

CST-KO mice had diminished ischemic tolerance and could not be protected. Fatty acid uptake and incomplete fatty acid oxidation was higher in left ventricles of CST-KO mice. Ultrastructural studies revealed decreased sarcomere length and altered mitochondrial morphology in CST-KO mice. Phospho AMPK as well as insulin-stimulated phosphorylation of Akt and GSK-3 β were decreased in CST-KO hearts. Additionally, we used proteomics and molecular simulations to identify CST as a binding partner for ATP synthase and describe possible binding sites as well as potential conformational changes within the ATP-synthase complex upon CST binding. Taken together, we show that KO of CST leads to decreased ischemic tolerance and loss of cardioprotective signaling and this appears to be dependent on altered structure of the contractile apparatus and impaired energy utilization by mitochondria.

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The phosphodiesterase-5 inhibitor vardenafil protects against diabetic cardiomyopathy in a type-2 diabetic animal model

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Purpose: Diabetes mellitus (DM) is associated with impaired cyclic guanosine monophosphate (cGMP) signaling which leads to the development of diabetic cardiomyopathy. The second messenger cGMP, broken down by the phosphodiesterase-5 enzyme (PDE5), has been shown to exert cytoprotective effects. We investigated the cardiac effects of chronic inhibition of PDE5 by vardenafil in type-2 DM.

Methods: For type-2 DM Zucker Diabetic Fatty (ZDF; homozygous recessive (*fa/fa*)) rats were used. Heterozygous (*fa/+*) or homozygous dominant (*+/+*) ZDF Lean (ZDFL) rats served as controls. Animals received vehicle (ZDFL, ZDF) or 10 mg/kgBW vardenafil per os (ZDFLVard, ZDFVard) from 7 to 32 weeks of age. Cardiac morphology was followed by echocardiography. Left ventricular (LV) function was assessed using a pressure-volume (PV) conductance microcatheter system. Gene expression analysis of atrial natriuretic factor (ANF; qRT-PCR), cardiomyocyte diameter/tibia length (CD/TL) and Masson's staining (fibrosis score (FS)) were used to prove pathological myocardium hypertrophy.

Results: Cardiac hypertrophy (echocardiography: LV anterior wall thickness in systole (LVAWs): 2.81 ± 0.1 mm; relative wall thickness (RWT): 0.49 ± 0.02 ; LVmass/TL: 0.30 ± 0.01 g/cm; CD/TL: 3.53 ± 0.02 μ m/cm; ANF: 3.04 ± 0.26 vs ZDFL (LVAWs: 2.53 ± 0.04 mm; RWT: 0.43 ± 0.02 ; LVmass/TL: 0.23 ± 0.004 g/cm; CD/TL: 3.09 ± 0.02 μ m/cm; ANF: 0.92 ± 0.17); $p < 0.05$) and fibrotic remodelling (FS: 1.05 ± 0.09 vs ZDFL (0.57 ± 0.13); $p < 0.05$) have been observed in ZDF. Drug treatment significantly decreased myocardial hypertrophy and fibrosis (LVAWs: 2.47 ± 0.05 mm; CD/TL: 3.15 ± 0.02 ; ANF: 1.39 ± 0.21 ; FS: 0.59 ± 0.08 vs ZDF; $p < 0.05$) in DM. PV analysis showed impaired diastolic function and increased cardiac stiffness (time constant of LV pressure decay (τ): 9.17 ± 0.25 ms; slope of end-diastolic pressure volume relationship (EDPVR): 0.078 ± 0.002 mmHg/ μ l vs ZDFL (τ : 8.18 ± 0.13 ms; EDPVR: 0.045 ± 0.003 mmHg/ μ l); $p < 0.05$) while contractility parameters and blood pressure remained unchanged in ZDF. Vardenafil

improved diastolic parameters (τ : 8.62 ± 0.34 ms, EDPVR: 0.062 ± 0.006 mmHg/ μ l vs ZDF; $p < 0.05$). Vardenafil did not have effect in ZDFL.

Conclusions: Chronic administration of vardenafil prevented DM associated myocardial complications. PDE5 inhibition might be an important target to improve the cardiovascular outcome in diabetic patients in the future.

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MuRF1 inhibits Cardiac Thyroid Hormone Signaling by TR α Mono-Ubiquitination and Localization to CAP350

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Thyroid hormone (TH) regulates cardiac physiological hypertrophy and is protective during heart failure. TH regulates cellular processes, in part, through its receptors, TR β and TR α . While ubiquitination of TR β has been described, the molecular detail of mechanisms governing TR activity remains undefined, including the identification of specific ubiquitin ligases involved. We recently demonstrated that the muscle specific ubiquitin ligase MuRF1 (Muscle Ring Finger-1) inhibits several nuclear transcription factors including serum response factor (SRF) and PPAR α *in vivo*. This led us to hypothesize that MuRF1 similarly regulates TR α through ubiquitination. MuRF1 overexpression inhibited TH (T3)-induced cardiac hypertrophy in α MHC-MuRF1 cardiac Tg+ mice and cardiomyocyte-derived cells in culture. MuRF1-/- mice challenged with daily T3 exhibited an exaggerated physiological cardiac hypertrophy. Mechanistically, MuRF1 attenuated TR DNA binding and increased co-localization with centrosome-associated protein (CAP350, a novel nuclear receptor mediator) in the perinuclear region. We also identified that MuRF1 binds and catalyzes mono-ubiquitination of lysines in the ligand-binding domain (LBD) of TR α , promoting perinuclear localization. Taken together, our working model describes MuRF1 mono-ubiquitinating the T3-TR α complex, which targets it to CAP350 resulting in decreased transcriptional activity in cardiomyocytes. This work demonstrates the first ubiquitin ligase to regulate thyroid receptors and illustrates MuRF1's critical function in TH-mediated cardiac hypertrophy, underscoring the role of ubiquitin ligases in cardiac homeostasis.

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In utero exposure to diesel exhaust promotes cardiac fibrosis through enhanced cardiac myocyte apoptosis

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