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## p21-activated kinase 3 aggravates pathological cardiac hypertrophy in mice

**Jun Xie**
Nanjing Drum Tower Hospital, China

**Background & Aim:** p21-activated kinase 3 (PAK3) is the critical downstream molecular in Rho GTPase signaling, and involved in cell survival, proliferation and cytoskeleton remodeling. The PAK family is expressed in the heart, while the detail role of PAK3 in cardiac hypertrophy is little to know. Here, we designed this study to explore the effects of PAK3 in cardiac hypertrophy.

**Methods & Results:** We observed the activation of PAK3 in failing human hearts, hypertrophic murine hearts and hypertrophic NRCMs. Then thoracic aortic constriction (TAC) was used to induce cardiac hypertrophy in PAK3 deficiency mice and wild-type control. PAK3 knockout mice displayed improved survival rate, relieved cardiac hypertrophy, well-preserved cardiac function, less fibrosis and decreased cardiomyocyte apoptosis compared with wild-type mice. In cell study, Ang II was used to induce NRCMs hypertrophy. The PAK3 and Raf1 were depressed by shRNAs and specific inhibitor. Cardiomyocyte hypertrophy was inhibited by selective knockdown of PAK3. Furthermore, the pro-hypertrophic effect of PAK3 was associated with activation of the Raf1-ERK1/2 signaling cascade. The rescue experiments revealed that the inactivation of Raf1-ERK1/2 pathway by pharmacological or RNAi rescued cardiac hypertrophy in cardiomyocytes with PAK3 overexpression.

**Conclusions:** Here, we concluded that PAK3 was a novel hypertrophic regulator via the positive regulation of Raf1-ERK1/2 signaling in pathological cardiac hypertrophy.

darcy_pann@hotmail.com

## Diminished excretion of cholesterol in the bile-independent risk factor for coronary artery disease

**Karyn Geiger, Ori Argov, Ori Rogowski** and **Gideon Charach**
Tel Aviv Sourasky Medical Center, Israel

**Aim:** The reasons for the increase in the coronary artery disease (CAD) risk related to bile acid alteration of excretion remain largely unexplained. The aim of this study was to elucidate the effect of alterations of bile acid excretion (BAE) and its long-term preventing action on CAD during a 20-year follow-up. Significantly low BAE was found in patients with CAD compared to non-CAD patients, leading to the hypothesis that the inability to efficiently excrete bile acids leads to coronary atherosclerosis development.

**Methods:** To investigate the long-term role of BAE in CAD development and related mortality, the BAE of 50 patients with proven CAD were compared with that of 50 patients with chest pain and found not to have CAD (controls). The two groups were matched for clinical and laboratory characteristics. All subjects received a four day standard diet that included ~500 mg of cholesterol. Fecal bile acids from 24-hour stool collections were measured by gas liquid chromatography.

**Results:** CAD patients excreted lower amounts of total bile acids (344.9, ICR 225.3-523.3 mg) than controls (597.5, ICR 401.3-725.5 mg; $p<0.001$), less deoxycholic acid (179.5, ICR 116.8-259.0 vs. 290.5, ICR 188.5-444.0 mg; $p<0.0001$) and less lithocholic acid (94.5 ICR±78.8 mg vs. 157.0 ICR131.3-234.3 mg; $p<0. 01$). BAE was the best significant independent laboratory factor that predicted CAD ($p<0.05$). Mortality and CAD development rates were significantly lower for the controls at the 20-year follow-up. Other vascular events, such as strokes and abdominal aortic aneurism were more common as well.

**Discussion & Conclusion:** BAE<415 mg/day was associated with increased CAD long-term mortality. CAD patients had markedly decreased BAE levels compared to non-CAD controls. Impaired ability to excrete cholesterol may be an additional independent risk factor for CAD development.

karynrg@gmail.com