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Atg7-Dependent Autophagy Is Essential for Cardiac Function with High Fat Diet.

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Heart is a high energy-demanding tissue. Since 60%-90% energy is from fatty acid oxidation in mitochondria, the regulation of lipid metabolism in the heart is critical. Autophagy, a self-degradative process, has been reported to be involved in lipid metabolism. Autophagy includes macroautophagy, microautophagy, and chaperone-mediated autophagy. It has been known that macroautophagy is essential not only for maintaining physiological cardiac function, but also in pathological stressors such as ischemia, and cardiac hypertrophy. However, the molecular pathway through which macroautophagy regulates cardiac lipid metabolism remains unclear. Therefore, it is critical to determine whether macroautophagy is essential in cardiac lipid metabolism.

In this study, we evaluated the function of autophagy in cardiac lipid metabolism. First, in order to evaluate the effects of high fat diet (HFD) on cardiac autophagy, cardiac-specific expression of Tandem fluorescent-tagged LC3 (mRFP-EGFP-LC3)(TF-LC3) mice were fed either normal diet (ND) or 60% HFD. Through the injection of Chloroquine, an inhibitor of the fusion between autophagosome and lysosome, we evaluated autophagy flux with ND and HFD. In TF-LC3 mice, autophagic flux was increased with 6 weeks' HFD, but inhibited with 3 months' HFD. Then, we detected mitophagy with HFD. Mitophagy was activated with HFD, as assessed in transgenic mice expressing the mitochondrial-targeted form of the fluorescent biosensor Keima(Mito-Keima). Mito-Keima fluorescence shows pH-dependent excitation characteristics, shifting excitation maxima to a higher wavelength after mitochondria come into contact with the acidic milieu of lysosomes in the content of mitophagy.

Next, to elucidate the role of autophagy in cardiac lipid metabolism, we used genetically altered mouse lines for Atg7, which is responsible for macroautophagy. We generated *atg7*-cardiac-specific knock out (*atg7cko*) mice. *Atg7cko* mice were fed HFD for two months. Then through measuring cardiac function by PV-Loop, *atg7cko* mice developed severe cardiac systolic (ESPVR=25±2.2 in WT with HF, ESPVR=15±1.3 in *atg7cko* with HF, p<0.05) and diastolic (EDPVR=0.11±0.02 in WT with HF, EDPVR=0.15±0.01 in *atg7cko* with HF, p<0.05) dysfunction. Electronic microscope (EM) analysis showed that dysfunctional mitochondria accumulated in *atg7cko* mice with HFD. Through Tg-mito-keima mice crossing with WT or *atg7cko* mice with ND or HFD, mitophagy was impaired in *atg7cko* mice with ND and HFD. Mitochondrial membrane potential, mitochondrial oxygen consumption rate (OCR) and fatty acid oxidation (FAO) were decreased in *atg7cko* mice with HFD. EM analysis and oil red o staining showed lipid droplets were accumulated and Fibrosis and cell death were increased in *atg7cko* mice during HFD. These results suggested that inhibition of mitophagy and accumulation of dysfunctional mitochondria developed in *atg7cko* mice with HFD.

Taken together, these data indicated that *atg7*-dependent autophagy is essential for cardiac function with HFD.

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