Hdac2 regulates the cardiac hypertrophic response by modulating Gsk3 beta activity.

Abstract:
In the adult heart, a variety of stresses induce re-expression of a fetal gene program in association with myocyte hypertrophy and heart failure. Here we show that histone deacetylase-2 (Hdac2) regulates expression of many fetal cardiac isoforms. Hdac2 deficiency or chemical histone deacetylase (HDAC) inhibition prevented the re-expression of fetal genes and attenuated cardiac hypertrophy in hearts exposed to hypertrophic stimuli. Resistance to hypertrophy was associated with increased expression of the gene encoding inositol polyphosphate-5-phosphatase f (Inpp5f) resulting in constitutive activation of glycogen synthase kinase 3beta (Gsk3beta) via inactivation of thymoma viral proto-oncogene (Akt) and 3-phosphoinositide-dependent protein kinase-1 (Pdk1). In contrast, Hdac2 transgenic mice had augmented hypertrophy associated with inactivated Gsk3beta. Chemical inhibition of activated Gsk3beta allowed 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 Gsk3beta are components of a regulatory pathway providing an attractive therapeutic target for the treatment of cardiac hypertrophy and heart failure.