G-protein coupled receptor kinase 2 (GRK-2), a new regulator in the pathological cardiac hypertrophy by interacting NFAT signaling

J. Reinkober, H. Tscheschner, P. Schlegel, T. Wieland, J. Backs, W. Koch, H. Katus, P. Most, Philip Raake

Angaben zur Veröffentlichung / Publication details:

Reinkober, J., H. Tscheschner, P. Schlegel, T. Wieland, J. Backs, W. Koch, H. Katus, P. Most, and Philip Raake. 2013. "G-protein coupled receptor kinase 2 (GRK-2), a new regulator in the pathological cardiac hypertrophy by interacting NFAT signaling." *European Heart Journal* 34 (suppl 1): 39–39. https://doi.org/10.1093/eurheartj/eht307.39.

39 | BENCH

G-protein coupled receptor kinase 2 (GRK-2), a new regulator in the pathological cardiac hypertrophy by interacting NFAT signaling

J. Reinkober[1], H. Tscheschner[1], P. Schlegel[1], T. Wieland[2], J. Backs[1], W. Koch[3], H. Katus[1], P. Most[1], P. Raake[1]. *[1]University Hospital of Heidelberg, Internal Medicine III, Dept Cardiology, Angiology & Pneumology, Heidelberg, Germany; [2]Medical Faculty Mannheim-Univ. of Heidelberg, Inst. of Experimental, Clinic. Pharma. & Toxicology, Mannheim, Germany; [3]Center for Translational Medicine, Department of Medicine, Thomas Jefferson University, Philadelphia, United States of America*

Purpose: G-protein coupled receptor kinase 2 (GRK2), a serin/threonin kinase, plays a crucial role in the regulation of cardiac myocytes β-adrenergic signaling thereby contributing to the development of heart failure. We could previously demonstrate that genetic GRK2 knockdown is beneficial in a mouse model of ischemic cardiomyopathy. Interestingly, adverse remodelling was halted by GRK2 knockdown in this model suggesting potential involvement of GRK2 in pathological cardiac hypertrophy. Thus, the present study was aimed at defining the role of GRK2 in pathological cardiac hypertrophy and to establish potential molecular mechanisms.

Methods: For our in vivo studies, pressure overload cardiac hypertrophy in conditional GRK2 knockout mouse was induced by transverse aortic constriction (TAC). Cardiac dysfunction and hypertrophic response was investigated using echocardiography, heart-to-body weight ratio and left ventricular wall thickness. Additionally neonatal rat ventricular cardiomyocyte (NRVCM) were stimulated with different agonists. The impairment of GRK2 was investigated using siRNA against GRK2. Cell area, fetal gene expression and total protein extracts were analysed. Additionally NFAT activity was investigated by using NFAT-promoter luciferase assay.

Results: In vivo GRK2 mRNA and protein levels were increased in pathological hypertrophy. In this regard, conditional GRK2 knockout mice showed improved survival and a significant reduction in heart-to-body weight ratio, myocardial hypertrophy, cardiac dysfunction and fetal gene expression following pressure overload. Consistent with these observations, in vitro NRVCM stimulated with angiotensin II and phenylephrine showed significant hypertrophy and upregulation of GRK2 mRNA and protein levels. GRK2 knockdown prevented the development of cardiac myocyte hypertrophy and inhibited activation of fetal genes. Downstream nuclear accumulation and activation of nuclear factor of activated T-cells (NFAT) is halted by GRK2 knockdown, as shown by confocal immunofluorescence and NFAT-promoter luciferase assay. Additionally, our in vitro studies reveal that GRK2 is associated with increased phosphorylation of glycogen synthase kinase-β (GSK3β) thereby modulating NFAT and promoting pathological cardiac hypertrophy. Respectively, GRK2 knockdown reduces GSk3β phosphorylation thus inhibiting nuclear translocation of NFAT.

Conclusion: Thus, GRK2 functions as a novel regulator of cardiac hypertrophy through regulation of nuclear NFAT activity and GRK2 knockdown could be a promising therapeutic approach targeting pathological cardiac hypertrophy.