

**003****A Novel Nuclear Function for GRK5 and Its Potential Role in the Hypertrophic Response**

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G-protein coupled receptor kinases (GRKs) are critical regulators of adrenergic signaling in the heart. During heart failure (HF) GRK2 and GRK5 protein are elevated, leading to a diminished cardiac function. Mice with cardiac-specific overexpression of GRK5 have a unique phenotype in response to overload hypertrophy compared to control or GRK2 overexpressing mice. GRK5 mice but not GRK2 or control (NLC) mice rapidly decompensate within 4 weeks with signs of HF. GRK5, unlike GRK2 can reside in the nucleus and contains a nuclear localization (NLS) and export sequence (NES). Our hypothesis is that cardiac decompensation after pressure-overload in GRK5 mice is due to its unique activity in the nucleus. Histone deacetylases (HDAC) reside in the nucleus and act as transcriptional repressors of cardiac hypertrophy at the level of MEF2. Phosphorylation of HDACs results in activation of MEF2 and other hypertrophic genes. We have found that GRK5 can phosphorylate HDAC5 and associates with HDAC5 in myocytes. Further, we found nuclear export of HDAC5 when co-transfected with a nuclear form of GRK5 (GRK5 $\Delta$ NES) while GRK5 $\Delta$ NLS induced no HDAC translocation. Pressure-overload hypertrophy is triggered by Gq activation and we found that expression a constitutively active mutant G $\alpha$ q in myocytes leads to GRK5 nuclear translocation and G $\alpha$ q and GRK5 overexpression increases MEF2 activity. Our results indicate that GRK5 possesses nuclear HDAC kinase activity and this novel non-G protein-coupled receptor activity may play a key role in cardiac hypertrophy and HF.