21st Annual European Pharma Congress

May 20-22, 2019 | Zurich, Switzerland

Mitophagy and oxidative stress in early stage acetaminophen-induced liver injury

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Background: Mitochondria go through frequent cycles of fusion and fission, a process required for mitochondrial quality control by eliminating ROS damaged mitochondria through mitophagy. Acetaminophen (APAP) overdose causes liver injury in animals and humans usually by mitochondria damage, which needed further study. Toxicity is mediated by the metabolism of APAP to the reactive metabolite N acetyl-p-benzoquinone imine, which forms adducts on cellular proteins in mitochondria. The aim of the current study is to assess the changes between oxidative stress and companied mitophagy in a rodent model which mimics APAP-induced liver injury (AILI) in humans.

Methods: Different approaches were used including different detective methods. Liver damage was monitored by measuring levels of biochemical indexes. Proteins associated with oxidative stress were inspected by western blot analyses.

Results: After given both Nrf2-/- and wild-type mice APAP, Nrf2-/- mice were highly susceptible to APAP treatment. Rapamycin can promote the process of autophagy, reducing the formation of giant mitochondria and lipid droplets. Both tBHQ and NAC can protect liver cells, promoting Nrf2 translocated into nucleus and increasing the expression of downstream enzymes and proteins. C57BL/6 mice with stabilization of Nrf2 had increased hepatic up-regulation of Nrf2 and other antioxidant enzymes and reduced mitochondria dysfunction. Interestingly, APAP-induced mitochondrial translocation of Drp1; however, the initiation of mitochondria fission was inhibited by MDIVI-1, resulting much more serious hepatic injury.

Conclusion: In the early stage of AILI, Nrf2 played a protective role in antioxidant activity while mitophagy protected against oxidative stress damage by scavenging function. Promoting Drp1 translocation and Nrf2 expression could be a promising new approach to AILI.