Prevention of Fas-Induced Liver Injury by Cytosolic Phospholipase A$_2$alpha

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The goal of this study was to explore the role of cytosolic phospholipase A$_2$alpha (cPLA$_2$alpha) in Fas-mediated apoptosis, in vivo. We generated transgenic (Tg) mice with targeted expression of cPLA$_2$alpha in the liver by using the albumin promoter-enhancer driven vector. The cPLA$_2$alpha Tg mice developed normally under normal housing conditions. Within 10 h of Jo2 injection, 100% wild type mice died of acute hemorrhagic liver failure; in contrast only 20% cPLA$_2$alpha Tg mice died during the same time period ($p<0.01$). 4 hours after Jo2 challenge, the wild type mice showed significantly higher serum ALT and AST levels, caspase-8, 9, 3 activity, more TUNEL-positive hepatocytes and more prominent liver tissue damage when compared to the cPLA$_2$alpha Tg mice ($p<0.01$). Higher levels of EGFR, gp130, phosphorylated PTEN, phosphorylated Akt, Akt, phosphorylated STAT3, STAT3, Mcl-1 were observed in the liver tissues from the cPLA$_2$alpha Tg mice than in the wild type mice. Pretreatment of wild type mice with the cPLA$_2$ inhibitor, AACOCF$_3$ (3 mg/kg body weight), aggravated Jo2-mediated liver injury and hepatocyte apoptosis. In parallel, pretreatment of cPLA$_2$alpha Tg mice with the STAT3 inhibitor, Stattic (25 mg/kg body weight), exacerbates Jo2-mediated liver injury and hepatocyte apoptosis. These results demonstrate that hepatocyte cPLA$_2$alpha protected against Fas-induced liver injury at least in part through activation of STAT3 pathway.

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