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Myocardin regulates mitochondrial calcium homeostasis and prevents permeability transition in cardiac myocytes.

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Topic(s):
Basic Science - Cardiac Biology and Physiology: Mitochondria

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S59

Funding Acknowledgements:
Research Manitoba, Natural Sciences & Engineering Council of Canada, Diabetes Research Envisioned and Accomplished in Manitoba

Myocardin is a transcriptional co-activator required for cardiovascular development and cardiomyocyte differentiation. Recent studies have shown that genetic inhibition of myocardin results in embryonic lethality with impaired cardiomyocyte proliferation and increased programmed cell death. Mitochondrial permeability transition, triggered by matrix calcium accumulation, has been implicated in regulated necrotic cell death, while permeability transition pore closure is involved with myocyte differentiation and mitochondrial maturation during development. We show that a genetic loss of myocardin function leads to endocardial necrosis, determined by HMGB1 staining, at embryonic day 9.5, concurrent with elevated expression of the death gene Nix. Mechanistically, we demonstrate that myocardin knockdown in primary ventricular myocytes reduces microRNA-133a levels to allow Nix accumulation, leading to mitochondrial permeability transition, reduced mitochondrial respiration, and necrosis. Using organelle-targeted calcium biosensors, we demonstrate that myocardin knockdown leads to sarcoplasmic reticulum (SR) calcium release and mitochondrial calcium accumulation, while mitochondrial permeability transition was prevented by pharmacological inhibition of the inositol triphosphate (IP3)-activated calcium channel or the mitochondrial calcium uniporter. Gain of function studies confirm that myocardin can desensitize myocytes to permeability transition elicited by protein kinase-A (PKA) activating agents by opposing SR calcium release. Furthermore, restoring microRNA-133a function with mimicking oligonucleotides, or knockdown of Nix rescues mitochondrial calcium accumulation induced by myocardin knockdown. Molecular studies using Nix constructs targeted to the SR or mitochondria revealed that only SR-targeted Nix leads to mitochondrial calcium accumulation, which could be attenuated by SR-targeted Bcl-2, but not mitochondrial-targeted Bcl-2. Finally, we observed reduced myocardin expression in vivo within the infarction border zone following coronary ligation in rodents, with corresponding reduced microRNA-133a and elevated Nix expression. These findings identify a novel myocardin-regulated genetic pathway that maintains cardiomyocyte calcium homeostasis and mitochondrial function during development, and is attenuated during ischemic heart disease.