p22^{phox} protects the heart against pressure overload

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Introduction: *p22^{phox}* forms a complex with NADPH oxidases, major sources of O_2^- and H_2O_2. However, the role of *p22^{phox}* during stress remains to be elucidated.

Purpose: To investigate the role of endogenous *p22^{phox}* during pressure overload (PO).

Methods and results: The level of *p22^{phox}* 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 *p22^{phox}* knockout (*p22^{phox}*cKO) mice was normal at baseline. However, four weeks after TAC, *p22^{phox}*cKO 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 *p22^{phox}* exacerbates TAC-induced cardiac dysfunction. The level of oxidative stress in the heart, evaluated by dityrosine immunoblot, was significantly lower in *p22^{phox}*cKO 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 *p22^{phox}*cKO 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 *p22^{phox}*cKO 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 *p22^{phox}*cKO 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 *p22^{phox}*cKO hearts than in control mouse hearts. Since cysteine oxidation decreases the stability of SERCA2a, our results suggest that *p22^{phox}* stabilizes SERCA2a by preventing cysteine oxidation.

Conclusion: Endogenous *p22^{phox}* is protective against PO, possibly by maintaining SERCA2a stability.