

P007 Identification of the macromolecular complex responsible for PI3Kgamma dependent regulation of cAMP levels
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PI3Kgamma is a phosphoinositide 3-kinase characterized by both lipid and protein kinase activity. It is activated by G protein-coupled receptors (GPCRs) and it is predominantly expressed in white blood cells; in addition, recent work showed its presence in the heart and its involvement in regulating cardiac functions. In this tissue, PI3Kgamma acts as a negative modulator of contractility, by decreasing cAMP concentration through a kinase-independent mechanism. Indeed, whereas PI3Kgamma-deficient mice show an abnormal cAMP elevation, cAMP levels in knock-in mouse mutants, expressing a kinase-dead PI3K gamma, are comparable to wild-type controls. PI3Kgamma regulates cardiac cAMP homeostasis by forming a macromolecular complex containing phosphodiesterase 3B (PDE3B). How PI3Kgamma controls PDE3B activity is still undefined. To address this question we tested whether known PDE3B activators, like PKA, were contained in the complex. Indeed immunoprecipitation studies revealed that PI3Kgamma co-immunoprecipitates with PKA alpha-catalytic subunit. This data suggests that PI3Kgamma could act as an A-kinase anchoring protein (AKAP), maintaining a cAMP signalling module, including PDE3B and PKA, that forms a negative feedback loop restoring basal cAMP levels. In progress studies using a peptide which specifically disrupts AKAP-PKA interaction (Ht31) might further demonstrate this hypothesis.