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Attenuation of Hepatic Steatosis and Insulin Resistance by Group VIA Phospholipase A2 Deficiencyin Ob/Ob Mice

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Obesity is a metabolic disorder often associated with non-alcohol fatty liver disease (NAFLD), insulin resistance and metabolic syndrome, despite the fact that the mechanisms involved into these pathology processes are far from understanding. Group VIA PLA2, also named iPLA2β, hydrolyzing fatty acyl bond at the sn-2 position of phospholipids, is recognized to take multiple roles in homeostatic membrane metabolism and energy homeostasis. We found that global iPLA2β null mice (PKO) exhibited lower body weight, liver and visceral fat weights as well as serum and hepatic lipids when compared with control wild type littermates (WT) in our previous study. We herein hypothesized that global deficiency of iPLA2β might attenuate adiposity and hepatic steatosis in obesity situation.

Our aim was to clarify whether iPLA2β deficiency can protect the leptin-deficient Ob/Ob (OB) mice against hepatic steatosis and insulin resistance and further to explore the possible mechanism.

We selected leptin-deficient OB mice as the obesity and NAFLD model. Cross-breeding between leptin$^{+/-}$ iPLA2β$^{+/-}$ mices was performed to generate leptin$^{-/-}$iPLA2$^{-/-}$ double-knockout (PKO/OB) mice. Male mice at 6-7 months old (n=5-9) were used. Serum transaminases, serum and liver lipids were determined using diagnostic kits. Fasting glucose, fasting insulin and intraperitoneal glucose tolerance test (IPGTT) was analyzed to evaluate glucose metabolism and insulin resistance. Formalin-fixed and optimal cutting temperature(OCT) compound

embedded liver sections were stained with hematoxylin-eosin and Oil Red O respectively.

To explore what underlies these changes, serum lipoprotein profiles were analyzed by Liposearch service, lipidomics analyses in mouse livers were determinated by using GC-MS and ESI-MS/MS, hepatic gene expression was studied by quantitative TaqMan RT-PCR, and hepatic protein expression was assessed by western blotting.

Compared with WT, OB mice had marked obesity with fatty liver and insulin resistance. By comparison with OB, PKO/OB mice revealed a significant decrease in metabolic parameter including body weight, visceral fat weight, liver enzyme and serum lipid; concomitantly with reduced liver lipid. Histology data revealed that PKO/OB mice exhibited decreased hepatic steatosis. Serum glucose and insulin displayed an improvement in hyperglycemia and insulin resistance in PKO/OB mice. PKO/OB mice also manifested the alteration of serum lipoprotein profiles and liver lipidomics, especially in reduction of multi-unsaturated fatty acids and elevation of n-3 poly-unsaturated fatty acids. Our PCR and western blotting data demonstrated that genes involved de novo lipogenesis such as SREBP-1, FAS, ELOVL6 and SCD1 may play key roles in the alleviation. Regulation of PPARγ genes and protein appeared to be important in both lipid synthesis and insulin resistance.

Deficiency of iPLA2β in obese mice decreased adiposity and elicited protection against hepatic steatosis and insulin resistance. Our data shed lights on the role of iPLA2β on hepatic lipid syntheses and insulin resistance in fatty liver and obesity, and that this gene may be used as a therapeutic target.