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The role of MBOAT7 on fatty liver disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet kommer att offentligen försvaras i Hjärtats Aula,
Blå Stråket 5, Göteborg, den 19 Mars, klockan 09:00.

av Andrea Marco Caddeo

Fakultetsopponent:
Docent Martijn C.G.J. Brouwers
Maastricht University, The Netherlands

Avhandlingen baseras på följande delarbeten

I. Caddeo A*, Jamialahmadi O*, Solinas G, Pujia A, Mancina RM, Pingitore P, Romeo S.
MBOAT7 is anchored to endomembranes by six transmembrane domains.
J Struct Biol. 2019 Jun 1;206(3):349-360

II. Caddeo A, Hedfalk K, Romeo S, Pingitore P.
LPIAT1/MBOAT7 contains a catalytic dyad transferring polyunsaturated fatty acids to lysophosphatidylinositol
Biochim. Biophys. Acta, Mol. Cell. Biol. Lipids 2021 Jan 26;158891

III. Tanaka Y*, Shimanaka Y*, Caddeo A*, Kubo T, Mao Y, Kubota T, Kubota N, Yamauchi T, Mancina RM, Baselli G, Luukkonen P, Pihlajamäki J, Yki-Järvinen H, Valenti L, Arai H, Romeo S, Kono N.
LPIAT1/MBOAT7 depletion increases triglyceride synthesis fueled by high phosphatidylinositol turnover
Gut. 2020 Apr 6. pii: gutjnl-2020-320646

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The role of MBOAT7 on fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the main health disorder in internal medicine, affecting one third of the population worldwide. Environmental and genetic factors contribute to NAFLD susceptibility and progression. Amongst these, a genetic variant in the *membrane bound O-acyltransferase domain-containing 7* (*MBOAT7*), also known as *lysophosphatidylinositol acyltransferase 1* (*LPIAT1*), robustly contributes to the entire spectrum of NAFLD.

MBOAT7 encodes for an O-acyltransferase that catalyses the transfer of free fatty acids to lysophospholipids, allowing the remodelling of phospholipids. The *MBOAT7 rs641738 C>T* genetic variant is associated with the development and progression of NAFLD and related end stage liver disease, namely cirrhosis and hepatocellular carcinoma (HCC). Despite the interest in MBOAT7, very little is known about the mechanisms by which this protein contributes to the pathogenesis and progression of fatty liver disease. In this thesis, we unveiled the topological organization, we assessed the enzymatic activity, we identified the catalytic site, and we unravelled how MBOAT7 depletion causes hepatic fat accumulation via a novel metabolic pathway.

In paper I, by using a combination of *in silico* and *in vitro* approaches, we showed that MBOAT7 is a multispanning membrane protein strongly attached to endomembranes by six transmembrane domains (TMDs) and two putative re-entrant loops.

In paper II, by producing in large scale the human MBOAT7 in the yeast species *Pichia pastoris*, we described MBOAT7 as an O-acyltransferase that esterifies free polyunsaturated fatty acids (PUFAs) to the *sn-2* position of lysophosphatidylinositol (LPI), releasing newly acyl-chain remodelled phosphatidylinositol (PI). Moreover, missense mutations at the position 321 and 356 of the protein almost abolished the enzymatic activity, indicating that this is the catalytic dyad for the O-acyl transferase activity of MBOAT7.

In paper III, we showed that MBOAT7 depletion led to triglycerides and collagen accumulation in 2D and 3D hepatic models. Similarly, hepatic specific *MBOAT7* knock-out mice developed steatosis and fibrosis. We demonstrated that MBOAT7 depletion on the one hand reduced the PI acyl chain remodelling rate, and on the other hand it boosted the PI synthesis and degradation. PI breakdown can be catalysed by a phospholipase C-like protein that releases newly synthesized diacylglycerols (DAGs). DAGs can undergo a final esterification step resulting in triacylglycerol (TAG) synthesis, the main lipid component of liver fat.

In conclusion, our studies demonstrate that MBOAT7: 1) is an integral membrane protein anchored to endomembranes by six TMDs; 2) has an O-acyltransferase activity that preferentially esterifies PUFAs to LPI with a catalytic site composed of the Asparagine and Histidine in position 321 and 356 of the protein, respectively; and 3) MBOAT7 depletion causes higher liver fat content by increasing triglyceride synthesis mediated by a novel non-canonical bio-metabolic pathway.

Keywords: MBOAT7, O-acyltransferase, phosphatidylinositol, arachidonic acid, NAFLD, steatosis.

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