

Review Article

Recent progress of lysophosphatidylcholine acyltransferases in metabolic disease and cancer

Chenze Shi¹, Shuxuan Qiao¹, Shuya Wang¹, Tao Wu^{1,2}, Guang Ji^{2,3}

¹Center of Chinese Medical Therapy and Systems Biology, Shanghai University of Traditional Chinese Medicine, Shanghai, China; ²Institute of Digestive Disease, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; ³China-Canada Center of Research for Digestive Diseases, Shanghai, China

Received July 5, 2017; Accepted June 14, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: With the rapid development of the economy, the updating of different diseases, especially metabolic diseases and cancers, is increasingly rapid and the difficulty of curing diseases is becoming greater. Lysophosphatidylcholine acyltransferase (LPCAT) has been shown to be more likely to participate in the development of related diseases. In the present review, we mainly focused on progress of the role of LPCAT in metabolic diseases and cancers and wish to provide new points to prevent and treat metabolic diseases and cancers. Related research of LPCAT in metabolic diseases, inflammatory diseases, and cancers have been reviewed. LPCAT 1-4 have different roles in metabolic diseases, such as diabetes, hyperlipidemia, hyperglycemia, and nonalcoholic steatohepatitis. Furthermore, LPCAT1 has been an independent predictor of early tumor recurrence and represents a novel prognostic biomarker for hepatocellular carcinoma, gastric cancer, breast cancer, oral squamous cell carcinoma, prostate cancer, colorectal cancer, and clear cell renal cell carcinoma. LPCAT2 is recognized as a novel aggressive prostate cancer susceptibility gene, and LPCAT4 participates in the elevated expression of PC (16:0/16:1) in colorectal cancer. LPCATs will provide a foundation for potential novel therapeutic approaches and highlight the important role of phospholipid metabolism in the prevention and treatment of metabolic diseases and cancers.

Keywords: LPCAT, metabolic diseases, cancer, phospholipid

Introduction

Lipids are a diverse family of biomolecules that are components of cell membranes and play important roles in signal transduction [1]. Phosphatidylcholine (PC) is synthesized through the Kennedy pathway, more than 50% of which is remodeled through the Lands cycle, i.e., the deacylation and reacylation of PC to attain final and proper fatty acids within PC, where the reacylation step is catalyzed by lysophosphatidylcholine (LPC) acyltransferase (LPCAT) [2]. LPC is generated through the hydrolysis of PC by phospholipase A2 (PLA2) and converts back to PC by LPCAT1. LPCAT and phosphatidic acid phosphatase (PAH) are two key enzymes of PC homeostasis, with PC being a key intermediate in the metabolic network of glycerolipid biosynthesis [3].

LPCAT enzymes have a role influencing the complex cell signaling network involved in

microbial responses, which contribute to their importance in the inflammatory response [4]. LPCAT enzymes are reported to be able to remodel membrane phospholipids (PLs) during inflammation [5]. LPCAT has 4 isoforms, including LPCAT1, LPCAT2, LPCAT3, and LPCAT4, using one lysophospholipid and one acyl-Coenzyme A (acyl-CoA) ester as substrates [6]. Among the four LPCAT isoforms, LPCAT1 and LPCAT2 are well defined. A major liver LPCAT isoform, named LPCAT3, has recently been characterized as being structurally different from other members of the glycerolipid acyltransferase family [2, 7]. More studies recently focused on the roles of LPCATs in disease, especially in regulating the composition of LPC and PC.

In the present review, we summarize the characteristics of LPCATs and mainly focus on the progress of the role of LPCAT in related diseases, including mainly metabolic diseases and

cancers. We wish to provide new points to prevent and treat these diseases clinically.

Structure and distribution of LPCAT

LPCAT1 is a protein-coding gene that displays a clear preference for saturated fatty acyl-Coenzyme A (acyl-CoA), and 1-myristoyl and 1-palmitoyl LPCs serve as acyl donors and acceptors, respectively [8]. They can synthesize PC in pulmonary surfactant, play a pivotal role in respiratory physiology [9], and are involved in the regulation of lipid droplet number and size [10]. LPCAT2, encoding a member of the LPCAT family, localizes to the endoplasmic reticulum (ER) and the Golgi body, and the encoded protein functions in membrane biogenesis and the production of platelet-activating factor (PAF) in inflammatory cells (<http://www.genecards.org>). LPCAT3, the major isoform in the liver and small intestine, belongs to the membrane-bound O-acyltransferase (MBOAT) family, encoding a protein of 487 amino acids with a molecular mass of 56 kDa [2]. LPCAT3 activity is involved in PC remodeling and has an impact on cell function [11, 12]. LPCAT3 is also a target of the liver X receptor (LXR), which regulates ER stress and inflammation [11]. LPCAT4 is a member of the 1-acylglycerol-3-phosphate O-acyltransferase family. It displays acyl-CoA-dependent LPCAT activity with a subset of LPCs as substrates. It converts lysophosphatidylethanolamine to phosphatidylethanolamine, LPC to phosphatidylcholine, 1-alkenyl-lysophosphatidylethanolamine to 1-alkenyl-phosphatidylethanolamine, and lysophosphatidylglycerol and alkyl-LPC to phosphatidylglycerol and alkyl-PC, respectively [13].

Biological characteristics and functions of LPCATs

Catalytic activity

LPCAT is involved in the conversion of “Acyl-CoA+1-acyl-sn-glycero-3-phosphocholine = CoA +1,2-diacyl-sn-glycero-3-phosphocholine” (<https://www.ncbi.nlm.nih.gov/gene/>). Acyl-CoA-dependent lysophosphatidylcholine (lysoPC) acyltransferase (LPCAT) catalyzes the reacylation of lysoPC in the remodeling pathway for the synthesis of phosphatidylcholine (PC) [14]. LPCAT catalyzes acylation of lysophosphatidylcholine to produce phosphatidylcholine, the main phospholipid in cellular membranes. This

reaction is a key component of the acyl-editing process, involving recycling of the fatty acids. Growing evidences indicate that the LPCAT reaction has an important impact on the synthesis and composition of triacylglycerols [15].

LPCAT1 is a calcium-independent PL metabolic enzyme with both acyltransferase and acetyltransferase activities, which could promote PL synthesis and remodeling and mediate conversion of 1-acyl-sn-glycero-3-phosphocholine into PC. LPCAT2 functions in two ways: to catalyze the biosynthesis of PAF (O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) from 1-O-alkyl-sn-glycero-3-phosphocholine and to catalyze synthesis of glycerophospholipid precursors from arachidonoyl-CoA and LPC. In recent years, results have suggested that plant LPCATs can operate reversely *in vivo* and thereby catalyze an acyl exchange between the acyl-coenzyme A (CoA) pool and the phosphatidylcholine. Jasieniecka-Gazarkiewicz K. et al. [16] investigated the abilities of Arabidopsis AtLPCAT2, and it showed good reversible activity. The results also showed that the capacity of reversibility that could be specific for a particular phospholipid, although the lysophospholipid derivatives of other phospholipids serve as good acyl acceptors for the forward reaction of the enzyme.

LPCAT3 has distinct substrate preferences, which are strikingly consistent with a role in the Lands cycle. It prefers lysoPC with a saturated fatty acid at the sn-1 position and exhibits an acyl donor preference toward PUFA-CoA at the sn-2 position, such as linoleoyl-CoA and arachidonoyl-CoA [2, 12]. LPCAT4 catalyzes the conversion of lysophosphatidic acid (LPA) to phosphatidic acid (PA), a precursor in the biosynthesis of all glycerolipids. Both LPA and PA are two PLs that are involved in signal transduction and in lipid biosynthesis. It has no lysophosphatidylinositol, glycerol-3-phosphate, diacylglycerol, or lysophosphatidic acid acyltransferase activity. LPCAT4 prefers long chain acyl-CoAs (C16, C18) as acyl donors (<https://www.ncbi.nlm.nih.gov/gene/>).

Pathways

LPCAT activity is a critical component of the phospholipid remodeling pathway in the function of the phospholipase A2 (PLA2) activity of peroxiredoxin (Prdx)6, which has important

physiological roles in the synthesis of lung surfactant and in repair of peroxidized cell membranes [17]. LPCAT1 mainly involves the pathways fatty Acyl-CoA biosynthesis and Acyl chain remodeling of PC, which are part of lipid metabolism [8]. Soupene E. et al. [18] concluded that PC formation by LPCAT1 was regulated by Ca^{2+} and the redox status of the cell. Mutant forms of LPCAT1 are not inhibited by Ca^{2+} , and sulfhydryl-alkylating and sulfhydryl-oxidizing agents provide a better understanding of the physiological function of the mechanism that dictates the formation of PC and the disposal of the bioactive species, LPC, under the control of the redox status and the Ca^{2+} concentration of the cell.

Pathways related to LPCAT2 are glycerophospholipid biosynthesis and acyl chain remodeling of PC. Gene Ontology annotations related to this gene include calcium ion binding and 1-acylglycerol-3-phosphate O-acyltransferase activity (<http://www.genecards.org>). Morimoto R. et al. [19] found that phosphorylation of LPCAT2 at Ser34 enhanced PAF production in endotoxin-stimulated macrophages. Further studies showed a new signaling pathway for the rapid biosynthesis of PAF, which is mediated by phosphorylation of LPCAT2 at Ser-34 [20]. Xu J. et al. [21] found that triglyceride (TG) synthesis by PL: diacylglycerol acyltransferase 1 (PDAT1) in the absence of diacylglycerol acyltransferase 1 (DGAT1) activity was dependent on the re-acylation of LPC by LPCAT2. It was also found that LPCAT2 activated and upregulated to produce PAF, which is a potent pro-inflammatory phospholipid mediator [22].

LPCAT3 involves the pathways glycerophospholipid biosynthesis and triacylglycerol biosynthesis. LPCAT3 is localized within the ER and is primarily expressed in metabolic tissues, including the liver, small intestine, and pancreas, as well as adipose tissue. Hepatic LPCAT3 has critical functions in TG transport and ER stress response because it can catalyze the incorporation of polyunsaturated fatty acids (PUFAs) into PLs. Li Z. et al. [23] indicated that hepatic LPCAT3 modulates VLDL production by regulating lysoPC levels and microsomal triglyceride transfer protein (MTP) expression. Demeur O. et al. [24] found, for the first time, that the chicken LPCAT3 gene was a direct target of LXR and therefore suggested a new role

for LXR in PL homeostasis. Singh R. et al. [25] identified LPCAT3 as a direct PPAR δ target gene and suggested a novel function of PPAR δ , which regulated many genes involved in lipid metabolism in the regulation of PL metabolism through LPCAT3. Singh AB and Liu J [26] also provided evidence *in vivo* that activation of PPAR δ by agonist L165041 in mice may increase hepatic LPCAT3 mRNA abundance and LPCAT enzymatic activity. It was closely associated with increased incorporation of arachidonate into liver phosphatidylcholine and phosphatidylethanolamine. Kabir I. et al. [27] investigated lipid metabolism in inducible intestine-specific and liver-specific LPCAT3 gene knock-out mice. At day 9, after treatment with tamoxifen, they found that LPCAT3 deficiency in enterocytes significantly reduced polyunsaturated PCs in the enterocyte plasma membrane and reduced Niemann-Pick C1-like 1 (NPC1L1), CD36, ATP-binding cassette transporter 1 (ABCA1), and ATP binding cassette subfamily G member 8 (ABCG8) levels on the membrane, and thus significantly reduced lipid absorption, cholesterol secretion through apoB-dependent and apoB-independent pathways, plasma TG, cholesterol, and PL levels. Inhibition of the small intestine of LPCAT3 might constitute a novel approach for treating hyperlipidemia. PUFAs in PLs affect the physical properties of membranes, but it is unclear which biological processes are influenced by their regulation. Hashidate-Yoshida T. et al. [28] showed that the lack of LPCAT3 lead to drastic reductions in membrane arachidonate levels and that LPCAT3-deficient mice were neonatally lethal due to extensive TG accumulation and dysfunction in enterocytes. It was found that high levels of PUFAs in the membrane enabled TGs to locally cluster at high density so that this clustering promoted efficient TG transfer. Rong X. et al. [29] discovered that LPCAT3 was a critical determinant of TG secretion due to its unique ability to catalyze the incorporation of arachidonate into membranes.

According to a series of experiments, it was found that mice lacking LPCAT3 in the intestine failed to thrive during weaning and exhibited enterocyte lipid accumulation and reduced plasma TGs. Mice lacking LPCAT3 in the liver showed reduced plasma TGs and hepatosteatosis, and secreted lipid-poor VLDL lacking arachidonoyl-PLs. Mechanistic studies indicat-

Recent progress of LPCATs in metabolic disease and cancer

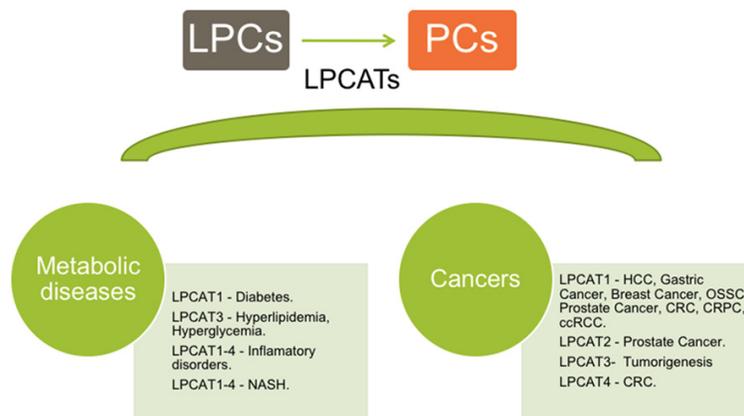


Figure 1. Schematic diagram of the association between LPCATs and metabolic diseases and cancers. LPCs, lysophosphatidylcholine; PC, phosphatidylcholine; LPCAT, lysophosphatidylcholine acyltransferase; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; OSCC, squamous cell carcinoma; CRC, colorectal cancer; CRPC, castration resistant prostate cancer; ccRCC, clear cell renal cell carcinoma.

ed that LPCAT3 activity impacted membrane lipid mobility in living cells, suggesting a biophysical basis for the requirement of arachidonoyl PLs in lipidating lipoprotein particles.

The fatty acyl composition of PLs determines the biophysical characteristics of the membranes and impacts the function of membrane proteins. Rong X. et al. [30] defined a nuclear receptor pathway for the dynamic modulation of membrane composition in response to changes in cellular lipid metabolism. Ligand activation of LXRs preferentially drove the combination of PUFAs in PLs through induction of the remodeling enzyme LPCAT3. Promotion of LPCAT3 activity ameliorated ER stress induced by saturated free fatty acids *in vitro* or by hepatic lipid accumulation *in vivo*. Conversely, LPCAT3 knockdown in the liver exacerbated ER stress and inflammation. Mechanistically, LPCAT3 modulated inflammation both by regulating inflammatory kinase activation through changes in membrane composition and by affecting substrate availability for inflammatory mediator production.

These results outlined an endogenous mechanism for the preservation of membrane homeostasis during lipid stress and identified LPCAT3 as an important mediator of LXR effects on metabolism. Ishibashi M. et al. [31] demonstrated that the LXR-mediated induction of LPCAT3 primed human macrophages for subsequent eicosanoid secretion by increasing the

pool of AA that can be mobilized from PLs. Eto M. et al. [32] found LPCAT3 was the key enzyme for incorporating arachidonic acid into glycerophospholipids during adipocyte differentiation. Pérez-Chacón G. et al. [33] defined LPCAT3 as a novel-signal-regulated enzyme that was centrally implicated in limiting free AA levels in activated cells. Jain S. et al. [11] concluded that reduced LPCAT3 expression resulted in more apoptosis and distinctly fewer lamellipodia, suggesting a necessary role for lysophospholipid esterification in maintaining cellular function and structure. Kazachkov M. et al. [34]

reported LPCAT3 had distinct substrate preferences that were strikingly consistent with a role in PC remodeling and modulating the fatty acid composition of PC. LPCAT3 preferred lysoPCs with saturated fatty acid at sn-1 position and exhibited acyl donor preference towards linoleoyl-CoA and arachidonoyl-CoA. Furthermore, LPCAT3 was active in mediating 1-O-alkyl-sn-glycero-3-phosphocholine acylation with long-chain fatty acyl-CoAs to generate 1-O-alkyl-PC, another very important constituent of mammalian membrane systems. These properties were the precisely known attributes of LPCAT that were previously ascribed to the isoform involved in Lands' cycle and thus strongly suggested that LPCAT3 was involved in PL remodeling to achieve appropriate membrane lipid fatty acid composition. Zhao Y. et al. [2] reported that membranes from HEK293 cells overexpressing LPCAT3 showed significantly increased LPCAT activity with a substrate preference toward unsaturated fatty acids. RNA interference-mediated knockdown of LPCAT3 in human hepatoma Huh7 cells resulted in the virtually complete loss of membrane LPCAT activity, suggesting that LPCAT3 was primarily responsible for hepatic LPCAT activity. Furthermore, PPAR α agonists dose-dependently regulated LPCAT3 in the liver in a PPAR alpha-dependent fashion, implicating the role of LPCAT3 in lipid homeostasis. The studies identified LPCAT3 as a key factor in lipoprotein production and provided an invaluable tool for future investiga-

tions on how PC remodeling may potentially impact glucose and lipid homeostasis. However, the pathways mediated by LPCAT4 have remained unclear.

LPCAT and metabolic diseases

LPCAT 1-4 have mainly been explored as having roles in metabolic diseases and different cancers. There are a few related studies that have shown the mechanism or pathway of LPCAT in diseases, as shown in **Figure 1**.

LPCAT1 and diabetes

LPC and PAF are potent inflammatory PLs implicated in diabetic complications [35]. Plasma LPC levels were significantly elevated in insulin-dependent and non-insulin-dependent diabetes mellitus patients, diabetic retinopathy patients, and experimental obesity models [36-38]. LPC has been proven to activate several signal transduction pathways implicated in insulin resistance, such as JNK and protein kinase C α [39, 40]. Among the four isoforms of LPCAT, LPCAT1, and LPCAT2 have also been shown to catalyze the synthesis of PAF from lyso-PAF, in addition to possessing acyltransferase activity toward LPC. Intriguingly, LPCAT2, but not LPCAT1, have been shown to play a role in the inflammatory response by catalyzing the synthesis of PAF from lyso-PAF [41]. LPCAT1, which can catalyze the synthesis of LPCs, could be regarded as a biomarker in the diagnosis of diabetes.

LPCAT3 and hyperlipidemia

In hyperlipidemia, LPCAT3 can offer the orientation of searching for biomarkers. It has played a novel and essential role in modulating PC composition in enterocyte plasma membranes, thereby influencing lipid uptake and plasma lipoprotein metabolism. LPCAT3 deficiency diminished the protein levels in enterocytes of NPC1L1, cluster of differentiation 36 (CD36), and fatty acid transport protein 4 (FATP4) and reduced lipid uptake in the small intestine. Further, LPCAT3 deficiency also decreased both very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) production from the liver. Additionally, all the plasma lipids (cholesterol, PLs, and TGs), as well as all the plasma lipoproteins (HDL and non-HDL), were significantly decreased. LPCAT3-mediated PC

remodeling was controlled by LXR in the liver and small intestine and PPARs in the liver but not in the small intestine. This showed that whole-body LPCAT3 deficiency resulted mainly in reduced polyunsaturated PCs in enterocyte membranes, which in turn increased membrane rigidity, causing reduced levels of lipid absorption-related proteins on the membrane and less circulating lipid. The activity of LPCAT is required for the addition of PUFAs to the sn-2 position of PCs and for maintaining cell membrane structure and function, inhibition of LPCAT3 in the small intestine, which could be developed as an approach to treat hyperlipidemia [42].

It has been reported that LPCAT3 activity is involved in PC remodeling and in turn has an impact on cell function [11]. LPCAT3 is also a target of LXR, which regulates ER stress and inflammation through the regulation of LPCAT3 [30]. Li Z. et al. [43] found that LPCAT3 KO mice had longer and larger small intestines than control mice, with shorter wide villi, reduced lipid absorption, and lower levels NPC1L1, CD36, and FATP4 proteins. Cash JG. et al. [43] found that liver-specific overexpression of LPCAT3 reduced postprandial hyperglycemia and improved the lipoprotein metabolic profile in mice. Wang B. et al. [44] demonstrated that the LXR-responsive PL-remodeling enzyme LPCAT3 modulated intestinal fatty acids and cholesterol absorption and was required for survival on a high-fat diet. Mice lacking LPCAT3 in the intestine thrived on carbohydrate-based chow but rapidly lost body weight and became moribund on a TG-rich diet. LPCAT3-dependent incorporation of PUFAs into PLs was required for the efficient transport of dietary lipids into enterocytes. Furthermore, loss of LPCAT3 amplified the production of gut hormones, including GLP-1 and oleoylethanolamide in response to high-fat diet, contributing to the paradoxical cessation of food intake in starvation. These results revealed that membrane PL composition was a gating factor in passive lipid absorption and implicated LXR-LPCAT3 signaling in a gut-brain feedback loop that coupled absorption to food intake.

In summary, LPCAT3 deficiency significantly reduced polyunsaturated PC levels in the plasma membrane of enterocytes, which in turn attenuated lipid absorption and decreased the

Recent progress of LPCATs in metabolic disease and cancer

plasma lipid levels. Inhibition of LPCAT3 in the small intestine could be a novel approach for the treatment of hyperlipidemia.

LPCAT3 and hyperglycemia

Hyperglycemia is a term referring to high blood glucose levels, often leading to the diagnosis of diabetes. Hyperglycemia is defined by certain high levels of blood glucose: fasting levels greater than 7.0 mmol/L; 2-hour postprandial levels greater than 11.0 mmol/L. Chronic hyperglycemia usually leads to the development of diabetic complications and other cardiometabolic diseases.

Cash JG. et al. [43] found that liver-specific overexpression of LPCAT3 reduced postprandial hyperglycemia and improved the lipoprotein metabolic profile in mice. Over-expression of LPCAT3 increased the utilization of lysophospholipid for PL synthesis, thereby alleviating lysophospholipid inhibition of fatty acid oxidation and improving glucose tolerance. Additionally, hepatic LPCAT3 overexpression may alter lipoprotein metabolism and increase HDL secretion. Additionally, the HDL secreted by LPCAT3 overexpressing hepatocytes was also enriched in apoE, which was similar to those characteristics induced by LXR agonists, and it was likely synthesized through mechanisms distinct from the synthesis of normal apoA-I HDL. Taken together, this was consistent with the interpretation that increased expression of LPCAT3 reduced the postprandial LPC levels in the liver and consequently enhanced mitochondrial fatty acid oxidation, improved postprandial glucose tolerance and promoted a favorable lipoprotein profile without adverse VLDL synthesis-promoting effects of LXR agonists. Hence, LPCAT3 has liver-specific overexpression and can help reduce postprandial hyperglycemia and improve the lipoprotein metabolic profile [45]. Hence, the overexpression of LPCAT3 in the liver could be a novel approach for the treatment of hyperglycemia.

LPCAT 1-4 and non-alcohol steatohepatitis (NASH)

NAFLD comprises a spectrum of progressive liver diseases, including simple steatosis, NASH, fibrosis, ultimately cirrhosis and HCC [46]. Yamazaki T. et al. [47] investigated the effect of fibrates (clofibrac acid, bezafibrate, and

fenofibrate) on the gene expression and activity of LPCATs. Eventually, they suggested (i) that fibrates induced LPCAT activity in hepatic microsomes by elevating the expression of LPCAT3 and LPCAT4, (ii) that the changes in the fatty acid profile of hepatic PC were, in part, due to the elevated expression of two isoforms, LPCAT3 and LPCAT4, and (iii) that the ability of fibrates to induce these changes were on the order of fenofibrate > bezafibrate > clofibrac acid.

It was found that hepatic LPCAT1, LPCAT2, and LPCAT3 mRNAs were all upregulated with two- to four-fold elevations in the NASH model [48]. Han MS. et al. [49] studied hepatocyte apoptosis induced by palmitic acid (PA) and measured the content of LPCs in the hepatocytes of rats. The results showed that LPC was a death effector of liver cell apoptosis. Wu T. et al. [50] detected that progressively lower levels of long-chain LPC a C18:2, LPC a C20:3, and LPC a C20:4 were observed from chronic hepatitis B to cirrhosis to carcinoma. Tanaka N. et al. [48] found that the content of LPC 16:0, LPC 18:0, and LPC 18:1 decreased significantly in the MCD diet-induced NASH rat model. Furthermore, they found that hepatic mRNAs encoding enzymes and proteins involved in LPC degradation (LPCAT 1-4), basolateral bile acid excretion (ATP-binding cassette subfamily C member [Abcc] 1/4/5 and organic solute transporter β [OST β]), and 12-hydroxyeicosatetraenoic acid (12-HETE) synthesis (arachidonate 12-lipoxygenase) were significantly up-regulated in accordance with these metabolite changes, with significant decreases in serum palmitoyl-, stearoyl-, and oleoyl-LPC and marked increases in tauro- β -muricholate, taurocholate and 12-HETE detected in NASH mice. LPC 22:5, LPC16:0 and other components were common markers of hepatitis B and C virus. The results suggest that LPCAT metabolic homeostasis was impaired in these common liver diseases and chemical hepatotoxicity models [51]. Beilstein F. et al. [52] had identified LPCAT1 as a modulator of liver lipid metabolism that was down-regulated by HCV, which suggested a viral strategy to increase the triacylglycerol content and hence the infectivity of viral particles. Targeting this metabolic pathway may represent an attractive therapeutic approach to reduce both the viral titer and hepatic steatosis.

Recent progress of LPCATs in metabolic disease and cancer

Inflammation is a fundamental component of acute and chronic cholestatic liver injury. PAF is a pro-inflammatory lipid, which may generate two independent pathways called the *de novo* and remodeling pathway, which are responsible for the synthesis of PAF during inflammation. In recent years, LPCAT enzymes are known to play a key role in PAF remodeling. Stanca E. et al. [53] reported that the level of lyso-PAF and PAF significantly increased in the liver of cirrhotic vs. control rats together with a significant decrease in both the mRNA abundance and protein level of both LPCAT1 and LPCAT2. Acyltransferase activities of both LPCAT1 and LPCAT2 were decreased in parallel in the liver of cirrhotic animals.

LPCAT 1-4 and inflammatory disorders

LPCAT is critical in the regulation of pro-inflammatory cytokine responses to gram-positive cell bacterial components, such as peptidoglycan, lipoteichoic acid, and the synthetic tri-palmitoylated lipopeptide Pam3CSK4, in monocytes and lung epithelial cells [42].

The degree of fatty acid unsaturation in membrane PLs influences many membrane-associated functions and cells must adapt to changes in the composition of membrane fatty acids by regulating lipid-metabolizing enzymes. Akagi S. et al. [54] investigated how cells responded to loading with excess PUFAs, such as arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid, and then they found that dipalmitoylphosphatidylcholine (DPPC) was increased after production of PUFA-containing PLs in cells loaded with PUFAs. LPCAT1 was involved in DPPC production. Moreover, LPCAT1 knock-down markedly enhanced cytotoxicity induced by excess PUFAs. PUFA-induced cytotoxicity was dependent on the caspase, unfolded protein response (UPR) sensor proteins, inositol requiring 1 α and protein kinase R-like ER kinase, suggesting that excess PUFAs triggered UPR-mediated apoptosis. DPPC was produced along with an increase in PUFA-containing PLs in the murine retina, in which PUFAs were highly enriched. In LPCAT1 knockout mice, the DPPC level was reduced and the UPR was activated in the retina. Cheng S. et al. [55] suggested that exogenous expression of LPCAT1 may attenuate eosinophil inflammation in the airway by down-regulating the LPC 16:0 and LPC 18:0

bronchoalveolar lavage fluid levels in asthmatic mice.

Ahn WG. et al. [56] found that levels of LPC and albumin and the enzyme activities of LPCAT, ATX, and PLA2 were decreased, whereas the levels of PC, LPA, and LPCAT1-3 were increased in the plasma of mice subjected to cecal ligation and puncture, a model of polymicrobial peritoneal sepsis. Bacterial peritonitis led to alterations in all the analyzed LPC-related metabolic parameters in the plasma, which could potentially contribute to a sepsis-induced decrease in plasma LPC levels. Taniguchi K. et al. [57] found that LPCAT3 played an important role in M1/M2-macrophage polarization, providing novel potential therapeutic targets for the regulation of immune and inflammatory disorders. Tanaka H. et al. [58] found that regulation of LPCAT3 expression might be associated with atherosclerotic progression in humans. LPCAT3 converts LPC and free Amino Acids (AA) into PC-containing AA (arachidonyl-PC) and thereby can regulate intracellular free-AA levels. A distribution of LPCAT3 expression and arachidonyl-PC was based on atherosclerotic progression. LPCAT3 was also found to be able to remodel phospholipid, which was shown to be pivotal for uptake of fatty acids by enterocytes, providing a mechanistic handle for therapeutic intervention in reducing atherosclerosis and risk of cardiovascular events [59].

LPCAT and cancers

Aberrant lipid metabolism is also an established hallmark of cancer cells. The alteration of the choline metabolite profile is a well-established characteristic of cancer cells.

LPCAT1 and cancers

LPCAT1 has been an independent predictor of early tumor recurrence and represents a novel prognostic biomarker for hepatocellular carcinoma (HCC), gastric cancer, breast cancer, oral squamous cell carcinoma (OSCC), prostate cancer, colorectal cancer (CRC), castration resistant prostate cancer (CRPC), and clear cell renal cell carcinoma (ccRCC) [60-62].

Because LPCAT is synthesized in the liver and mediates the conversion LPC into PC, LPCAT can also be a novel biomarker of liver cancer. It was visible that LysoPCs in the HCC model and

Recent progress of LPCATs in metabolic disease and cancer

clinical patients were obviously changed [63]. Morita Y. et al. [64] performed a molecular lipidomic screening by imaging mass spectrometry in 37 resected HCC specimens, and the increase of PC species with palmitoleic acid or oleic acid at the sn-2-position and the reduction of LPC with palmitic acid at the sn-1-position were found in HCC tissues. Expression of the mRNA and protein of LPCAT1 were more abundant in HCCs than in the surrounding parenchyma. In the cell line experiments, LPCAT1 overexpression enriched PCs and promoted cell proliferation, migration, and invasion, while LPCAT1 knockdown did the opposite. Thus, LPCAT1 may be a potential target molecule to inhibit HCC progression because it modulates PL composition to create favorable conditions in HCC cells.

Uehara T. et al. [62] found that LPCAT1 was highly expressed in cancer lesions compared to the non-neoplastic mucosa, predominantly in differentiated adenocarcinoma, and overexpressed LPCAT1 protein in the gastric mucosa played important roles in the tumorigenic process of gastric cancer by converting LPC to PC.

Abdelzaher E. et al. [60] evaluated immunohistochemical expression of LPCAT1 in 80 primary breast carcinomas, 24 metastatic lymph nodes, and 30 non-neoplastic breast tissue specimens. LPCAT1 protein was significantly upregulated in primary breast carcinoma and showed a significant ascending pattern being the lowest in normal breast tissues, relatively increased in fibrocystic disease, and the highest in primary carcinoma. LPCAT1 expression was significantly higher at the tumor's advancing edge and correlated positively with tumor's grade and TNM stage. LPCAT1 overexpression was significantly associated with increased proliferative activity, negative estrogen receptor (ER) and progesterone receptor (PR) status, positive human epidermal growth factor receptor 2 (HER2) status, and triple-negative and HER2 disease molecular subtypes. LPCAT1 was implicated in breast cancer pathogenesis, evolution, and progression and played a crucial role as a determinant of local invasiveness and metastasis.

Shida-Sakazume T. et al. [65] explored whether down-regulation of LPCAT1 resulted in a decreased intercellular PAF concentration and PAF-receptor (PAFR) expression. Finally, they concluded that LPCAT1 was overexpressed in

OSCC and correlated with cellular invasiveness and migration.

It was estimated that approximately 233,000 new prostate cancer cases will be diagnosed in the United States alone in 2014 [25]. To assess its role in prostate cancer, Grupp K. et al. [61] analyzed LPCAT1 expression on a tissue microarray containing samples from 11,152 prostate cancer patients. In benign prostate glands, LPCAT1 immunostaining was absent or weak. In prostate cancer, LPCAT1 positivity was found in 73.8% of 8786 interpretable tumors, including 29.2% with strong expression. Increased LPCAT1 expression was associated with advanced tumor stage (pT3b/T4), high Gleason score, positive nodal involvement, positive surgical margin, and early PSA recurrence. High LPCAT1 expression was strongly linked to ERG-fusion type prostate cancer. Strong LPCAT1 staining was detected in 45.3% of ERG-positive cancers but in only 16.7% of ERG negative tumors. Within the ERG negative cancers, LPCAT1 staining was strongly increased within the subgroup of PTEN-deleted cancers. Further subgroup analyses revealed that associations of high LPCAT1 expression with PSA recurrence and unfavorable tumor phenotype were largely driven by ERG negative cancers, while these effects were substantially mitigated in ERG-positive cancers. The prognostic impact of LPCAT1 expression was independent of the histological and clinical parameters. It was concluded that LPCAT1 measurement, either alone or in combination, may be utilized for better clinical decision-making.

PCs are the most prominent PLs in colorectal cancer (CRC). Mansilla F. et al. [66] reported that LPCAT1 was highly overexpressed in colorectal adenocarcinomas when compared to normal mucosa, and LPCAT1 may contribute to total choline metabolite accumulation via PC remodeling, thereby altering the CRC lipid profile, which is characteristic of malignancy.

Bin X. et al. [67] have found that LPCAT1 was overexpressed in castration resistant prostate cancer (CRPC) and regulated by androgen through the Wnt-dependent signaling pathway. They also found that LPCAT1 promoted to the progression of CRPC in terms of proliferation, invasion and migration *in vitro* and *in vivo*. LPCAT is likely to be a significant therapeutic target for CRPC treatment.

Recent progress of LPCATs in metabolic disease and cancer

A recent study explored the role of phospholipid profile alterations in clear cell renal cell carcinoma (ccRCC) [68]. Selective changes in PC and LPC composition were observed in ccRCC tissues. The mRNA and protein levels of LPCAT1 were up-regulated in ccRCC tissues compared with normal renal tissues, and LPCAT1 expression was significantly correlated with unfavorable pathological features (higher tumor grade, higher TNM stage and larger tumor size) and overall survival. In cell line experiments, LPCAT1 knockdown depleted PCs, inhibited cell proliferation, migration and invasion and induced cell cycle arrest at the G0/G1 phase. They concluded that the overexpression of LPCAT1 promoted the development and progression of ccRCC through the conversion of LPC to PC.

Altogether, the above studies imply that the recently isolated LPCAT1 is labeled in cancer development and progression as the most important enzyme in membrane biogenesis.

LPCAT2 and prostate cancer

Williams KA. et al. [69] performed a systems genetic approach, which identified CXCL14, ITGAX, and LPCAT2 as novel aggressive prostate cancer susceptibility genes. However, until now there are only a few studies about the relationship between LPCAT2 and cancers.

LPCAT3 and tumorigenesis

Wang B. et al. [70] revealed that disruption of LPCAT3-dependent phospholipid and cholesterol homeostasis dramatically enhanced tumor formation in *Apc^{min}* mice, which identified a critical dietary-responsive phospholipid-cholesterol axis regulating intestinal stem cell (ISC) proliferation and tumorigenesis.

LPCAT4 and CRC

It has been reported that the overall levels of PC are elevated in CRC. Kurabe N. et al. [71] identified a novel biomarker, PC (16:0/16:1), in CRC using imaging mass spectrometry, which was based on a panel of non-neoplastic mucosal and CRC tissues. Specifically, elevated levels of PC (16:0/16:1) expression were observed in the more advanced stage of CRC and were specifically localized in the cancer region. This indicated the potential usefulness of PC (16:0/16:1) in the clinical diagnosis of CRC and

implicated LPCAT4 in the elevated expression of PC (16:0/16:1) in CRC. In conclusion, LPCATs play important roles in different kinds of cancers and may become biomarkers or targets in the prevention and therapy of cancers.

Conclusions and prospective

Despite much interest in the above findings, the role of LPCATs in pathological conditions remains unknown. It is obvious that LPCAT has been presumed to be a possible biomarker of many metabolic diseases and cancers. Because of the differences between the detection methods and the experimental design, studies could not exclude whether the diseases have common markers, and the mechanism of these LPCATs has not been systematically studied. Adopting a uniform experimental design and platform, discovery and confirmation of the common biomarkers, and the illustration of the biochemical mechanism of LPCATs are all important issues that scientists need to face in the near future.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (81620108030), the 3-Year Action Plan of Shanghai Municipal Committee of Health and Family Planning (ZY3-CCCX-2-1002), the Shanghai Rising-Star Project (15QA1403500), and the Shanghai Talents development fund Project (2017090).

Disclosure of conflict of interest

None.

Address correspondence to: Guang Ji, Institute of Digestive Disease, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 Wanping Road, Shanghai 200032, China. Tel: +86-21-64286261; E-mail: jiliver@vip.sina.com; Tao Wu, Center of Chinese Medical Therapy and Systems Biology, Shanghai University of Traditional Chinese Medicine, 1200 Cailun Road, Shanghai 201203, China. Tel: +86-21-51322748; E-mail: wutao0018-27@163.com

References

- [1] Serhan CN, Chiang N and Van Dyke TE. Resolving inflammation: dual anti-inflammatory and

Recent progress of LPCATs in metabolic disease and cancer

- pro-resolution lipid mediators. *Nat Rev Immunol* 2008; 8: 349-361.
- [2] Zhao Y, Chen YQ, Bonacci TM, Bredt DS, Li S, Bensch WR, Moller DE, Kowala M, Konrad RJ and Cao G. Identification and characterization of a major liver lysophosphatidylcholine acyltransferase. *J Biol Chem* 2008; 283: 8258-8265.
- [3] Wang L, Kazachkov M, Shen W, Bai M, Wu H and Zou J. Deciphering the roles of arabidopsis LPCAT and PAH in phosphatidylcholine homeostasis and pathway coordination for chloroplast lipid synthesis. *Plant J* 2014; 80: 965-976.
- [4] Hughes JA. The role of LPCAT in regulating cellular inflammatory responses to toll-like receptor ligands. PhD, University of the West of England, 2014. Available from: <http://eprints.uwe.ac.uk/24099>.
- [5] Chen J, Yang L, Foulks JM, Weyrich AS, Marathe GK and McIntyre TM. Intracellular PAF catabolism by PAF acetylhydrolase counteracts continual PAF synthesis. *J Lipid Res* 2007; 48: 2365-2376.
- [6] Martin SA, Gijon MA, Voelker DR and Murphy RC. Measurement of lysophospholipid acyltransferase activities using substrate competition. *J Lipid Res* 2014; 55: 782-791.
- [7] Hishikawa D, Shindou H, Kobayashi S, Nakaniishi H, Taguchi R and Shimizu T. Discovery of a lysophospholipid acyltransferase family essential for membrane asymmetry and diversity. *Proc Natl Acad Sci U S A* 2008; 105: 2830-2835.
- [8] Moessinger C, Kuerschner L, Spandl J, Shevchenko A and Thiele C. Human lysophosphatidylcholine acyltransferases 1 and 2 are located in lipid droplets where they catalyze the formation of phosphatidylcholine. *J Biol Chem* 2011; 286: 21330-21339.
- [9] Nakanishi H, Shindou H, Hishikawa D, Harayama T, Ogasawara R, Suwabe A, Taguchi R and Shimizu T. Cloning and characterization of mouse lung-type acyl-CoA:lysophosphatidylcholine acyltransferase 1 (LPCAT1). Expression in alveolar type II cells and possible involvement in surfactant production. *J Biol Chem* 2006; 281: 20140-20147.
- [10] Moessinger C, Klizaitė K, Steinhagen A, Philippou-Massier J, Shevchenko A, Hoch M, Ejsing CS and Thiele C. Two different pathways of phosphatidylcholine synthesis, the Kennedy pathway and the Lands cycle, differentially regulate cellular triacylglycerol storage. *BMC Cell Biol* 2014; 15: 43.
- [11] Jain S, Zhang X, Khandelwal PJ, Saunders AJ, Cummings BS and Oelkers P. Characterization of human lysophospholipid acyltransferase 3. *J Lipid Res* 2009; 50: 1563-1570.
- [12] Ariyama H, Kono N, Matsuda S, Inoue T and Arai H. Decrease in membrane phospholipid unsaturation induces unfolded protein response. *J Biol Chem* 2010; 285: 22027-22035.
- [13] Cao J, Shan D, Revett T, Li D, Wu L, Liu W, Tobin JF and Gimeno RE. Molecular identification of a novel mammalian brain isoform of acyl-CoA:lysophospholipid acyltransferase with prominent ethanolamine lysophospholipid acylating activity, LPEAT2. *J Biol Chem* 2008; 283: 19049-19057.
- [14] Zhang D, Jasieniecka-Gazarkiewicz K, Wan X, Luo L, Zhang Y, Banas A, Jiang M and Gong Y. Molecular characterization of two lysophospholipid: acyl-coa acyltransferases belonging to the MBOAT family in *Nicotiana benthamiana*. *PLoS One* 2015; 10: e0144653.
- [15] Arroyo-Caro JM, Chileh T, Alonso DL and Garcia-Maroto F. Molecular characterization of a lysophosphatidylcholine acyltransferase gene belonging to the MBOAT family in *Ricinus communis* L. *Lipids* 2013; 48: 663-674.
- [16] Jasieniecka-Gazarkiewicz K, Demski K, Lager I, Szymne S and Banas A. Possible role of different yeast and plant lysophospholipid:acyl-coa acyltransferases (LPLATs) in acyl remodeling of phospholipids. *Lipids* 2016; 51: 15-23.
- [17] Fisher AB, Dodia C, Sorokina EM, Li H, Zhou S, Raabe T and Feinstein SI. A novel lysophosphatidylcholine acyl transferase activity is expressed by peroxiredoxin 6. *J Lipid Res* 2016; 57: 587-596.
- [18] Soupene E and Kuypers FA. Phosphatidylcholine formation by LPCAT1 is regulated by Ca(2+) and the redox status of the cell. *BMC Biochem* 2012; 13: 8.
- [19] Morimoto R, Shindou H, Oda Y and Shimizu T. Phosphorylation of lysophosphatidylcholine acyltransferase 2 at Ser34 enhances platelet-activating factor production in endotoxin-stimulated macrophages. *J Biol Chem* 2010; 285: 29857-29862.
- [20] Morimoto R, Shindou H, Tarui M and Shimizu T. Rapid production of platelet-activating factor is induced by protein kinase C α -mediated phosphorylation of lysophosphatidylcholine acyltransferase 2 protein. *J Biol Chem* 2014; 289: 15566-15576.
- [21] Xu J, Carlsson AS, Francis T, Zhang M, Hoffman T, Giblin ME and Taylor DC. Triacylglycerol synthesis by PDAT1 in the absence of DGAT1 activity is dependent on re-acylation of LPC by LPCAT2. *BMC Plant Biol* 2012; 12: 4.
- [22] Tarui M, Shindou H, Kumagai K, Morimoto R, Harayama T, Hashidate T, Kojima H, Okabe T, Nagano T, Nagase T and Shimizu T. Selective inhibitors of a PAF biosynthetic enzyme lysophosphatidylcholine acyltransferase 2. *J Lipid Res* 2014; 55: 1386-1396.

Recent progress of LPCATs in metabolic disease and cancer

- [23] Li Z, Ding T, Pan X, Li Y, Li R, Sanders PE, Kuo MS, Hussain MM, Cao G and Jiang XC. Lysophosphatidylcholine acyltransferase 3 knock-down-mediated liver lysophosphatidylcholine accumulation promotes very low density lipoprotein production by enhancing microsomal triglyceride transfer protein expression. *J Biol Chem* 2012; 287: 20122-20131.
- [24] Demeure O, Lecerf F, Duby C, Desert C, Ducheix S, Guillou H and Lagarrigue S. Regulation of LPCAT3 by LXR. *Gene* 2011; 470: 7-11.
- [25] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9-29.
- [26] Singh AB and Liu J. Identification of hepatic lysophosphatidylcholine acyltransferase 3 as a novel target gene regulated by peroxisome proliferator-activated receptor delta. *J Biol Chem* 2017; 292: 884-897.
- [27] Kabir I, Li Z, Bui HH, Kuo MS, Gao G and Jiang XC. Small intestine but not liver lysophosphatidylcholine acyltransferase 3 (*Lpcat3*) deficiency has a dominant effect on plasma lipid metabolism. *J Biol Chem* 2016; 291: 7651-7660.
- [28] Hashidate-Yoshida T, Harayama T, Hishikawa D, Morimoto R, Hamano F, Tokuoka SM, Eto M, Tamura-Nakano M, Yanobu-Takanashi R, Mukumoto Y, Kiyonari H, Okamura T, Kita Y, Shindou H and Shimizu T. Fatty acid remodeling by LPCAT3 enriches arachidonate in phospholipid membranes and regulates triglyceride transport. *Elife* 2015; 4.
- [29] Rong X, Wang B, Dunham MM, Hedde PN, Wong JS, Gratton E, Young SG, Ford DA and Tontonoz P. *Lpcat3*-dependent production of arachidonoyl phospholipids is a key determinant of triglyceride secretion. *Elife* 2015; 4.
- [30] Rong X, Albert CJ, Hong C, Duerr MA, Chamberlain BT, Tarling EJ, Ito A, Gao J, Wang B, Edwards PA, Jung ME, Ford DA and Tontonoz P. LXRs regulate ER stress and inflammation through dynamic modulation of membrane phospholipid composition. *Cell Metab* 2013; 18: 685-697.
- [31] Ishibashi M, Varin A, Filomenko R, Lopez T, Athias A, Gambert P, Blache D, Thomas C, Gautier T, Lagrost L and Masson D. Liver x receptor regulates arachidonic acid distribution and eicosanoid release in human macrophages: a key role for lysophosphatidylcholine acyltransferase 3. *Arterioscler Thromb Vasc Biol* 2013; 33: 1171-1179.
- [32] Eto M, Shindou H, Koeberle A, Harayama T, Yanagida K and Shimizu T. Lysophosphatidylcholine acyltransferase 3 is the key enzyme for incorporating arachidonic acid into glycerophospholipids during adipocyte differentiation. *Int J Mol Sci* 2012; 13: 16267-16280.
- [33] Perez-Chacon G, Astudillo AM, Ruiperez V, Balboa MA and Balsinde J. Signaling role for lysophosphatidylcholine acyltransferase 3 in receptor-regulated arachidonic acid reacylation reactions in human monocytes. *J Immunol* 2010; 184: 1071-1078.
- [34] Kazachkov M, Chen Q, Wang L and Zou J. Substrate preferences of a lysophosphatidylcholine acyltransferase highlight its role in phospholipid remodeling. *Lipids* 2008; 43: 895-902.
- [35] Cheng L, Han X and Shi Y. A regulatory role of LPCAT1 in the synthesis of inflammatory lipids, PAF and LPC, in the retina of diabetic mice. *Am J Physiol Endocrinol Metab* 2009; 297: E1276-1282.
- [36] Rabini RA, Galassi R, Fumelli P, Dousset N, Solera ML, Valdiguie P, Curatola G, Ferretti G, Taus M and Mazzanti L. Reduced Na(+)-K(+)ATPase activity and plasma lysophosphatidylcholine concentrations in diabetic patients. *Diabetes* 1994; 43: 915-919.
- [37] Shi AH, Yoshinari M, Wakisaka M, Iwase M and Fujishima M. Lysophosphatidylcholine molecular species in low density lipoprotein of type 2 diabetes. *Horm Metab Res* 1999; 31: 283-286.
- [38] Galili O, Versari D, Sattler KJ, Olson ML, Mannheim D, McConnell JP, Chade AR, Lerman LO and Lerman A. Early experimental obesity is associated with coronary endothelial dysfunction and oxidative stress. *Am J Physiol Heart Circ Physiol* 2007; 292: H904-911.
- [39] Motley ED, Kabir SM, Gardner CD, Eguchi K, Frank GD, Kuroki T, Ohba M, Yamakawa T and Eguchi S. Lysophosphatidylcholine inhibits insulin-induced Akt activation through protein kinase c-alpha in vascular smooth muscle cells. *Hypertension* 2002; 39: 508-512.
- [40] Fang X, Gibson S, Flowers M, Furui T, Bast RC Jr and Mills GB. Lysophosphatidylcholine stimulates activator protein 1 and the c-Jun N-terminal kinase activity. *J Biol Chem* 1997; 272: 13683-13689.
- [41] Shindou H, Hishikawa D, Nakanishi H, Harayama T, Ishii S, Taguchi R and Shimizu T. A single enzyme catalyzes both platelet-activating factor production and membrane biogenesis of inflammatory cells. Cloning and characterization of acetyl-CoA: LYSO-PAF acetyltransferase. *J Biol Chem* 2007; 282: 6532-6539.
- [42] Li Z, Jiang H, Ding T, Lou C, Bui HH, Kuo MS and Jiang XC. Deficiency in lysophosphatidylcholine acyltransferase 3 reduces plasma levels of lipids by reducing lipid absorption in mice. *Gastroenterology* 2015; 149: 1519-1529.
- [43] Cash JG and Hui DY. Liver-specific overexpression of LPCAT3 reduces postprandial hyperglycemia and improves lipoprotein metabolic profile in mice. *Nutr Diabetes* 2016; 6: e206.

Recent progress of LPCATs in metabolic disease and cancer

- [44] Wang B, Rong X, Duerr MA, Hermanson DJ, Hedde PN, Wong JS, Vallim TQ, Cravatt BF, Gratton E, Ford DA and Tontonoz P. Intestinal phospholipid remodeling is required for dietary-lipid uptake and survival on a high-fat diet. *Cell Metab* 2016; 23: 492-504.
- [45] Patterson AD, Maurhofer O, Beyoglu D, Lanz C, Krausz KW, Pabst T, Gonzalez FJ, Dufour JF and Idle JR. Aberrant lipid metabolism in hepatocellular carcinoma revealed by plasma metabolomics and lipid profiling. *Cancer Res* 2011; 71: 6590-6600.
- [46] Ilan Y. Review article: novel methods for the treatment of non-alcoholic steatohepatitis - targeting the gut immune system to decrease the systemic inflammatory response without immune suppression. *Aliment Pharmacol Ther* 2016; 44: 1168-1182.
- [47] Yamazaki T, Wakabayashi M, Ikeda E, Tanaka S, Sakamoto T, Mitsumoto A, Kudo N and Kawashima Y. Induction of 1-acylglycerophosphocholine acyltransferase genes by fibrates in the liver of rats. *Biol Pharm Bull* 2012; 35: 1509-1515.
- [48] Tanaka N, Matsubara T, Krausz KW, Patterson AD and Gonzalez FJ. Disruption of phospholipid and bile acid homeostasis in mice with non-alcoholic steatohepatitis. *Hepatology* 2012; 56: 118-129.
- [49] Han MS, Park SY, Shinzawa K, Kim S, Chung KW, Lee JH, Kwon CH, Lee KW, Park CK, Chung WJ, Hwang JS, Yan JJ, Song DK, Tsujimoto Y and Lee MS. Lysophosphatidylcholine as a death effector in the lipoapoptosis of hepatocytes. *J Lipid Res* 2008; 49: 84-97.
- [50] Wu T, Zheng X, Yang M, Zhao A, Li M, Chen T, Panee J, Jia W and Ji G. Serum lipid alterations identified in chronic hepatitis B, hepatitis B virus-associated cirrhosis and carcinoma patients. *Sci Rep* 2017; 7: 42710.
- [51] Beier JI, Arteel GE and McClain CJ. Advances in alcoholic liver disease. *Curr Gastroenterol Rep* 2011; 13: 56-64.
- [52] Beilstein F, Lemasson M, Pene V, Rainteau D, Demignot S and Rosenberg AR. Lysophosphatidylcholine acyltransferase 1 is downregulated by hepatitis C virus: impact on production of lipo-viro-particles. *Gut* 2016; 66: 2160-2169.
- [53] Stanca E, Serviddio G, Bellanti F, Vendemiale G, Siculella L and Giudetti AM. Down-regulation of LPCAT expression increases platelet-activating factor level in cirrhotic rat liver: potential antiinflammatory effect of silybin. *Biochim Biophys Acta* 2013; 1832: 2019-2026.
- [54] Akagi S, Kono N, Ariyama H, Shindou H, Shimizu T and Arai H. Lysophosphatidylcholine acyltransferase 1 protects against cytotoxicity induced by polyunsaturated fatty acids. *FASEB J* 2016; 30: 2027-2039.
- [55] Cheng S, Chen H, Wang A, Xie M, Xie J, Osanai K, Zhao J, Xu Y, Xiong W and Zhou M. Lentiviral vector-mediated delivery of lysophosphatidylcholine acyltransferase 1 attenuates airway inflammation in ovalbumin-induced allergic asthmatic mice. *Asian Pac J Allergy Immunol* 2015; 33: 320-329.
- [56] Ahn WG, Jung JS, Kwon HY and Song DK. Alteration of lysophosphatidylcholine-related metabolic parameters in the plasma of mice with experimental sepsis. *Inflammation* 2017; 40: 537-545.
- [57] Taniguchi K, Hikiji H, Okinaga T, Hashidate-Yoshida T, Shindou H, Ariyoshi W, Shimizu T, Tomimaga K and Nishihara T. Essential role of lysophosphatidylcholine acyltransferase 3 in the induction of macrophage polarization in PMA-treated U937 cells. *J Cell Biochem* 2015; 116: 2840-2848.
- [58] Tanaka H, Zaima N, Sasaki T, Yamamoto N, Inuzuka K, Yata T, Iwaki T, Umemura K, Sano H, Suzuki Y, Urano T, Setou M, Unno N. Lysophosphatidylcholine acyltransferase-3 expression is associated with atherosclerosis progression. *J Vasc Res* 2017; 54: 200-208.
- [59] Paalvast Y, de Boer JF and Groen AK. Developments in intestinal cholesterol transport and triglyceride absorption. *Curr Opin Lipidol* 2017; 28: 248-254.
- [60] Abdelzaher E and Mostafa MF. Lysophosphatidylcholine acyltransferase 1 (LPCAT1) upregulation in breast carcinoma contributes to tumor progression and predicts early tumor recurrence. *Tumour Biol* 2015; 36: 5473-5483.
- [61] Grupp K, Sanader S, Sirma H, Simon R, Koop C, Prien K, Hube-Magg C, Salomon G, Graefen M, Heinzer H, Minner S, Izbicki JR, Sauter G, Schlomm T and Tsourlakakis MC. High lysophosphatidylcholine acyltransferase 1 expression independently predicts high risk for biochemical recurrence in prostate cancers. *Mol Oncol* 2013; 7: 1001-1011.
- [62] Uehara T, Kikuchi H, Miyazaki S, Iino I, Setoguchi T, Hiramatsu Y, Ohta M, Kamiya K, Morita Y, Tanaka H, Baba S, Hayasaka T, Setou M and Konno H. Overexpression of lysophosphatidylcholine acyltransferase 1 and concomitant lipid alterations in gastric cancer. *Ann Surg Oncol* 2016; 23 Suppl 2: S206-213.
- [63] Tan Y, Yin P, Tang L, Xing W, Huang Q, Cao D, Zhao X, Wang W, Lu X, Xu Z, Wang H and Xu G. Metabolomics study of stepwise hepatocarcinogenesis from the model rats to patients: potential biomarkers effective for small hepatocellular carcinoma diagnosis. *Mol Cell Proteomics* 2012; 11: M111.010694.

Recent progress of LPCATs in metabolic disease and cancer

- [64] Morita Y, Sakaguchi T, Ikegami K, Goto-Inoue N, Hayasaka T, Hang VT, Tanaka H, Harada T, Shibasaki Y, Suzuki A, Fukumoto K, Inaba K, Murakami M, Setou M and Konno H. Lysophosphatidylcholine acyltransferase 1 altered phospholipid composition and regulated hepatoma progression. *J Hepatol* 2013; 59: 292-299.
- [65] Shida-Sakazume T, Endo-Sakamoto Y, Unoza-wa M, Fukumoto C, Shimada K, Kasamatsu A, Ogawara K, Yokoe H, Shiiba M, Tanzawa H and Uzawa K. Lysophosphatidylcholine acyltransferase1 overexpression promotes oral squamous cell carcinoma progression via enhanced biosynthesis of platelet-activating factor. *PLoS One* 2015; 10: e0120143.
- [66] Mansilla F, da Costa KA, Wang S, Kruhoffer M, Lewin TM, Orntoft TF, Coleman RA and Birkenkamp-Demtroder K. Lysophosphatidylcholine acyltransferase 1 (LPCAT1) overexpression in human colorectal cancer. *J Mol Med (Berl)* 2009; 87: 85-97.
- [67] Xu B, Cheng Y, Yu G, Li W, Wan X, Zhou J and Wang Z. LPCAT1 promotes castration resistant prostate cancer progression by increasing PAF release and mRNA synthesis. *Oncotarget* 2018.
- [68] Du Y, Wang Q, Zhang X, Wang X, Qin C, Sheng Z, Yin H, Jiang C, Li J and Xu T. Lysophosphatidylcholine acyltransferase 1 upregulation and concomitant phospholipid alterations in clear cell renal cell carcinoma. *J Exp Clin Cancer Res* 2017; 36: 66.
- [69] Williams KA, Lee M, Hu Y, Andreas J, Patel SJ, Zhang S, Chines P, Elkahloun A, Chandrasekharappa S, Gutkind JS, Molinolo AA and Crawford NP. A systems genetics approach identifies CXCL14, ITGAX, and LPCAT2 as novel aggressive prostate cancer susceptibility genes. *PLoS Genet* 2014; 10: e1004809.
- [70] Wang B, Rong X, End P, Wang J, Fogelman AM, Martín MG, Alrefai WA, Ford DA and Tontonoz P. Phospholipid remodeling and cholesterol availability regulate intestinal stemness and tumorigenesis. *Cell Stem Cell* 2018; 22: 206-220.
- [71] Kurabe N, Hayasaka T, Ogawa M, Masaki N, Ide Y, Waki M, Nakamura T, Kurachi K, Kahyo T, Shinmura K, Midorikawa Y, Sugiyama Y, Setou M and Sugimura H. Accumulated phosphatidylcholine (16:0/16:1) in human colorectal cancer; possible involvement of LPCAT4. *Cancer Sci* 2013; 104: 1295-1302.