**Nuclear GRK5 binds Class I HDACs and the transcriptional repressor Sin3A.**

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G-protein coupled receptor kinase 5 (GRK5), known for its role in G-protein coupled receptor (GPCR) desensitisation, can also adopt a nuclear localisation. Nuclear GRK5 has been shown to have a causative role in pathological cardiac hypertrophy when overexpressed in the hearts of transgenic (TG) mice. Hypertrophy is a cardiovascular disease that represents a milestone in the progression to heart failure. At the cellular level, pathological cardiac hypertrophy is concomitant with the aberrant expression of foetal cardiac genes and the upregulation of the prohypertrophic transcription factor, MEF2. This aberrant cardiac remodelling ensues following pathological hypertrophic stimuli, which signal through Gq coupled GPCRs to activate multiple signalling pathways many of which converge upon histone deacetylase (HDAC) regulation.

HDACs play a dual role in cardiac hypertrophy; with class I (HDAC1, 2, 3 and 8) acting in a prohypertrophic manner while class IIa (HDAC4, 5, 7 and 9) are antihypertrophic. HDAC5 is a GRK5 substrate whose phosphorylation induces nuclear export, which relieves the inhibition of MEF2, thus resulting in the activation of hypertrophy.

Here we demonstrate a novel and direct interaction between GRK5 and the class I HDACs, with the exception of HDAC2. Additionally, we show that GRK5 can also interact indirectly with both HDAC1 and 2 via its direct binding to the transcriptional repressor protein Sin3A. Considering that HDAC1 and GRK5 function to activate hypertrophy, we hypothesize that both proteins may function in the same prohypertrophic signalling pathway, potentially via the Sin3A repressor complex. We have used GRK5 peptide arrays to map the binding sites of HDAC1 and Sin3A on GRK5. It is anticipated that GRK5 mutant constructs lacking the ability to bind HDAC1, Sin3A or both proteins will allow an assessment of the role of these interactions in mediating pathological hypertrophy both in neonatal rat ventricular myocytes (NRVM) *in vitro* and TG mice *in vivo*. Our results suggest that in addition to the regulation of MEF2 activity via GRK5-mediated phosphorylation and nuclear export of HDAC5, GRK5 may also be potentiating cardiac hypertrophy via a GRK5/HDAC1/Sin3A transcriptional repressor complex. Patients with ventricular overload disease have high cardiac levels of GRK5 expression. Elucidation of the molecular pathways by which GRK5 is causing cardiac hypertrophy could potentially lead to the development of novel specific inhibitors.