hearts exposed to hypertrophic stimuli. Resistance to hypertrophy is associated with activation of an inositol polyphosphate phosphatase, INPP5F, resulting in constitutive activation of glycogen synthase kinase 3β (GSK3β) via inactivation of AKT and PDK1. Conversely, transgenic HDAC2 gain-of-function augments hypertrophy and inactivates GSK3β. Chemical inhibition of activated GSK3β allows HDAC2-deficient adults to become sensitive to hypertrophic stimulation. These results suggest that HDAC2 is an important molecular target of HDAC inhibitors in the heart, and that HDAC2 and GSK3β are components of a regulatory pathway that is a therapeutic target for the treatment of cardiac hypertrophy and heart failure.

Key Words: Cardiac hypertrophy, Fetal gene program, Histone deacetylase 2, Glycogen synthase kinase 3β