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Research progress, challenges and perspectives of phospholipids metabolism in the LXR-LPCAT3 signaling pathway and its relation to NAFLD (Review)

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Abstract. Phospholipids (PLs) are principle constituents of biofilms, with their fatty acyl chain composition significantly impacting the biophysical properties of membranes, thereby influencing biological processes. Recent studies have elucidated that fatty acyl chains, under the enzymatic action of lyso-phosphatidyl-choline acyltransferases (LPCATs), expedite incorporation into the sn-2 site of phosphatidyl-choline (PC), profoundly affecting pathophysiology. Accumulating evidence suggests that alterations in LPCAT activity are implicated in various diseases, including non-alcoholic fatty liver disease (NAFLD), hepatitis C, atherosclerosis and cancer. Specifically, LPCAT3 is instrumental in maintaining systemic lipid homeostasis through its roles in hepatic lipogenesis, intestinal lipid absorption and lipoprotein secretion. The liver X receptor (LXR), pivotal in lipid homeostasis, modulates cholesterol, fatty acid (FA) and PL metabolism. LXR's capacity to modify PL composition in response to cellular sterol fluctuations is a vital mechanism for protecting biofilms against lipid stress. Concurrently, LXR activation enhances LPCAT3 expression on cell membranes and elevates polyunsaturated PL levels. This activation can ameliorate saturated free FA effects *in vitro* or endoplasmic reticulum stress *in vivo* due to lipid accumulation in hepatic cells. Pharmacological interventions targeting LXR, LPCAT and membrane PL components could offer novel therapeutic directions for NAFLD management. The present review primarily focused on recent advancements in understanding the LPCAT3 signaling pathway's role in lipid metabolism related to NAFLD, aiming to identify new treatment targets for the disease.

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Abbreviations: ABCA1, ATP-binding cassette transporter A1; ApoB, apolipoprotein B; ATF-6, activating transcription factor-6; CTP, cytidine triphosphate; CCT, CTP: phosphocholine cytidylyltransferase; ERS, endoplasmic reticulum stress; FATP4, fatty acid transporter protein 4; FA, fatty acid; FFA, free fatty acid; HDL, high density lipoprotein; IRE-1α, inositol requiring enzyme-1α; LPC, lyso-phosphatidyl-choline; LPCATs, lyso-phosphatidyl-choline acyltransferases; LXR, liver X receptor; MBOAT, membrane-bound O-acyltransferase; MTTP, microsomal TG transfer protein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PC, phosphatidylcholine; PLs, phospholipids; PLTP, phospholipid transfer protein; PERK, protein kinase-like ER kinase; PEMT, phosphatidylethanolamine N-methyltransferase; PPAR, peroxisome proliferation-activated receptor; RXR, retinoic acid receptor; SCD-1, stearoyl-CoA desaturase 1; SFA, saturated fatty acids; SREBP-1c, sterol response element-binding protein 1a; TG, triglyceride; UPR, unfolded protein response; VLDL, very low density lipoprotein

Key words: NAFLD, LXR, LPCAT 3, ERS, NASH

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome, which is characterized by excessive fat deposition in hepatic cells (1,2), affecting over 1.7 billion individuals globally and representing a significant public health concern (3). Lifestyle changes have led to NAFLD becoming the predominant chronic liver disease in China (4). The advanced stages of NAFLD, particularly non-alcoholic steatohepatitis (NASH), are associated with escalating mortality rates (4,5). Consequently, the condition has garnered increasing global research attention, emphasizing the necessity of identifying preventative and therapeutic targets.

The pathogenesis of NAFLD is multifaceted and not entirely elucidated, encompassing metabolic, environmental, genetic and microbial factors (6-9). The prevailing conceptual framework posits NAFLD as a 'multiple hits' phenomenon (10). Central to NAFLD's etiology is elevated circulating free fatty acids (FFAs) and insulin resistance, culminating in excessive triglyceride (TG) accumulation in hepatocytes. FFAs are also implicated in lipotoxicity, oxidative stress and inflammation, contributing to progressive hepatic injury (10,11). Furthermore, recent studies indicated that a confluence of mechanisms, particularly in genetically susceptible individuals, plays a crucial role in NAFLD's onset and progression (12,13). Consequently, devising effective preventive and therapeutic approaches for NAFLD represents a pressing scientific challenge.

The pathophysiology of NAFLD is complex, marked by significant individual heterogeneity. Currently, no efficacious pharmacological treatments exist. Current therapeutic approaches, including weight management, intestinal glucagon-like peptide-1 agonists, sodium-glucose cotransporter inhibitors, peroxisome proliferator-activated receptor (PPAR) agonists, farnesoid derivative X receptor-bile acid axis modulators, hormonal therapies, lipid synthesis inhibitors, antioxidants, targeted apoptosis-targeting agents, anti-inflammatory drugs, microbiome modulators and anti-fibrotic treatment and combination therapies (14-17), have demonstrated limited clinical efficacy and are often accompanied by adverse effects, such as elevated serum transaminases, edema, gastrointestinal discomfort and increased liver burden (18,19). Given the complexity and interconnectedness of NAFLD's pathogenic factors, identifying effective therapeutic targets and pathways remains a formidable task.

Phospholipids (PLs) are the principal components of biofilms, and their biophysical membrane properties are largely determined by the composition of their fatty acyl chains, which significantly influences biological processes. It has been established that lyso-phosphatidyl-choline acyltransferase (LPCAT) plays a crucial role in catalyzing the integration of fatty acyl chains into the sn-2 site of phosphatidyl-choline (PC), profoundly impacting pathophysiology (20,21). Increasing evidence suggests that alterations in LPCAT activity are implicated in various diseases, including NAFLD, hepatitis C, atherosclerosis and cancers (22-24). Specifically, LPCAT3 is key in maintaining lipid homeostasis by regulating hepatic lipogenesis, intestinal lipid absorption and lipoprotein secretion (21). The liver X receptor (LXR) is instrumental in regulating metabolism of cholesterol, FAs and PLs, thereby playing a significant role in lipid homeostasis (25). LXR provides a mechanism to protect biofilms from lipid stress by altering PL composition in response to cellular sterol level fluctuations. Concurrently, LXR activation enhances LPCAT3 expression of LPCAT3 on cell membranes and increases the abundance of polyunsaturated PLs. This activation strategy can ameliorate saturated FFA-induced effects *in vitro* or endoplasmic reticulum stress (ERS) *in vivo*, arising from lipid accumulation in hepatic cells (24,26). Pharmacological regulation focusing on LXR, LPCAT and membrane PL may offer new avenues in NAFLD treatment. The present review mainly discussed the potential role of the LXR-LPCAT3 signaling pathway in NAFLD, aiming to identify novel targets and pathways that could facilitate the development of effective therapeutics.

2. Main metabolic pathways of PLs

Characteristics of PLs. PLs are composed of two hydrophobic fatty acyl chains and one hydrophilic head group. Their bilayer membrane structure plays a critical role in compartmentalizing intracellular contents and facilitating the formation of subcellular organelles, essential for various cellular processes (27,28). In signal transduction, PLs serve as matrices for bioactive molecules such as eicosanoids, lyso-phosphatidyl-choline (LPC), lysophosphatidic acid and diacylglycerol (DAG) (29,30). Glycerophospholipids, including PC, phosphatidylethanolamine and phosphatidylserine, constitute the main structure of mammalian cell membranes. PC, particularly abundant in mammalian cell membranes and organelles, accounts for ~40-50% of total PLs (27). In the liver, PLs primarily derive from DAG and phosphatidylethanolamine (Fig. 1).

Metabolic processing of PC

Biosynthesis of PC (Kennedy pathway). The Kennedy pathway, the primary route for PC synthesis, operates predominantly via the CDP choline pathway (31). This pathway involves three enzymatic reactions: Choline kinase catalyzes the conversion of choline to phosphocholine; CTP:phosphocholine cytidylyltransferase (CCT) then catalyzes the formation of cytidine diphosphate (CDP) choline, which subsequently forms PC under the catalysis of 1,2-DAG choline-phosphotransferase (32) (Fig. 2, left).

Remodeling of PC (Lands' cycle). Beyond the Kennedy pathway, the liver synthesizes PC through an alternative route, largely via the methylation of phosphatidylethanolamine by phosphatidylethanolamine N-methyltransferase (PEMT), contributing to ~30% of hepatic PC synthesis (33). Fatty acyl chains in PLs exhibit not only diversity in structure but also asymmetric distribution on each side of the molecule. In mammalian cells, the sn-1 position typically hosts saturated and monounsaturated FAs, while the sn-2 position is reserved for polyunsaturated FAs. This asymmetry arises from the deacylation-reacylation process known as Lands' cycle (33). Calcium-independent A2 [phospholipase A2 (iPLA2] mediates the deacylation step, removing saturated or monosaturated FAs from the sn-2 position of PCs. The subsequent reacylation step, characterized by the addition of polyunsaturated FAs at the sn-2 position, is regulated by LPCAT (24) (Fig. 2, right).

3. The integral role of LXRs in PL metabolism

LXRs are categorized into two subtypes: LXR α and LXR β. LXR α exhibits high expression levels in the liver, particularly in Kupffer cells, and is also present in the adrenal gland, small intestine, adipose tissue, lungs and kidneys. Conversely, LXR β is expressed ubiquitously throughout the body (34-37). LXRs feature a highly conserved structure, including a hydrophobic ligand-binding domain, a DNA binding domain, a ligand-independent N-terminal domain and a ligand-dependent C-terminal domain. LXRs form a heterodimer with the retinoic acid receptor (RXR), binding

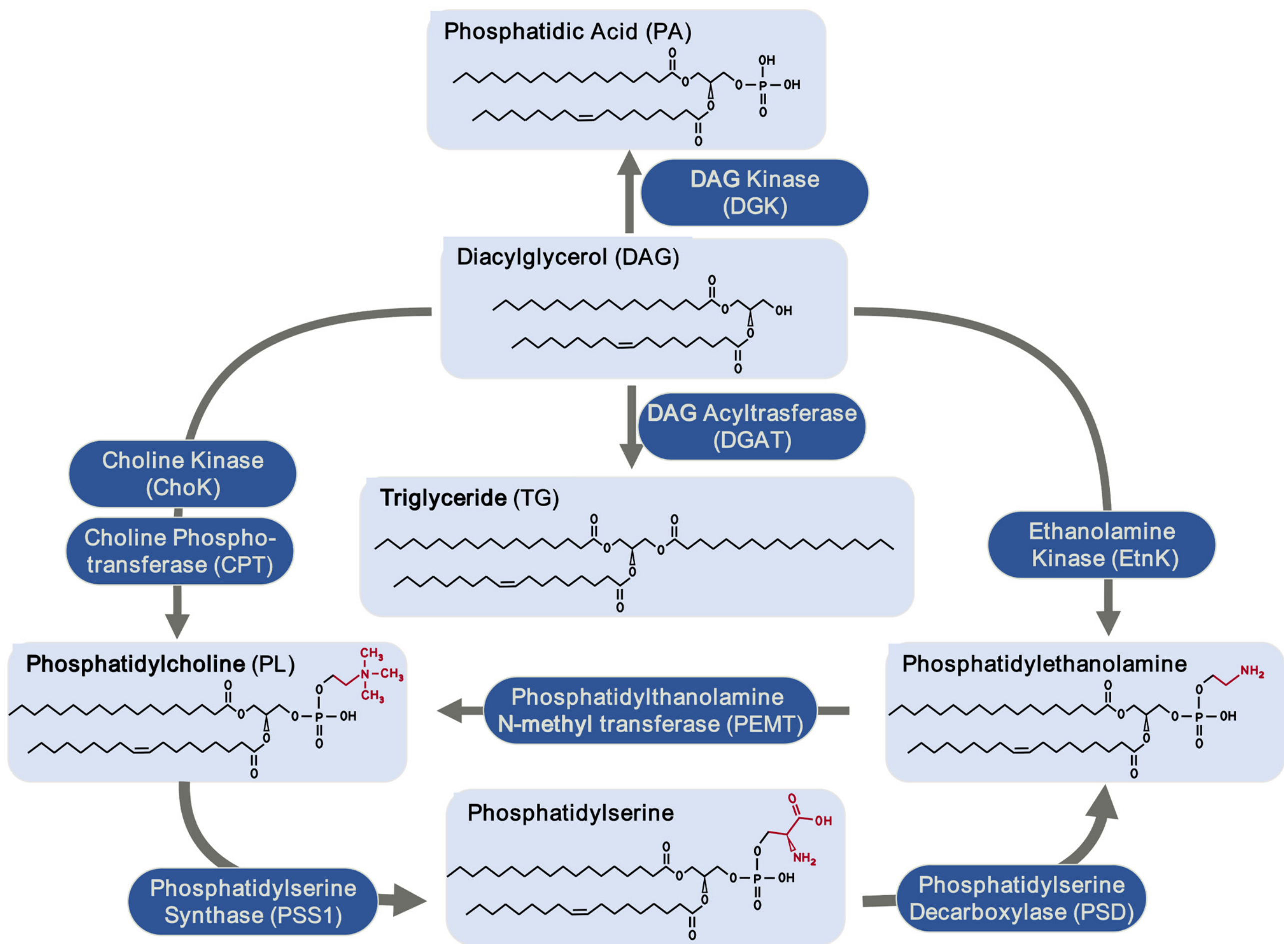

Figure 1. Hepatic phospholipid biosynthesis pathways. DAG is converted into PA by DGK. TG formation is catalyzed by DGAT. Phosphatidylethanolamine is synthesized under the action of EtnK and phospholipids are produced through the activity of ChoK and CTP: phosphocholine cytidylyltransferase (CPT). PL forms phosphatidylserine under the catalysis of PSS1, which in turn is converted into phosphatidylethanolamine by PSD. Additionally, phosphatidylethanolamine can be converted back into PL via PEMT. DAG, diacylglycerol; PA, phosphatidic acid; DGK, DAG kinase; TG, triglyceride; DGAK, DAG acyltrasferase; EtnK, ethanolamine kinase; ChoK, choline kinase; CPT, choline phosphotransferase; PL, phosphatidylcholine; PSS1, phosphatidylserine synthase 1; PSD, phosphatidylserine decarboxylase; PEMT, phosphatidylethanolamine N-methyl transferase.

to specific nucleotide sequences in the LXR response element to regulate the transcription of the target genes (38). In the nucleus, LXRs remain inactive and bound to DNA, forming complexes with corepressors such as the retinoic acid silencing regulator, thyroid hormone receptor, and nuclear receptor co-repressor proteins (38-40). These complexes can inhibit the transcriptional activity of LXR target genes in the absence of ligands. Ligand binding to the LXR/RXR heterodimer induces a conformational change in LXR. This change results in corepressor detachment and coactivator recruitment, thereby activating LXR and inducing expression of target genes (41-44).

Function of LXRs in lipid metabolism. The pivotal role of LXRs in lipid metabolism regulation is multifaceted: LXRs, as ligand-activated nuclear receptors, are central to lipid homeostasis (45); LXRs govern cellular and systemic cholesterol homeostasis through the regulation of cholesterol assimilation, cellular uptake and excretion, reverse transport and biosynthesis in various tissues and cells (39,46); LXRs enhance adipogenesis by regulating sterol response element-binding protein-1c (SREBP-1c) and its downstream genes in the hepatic tissues (47,48); LXRs also regulate the expression of membrane PL components through the induction of LPCAT3 (49) (Fig. 3).

LXR-dependent PL remodeling in the liver. Activation of LXRs facilitates very low-density lipoprotein (VLDL) secretion in mouse livers by regulating SREBF-1c and its downstream lipogenesis-related genes, and by enhancing the expression of phospholipid transfer proteins (PLTP). PLTP contributes to VLDL maturation by incorporating PLs into nascent VLDL, expanding lipoprotein particles (50). Given that PLs constitute a major component of lipoprotein particles, their efficiency influences lipoprotein production (51). Studies have demonstrated that LPCAT3 and PL remodeling significantly affect lipoprotein production, underscoring the importance of PL quantity and composition in lipoprotein secretion (52-54). Rong *et al* (26) demonstrated that LXRs regulate the membrane PL composition by activating LPCAT3, an enzyme that catalyzes the incorporation of polyunsaturated FAs at sn-2 position of lyso-phospholipids.

The induction of LPCAT3 expression in hepatic tissues is a critical aspect of LXR agonists' pharmacological

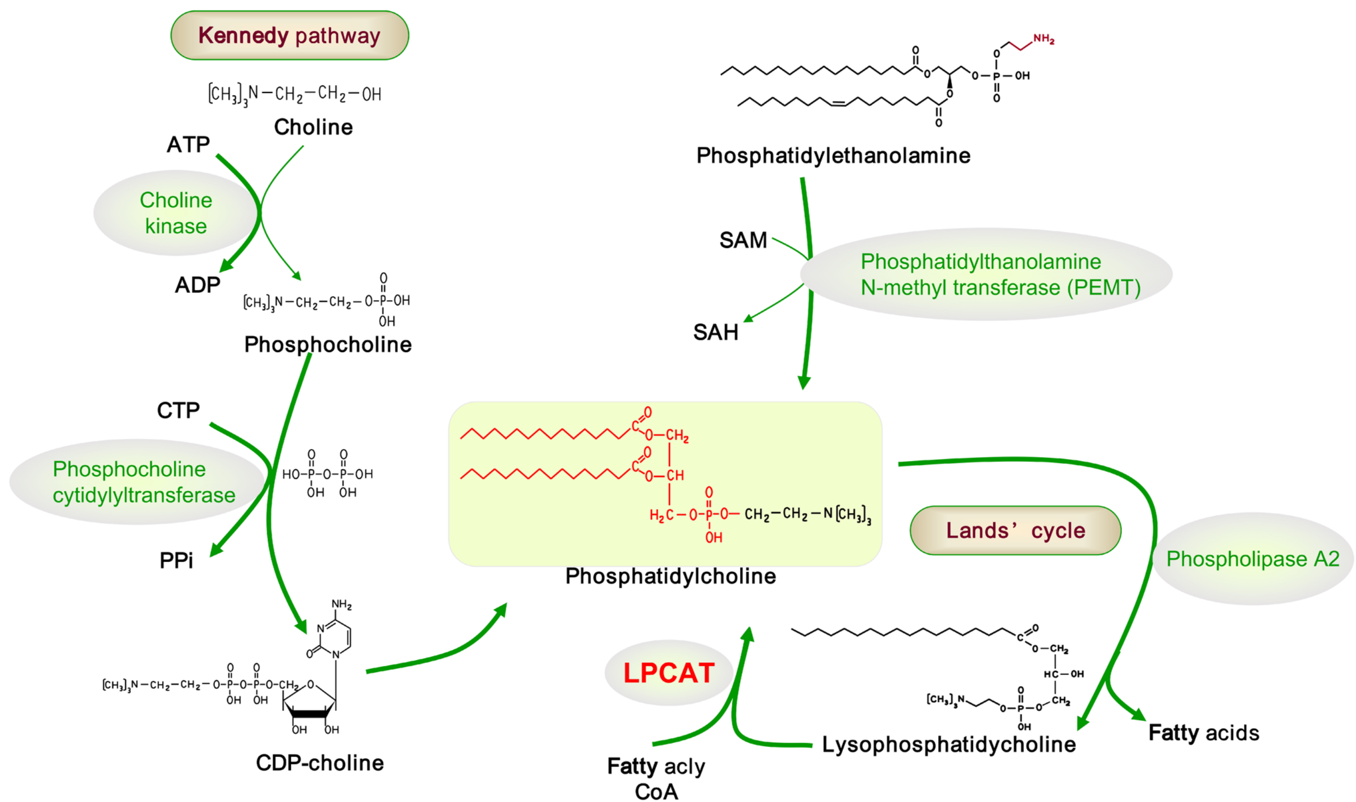

Figure 2. Pathways of phosphatidylcholine metabolism: Kennedy pathway and Lands' cycle. In the Kennedy pathway, choline kinase catalyzes the conversion of choline into PC. PC is then converted to CDP-choline by phosphocholine cytidylyltransferase, and subsequently, CDP-choline forms PC under the action of 1,2-diacylglycerol choline-phosphotransferase. Phosphatidylethanolamine synthesizes PC through PEMT. In phospholipids, saturated and monounsaturated fatty acids typically esterify at the sn-1 position, while polyunsaturated fatty acids are esterified at the sn-2 position. The asymmetric distribution of fatty acids at sn-1 and sn-2 is established through a deacylation-reacylation process known as the Lands' cycle. The deacylation step, catalyzed by phospholipase A2, removes saturated or monounsaturated fatty acids from the sn-2 position of PCs. The reacylation step, facilitated by LPCAT, incorporates polyunsaturated fatty acids at the sn-2 position of PC. PC, phosphocholine; PEMT, phosphatidylethanolamine N-methyl transferase; LPCAT, lyso-phosphatidyl-choline acyltransferase; ATP, adenosine-triphosphate; ADP, adenosine diphosphate; CTP, cytidine triphosphate; PPi, pyrophosphoric acid; CDP, cytidine diphosphate; SAM, S-adenosyl methionine; SAH, S-Adenosyl-L-homocysteine; CoA, coenzyme A.

action. The mice with liver-specific LPCAT3 gene knockout (LPCAT3-LKO) exhibited reduced VLDL secretion compared with controls following LXR agonist treatment, indicating that LXRs' ability to enhance hepatic VLDL production is contingent upon LPCAT3 activity (52). LPCAT3 mediates the integration of polyunsaturated FAs into PLs, which is essential for the processing and lipogenesis of SREBP-1c. As liver lipogenesis largely depends on interaction of LXRs with SREBP-1c, LPCAT3 activity also plays a role in hepatic lipogenesis (55). Notably, obese mice display elevated levels of polyunsaturated PLs in the endoplasmic reticulum, a consequence of increased LPCAT3 activity. Reducing expression of LPCAT3 in obese mice can attenuate the activation of the SREBP-1c pathway, thereby decelerating fat production and accumulation and delaying the progression of fatty liver disease (56).

4. Regulation of polyunsaturated fatty acid PLs by LPCAT3

The LPCAT family. LPCATs are categorized based on amino acid sequence variations into two distinct groups. LPCAT1 and LPCAT2, characterized by four conserved domain localization sequences known as LPA acyltransferase motifs 1-4 and an ER localization, are part of the acyl-glycerol phosphate acyltransferase family (57). LPCAT3 and LPCAT4, classified under the membrane-bound O-acyltransferase (MBOAT) family as MBOAT5 and MBOAT2 respectively, lack the LPA acyltransferase moiety but contain the MBOAT moiety (57).

Each LPCAT exhibits specific acyl-CoA substrate preferences: LPCAT1 favors 16:0-acyl-CoA for palmitoyl PC synthesis, whereas LPCAT2 utilizes acetyl-CoA or 20:4-acyl-CoA. LPCAT3 and LPCAT4 preferentially use polyunsaturated fat-acyl-CoA substrates, such as 18:2-acyl-CoA or 20:4-acyl-CoA and 18:1-acyl-CoA, respectively (57-60). Consequently, tissue-selective remodeling of membrane PC species may be optimized by leveraging the distinct substrate preferences of specific LPCAT isoforms in various tissues.

Impact of LPCAT3 on lipid metabolism via PLs composition regulation. LPCAT3, a direct transcriptional target of lipid-activated nuclear receptors such as LXR, PPAR-α and PPAR-γ, plays a crucial role in lipid homeostasis (26,61) (Fig. 3). Highly expressed in liver, intestinal and adipose tissues, LPCAT3 accounts for >90% of LPC acyltransferase activity, making it the most abundant LPCAT in the liver tissue (53). PC, the primary PL component of all plasma lipoproteins, and its FA chain synthesis are key regulators of lipoprotein secretion and lipid metabolism in hepatic and intestinal tissues (62). The diversity and saturation of fatty acyl

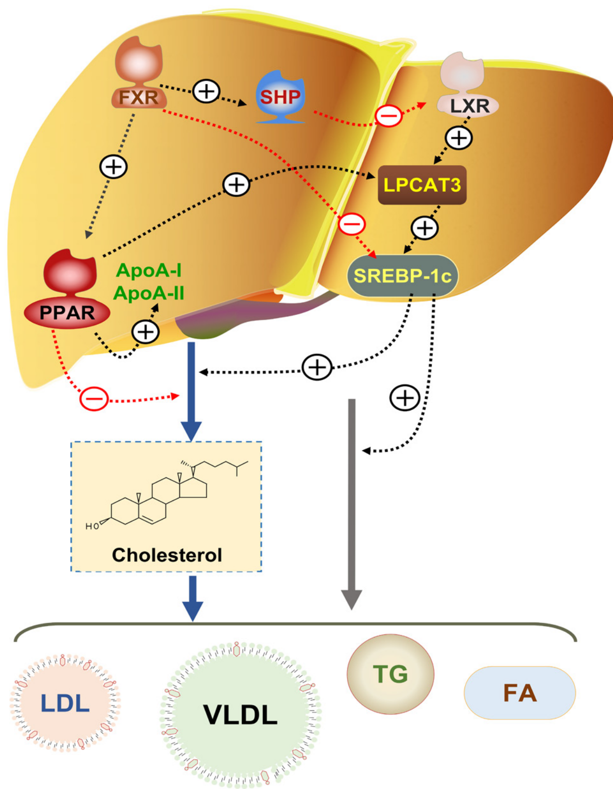

Figure 3. LPCAT3-dependent hepatic lipid metabolism pathway. In the liver, the FXR regulates cholesterol metabolism by upregulating the expression of PPAR. PPAR directly influences LPCAT3, thereby promoting the expression of SREBP-1c to regulate lipid metabolism. FXR also enhances the expression of SHP, leading to the downregulation of LXR. LXR, an upstream regulator of LPCAT3, upregulates LPCAT3 expression, which subsequently elevates SREBP-1c expression and promotes lipid metabolism. Additionally, FXR directly inhibits SREBP-1c expression, further influencing lipid metabolism. LPCAT3, lyso-phosphatidyl-choline acyltransferase 3; FXR, farnesoid X receptor; PPAR, peroxisome proliferation-activated receptor; SREBP-1c, sterol regulatory element-binding protein-1c; SHP, small heterodimer partner; LXR, liver X receptor alpha; FA, fatty acid; LDL, low density lipoprotein; TG, triglyceride; VLDL, very LDL.

groups in membrane PLs, attributable to the differences in double bond and single bonds, determine the biophysical properties of the cell membranes, including its fluidity, curvature and subdomain structure. These properties, in turn, influence biological processes involving membranes, such as signaling and protein transport (63). The important role of LPCATs in lipid metabolism and homeostasis has been corroborated through genetic model studies, and the regulation of a variety of PC species by LPCATs in different cells and tissues, thereby influencing membrane PL composition and affecting biological functions (20-22).

Role of LPCAT3 in regulating VLDL secretion through membrane polyunsaturated PLs composition. Studies have indicated that inducing acute LPCAT3-LKO in mice via adenovirus elevates plasma TG levels while concurrently reducing liver TG content (26,64). This phenomenon may be attributed to an increase in LPC, while enhances the expression of microsomal TG transfer protein (MTTP) and apolipoprotein B (ApoB), thereby facilitating the assembly and secretion of VLDL (64). By contrast, mice with acute overexpression of human LPCAT3 exhibited reduced VLDL secretion and liver TG levels, potentially due to low LPC levels no longer inhibiting FA β-oxidation in hepatic cells (65). These mice also presented elevated plasma levels of high-density lipoprotein (HDL) levels, enriched with protective ApoE. However, contradictory studies suggested that LPCAT3-deficient mice display decreased plasma TG levels, increased VLDL fat deposition and decreased secretion, leading to liver steatosis. This outcome might relate to the role of LPCAT3 activity and polyunsaturated PLs in influencing membrane surface fluidity and curvature, thus diminishing TG mobilization to VLDL (52,53).

The long-term effects of LPCAT3 activation or overexpression remain unclear. Permanent LPCAT3 deletion in mouse hepatocytes resulted in a metabolic phenotype distinct from the acute knockout. Unlike acute LPCAT3 knockout, chronic LPCAT3 knockout mice did not exhibit significantly higher LPC accumulation, possibly due to the redirection of LPC into the biosynthesis of both saturated and monounsaturated PCs (52,53).

A previous study revealed that hepatic deletion of genes involved in *de novo* PC synthesis in the liver (such as PEMT and CT-α) impairs VLDL secretion, as evidenced by reduced plasma ApoB protein levels (66). However, LPCAT3-deficient mice maintained stable plasma ApoB levels, suggesting preserved ApoB secretion functionality (52). Decreased plasma VLDL particles and TG-rich ApoB particles in the Golgi apparatus of LPCAT3-deficient mice underscore LPCAT3's influence on VLDL assembly: TG is assembled, low-fat ApoB particles are incorporated, and mature VLDL is produced. Mechanistically, these phenotypes are linked to diminished ER membrane mobility and altered curvature, stemming from the loss of linoleic acid and arachidonic acid PLs. The presence of these polyunsaturated PLs enhance membrane fluidity and dynamics (67,68). Proteomic studies have elucidated the composition of VLDL transport vesicles containing LPCAT3, indicating that LPCAT3 and the nascent VLDL particles originate from the ER and transit to the Golgi apparatus (52). Further investigations reveal that LPCAT3-mediated accumulation of polyunsaturated PLs in membrane, particularly at high local concentrations, facilitates efficient TG transfer (52,53).

Therefore, LPCAT3's modulation of linoleic acid and arachidonic acid PL composition in membranes plays a pivotal role in creating an environment conducive to lipid transport and substantial fat deposition during VLDL assembly.

Influence of LPCAT3 on SREBP-1c production via polyunsaturated PLs levels in the ER membrane. LXR activation significantly stimulates hepatic lipogenesis, primarily through the upregulation of genes such as SREBP-1c, fatty acid synthase, and stearoyl-CoA desaturase 1 (SCD-1) (25,48) (Fig. 3). Certain studies have reported that LXR activation promotes the post-translational processing of SREBP-1c by inducing LPCAT3 expression (50,55). The integration of polyunsaturated FAs into PLs in the ER membrane, mediated by LPCAT3, enhances SREBP-1c expression, thereby promoting adipogenesis. On the contrary, hepatocytes deficient in LPCAT3 exhibit reduced polyunsaturated PL levels in the ER, diminished nuclear SREBP-1c levels, and a muted adipogenic response to LXR agonist treatment (47,55). The specific role of ER membrane PL components in regulating the SREBP-1c pathway remains to be fully elucidated. Notably, the impact of PL metabolism on the SREBP1 and SREBP2 pathways varies by the tissue specificity. In the liver, LPCAT3 does

not selectively influence SREBP-1c due to the absence of corresponding target genes, while in the intestine, SREBP2 is significantly affected due to the presence of corresponding target genes (20,47,50,63). These findings suggested that membrane PL remodeling differentially modulates SREBP maturation in response to cellular lipids. The involvement of LPCAT3 and membrane lipid acyl chain composition in SREBP-1c processing is considered to hinge on the SREBP cleavage-activating protein, potentially influencing the transport of SREBP-1c from the ER to the Golgi matrix. The total cellular PL level also affects SREBP-1 activity (55). Inhibiting enzymes in the PL *de novo* biosynthesis pathway reduces total cellular PL levels, activating the SREBP1 process and leading to the mislocalization of sphingosine 1-phosphate and sphingosine 2-phosphate, thereby disrupting CopII-dependent ER-to-Golgi transport (69).

Under both physiological (such as feeding) and pathological (such as obesity) conditions, LPCAT3 is known to enhance SREBP-1c activity and lipogenesis (69). Mass spectrometry analysis revealed a selective increase in polyunsaturated PLs in the ER of both wild-type and obese mice during feeding, a change dependent on LPCAT3 activity. Inhibition of LPCAT3 activity in obese mice using adenoviral LPCAT3shRNA has been demonstrated to reduce SREBP-1c processing, slow down fat production and improve fatty liver symptoms (69). These findings suggested that LPCAT3 could be a potential target for NAFLD treatment.

Impact of LPCAT3 on lipogenesis through polyunsaturated PL levels. LPCAT3 is the most highly expressed LPCAT in adipose tissue (21). Eto *et al* (70) demonstrated that LPCAT3 may play a role in adipogenesis, with its expression and activity markedly increasing during adipocyte differentiation, as observed *in vitro* in studies using C3H10T1/2 cells. These mesenchymal stem cells have the capacity to differentiate into adipocyte-like cells. Correlating with gene expression changes, both PC and PE, as well as arachidonic PLs, were found to increase in adipocytes. Arachidonic acid in PLs, a substrate for eicosanoid biosynthesis, is considered as an endogenous ligand for PPAR-γ. It is posited that the enhancement of the endogenous lipid ligand PPAR-γ may result from the incorporation of arachidonic acid into PLs, a process mediated by LPCAT3 (70). Further studies indicated that LPCAT3 knockout in 3T3-L1 preadipocytes impairs lipogenesis and differentiation (71). Limiting LPCAT3 reduces levels of polyunsaturated PLs, such as linoleic acid and arachidonic acid PLs, and reduces the expression of adipogenesis-related genes, including SREBPs, PPAR-γ and C/EBPs. This mechanism involves regulation of the Wnt/β-catenin signaling pathway (71). Although these cell studies confirm the role of LPCAT3 in impaired adipogenesis, the specific effects of LPCAT3 on adipose tissue and systemic metabolism *in vivo* remain to be fully elucidated.

Role of LPCAT3 in intestinal lipid absorption by regulating PC levels. PC in the intestinal lumen has long been recognized for its essential role in lipid absorption. LPCAT3 is the predominant LPCAT in the intestinal tract, accounting for 80-90% of the total LPC acyltransferase activity (53,54). Previous studies have identified the significance of LPCAT3 in the lipid metabolism of the small intestine (54,72). Mice with systemic LPCAT3 knockout can be born normally but typically succumb to hypoglycemia and mortality shortly after birth, around postnatal day 2 (P2) (53). Similarly, mice with intestinal-specific LPCAT3 knockout, induced by Vilin-Cre, also experience hypoglycemia and increased mortality during lactation, highlighting the vital role of intestinal LPCAT3 l in neonatal survival (72). LPCAT3 activity is crucial in mediating intestinal fat absorption (54,72). Mice with intestinal LPCAT3 deficiency ($LPCAT3^{Vil-Cre}$) display reduced serum TG and TC levels, indicative of impaired uptake of FAs by intestinal cells and the secretion of smaller chylomicron particles. The absence of LPCAT3 predominantly affects intestinal lipid metabolism, rather than hepatic VLDL production. A deficiency in LPCAT3 leads to decreased levels of ApoB in chylomicrons and its accumulation in the intestine (73), suggesting that not only the lipid loading of chylomicrons is compromised, but their secretion is also impaired. The loss of intestinal LPCAT3 results in altered binding of linoleic acid and arachidonic acids to membrane PLs. This change, coupled with a significant increase in saturated and monounsaturated PCs, leads to reduced membrane fluidity, thereby impairing passive FA transport across the apical membrane of intestinal epithelial cells (73).

Li *et al* (54) demonstrated the impact of LPCAT3 deficiency on FA transport in the intestine, noting a decreased expression of FA transporters, including FA transporter (FAT/CD36) and FA transporter protein 4 (FATP4), in intestinal cells of LPCAT3 knockout mice. This reduction in transporter expression may contribute to impaired FA uptake. However, another study indicated that the loss of CD36 or FATP4 in the intestinal tract of mice does not appear to significantly alter FA intake (74). The potential connection between altered membrane fluidity and kinetics due to LPCAT3 deficiency and the transport and secretion of chylomicrons warrants further investigation.

In addition to impaired TG absorption, $LPCAT3^{Vil-Cre}$ mice also exhibit reduced serum cholesterol levels (54,72,75), potentially resulting from diminished production of intestinal chylomicrons and HDL. Niemann-Pick C1-like 1, a crucial protein in intestinal cholesterol absorption, is significantly reduced in LPCAT3-deficient intestinal tissues (76). The decrease in HDL levels in $LPCAT3^{Vil-Cre}$ mice has been attributed to lower ATP-binding cassette transporter A1 (ABCA1) expression and ApoA-I secretion (77). Notably, ~30% of total plasma HDL is generated via intestinal ABCA1 activity, as evidenced by mouse experiments (78). However, the extent to which LPCAT3 deficiency affects the expression of cholesterol transport-related genes and alters membrane PL components remains to be fully elucidated.

5. The role of lipo-apoptosis related to the LXR-LPCAT3-ERS signaling pathway in NAFLD

Connection between PL metabolism and lipo-apoptosis in NAFLD development. NAFLD has emerged as a significant global health issue. A proportion of NAFLD patients progress to NASH, marked by steatosis, hepatocyte death and inflammation. A positive correlation exists between serum FFAs, hepatocyte death and liver inflammation (79). Saturated FFAs can induce hepatocyte apoptosis, a process termed lipo-apoptosis, which is linked to the severity of NAFLD (80). Numerous studies have revealed that saturated fatty acids (SFAs) are more toxic than their unsaturated counterparts, leading to

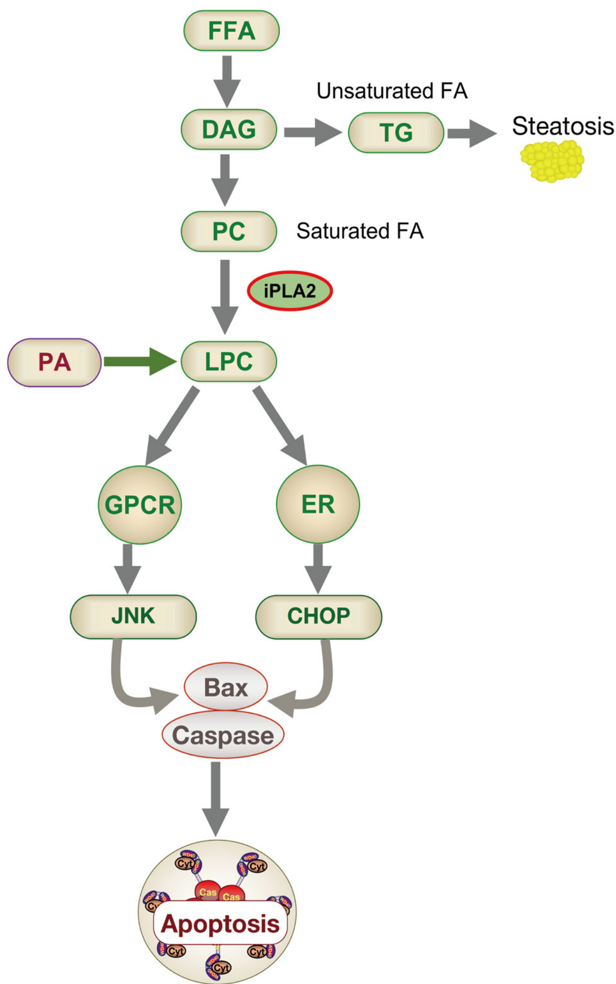

Figure 4. Schematic diagram of apoptosis model induced by fatty acid metabolism. DAG is produced when FFA entering the glycerol backbone can be converted into LPC or TG. Steatosis or hepatitis may occur when the TG pathway or the LPC pathway, respectively, is dominant. LPC can also be derived from PA. LPC may activate the JNK pathway by activating GPCR, and may also activate the ER stress pathway, thereby inducing cell apoptosis. DAG, diacylglycerol; FFA, free fatty acid; LPC, lyso-phosphatidyl-choline; TG, triglyceride; PA, phosphatidic acid; JNK, c-Jun N-terminal kinase; GPCR, G protein-coupled receptor; ER, endoplasmic reticulum; CHOP, C/EBP homologous protein; PC, phosphatidylcholine.

a progressive lipotoxic cascade (Fig. 4). Malhi *et al* (81) confirmed that SFAs induce JNK-dependent hepatocyte lipo-apoptosis by activating the pro-apoptotic proteins Bim and Bax.

Palmitic acid (PA) is an SFA. Gu *et al* (82) found that PA induced HepG2 cytotoxicity and apoptosis in a dose-dependent manner, and induced ER stress, which was manifested by increased phosphorylation of eIF2α and upregulation of IRE1α and CHOP. After PA treatment, BIP expression levels were slightly downregulated. Overexpression of Bip attenuated PA-induced ERS and resulted in a significant reduction in PA-mediated apoptosis, indicating that ERS is necessary for the lipotoxic effect of hepatocytes (82). Similarly, Guo *et al* (83) demonstrated that PA modulates intracellular signaling in mouse 3T3-L1 and rat primary preadipocytes, induces ERS, and leads to their apoptosis. It induces multiple ERS responses, including increased CHOP and GRP78 protein levels, XBP-1 mRNA splicing, and changes in eIF2 phosphorylation. It also increases the phosphorylation of JNK and ERK1/2 (83). In addition, oleic acid counteracts PA-induced hepatocyte death by converting PA to triglycerides and decreasing LPC levels, indicating that FFAs contribute to steatosis or lipid metabolism depending on the balance of saturated/unsaturated Fas (84).

Normally, FFAs undergo metabolism into PLs, in addition to being oxidized in mitochondria, esterified into triglycerides, and incorporated into lipoprotein complexes (85). For instance, saturated FFAs can combine with DAG, subsequently forming PC. LPC is a major plasma PL derived from PC through PLA2 activity (86). Under physiological conditions, LPCAT convert LPC back to PC, maintaining a dynamic equilibrium known as the Lands' cycle. However, previous studies have indicated that elevated hepatic LPC levels in NAFLD patients correlate with disease severity (87). In two small biopsy studies, liver LPC concentrations in NASH patients were higher compared with healthy controls (88,89). Intravenous LPC administration in ICR mice significantly increased *in vivo* AST/ALT levels, lobular hepatitis and apoptosis, albeit without steatosis (89), suggesting LPC's crucial role in hepatocyte lipo-apoptosis. Kakisaka *et al* (84) demonstrated that *in vivo* LPC administration induces hepatitis in mice, observing that PA converts to LPC, triggering hepatocyte apoptosis through G-protein-coupled receptor activation, mitochondrial events and JNK activation (Fig. 4). Han *et al* (89,90) identified LPC as an active metabolite of palmitate, noting its activation of ERS and JNK signaling, which promotes hepatocyte lipo-apoptosis. Exogenous LPC exposure mimics lipotoxic phenotypes observed in SFA overexposure, characterized by ERS markers, caspase activation and apoptosis (84,89). Exploring the role of LPC in PA-derived SFA-induced lipotoxicity, Kakisaka *et al* (84) used Huh-7 cells and isolated mouse and human primary hepatocytes. Their findings indicated that substituting LPC for PA leads to caspase-dependent cell death, c-JUN phosphorylation, JNK activation, increased PUMA expression and ERS induction, as evidenced by eIF2 activation (84). It was deduced that saturated FFA itself may not be necessary to induce hepatocyte cytotoxicity pathways as long as its downstream lipo-phospholipid metabolite LPC is present. While investigating LPC in SFA-induced lipotoxicity is a promising research direction, further studies are needed to clarify the direct relationship between these two mechanisms.

The breakdown and transformation of PLs have long been recognized as having a significant impact on the occurrence of NAFLD (91,92). Lipidomic analysis of liver tissues has revealed that levels of polyunsaturated PCs, including linoleic acid and arachidonic acid PCs, are significantly reduced in patients with non-alcoholic fatty liver and NASH compared with control groups (93). Hall *et al* (94) observed altered PL partitioning characteristics in both NASH animal models and human patients. Given that PC is the main component of PLs, alterations in the FA composition of structural PLs have been shown to protect hepatocytes from PA-induced ERS and associated lipotoxicity (95). In the context of NAFLD, the specific mechanism between PL metabolites, such as PC, PE, PS and lipid apoptosis needs further study.

Lipo-apoptosis related to LXR-LPCAT3-ERS pathway in NAFLD. It has been previously suggested that elevated levels of FFAs, especially SFAs, are key contributors to lipotoxicity,

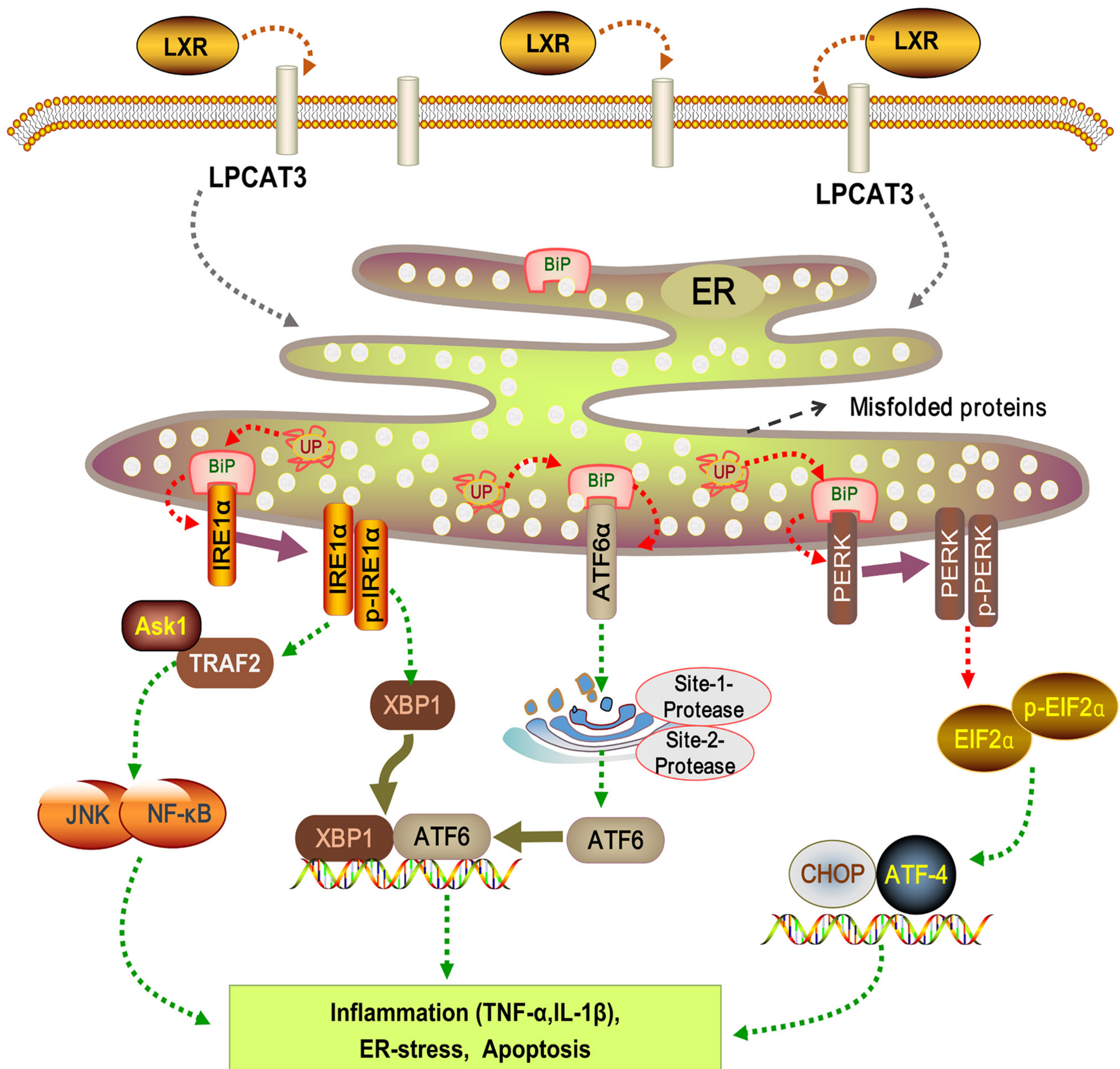

Figure 5. LXR-LPCAT3-ERS signaling pathway. LXR affects LPCAT3 on the cell membrane, thus regulating signaling molecules associated with the ER. ER stability is maintained by three UPR pathways: PERK, ATF6 and IRE1α. Phosphorylated of PERK activates downstream EIF2α phosphorylation, regulating the expression of downstream ATF4 and CHOP expression. ATF6 directly influences XBP1 expression. IRE1α modulates the expression of downstream molecules such as ASK1, JNK and NF-κB. Under pathological conditions, aberrant activation of these pathways can alter inflammatory factor expression, leading to ER stress and cell apoptosis. LXR, liver X receptor alpha; LPCAT3, lyso-phosphatidyl-choline acyltransferase 3; ERS, ER stress; ER, endoplasmic reticulum; UP, unfolded protein; UPR, UP response; PERK, protein kinase-like ER kinase; ATF, activating transcription factor; IRE1α, inositol requiring enzyme-1α; EIF2α, eukaryotic initiation factor 2 alpha; CHOP, C/EBP homologous protein; XBP1, X-box binding protein 1; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; NK-κB, nuclear factor kappa B; TRAF2, TNF receptor associated factor 2.

both in experimental models and in patients with NAFLD. In NASH patients, serum SFA levels are notably higher than in those with simple steatosis (96). SFAs are absorbed by hepatocytes and can directly induce hepatocellular toxicity, leading to lipo-apoptosis (97). Increasing evidence indicates that ERS is an upstream signal of SFA-induced cellular dysfunction and apoptosis. SFAs can increase the saturation of cell membrane phospholipids, thereby initiating unfolded protein response (UPR) and causing ERS (98-100). The JNK signaling pathway responds to prolonged ERS and activates downstream apoptotic pathways (99). SFAs have demonstrated the ability to potentially induce ERS in multiple cell types *in vitro*, including hepatocytes (98), pancreatic B cells (101), adipocytes (83) and CHO cells (102). Therefore, previous studies have identified ERS as a key factor in the pathogenesis of NAFLD.

The ER is crucial for protein processing, maturation, lipid synthesis and redox stability maintenance (103). Disruption of ER homeostasis triggers leads to ERS and activates the UPR. Chronic UPR activation can lead to inflammation and contribute to metabolic diseases, including obesity, type 2 diabetes, liver disease and atherosclerosis (102). Elevated FFA levels can induce ERS and UPR, potentially linked to alterations in ER membrane composition (102,104) (Fig. 5). Following FFA exposure, ER stress is initiated via UPR,

primarily mediated by three transmembrane protein pathways (105-107). Protein kinase RNA-like ER kinase (PERK) pathway: PERK activation and subsequent C/EBP homologous protein (CHOP) induction lead to apoptosis. Inositol-requiring enzyme-1α (IRE-1α) pathway: Activated IRE-1α interacts with tumor necrosis factor receptor-associated factor 2 and signal-regulating kinase 1, impacting JNK activation, cell apoptosis, NF-κB activation and downstream inflammatory factors expression. Activating transcription factor-6 (ATF-6) pathway: N-terminal phosphorylation of ATF-6 activates NF-κB and triggers inflammation (107,108). ERS plays a significant role in NAFLD progression. These pathways induce the expression of inflammatory cytokines (TNF-α and IL-1β), mediate inflammatory response, promote cell apoptosis, and exacerbate liver injury and fibrosis (109) (Fig. 5). Importantly, activation of JNK has been identified as a central mediator of FFA-induced hepatocyte apoptosis.

In vitro studies across various cell types have revealed that excessive exposure to SFAs enhances pro-inflammatory cytokine expression, disrupts insulin signaling, and initiates apoptosis, marked by ER damage and oxidative stress (110-113). Conversely, monounsaturated fatty acids predominantly lead to steatosis and triglyceride formation, without inducing apoptosis (111,114). A particular study focused on the impact of increased PL saturation in cell membranes (115). This research examined the functions of SCD-1, involved in desaturating SFAs for lipid biosynthesis, and LPCAT3, known for its preferential integration of polyunsaturated FAs into PCs. Notably, SCD-1 and LPCAT3 knockout cells exhibited marked PL saturation and UPR activation even in the absence of SFA supplementation. This was evidenced by increased X-box binding protein splicing and PERK phosphorylation, effects that were intensified with the combined knockout of LPCAT3/SCD-1 and additional palmitate supplementation (115). These findings underscore the importance of incorporating unsaturated FAs into PLs for maintaining ER membrane functionality, highlighting that SFA overexposure can disrupt this balance. Further research on the mechanism and role of SFA in controlling the composition of cell membrane phospholipids is of great significance for establishing a complete lipotoxic cell death mechanism.

Studies have identified that LXR activation can increase the expression of cell membrane LPCAT3 and the abundance of polyunsaturated PLs, thereby improving ERS caused by saturated FFA *in vivo* and *in vitro* or liver lipid accumulation *in vivo* (26,45). Rong *et al* (26) discovered that LPCAT3 plays a pivotal role in maintaining ER homeostasis by regulating membrane PLs composition. This maintenance is evident both *in vitro*, where LPCAT3 inhibits ERS induced by FFAs, and *in vivo*, as demonstrated by reduced liver lipid accumulation in ob/ob mice. These effects are manifestations of LPCAT3's mediation of LXR activation and its function as an LXR target. Enhanced LPCAT3 expression, prompted by LXR activation, fosters an increase in polyunsaturated FAs that integrate with PLs, thereby reducing ER membrane saturation. By contrast, acute liver LPCAT3 knockout in mice, facilitated via adenovirus, exacerbates ERS (26). Furthermore, impaired LPCAT3 activity can elevate liver inflammation and modulate c-Src activity by altering membrane microdomain components (116). The activity of LPCAT3 influences arachidonic acid levels, which are instrumental in the production of prostaglandin E2, a lipid inflammatory mediator contributing to inflammation (117). A recent study highlighted that inhibiting the SCAP/SREBP pathway exacerbates liver damage and carcinogenesis in NASH mice (118). The underlying mechanism involves not only the inhibition of FA synthesis but also a disruption in FA incorporation into PC due to downregulation of LPCAT3. This alteration in FA composition leads to ERS and hepatocellular damage. It was also found that the activity of LXR, a key transcription factor that regulates LPACT3 expression, was downregulated in hepatocytes of PTEN/SCAP double-knockout mice, and LXR agonists restored the expression of LPCAT3 in hepatocytes of PTEN/SCAP double-knockout mice. Therefore, LXR-mediated LPCAT3 expression was suppressed in the livers of PTEN/SCAP double-knockout mice, which may be partly responsible for the reduced number of PCs containing PUFAs (118).

Jiang *et al* (119) investigated the impact of LPCAT3 on serum lipid levels through systemic knockdown, as well as intestinal and liver-specific knockouts in mice. It was revealed that these alterations were primarily associated with a decrease in polyunsaturated PC on the plasma membrane. By contrast, Feng *et al* (71) posited that suppression of LPCAT3 attenuates lipid production in 3T3-L1 cells via activation of the Wnt/β-catenin signaling pathway, a finding echoed by Rong *et al* (52). LPCAT3 is also implicated in the biosynthesis of inflammatory lipid mediators in humans (117). Cell and animal studies have demonstrated that LPCAT3 expression is related to the mitigation of ERS and inflammation in response to saturated Fas (26). LPCAT3 knockdown leads to the accumulation of LPC in the liver, which enhances the production of VLDL through upregulated expression of MTTP (64). A previous genome-wide association study highlighted a significant link between genetic variations at the LPCAT3 locus and cellular FAs composition, underscoring the essential role of LPCAT3 in human PL component regulation (120).

Rong *et al* (52) have highlighted the critical role of LPCAT3-mediated arachidonic acid accumulation in PC for the production of TG-rich lipoproteins. Their prior research indicated that an acute decrease in LPCAT3 in the liver of obese mice exacerbated lipid-induced ERS (26). Interestingly, it was also observed that LPCAT3 gene deletion in the liver did not affect the expression of ERS markers (121). These findings suggested a potential compensatory response in membrane components to mitigate the induction of ERS when LPCAT3 is chronically deleted. A study from Xiang *et al* (122) demonstrated that the LXR α-LPCAT3 pathway can regulate ER stress to ameliorate liver damage in NASH.

In a previous study, LPCAT3 expression was reduced in the liver in a mouse model of HDF-induced NASH (123). To confirm the protective role of LPCAT3 in lipotoxicity, the LPCAT3-overexpressing Huh7 cells (LPCAT3-OE) were established. In LPCAT3-OE cells, PA-induced expression of CHOP, a transcription factor that serves as a marker of ERS, was significantly reduced. Furthermore, the phosphorylation of eIF2α and PA-induced cell death were significantly reduced in LPCAT3-OE cells compared with WT cells. Finally, PA-induced LPC increase in LPCAT3-OE cells was significantly attenuated compared with WT cells. In-depth mechanistic research demonstrated that PA-induced

hepatocyte death under LPCAT3 depletion is performed by a caspase-independent mechanism and is mediated by LPC (123). These results suggested that LPCAT3 may be a therapeutic target for NASH by reducing hepatocyte death.

LXR functions as an upstream regulator of LPCAT3. LPCAT3 itself is pivotal in PL metabolism, governing the physiological conversion between LPC and PC. Under pathological conditions, the role of LPCAT3 extends beyond influencing the composition of the endoplasmic reticulum membrane to impacting FA metabolism. This impact is a crucial factor in ERS. Therefore, the stable modulation of ERS by the LXR-LPCAT3 pathway is vital in maintaining normal adipocyte metabolism in the liver. Among the existing studies, research on the regulation of endoplasmic reticulum stress by LXR-LPCAT3 is available, but there is no clear experimental study to fully elucidate the role of LXR-LPCAT3-ERS pathway in the development of NAFLD. It is anticipated that more experiments will be conducted in the future to clarify this mechanism and provide new targets for the treatment of NAFLD.

6. Controversy and prospects

The significance of the LXR-LPCAT3 signaling pathway in NAFLD has not been extensively studied, and the existing research on LPCAT3 presents some controversial findings.

While some researchers posit that LPCAT3 mitigates ERS and inflammation, others argue that inhibiting LPCAT3 expression exacerbates these conditions. Rong *et al* (26) suggested that LXR activation leads to increased LPCAT3 expression, which in turn reduces the saturation of ER membrane. On the contrary, acute liver-knockout of LPCAT3 is associated with aggravated ERS, and inhibiting LPCAT3 activity appears to enhance liver inflammation. Adding another dimension to this discourse, Wang *et al* (124) observed that disruptions in LPCAT3-dependent sphingomyelin and cholesterol metabolism in Apc^{min} mice promote tumor formation, suggesting broader implications of LPCAT3 beyond NAFLD.

Some researchers proposed that LPCAT3 facilitates adipogenesis, and thus suppressing LPCAT3 expression could reduce adipogenesis. Rong *et al* (52) highlighted that LPCAT3-mediated accumulation of arachidonic acid in PC is essential for the production of TG-rich lipoproteins. Li *et al* (54) suggested that inhibiting intestinal LPCAT3 might be an effective strategy for hyperlipidemia treatment. In obese mice, the increase in LPCAT3 expression leads to a selective rise in polyunsaturated PLs in ER; consequently, inhibiting LPCAT3 activity can reduce the activation of SREBP1c pathway, slow down fat production, and delay the progression of fatty liver (56). LXR activation is known to promote the post-translational processing of SREBP-1c by inducing LPCAT3 expression, where LPCAT3's integration of polyunsaturated FAs into PLs aids in SREBP1c processing and lipid formation. Conversely, LPCAT3 deficiency in hepatocytes leads to reduced levels of polyunsaturated PLs in the ER, lowered nuclear SREBP-1c levels, and a decreased adipogenic response to LXR agonist treatment (55). Studies using LPCAT3shRNA adenovirus in obese mice have demonstrated a reduction in SREBP-1c processing, a slowdown in fat production, and an improvement in fatty liver condition (69). Additionally, LPCAT3 knockout in 3T3-L1 preadipocytes impairs fat generation and differentiation (71). LPCAT3 inhibition decreases levels of polyunsaturated PLs, such as linoleic acid and arachidonic acid PLs, and reduces the expression of adipogenesis-related genes expression including SREBPs, PPAR-γ and C/EBPs, with the mechanism being related to the regulation of the Wnt/β-catenin pathway (71). Feng *et al* (71) revealed that LPCAT3 deficiency attenuates lipid production in 3T3-L1 cells by activating the Wnt/β-catenin signaling pathway, a finding corroborated by Rong *et al* (52). Furthermore, LPCAT3 is considered to be directly involved in the biosynthesis of inflammatory lipid mediators in humans (117).

LXR can modulate adipogenesis-related factors through the regulation of LPCAT3. LPCAT3 itself influences FA metabolism and the saturation level of the ER membrane. Research has demonstrated that saturated FAs can induce hepatocyte lipo-apoptosis through JNK-dependent activation of pro-apoptotic proteins Bim and Bax (81). ERS is recognized as a critical factor in FFA-induced apoptosis. However, the specific role of the LXR-LPCAT3-ERS pathway in fat apoptosis within the context of NAFLD remains incompletely understood, necessitating further experimental research to elucidate the underlying mechanisms.

At present, the international and domestic research on LPCAT3 has not converged to a unified conclusion, highlighting the need for more studies to clarify its critical role. Questions such as whether receptors other than LXR, PPAR-α and PPAR-γ regulate LPCAT3 expression, and whether LPCAT3 is involved in other physiological and pathological processes beyond ER stress and inflammation, remain open for investigation. These areas warrant in-depth exploration. Therefore, a detailed examination of the LXR-LPCAT3 signaling pathway's role in NAFLD is essential. Such research could provide a foundational understanding of NAFLD pathogenesis and hold significant theoretical and practical value in advancing the treatment of NAFLD.

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Authors' contributions

JW contributed to acquisition, analysis, interpretation and drafted the manuscript. LL, YF, YZ and JL contributed to acquisition and analysis. YL contributed to conception and design and critically revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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