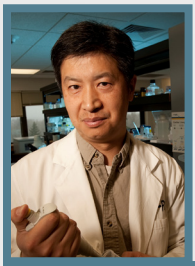

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# Deficiency in the E3 Ubiquitin Ligase Parkin Exacerbates Alcoholic Cardiomyopathy: Role of Mitophagy

**Background:** Long-term heavy alcohol consumption has been shown to promote mitochondrial injury, unfavorable geometric and contractile changes in the heart. Parkin, a cytosolic E3 ubiquitin ligase encoded by PARK2 gene, plays an important role in the regulation of selective mitophagy. This study was designed to examine the role of Parkin in alcohol-induced myocardial injury (aka alcoholic cardiomyopathy) and the underlying mechanism with a focus on mitophagy.

**Methods:** Adult male wild-type C57 and PARKIN2 knockout (Parkin-/-) mice were placed on alcohol (4%) or control diet for 4 weeks. Echocardiographic and cardiomyocyte mechanical properties were assessed. Mitochondrial morphology, function and mitophagy were examined using transmission electronic microscopy, Clark-type oxygen electrode, and Western blot, respectively.

**Results:** Our results revealed that chronic alcohol consumption triggered unfavorable geometric and contractile changes [decreased fractional shortening (FS) and ejection fraction (EF), with enlarged left ventricular chamber; decreased peak shortening (PS) and velocity of shortening +dL/dt, increased time-to-90% relengthening $TR_{90}$], the effects of which were exacerbated by Parkin deficiency. In addition, our data showed that chronic alcohol intake promoted myocardial mitochondrial swelling with cristae disarrangement, induced myocardial mitochondrial depolarization and respiration inhibition, which were exacerbated by Parkin knockout. Furthermore, chronic alcohol consumption promoted accumulation of Parkin and LC3BII in mitochondria and mitochondrial ubiquitination in the heart, the effects of which were nullified by Parkin knockout.

**Conclusion:** These data suggest that chronic alcohol consumption triggered mitophagy by stimulating Parkin translocation to the mitochondria, which may be an adaptive response in the heart. Our findings implicated the therapeutic potential of mitophagy as a target in the management of alcoholic cardiomyopathy.