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Downregulation of PGC-1 leads to decreased expression of mitochondrial antioxidant enzymes in the mouse model of obstructive cholestasis

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Introduction : Several studies have indicated that cholestatic liver damage is mitochondria-mediated. However, the precise mechanism by which hydrophobic bile salts cause mitochondrial dysfunction is not clear. In this study, we intended to determine the pathogenesis of cholestatic liver injury associated with peroxisome proliferator activated receptor co-activator 1α (PGC-1α).

Methods : The mouse model of cholestatic livers was generated by surgical ligation of the bile duct (BDL), and the mouse model of fibrosis was developed following serial administration of thioacetamide. Next, after obtaining liver specimens on scheduled days, we compared the expression of the antioxidant enzymes (superoxide dismutase2 [SOD], catalase, and glutathione peroxidase-1[GPx]), and PGC-1α in livers from mice with fibrosis and cholestasis using western blotting, immunohistochemistry and immunofluorescence.

Results : We found that a cholestatic liver exhibits lower expression of antioxidant enzymes, such as SOD, catalase, and PGC-1α. Contrastingly, a fibrotic liver exhibits higher expression of antioxidant enzymes and PGC-1α. In addition, cholestatic livers were found to show significantly lower expression of pro-apoptotic markers (Bax) than that seen in fibrotic livers.

Conclusions : It was well known that overexpression of PGC-1α increases mitochondrial antioxidant enzyme expression, and vice versa. Thus, we concluded that obstructive cholestasis decreases expression of PGC-1α, which leads to decreased expression of mitochondrial antioxidant enzymes, rendering mice with cholestatic livers vulnerable to ROS-induced cell death.

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