**p22phox** protects the heart against pressure overload

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**Introduction**: p22phox forms a complex with NADPH oxidases, major sources of O$_2^-$ and H$_2$O$_2$. However, the role of p22phox during stress remains to be elucidated.

**Purpose**: To investigate the role of endogenous p22phox during pressure overload (PO).

**Methods and results**: The level of p22phox protein in isolated cardiomyocytes after 4 weeks of transverse aortic constriction (TAC) was significantly higher than after sham operation (1.7-fold, p<0.05). The cardiac phenotype of cardiac-specific p22phox knockout (p22phoxcKO) mice was normal at baseline. However, four weeks after TAC, p22phoxcKO mice exhibited a lower left ventricular ejection fraction (32.0±10.0 vs 53.2±8.4%, p<0.05), a higher lung weight to tibial length ratio (23.0±6.0 vs 13.1±6.6, p<0.05), and more interstitial fibrosis (6.1±1.0 vs 4.4±1.1%, p<0.05) than control mice, indicating that the loss of p22phox exacerbates TAC-induced cardiac dysfunction. The level of oxidative stress in the heart, evaluated by dityrosine immunoblot, was significantly lower in p22phoxcKO mice than in control mice (0.71±0.04 vs 1.00±0.04, p<0.01). The peak Ca$^{2+}$ amplitude in isolated cardiomyocytes was lower in p22phoxcKO mice than in control mice at baseline (2.4±0.1 vs 3.0±0.2, p<0.01). Although mRNA expression of SERCA2a did not differ, there was significantly less SERCA2a protein in p22phoxcKO mice than in control mice (0.62±0.10 vs 1.00±0.23, p<0.01) at baseline. The amount of biotinylated iodoacetamide labeled SERCA2a was significantly smaller in p22phoxcKO hearts than in control mouse hearts (0.4-fold, p<0.01), indicating that cysteine residues in SERCA2a are oxidized to a greater extent in p22phoxcKO hearts than in control mouse hearts. Since cysteine oxidation decreases the stability of SERCA2a, our results suggest that p22phox stabilizes SERCA2a by preventing cysteine oxidation.

**Conclusion**: Endogenous p22phox is protective against PO, possibly by maintaining SERCA2a stability.