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Complex effects of iPLA$_2$β deficiency on hepatic lipid metabolism in methionine-choline-deficient diet-induced fatty liver

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Nonalcoholic fatty liver disease (NAFLD) is a major chronic liver disease with a progression from fatty liver, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Group VIA phospholipase A2, PLA2G6 or iPLA$_2$β hydrolyzes phospholipids (PL) to lysoPL and a free fatty acid (FA) thus is involved in FA metabolism, PL remodeling, and membrane homeostasis. PLA2G6 has been identified as one of the NAFLD modifier genes. We have shown that the deletion of iPLA$_2$β protects fatty liver in morbidly obese ob/ob mice by inducing hepatic remodeling and replenishing the loss of PL (BBA 1861, 449, 2016). As methionine and choline are substrates for PL synthesis pathways, we aimed to test whether the protection and PL remodeling could still be observed under an induction of fatty liver by feeding iPLA$_2$β-knockout (iPLA$_2$β$^{-/-}$) mice with methionine and choline deficient (MCD) diet.

Female iPLA$_2$β$^{-/-}$ mice and aged-matched wild-type (WT) littermates were fed with an MCD diet for 5 weeks. Phenotypes were characterized by histology, immunohistochemistry (IHC), quantitative RT-PCR, and Western blot (WB). Liver FA and PL profiles were, respectively, determined by gas- and liquid- chromatography

mass spectrometry.

MCD feeding induced hepatic steatosis with reduction of body and liver weights to the same extent in both genotypes - WT and iPLA$_2$β$^{-/-}$ mice. However, iPLA$_2$β deficiency attenuated MCD-induced elevation of serum transaminase activities as well as the contents of hepatic FA and cholesterol esters (CE). Compared to livers of MCD-fed WT mice, those of iPLA$_2$β$^{-/-}$ mice showed increased levels of collagen fibers (by sirus-red staining) and profibrogenic markers (α-smooth muscle actin IHC/WB and vimentin WB). Compared to WT mice, MCD diet caused insignificant changes in expression of hepatic pro-inflammatory cytokines in iPLA$_2$β$^{-/-}$ mice. PL profiling showed that MCD feeding of WT mice caused a severe reduction in liver PL contents which were not modified by iPLA$_2$β deficiency.

By depleting PL substrates, iPLA$_2$β deficiency did not protect from MCD diet-induced hepatic steatosis concomitant with the lack of the rescue of PL remodeling loss. iPLA$_2$β deficiency attenuated the elevation of liver enzymes and hepatic FA and CE while increasing liver fibrosis. Thus, iPLA$_2$β deletion elicited partial protection in MCD-induced NAFLD model.