

8th World Congress on

PHARMACOLOGY AND TOXICOLOGY

July 24-25, 2017 Melbourne, Australia

Bax inhibitor-1 inhibits Acetaminophen-induced hepatotoxicity by reducing ER stress through regulating the RIDD activity of IRE1 α **Raghupatil Junjappa, Geum Hwa Lee, Hyung Ryong Kim and Han Jung Chae**
Chonbuk National University, South Korea

Acetaminophen (APAP) overdose is the most frequent cause of acute liver failure in young adults and is primarily caused by CYP2E1 driven conversion of APAP into NAPQI, a hepatotoxic metabolite. This will lead to the ER stress, activation of UPR and the proapoptotic events, due to the reduced glutathione level and perturbation in the redox balance. Bax inhibitor-1 (BI-1) is an evolutionarily conserved ER-membrane resident protein that suppresses cell death by regulating ER stress response. In this study we examined the role of BI-1 in APAP induced ER stress and in regulation of IRE1 α , an endoribonuclease UPR molecule known to degrade the mRNA through the process called RIDD. Our result showed that APAP induced ER stress was reduced in BI-1 over expressing cells. BI-1 knockout mice showed massive hepatic toxicity and large number of cytoplasmic vacuoles as revealed by H&E staining. Further it increased ALT and AST levels, protein oxidation and lipid peroxidation. We observed reduction of CYP2E1, a RIDD substrate, expression in BI-1 overexpressing cells. To examine the possible relation of BI-1 in CYP2E1 lower expression in the ER stress, we hypothesized that BI-1 may regulate the IRE1 response. As, it is known that XBP1s requires oligomer state of activated IRE1 α and this XBP1s is reduced in BI-1 expressing cells but at the same time phosphorylation of IRE1 was also observed. So, it indicates that in BI-1 overexpressing cells IRE1 α is activated but held in dimer state for extended time compare to PC cells. In consequence, the dimer state of activated IRE1 α has the RIDD activity and helps in initial adaptive stress response by reducing the further load of protein synthesis during ER stress. As a consequence CYP2E1 mRNA degraded and resultantly lesser conversion of APAP to toxic metabolite. So, our results suggest a role for BI-1 in the regulation of RIDD activity in early adaptive responses against APAP induced ER stress.

raghupatij@gmail.com