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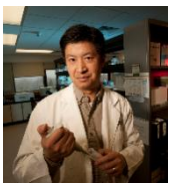
Deficiency in the E3 Ubiquitin Ligase Parkin Exacerbates Alcoholic Cardiomyopathy: Role of Mitophagy

Jun Ren
University of Wyoming College of Health Sciences, USA.



Abstract

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 TR90], 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.

Biography:

Dr. Ren earned his Ph.D. in 1994 from the University of Alberta, Canada, in the area of cellular physiology, following his medical training in China (Beijing University and Peking Union Medical College). In 1994, he became a post-doctoral fellow in the Wayne State University School of Medicine (Internal Medicine), where he served for two years. He remained at Wayne State University until 1998, working as a research instructor of physiology. He was an Assistant Professor of Physiology at the University of North Dakota School of Medicine and Health Sciences from 1998-2002 and then an Associate Professor of University of Wyoming from 2002-2005. He was promoted to full professor in 2005 and was appointed as Associate Dean for Research in the College of Health Sciences at the University of Wyoming. Dr. Ren recently relocated to the Department of Cardiology at Zhongshan Hospital Fudan University. His major area of research is related to cardiac pathophysiology in alcoholism, diabetes, obesity and aging. His research has been funded by the American Heart Association, American Diabetes Association and NIH.

He is a first or corresponding author of more than 500 peer-reviewed papers and 200 published abstracts. He is editor or on editorial board for a number of journals including Hypertension, Diabetes, Journal of Molecular and Cellular Cardiology, BBA Molecular Basis of Disease, American Journal of Physiology, Cardiovascular Toxicology and Clinical and Experimental Pharmacology and Physiology.

Speaker Publications:

1.Jun Ren (2015) Discovering essential proteins based on PPI network and protein complex. International Journal of Data Mining and Bioinformatics (IJDMB,12(1):24-43.

2. Jun Ren (2013) Identifying protein complexes based on local fitness method . Systems Biology, 2013; 7(Suppl 4): S12.

3.Jun Ren (2018) Prediction of essential proteins by integration of PPI network topology and protein complexes information. International Journal of Data Mining and Bioinformatics, 13(4): e0195410.

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