Understanding the underlying molecular pathways by which \textit{Mboat7/Lpiat1} depletion induces hepatic steatosis

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Nonalcoholic fatty liver disease (NAFLD) is becoming the leading cause of chronic liver disease worldwide, paralleling the global epidemic of obesity and type 2 diabetes \cite{1}. In addition to the well-established metabolic and environmental risk factors, a body of evidence supports genetic predisposition as a pivotal driver of NAFLD development and progression to its life-threatening complications, namely cirrhosis and hepatocellular carcinoma. To date, several genetic loci have been identified contributing to NAFLD. Noteworthy, the majority of these genetic variations are located in genes involved in lipid biology, including \textit{PNPLA3}, \textit{TM6SF2}, membrane-bound O-acyltransferase domain–containing 7 (MBOAT7), and \textit{HSD17B13} \cite{2}.

The common sequence variant rs641738 C>T near the \textit{MBOAT7} gene confers increased susceptibility to NAFLD and the entire spectrum of its conditions by downregulating \textit{MBOAT7} expression in the liver \cite{3}. In a recent meta-analysis of 42 studies including more than one million participants, this major variant has been firmly associated with the presence and severity of NAFLD in European adults \cite{4}. Interestingly, homozygotes for very rare and severe loss-of-function mutations in \textit{MBOAT7} display severe cognitive impairment with neurodevelopmental defects \cite{5}, showing how common and rare genetic variants in the same \textit{locus} may lead to extremely diverse phenotypes.

\textit{MBOAT7} encodes lysophosphatidylinositol acyltransferase 1, a 472-amino acids–long protein with six transmembrane domains present on the ER, lipid droplets, and mitochondrion–associated membranes \cite{3,6}. The pronounced effect on the nervous system may be due to an alteration of protein trafficking, a key intracellular pathway for nervous system development. \textit{MBOAT7} is involved in the acyl-chain remodeling of membrane phospholipids in the Lands’ cycle. Specifically, \textit{MBOAT7} has a lysophospholipid acyltransferase activity thought to preferentially incorporate arachidonic acid (AA; 20:4 n-6) into phosphatidylinositol (PI) \cite{3,6,7}.

In the past year, several lines of research have focused on unraveling the molecular mechanism(s) by which \textit{MBOAT7} deficiency induces hepatic steatosis. In this issue of the Journal of Lipid Research, Xia \textit{et al.} \cite{8} elegantly showed that hepatocyte-specific \textit{Mboat7} depletion caused an increased liver fat content (mostly triglycerides and cholesterol esters) and liver damage (i.e., higher transaminases) in mice fed a chow diet with a fasting-refeeding regime. In addition, by using MS, authors analyzed in detail the phospholipid composition in the liver, showing that the concentration of PI 38:4(18_0_20_4), the most abundant PI in the liver, was decreased by approximately 50% in \textit{Mboat7} hepatocyte-specific KO (LKO) mice. Similarly, the concentration of other PI species containing 20-carbon polyunsaturated fatty acids, including PI 36:3 (16_0_20_3), PI 38:2 (18_0_20_2), and PI 38:3 (18_0_20_3), was markedly decreased in the \textit{Mboat7} LKO liver. Conversely, \textit{Mboat7} depletion led to increased hepatic levels of PIs containing monounsaturated or polyunsaturated without 20-carbon fatty acids, including PI 34:1 (16_0_18_1), PI 36:2 (18_1_18_1), and PI 40:6 (18_0_22_6).

In this work, \textit{Mboat7} depletion induced hepatic steatosis by increasing de novo lipogenesis driven by the activation of sterol regulatory element–binding protein–Ic (SREBP-Ic), a key lipogenic transcription factor involved in fatty acid biosynthesis. In agreement, the mRNA expression and synthesis of SREBP-Ic target genes was found to be increased in the \textit{Mboat7} LKO liver. In addition, the hepatocyte-specific depletion of both \textit{Mboat7} and SREBP cleavage–activating protein (Scap) normalized hepatic fat content similarly to \textit{Scap} depletion alone, supporting that \textit{Mboat7}–mediated hepatic steatosis was due to SREBP-Ic processing. The strength of this study resides in the detailed and accurate lipidomics with lipid flux analysis in genetically engineered \textit{Mboat7} LKO mice.

Serendipitously, a recent study in a similar mouse model showed remarkably consistent results \cite{9}.
In agreement with the study by Xia et al., Tanaka et al. showed that hepatocyte-specific Mboat7 depletion spontaneously caused liver fat accumulation in LKO mice (9) with increase in the triglyceride content. However, this study (9) did not see any differences in the cholesterol amount, although the trend was in the same direction as the study by Xia et al., indicating a potential lack of power for detecting changes in cholesterol in the study from Tanaka et al.

In agreement with the study by Xia et al., the study by Tanaka et al. (9) reported similar changes in PI composition in the Mboat7 LKO liver. Indeed, the authors showed that the hepatic amount of AA-containing PI (PI 38:4) was dramatically reduced in Mboat7 LKO mice. However, the total amount of PIs was found to be slightly decreased in the LKO liver, whereas it was significantly increased in the study by Xia et al. The changes in the levels of other PI species containing monounsaturated and polyunsaturated fatty acids were similar in both studies.

In addition to the mouse model, Tanaka et al. (9) investigated the impact of MBOAT7 depletion on hepatic fat content and PI composition in cultured human hepatocytes, obtaining results similar to in vivo experiments. Within this context, the authors robustly demonstrated that MBOAT7 deficiency in vitro resulted in hepatic fat accumulation specifically by upregulating triglyceride synthesis, without affecting either triglyceride degradation or secretion. The authors proposed a non-canonical pathway underpinning the association between MBOAT7 deficiency and hepatic steatosis. Indeed, they suggested that the depletion of AA-containing PI in hepatocytes caused simultaneously an increased PI synthesis and PI degradation mediated by an unknown protein with PLC activity resulting in DAG, a substrate of triglyceride synthesis. These mechanisms contribute to the development of MBOAT7-induced hepatic steatosis, although they have yet to be entirely elucidated.

Fig. 1. Molecular pathways by which MBOAT7/LPIAT1 depletion induces hepatic steatosis. MBOAT7/LPIAT1 has an acyltransferase activity, incorporating arachidonic acid into lysophosphatidylinositol in the Lands’ cycle. Xia et al. recently suggest that MBOAT7 depletion promotes an increase in de novo lipogenesis driven by the activation of SREBP-1c. In an independent work, Tanaka et al. propose that MBOAT7 depletion simultaneously causes an increased PI synthesis and PI degradation mediated by an unknown protein with PLC activity resulting in DAG, a substrate of triglyceride synthesis. These mechanisms contribute to the development of MBOAT7-induced hepatic steatosis, although they have yet to be entirely elucidated. AA, arachidonic acid; AGPAT, 1-acylglycerol-3-phosphate-O-acyltransferase; CDP-DAG, cytidine diphosphate diacylglycerol; CDS, cytidine diphosphate diacylglycerol synthase; DAG, diacylglycerol; DGAT, diacylglycerol O-acyltransferase; FA, fatty acids; G-3-P, glycerol-3-phosphate; GPAT, glycerol-3-phosphate acyltransferase; IP$_1$, inositol monophosphate; LPA, lysophosphatidic acid; LPI, lysophosphatidylinositol; MBOAT7, membrane-bound O-acyltransferase domain–containing 7; OA, oleic acid; PA, phosphatidic acid; PAP, phosphatidate phosphatase; PIAA, phosphatidylinositol with arachidonic acid; PI$^{OA}$, phosphatidylinositol with oleic acid; PIS, PI synthase; PLA$_2$, phospholipase A$_2$; PLC, phospholipase C; SCAP, SREBP cleavage–activating protein; SREBP-1c, sterol regulatory element–binding protein-1c; TG, triglyceride.

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Of note, while both studies found a remarkably consistent phenotype (i.e., increased hepatic triglyceride content), the mechanism leading to this phenotype was found to be different (Fig. 1). Xia et al. found that the
increase in liver lipids was due to an increase in triglyceride synthesis mediated by SREBP-1c, while Tanaka et al. found that this increase was due to a novel non-canonical pathway supplying substrates from PI to triglycerides through a futile cycle. These differences may be partially explained by the different administration of the diet in the two studies. Indeed, in the study by Xia et al. (8), mice were fed a fasting-refeeding regime that is known to enhance the activation of SREBP pathway (10), whereas Tanaka et al. have used an ad libitum diet that does not affect this pathway. Perhaps the truth is somewhere in the middle, and both mechanisms contribute to the observed phenotype.

To conclude, Xia et al. robustly show that liver-specific Mboat7 depletion causes an increase in liver fat content because of SREBP-1c–mediated increase in triglyceride synthesis. There are several other questions that remain to be solved: (a) what is the catalytic site of this protein, (b) how does MBOAT7 depletion increase the susceptibility to liver inflammation, fibrosis, and hepatocellular carcinoma, and (c) last but not least, what is the mechanism by which the depletion of this gene causes liver and at the same time neurological disease. Further experimental studies are needed to answer these questions and to assess whether MBOAT7 may represent a novel pharmacological target(s) for NAFLD treatment in humans. #

Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Abbreviations

AA, arachidonic acid; LKO, hepatocyte-specific KO; MBOAT7, membrane-bound O-acyltransferase domain-containing 7; NAFLD, nonalcoholic fatty liver disease; PI, phosphatidylinositol; Scap, SREBP cleavage-activating protein; SREBP-1c, sterol regulatory element–binding protein-1c.

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