

## **HEART/MUSCLE-SPECIFIC MNSOD DEFICIENCY CONFERS HEART FAILURE WITH IMPAIRED MITOCHONDRIAL RESPIRATION IN MICE**

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Heart failure in elderly people insidiously manifests symptoms such as dyspnea and/or physical disabilities in an age-dependent manner. Although previous studies suggested that oxidative stress plays a pathological role in the development of heart failure, the direct evidence has been little documented. In order to investigate the pathological significance of oxidative stress in the heart, we generated heart/muscle-specific manganese superoxide dismutase (MnSOD)-deficient mice. The mutant mice developed progressive congestive heart failure with specific molecular defects in mitochondrial respiration. We, for the first time in this paper, showed that the oxidative stress caused specific morphological changes of mitochondria, metabolic compensations for energy balance, and transcriptional alterations of genes associated with heart failure in respect to cardiac contractility or cardiac cell death. Accordingly, administration of an SOD mimic significantly ameliorated the symptoms. These results implied that the superoxide generated in mitochondria played a pivotal role in the development and progression of heart failure in aging heart. We here provide a bona fide model for human cardiac aging with the molecular alterations valuable for therapeutic interventions.