Heart-Specific Knockout of the Mitochondrial Thioredoxin Reductase (Txnrd2) Induces Metabolic and Contractile Dysfunction in the Aging Myocardium.

Abstract:
Ubiquitous deletion of thioredoxin reductase 2 (Txnrd2) in mice is embryonically lethal and associated with abnormal heart development, while constitutive, heart-specific Txnrd2 inactivation leads to dilated cardiomyopathy and perinatal death. The significance of Txnrd2 in aging cardiomyocytes, however, has not yet been examined. The tamoxifen-inducible heart-specific \textit{MHC-MerCreMer} transgene was used to inactivate loxP-flanked Txnrd2 alleles in adult mice. Hearts and isolated mitochondria from aged knockout mice were morphologically and functionally analyzed. Echocardiography revealed a significant increase in left ventricular end-systolic diameters in knockouts. Fractional shortening and ejection fraction were decreased compared with controls. Ultrastructural analysis of cardiomyocytes of aged mice showed mitochondrial degeneration and accumulation of autophagic bodies. A dysregulated autophagic activity was supported by higher levels of lysosome-associated membrane protein 1 (LAMP1), microtubule-associated protein 1A/1B-light chain 3-I (LC3-I), and p62 in knockout hearts. Isolated Txnrd2-deficient mitochondria used
less oxygen and tended to produce more reactive oxygen species. Chronic hypoxia inducible factor 1, α subunit stabilization and altered transcriptional and metabolic signatures indicated that energy metabolism is deregulated. These results imply a novel role of Txnrd2 in sustaining heart function during aging and suggest that Txnrd2 may be a modifier of heart failure.