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Inhibition of Drp-1 dependent mitochondrial fission augments alcohol-induced cardiotoxicity via dysregulated Akt signaling

Anusha Sivakumar, Ramasamy Subbiah* and Rekha Balakrishnan

Cardiac Hypertrophy Laboratory, Department of Molecular Biology, School of Biological Sciences, Madurai Kamaraj University, Madurai 625 021, NDIA

*Corresponding author: subbiahr@nrcbsmku.org

Abstract

Cardiovascular disorders (CVDs) still claim high mortality in spite of advancements in prognosis and treatment strategies. Alcohol is one of the most commonly consumed drugs globally and chronic/binge consumption (BAC 0.08 g/dL in 2 hours) is a risk factor for CVDs. However, the aetiology and pathophysiological mechanisms of alcohol induced cardiotoxicity are still poorly understood. Mitochondria are the prime site for the ATP demands of the heart and also ethanol metabolism. These subcellular organelles depict dynamic fusion and fission events that are vital for structure and functional integrity. While fused mitochondrial improve ATP production and cell survival, increased fragmentation can be the cause or result of apoptosis. In this study, we proposed to analyze the mechanism of mitochondrial fission protein Drp-1-dependent apoptosis during alcohol toxicity. Male Wistar rats (220-250 kg body weight) were given isocaloric sucrose or ethanol for 45 days, orally, via drinking water and intermittent gavage twice a week. Histopathological examination of the heart displayed hypertrophy with mild inflammation. Drp-1 immunoblotting showed over-expression of the protein during ethanol treatment. We next hypothesized that inhibiting Drp-1 could attenuate alcohol-induced cardiotoxicity. Interestingly, silencing Drp-1 with siRNA *in-vitro* augmented cytotoxicity. Also, crude mitochondrial fraction showed increased Bak aggregation, reduced cytochrome c release but increased SMAC/DIABLO. We analyzed the Akt cell survival signaling and found that PTEN showed over-expression at both transcriptional and translational level with no significant change in total Akt but down-regulation of p-Akt (Ser473). In conclusion, we have shown that inhibition of Drp-1 dependent mitochondrial fission is not cardioprotective against alcohol-induced apoptotic signaling and augments the cytotoxicity. To our knowledge, this study is the first to interlink cell survival AKT signaling as the cause for cytotoxicity during Bax/Bak dependent apoptosis, where inhibition of Drp-1 dependent fission fails to protect.

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