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Adipose-specific fatty acid transport protein 4 (FATP4) deletion increases adipose lipolysis and liver fibrosis in mice fed with methionine-choline-deficient diet

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease ranging from fatty liver, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Although the mechanisms of NAFLD progression are not completely understood, lipolytic events resulting in fibrosis in the liver appear to be one of the central mechanisms in NAFLD. FFA and their metabolites are potentially lipotoxic mediators triggering liver injury, suggesting a central role of lipolysis. Fatty acid transport protein 4 (FATP4) catalyzes the activation of fatty acids in specific complex lipids by its acyl-CoA synthetase activity. Previous results from our department have shown that adipocyte-specific FATP4 deficiency sensitizes with high-fat diet for disturbances in

adipose tissue lipid composition concomitant with obesity and hepatic steatosis. However, the role of FATP4 in the lipolysis of adipose triglycerides and thus affecting hepatic steatosis has not been investigated. Since feeding mice with methionine and choline-deficient (MCD) diet is shown to induce adipose lipolysis, we therefore investigated possible FATP4 effect on adipose tissues as well as liver by feeding adipose tissue-specific FATP4 knockout mice with MCD diet.

Female FATP4A-/- mice and age-matched wide-type (WT) littermate were fed with MCD diet for 1 or 4 weeks. Lipolytic products (FAs and glycerol) were measured from adipose tissue pads. Phenotypes were characterized by histology, immunohistochemistry (IHC), quantitative RT-PCR, and western blot (WB). Phospholipid profiles in adipose tissue and liver were determined by liquid-chromatography mass spectrometry.

When exposed to MCD medium, adipose tissue pads of FATP4A-/- mice showed increased lipolytic activities compared to that of WT mice. In vivo studies, MCD feeding of FATP4A-/- mice enhanced lipolysis by increasing glycerol release and the expression of phosphorylated hormone-sensitive lipase (P-HSL). This was concomitant with

reduction of adipose ceramides (Cer) and sphingomyelins (SM). Adipose FATP4 deficiency increased serum triglyceride (TG) levels. When challenged with MCD diet, the elevation was further increased while hepatic TG levels were attenuated. Hence, adipose FATP4 deficiency caused a metabolic shift from sphingolipids to TG, which underwent lipolysis to glycerol, and fatty acid (FA) that were released to blood. Compared to liver of WT mice, MCD diet feeding of FATP4A-/- mice caused significant increase in expression of pro-fibrogenic markers (α-smooth muscle actin, plasminogen activator inhibitor-1 and E-cadherin). Such fibrosis sensitization in FATP4A-/- mice was likely due to increased lipolysis products released by adipose tissues.

Adipocyte-specific FATP4 deficiency in mice fed with MCD diet results in enhanced adipose lipolytic activities and disturbances in adipose phospholipids, and sphingolipids. These events consequently lead to an increase of liver fibrosis. Thus, FATP4 plays a role in NAFLD development by suppressing adipose lipolysis and blood lipids. Our results are in line with the reported insulin resistance in patients with FATP4 mutations.