HDAC signalling through post-translational modification exerts hypertrophic action

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Cardiomyocyte hypertrophy is an integral component of pathological cardiac remodelling, which occurs in settings of cardiovascular disease. Class IIa histone deacetylases, such as HDAC5, are important regulators of cardiomyocyte hypertrophy, repressing cell growth when localized in the nucleus, and promoting cell enlargement upon export into the cytoplasm. Post-translational modifications, such as phosphorylation, oxidation and proteolytic cleavage, regulate the shuttling of class IIa HDACs between the nucleus and the cytoplasm. Phosphorylation of HDAC5 at two conserved serine residues (Ser259 and Ser498) promotes nuclear export in response to G_q protein-coupled receptor activation. The signalling cascades responsible for increased phosphorylation of HDAC5 in these settings are well established, and involve the HDAC kinases Ca^{2+}/calmodulin-dependent protein kinase II and protein kinase D. Interestingly, recent work shows that activation of β-adrenergic receptors (β-ARs) leads to reduced phosphorylation of HDAC5 and nuclear accumulation, which, in turn, suppresses cardiomyocyte hypertrophy. The dephosphorylation of HDAC5 downstream of β-AR activation is dependent upon protein kinase A and protein phosphatase 2A (PP2A) activity, and the PP2A regulatory subunit B55α is responsible for targeting the PP2A holoenzyme to HDAC5 in response to acute β-AR activation *in vitro*. Ongoing *in vivo* studies are investigating the role of B55α in the heart and the biological significance of β-AR-induced association of B55α-PP2A with HDAC5 in the context of cardiac remodelling and heart failure.