# Lipid alterations in chronic liver disease and liver cancer

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## Summary

**Lipids are a complex and diverse group of molecules with crucial roles in many physiological processes, as well as in the onset, progression, and maintenance of cancers. Fatty acids and cholesterol are the building blocks of lipids, orchestrating these crucial metabolic processes. In the liver, lipid alterations are prevalent as a cause and consequence of chronic hepatitis B and C virus infections, alcoholic hepatitis, and non-alcoholic fatty liver disease and steatohepatitis. Recent developments in lipidomics have also revealed that dynamic changes in triacylglycerols, phospholipids, sphingolipids, ceramides, fatty acids, and cholesterol are involved in the development and progression of primary liver cancer. Accordingly, the transcriptional landscape of lipid metabolism suggests a carcinogenic role of increasing fatty acids and sterol synthesis. However, limited mechanistic insights into the complex nature of the hepatic lipidome have so far hindered the development of effective therapies.**

## Introduction

Liver cancer is the fourth leading cause of cancer-related deaths worldwide,[1] and incidence and mortality rates are steadily increasing.[2] It is estimated that, by 2025, more than 1 million people will be affected by primary liver cancer annually,[3] posing a severe health challenge and societal burden. The most frequent types of primary liver cancer are hepatocellular carcinoma (HCC), accounting for up to 90%[4] of all cases, and cholangiocarcinoma (CCA), accounting for 10-15%.[5,6] The complex heterogeneity of these malignancies makes their early diagnosis and the development of therapies difficult. The common risk factors for liver cancer development are chronic HBV[4] and HCV infections (whose frequency has decreased considerably due to successful vaccination programmes and antiviral drugs),[7] alcohol abuse,[1] and metabolic diseases including non-alcoholic fatty liver disease (NAFLD),[8] ranging from simple steatosis to non-alcoholic steatohepatitis (NASH),[8] obesity,[1] and diabetes mellitus.[1] Additional risk factors include aflatoxin exposure in HCC,[1] and inflammation of the biliary tract in CCA,[9] with underlying causes including primary sclerosing cholangitis (PSC), cholestasis, bile stones and liver fluke infestation.

Metabolic alterations are a well-established hallmark of cancer.[10] The liver is the central organ for metabolism in the body[11–15]; thus, metabolic processes are often highly altered in liver cancer (reviewed in[16]). Distinct metabolic alterations have been uncovered in glucose, nucleotide, amino acid, and lipid metabolism in liver cancer.[16] Dysregulation of lipids plays important roles in both the development[17] and the progression[18] of liver cancer, which is a consequence of lipids being a vast and multifarious group of complex structured biomolecules. Lipids are involved in diverse biological processes in the body from energy storage[19] and metabolism,[20] to epigenetic regulation,[21] signal transduction,[22] immunoregulation,[23] inflammation,[24] and cell-cell recognition.[25]

The study of the lipidome and its dynamic nature used to pose a significant technical challenge. However, advances in mass spectrometry and chromatography techniques in the past decade have provided deeper insights into the metabolic heterogeneity and biological function(s) of the lipidome in both normal homeostasis and disease.[26–29] In this review, we will highlight the major lipidomic rearrangements that occur in the development and progression of liver cancer, focusing on lipids structural function and roles in energy storage and signal transduction.

## The origin and role(s) of hepatic lipids

Fatty acids (FAs), including carboxylic acids with a chain from 2 to 36 carbon atoms,[28] and cholesterol, consisting of 4 linked hydrocarbon rings,[30] are the fundamental building blocks of all lipids. The hepatic FA pool is mainly dependent on the FA uptake of serum non-esterified FAs from dietary sources[31] (in the fed state) or adipose tissue lipolysis[31,32] (in the fasting state) (Fig. 1). However, 15-25% of all FAs originate from a process termed *de novo*

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lipogenesis (DNL).[32,33] This process allows for FA synthesis up to the Δ9 position, while other FAs need to be taken up from dietary sources.[34,35] Contrary to FAs, the majority (80%) of cholesterol is synthesised internally, and almost 50% of cholesterol synthesis is controlled by the liver.[36] With a body mass of 70 kg, a human contains around 100 grams of cholesterol with a synthesis rate of 1.2 grams per day.[37] Whereas cholesterol can be sufficiently synthesised, the dietary intake can range from 300-500 mg per day.[37] FA and cholesterol are the backbone of a very diverse group of biomolecules that can be classified based on their structure, chemical properties (such as hydrophobicity or hydrophilicity), and biological function(s)[30] (Fig. 1).

## Energy storage

The human body stores energy as fat and carbohydrates. The neutral storage of FAs in the healthy liver is in the form of triglycerides (TGs), which are 3 FAs attached to a glycerol moiety, and sterol esters (SEs), in which FA is esterified to sterol.[30] Neutral lipids (SEs and TGs) are stored in lipid droplets, and in a healthy liver, these lipids should not exceed 5%.[38] FAs stored in TGs and SEs can be utilised at any time during liver homeostasis to generate energy (ATP) via fatty acid oxidation (FAO) or be transported to other organs in very-low-density lipoprotein.

### Key points

- Lipidomic alterations are a common feature of primary liver cancers (hepatocellular carcinoma and cholangiocarcinoma) and their risk factors.
- Unique changes in the lipid landscape of hepatocellular carcinoma and cholangiocarcinoma allow for differential diagnosis of these malignancies.
- Hepatocellular carcinoma and cholangiocarcinoma show differential dependency on *de novo* lipogenesis.
- Transcriptional deregulation of lipid metabolism differs between hepatocellular carcinoma and cholangiocarcinoma.

## Structural lipids

Glycerophospholipids, sphingolipids, and cholesterol are major building blocks of the cellular membrane (Fig. 1). Glycerophospholipids include phosphatidylcholine (PC), phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidic acid. PC accounts for more than 50% of the phospholipids in most eukaryotic membranes.[39] The second most abundant lipid in the mammalian membrane is cholesterol, which accounts for 30% of lipids, and increases the lipid-packing density to maintain a high membrane fluidity.[40] Lastly,
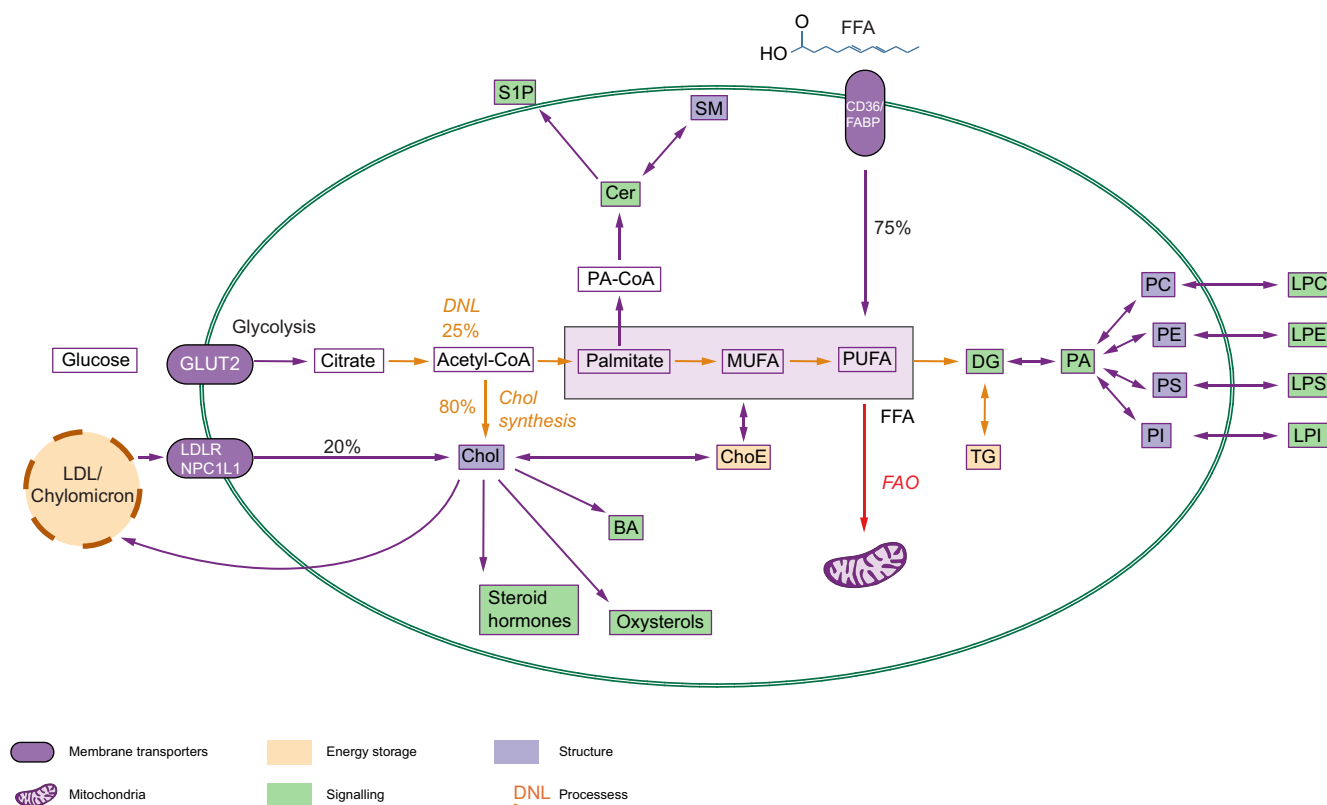


Fig. 1. **Simplified representation of the major metabolic pathways responsible for the uptake, transport, synthesis, and utilisation of lipids in the liver.** FA and cholesterol are the building blocks of most complex lipids. They can either be synthesised (orange arrows) via DNL (up to 25% of FA pool) and cholesterol synthesis (up to 80% of cholesterol pool) or they can be taken directly from the circulation. FA are subjected to FAO (red arrow) via a series of catabolic reactions, which are carried out in the mitochondria to generate ATP or used to form complex lipids. Lipids play structural (blue), signalling (green) or energy storage (yellow) functions. BA, bile acids; Cer, ceramides; Chol, cholesterol; ChoE, cholesterol esters; DG, diglyceride; DNL, *de novo* lipogenesis; FAO, fatty acid oxidation; FFA, free fatty acids; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; LPI, lysophosphoinositide; LPS, lysophosphatidylserine; MUFA, monounsaturated FA; PA, phosphatidate; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphoinositide; PS, phosphatidylserine; PUFA, polyunsaturated FA; S1P, sphingosine-1-phosphate; SM, sphingomyelin; TG, triglyceride.

sphingomyelin (SM) is the most abundant sphingolipid in mammalian cells and this lipid plays a crucial role in the formation of sterol-enriched ordered membrane domains and in cell-cell signalling.[39]

## Signalling molecules

Lipids act as first (extracellular) and second (intracellular) messengers in signal transduction and molecular recognition processes (reviewed in[39,41]). As such, membrane glycerolipids and sphingolipids transduce signals through hydrolysis to generate bioactive molecules: ceramides and sphingosine-1-phosphate (S1P),[42] while steroids (oxysterols, bile acids [BAs], steroid hormones) and FAs interact directly with receptors,[43–47] such as CD36 (FA translocase) (Fig. 1).

## Lipid alterations in liver diseases associated with the development of liver cancer

Prominent steatosis is caused by FA uptake and DNL exceeding FAO and secretion,[48–50] and is a shared feature underlying several risk factors of liver cancer. Accordingly, increased intrahepatic lipid accumulation is observed in viral hepatitis,[51,52] alcoholic hepatitis,[53] and among individuals suffering from metabolic diseases (obesity,[54] diabetes,[55] and NAFLD[56,57]), all of which pose a risk for liver cancer development. Conversely, steatosis is rarely observed alongside PSC or primary biliary cholangitis,[58] which are conditions associated with BA deregulation.[59,60]

## Viral hepatitis

HBV and HCV infections are important risk factors for liver cancer development. HBV is the main aetiology for HCC in most regions of Asia, Africa, and South America. HCV is the predominant cause in Western Europe, North America, and Japan.[1]

Hepatic steatosis is often associated with both HBV and HCV infections,[51,52,61] as well as being observed in HBx (HBx protein is crucial in HBV tumorigenesis) transgenic[62,63] and HCV transgenic mouse models.[64] Hence, viral hepatitis leads to prominent changes in both the serum[61] and hepatic (tumour and tumour-adjacent compartments)[65] lipidomes (Table 1). Indeed, the blood FA composition is significantly altered in HBV- and HCV-infected patients. As such, serum levels of saturated FAs (SFAs) and monounsaturated FAs (MUFAs) are significantly increased[66–68] in HBV-positive patients, and increase in parallel with disease severity.[67,69] Concurrently, the class of poly-unsaturated FA (PUFAs) is depleted.[66–68] This change in FA composition is also observed in mouse HBV-positive liver tumours.[70] Moreover, PUFAs are necessary for HCV particle replication[71] as knockdown of fatty acid desaturase 2 (FADS2) - the first step in PUFA synthesis – impairs HCV virus particle production. Similarly, FAs are involved in stabilisation of the HBx protein.[72] HBx can also increase the cholesterol levels in HCC cells, both in vitro[73] and in vivo.[74] Conversely, in both patients and HCV transgenic mice, cholesterol,[66,67] TG,[66] and lysophosphatidylcholine (LPC)[75,76] of longer FA chains have been shown to be significantly depleted.[77]

## Alcohol-related liver disease

Excessive alcohol consumption is the main aetiological factor for liver cancer development in Central and Eastern Europe.[1] In patients with alcohol-related liver disease (ALD), FAs that accumulate in the liver are predominantly released from the adipose tissue.[78] Ethanol increases the uptake of FAs by the liver in vivo[79] and in vitro[80] leading to intrahepatic accumulation of TGs.[81] Abstinence has been shown to reduce serum FA and LPC levels, while TGs stay elevated[82] in patients with ALD (Table 1). Moreover, in several models, FA synthesis pathways are significantly upregulated in mice fed alcohol ad libitum in their drinking water.[83–85]

## Non-alcoholic fatty liver disease

NAFLD, ranging from steatosis to its progressive form NASH, is the most common liver disease in the developed world,[1] and is an important risk factor for liver cancer development. NAFLD is associated with prominent changes in both the hepatic and serum lipidomes at the onset of steatosis, but as the disease progresses to NASH, only certain TGs[86–88] and steroids[89] change progressively. However, NAFLD-HCC is reflected by a complete rearrangement of the serum lipidome[90] (Table 1). Patients with NAFLD have significantly increased levels of FAs, TGs, ceramides

**Table 1. Deregulation of blood (and tissue) lipids as risk factors for liver cancer, HCC and CCA.**

| Lipid | Serum/plasma | | | | | | Tissue |
|---|---|---|---|---|---|---|---|
| | Viral hepatitis | Alcoholic hepatitis | NAFLD | PSC[59] | CCA[59] | HCC | HCC T vs. SL |
| SFA | ↑[66–68] | ↑[82] | ↑[86,87,91,92] | = | = | ↑[117,118,121] | ↑[118] |
| MUFA | ↑[66–68] | ↑[82] | ↑[86,87,91,92] | = | = | ↑[117,118,121] | ↑[118] |
| PUFA | ↓[66–68] | ↑[82] | ↑[86,87,91,92] | = | = | ↓[90,118,122] | ↓ |
| TG | ↓[66] | ↑[82] | ↓[86,87,91,92,99,100] | ↑ | = | ↑[90] | ↓[216] |
| Cholesterol | ↓[66,67] | | | ↑ | ↑ | ↑[122,134,140,141] ↓[146] | |
| BA | | | ↑[86,87,91,92] | ↑ | ↑ | ↑[59,90] | ↓[311] |
| Cholesterol ester | | | | ↑ | ↓ | ↑[90] | ↑[216,249] |
| LPC | ↓[75,76] | ↓[82] | ↓[100,103] | ↑ | ↓ | ↓[135] | = |
| PC | | | ↓[100,103] | | | | ↑[134] |
| Ceramide | | | ↑[86,87,91,92,107,312] | = | = | ↑[123] | ↑[124,132] ↓[132] |
| S1P | | | | ↑ | ↑ | ↑[123] | ↑[126–128] |
| Sphingomyelin | | | | | ↓ | ↑[135] | ↓[134] |

Data for PSC and CCA are based on single reference (Banales et al.[59])
↑Upregulated metabolites; ↓ downregulated metabolites.
BA, bile acids; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; LPC, lysophosphatidylcholine; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; PC, phosphatidylcholine; PSC, primary sclerosing cholangitis; PUFA, polyunsaturated fatty acid; S1P, sphingosine-1-phosphate; SFA, saturated fatty acid; SL, surrounding liver; SM, sphingomyelin; T, tumour; TG, triglyceride.

(Cer), and BAs, while phospholipids in the blood are depleted.[86,87,91,92] In NAFLD, the most important metabolic dysregulation is a result of high lipolysis and non-esterified FAs released into the bloodstream.[93] Hepatic FA profiles in patients with NAFLD are severely deregulated.[86,92] Specifically, SFAs and PUFAs are significantly increased in NAFLD compared to normal livers.[92] Conversely, in murine models, a higher consumption of n-6 FAs leads to the onset of NASH by inducing mitochondrial dysfunction and altered apoptosis.[94] Furthermore, palmitic acid and linoleic acid (LA) have been found to modulate the immune response in murine models of NASH.[95] Palmitic acid and LA stimulate neutrophils[95] as well as macrophages[24] to express and secrete inflammatory proteins (for example, interleukin-6, interleukin-10, chemokine (C-C motif) ligand 2, interferon-γ, and tumour necrosis factor). LA also upregulates carnitine palmitoyltransferase (CPT) leading to increased apoptosis of CD4^{+} T cells.[96] This LA-mediated loss of intrahepatic CD4^{+} T cells, but not CD8^{+} T lymphocytes, results in HCC progression.[97] On a background of NASH, CD8^{+} T cells promote the incidence of murine HCC because of impaired tumour surveillance and increased tissue damage by lymphocytes.[98]

NAFLD is characterised by a significant increase of TGs in the circulation[86,99,100] and liver.[86,92] These are TGs with longer carbon chains and fewer double bonds.[92,101,102] Among the lipids increased in both the blood and livers of NAFLD patients are Cer,[86,103,104] with an increase in dihydroceramides[105,106] that are basic markers of *de novo* Cer synthesis.[107] As such, murine models have shown a decrease in hepatic steatosis when levels of liver Cer are lowered by an increase in acid ceramidase activity[108] or deletion of dihydroceramide desaturase 1[109]. Moreover, several studies have shown that BA levels are increased in the liver,[110,111] plasma[91,110,112] and faeces[112] of patients with NASH. Elevated plasma levels of glycocholate, taurocholate, and taurochenodeoxycholate[91,110] are associated with progressive liver deterioration and dysfunction. Furthermore, increased levels of cholic, chenodeoxycholic, and deoxycholic acids are present in liver tissue,[111] leading to altered expression and activity of genes involved in BA, lipid and carbohydrate metabolism, energy expenditure, and inflammation.[113] Meanwhile, PCs and LPCs (particularly classes that contain PUFAs) are depleted in livers[86] and blood obtained from patients with NAFLD[100] and NASH.[103] Interestingly, sphingolipids, phospholipids, and TGs are putative biomarkers of NAFLD progression.[87,103] Furthermore, cholesterol promotes NAFLD development.[114]

**Primary sclerosing cholangitis**
Previously, studies with relatively limited sample sizes (n <30) have investigated lipidomic changes in patients with PSC compared to healthy individuals.[59,115,116] The most comprehensive lipidomic study[59] has shown prominent changes in patients with PSC compared to healthy individuals, reporting over 150 altered metabolites. Overall, serum obtained from patients with PSC comprised augmented levels of BAs, phosphatidylethanolamines, PCs and LPCs, and lysophosphatidylinositols, as well as decreased levels of some FA, SM and TG species (Table 1). Previously, FA deregulation has been observed in PSC.[115] The liver plays a major role in cholesterol clearance via BA secretion; thus, it is not surprising that BAs are among the most deregulated lipids.[59,60,115,116] Particularly, taurine and glycine conjugates of primary BAs have been found elevated in patients with PSC compared to non-cholestatic individuals.[59,60,115,116]

## Deregulation of lipid metabolism in liver cancer
Deregulated lipid metabolism has been strongly associated with the onset and progression of HCC in several epidemiological studies[90,117–119] as well as in *in vitro* and *in vivo* modelling (Table 1). In comparison, CCA lipidomic studies are currently limited to biomarker discovery[16,59,120]; thus, a comprehensive investigation of the biliary tract and CCA lipidome landscapes are still lacking.

**Lipidomic landscape is deregulated in liver cancer**
Several lipidomic studies have investigated the blood lipidome to understand the progressive nature of CCA,[59] HCC[61,67,75,76,117,121] of viral origin, and more recently NAFLD-HCC.[90] As such, the FA composition in the circulation dynamically changes as the liver deteriorates and progresses towards HCC[59] (this is not seen in CCA). Several SFAs and MUFAs are increased during disease progression: chronic hepatitis -> cirrhosis -> HCC.[117,121] Particularly, the MUFAs (16:1) and (18:1) progressively increase during development of viral-associated HCC[117,118]; however, these observations have not been corroborated in NAFLD-HCC.[90] Conversely, serum levels of PUFAs are decreased in the blood of patients with HCC.[90,118,122]

Sphingolipids are an important lipid class that is upregulated in HCC[90,123,124] and CCA.[125] As such, S1P, a biologically active sphingolipid, has been shown to promote cell proliferation, migration, invasion, and epithelial-to-mesenchymal transition (EMT) in HCC[126–128] as well as lymph node metastasis in CCA.[125] Accordingly, sphingosine-1-phosphate receptor (S1PR) could be a potential therapeutic target in HCC, as it is known to promote HCC invasion[129–131] and progression[131] (Fig. 2). Similarly, Cer as a class accumulate in the serum of patients with HCC,[123] but the function of specific Cer remains unknown and contradictory.[132,133] Furthermore, an increase of SM (40:1) in mice[134] and SM (18:2/24:1) in patients with HCC,[135] as well as the utility of SM as a biomarker in distinguishing HCC and CCA[59] suggest that sphingolipid metabolism may present a therapeutic target in liver cancer.[136,137]

Phospholipids are also significantly implicated in hepatocarcinogenesis.[133,138] MUFA-PCs accumulate in HCC tumours,[134] while PUFA-PCs and SFA-PCs are depleted. Moreover, MUFA-PCs are associated with a switch in the proliferative capacity of hepatocytes and with the onset of HCC.[134] Additionally, LPCs, a highly anti-inflammatory class of molecules, are progressively decreased during chronic hepatitis and HCC onset.[75,139] LPCs are highly upregulated in PSC, but significantly depleted in CCA,[59] which follows the opposite trajectory compared to HCC. We can only speculate that LPCs are increased in PSC as a response to bile duct inflammation.

Several studies have demonstrated that a high-fat, high-cholesterol diet can trigger HCC in mice,[122,134,140,141] via a neoplastic transformation of hepatocytes caused by broad transcriptional deregulation of genes involved in metabolic pathways (`metabolism in cancer´ hallmark) and calcium signalling.[140] It has been shown that statins, which block hepatic cholesterol synthesis, protect against HCC[142] and CCA[143] development, as well as resulting in decreased risk of mortality.[144] On the other hand, a higher serum cholesterol level was shown to be reflective of conserved liver function and decreased mortality.[145] A recent population study showed that low serum cholesterol in patients (not using statins) was significantly associated with an increased risk of developing HCC.[119] Interestingly, in patients with HCV-associated HCC, serum cholesterol levels and genes involved in
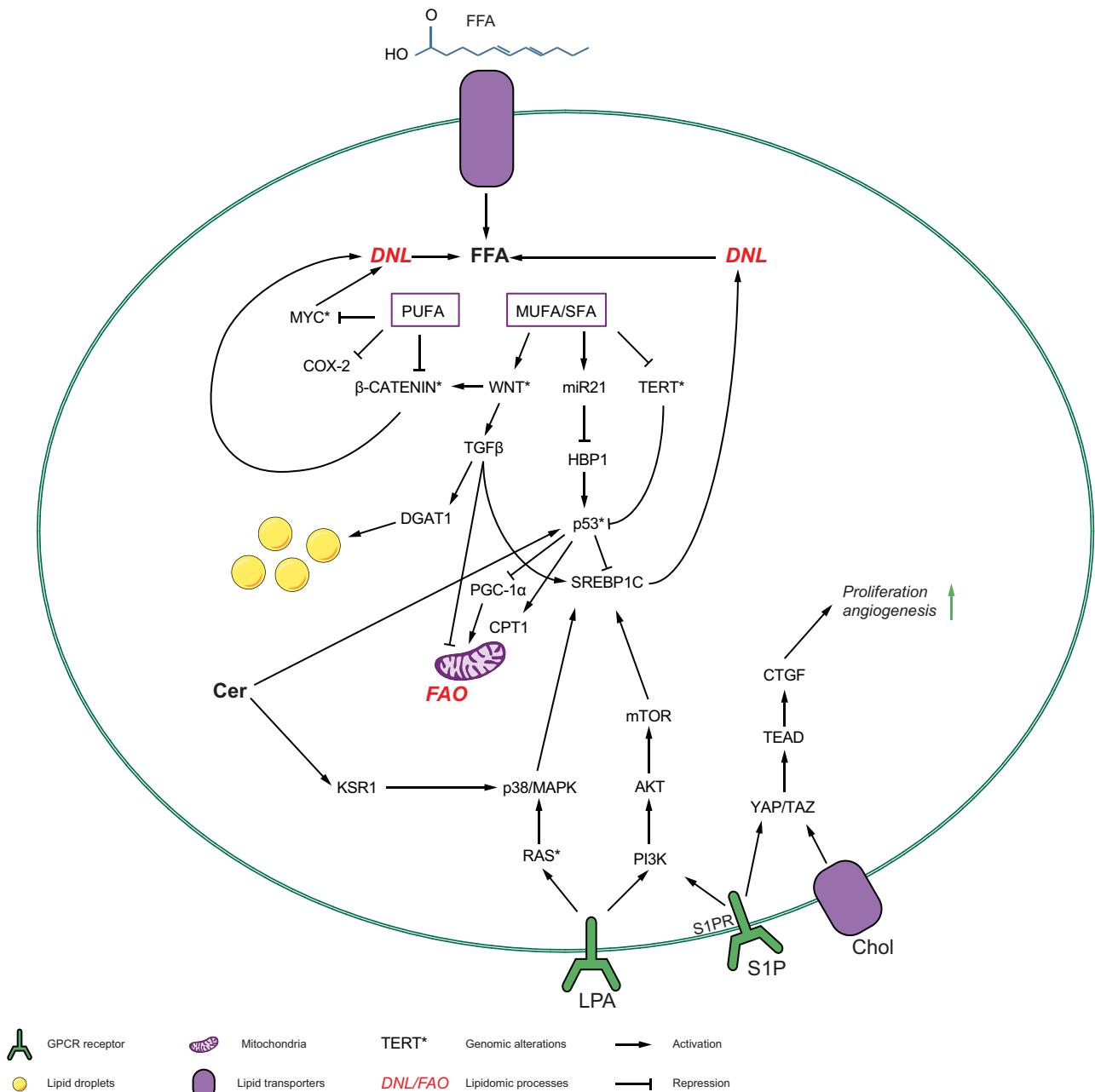
**Fig. 2. The interplay between lipid metabolism and oncogene pathways that leads to tumorigenesis in the liver.** Various lipids influence and are influenced by the recurrently deregulated oncogenic pathways, p53, RAS/MAPK, PI3K/AKT/mTOR signalling axis, Wnt/β-catenin signalling axis, TGF-β signalling axis and myc and TAZ/YAP pathways to cause hepatocarcinogenesis. The inhibited genes are marked with (⊥) and activated with (↓). The recurrent molecular alterations in oncogenes are marked with (*). CL, cardiolipin; CTGF, connective tissue growth factor; DNL, de novo lipogenesis; FA, fatty acid; GlcCer, glucosylceramide; mTOR, mammalian target of rapamycin; NPC1, NPC intracellular cholesterol transporter 1; PI3K, phosphoinositide 3-kinase; PDK1, phosphoinositide-dependent protein kinase 1; S1P, sphingosine-1-phosphate; SL, sphingolipid; TG, triglycerides; TGF-β, transforming growth factor-β; YAP, Yes-associated protein.

the cholesterol synthesis pathway are significantly reduced.[61] High serum levels of cholesterol suppress HCC tumorigenesis through the activation of natural killer cells[146]; however, further studies are necessary to understand this disagreement. This may not be the situation in CCA, where high levels of cholesterol have been observed in the sera of patients.[147]

The nature and regulation of BAs is less controversial than that of cholesterol itself. Conjugated primary BAs are significantly elevated at the stage of cirrhosis and continue to increase with the progression of HCC.[148,149] The role of BAs in the development of HCC is well-established and was extensively reviewed elsewhere.[150] Fundamentally, BAs activate farnesoid X receptor (FXR) and G-protein coupled BA receptor 1 (GPBAR1) that both control numerous oncogenic processes, including inflammation, oxidative stress, and the regulation of many cancer-related genes.[150] BAs act through FXR in different cell

types and organs, including the gut,[151] hepatocytes,[152] hepatic stellate cells (HSCs)[152] and immune cells.[153] Conversely, a step-wise increase in plasma-conjugated BAs has been observed in the trajectory from healthy control to benign biliary disease, and further to CCA.[154] Indeed, conjugated BAs promote the growth of CCA through control and activation of the NF-kB pathway and decreased expression of FXR.[155,156]

Lastly, steroid hormones play an important role in hepatocarcinogenesis.[157,158] Oestrogen shows a significantly protective effect against HCC,[159] while elevated serum oestrogen and high expression levels of oestrogen-related proteins are associated with CCA[160,161] and poor clinical outcomes.[161] Thus, tamoxifen may potentially aid CCA therapy.[162] As such, the use of oral contraception is associated with an increased risk of CCA,[158] but not HCC development.[163]

### Lipids reshape oncogenic processes

While many studies have investigated how alterations of lipids alter transcriptomic processes, there are still gaps in our knowledge of how specific lipids alter the metabolic landscape in liver diseases. Herein, we will highlight how specific lipids,

acting as signalling molecules, may promote tumorigenesis (Fig. 2, Table 2). We will focus on alterations in cancer cells, as lipid reprogramming of immune cells in the tumour microenvironment has been reviewed elsewhere.[164]

FAs play a crucial role in the regulation of several oncogenic processes (Fig. 2, Table 2). For instance, telomere length and telomerase reverse transcriptase (TERT) activity are affected by FAs.[165] In obese children, the TERT promoter was shown to be hypermethylated, reducing TERT activity compared to in control individuals. Telomere length in leukocytes obtained from obese children showed a positive association with total SFAs and docosahexaenoic acid, as well as a negative association with the arachidonic acid to docosahexaenoic acid ratio.[165] Conversely, TERT deficiency in murine models promotes hepatic injury, increasing steatosis upon high-fat diet feeding, and inhibits liver regeneration via the activation of the tumour suppressor p53-peroxisome proliferator-activated receptor gamma coactivator 1 alpha (p53-PGC1$\alpha$) axis.[166] However, TERT expression and its activity are restored with cancer initiation as 80% of HCCs exhibit TERT promoter mutations or gene amplifications.[167] Moreover, oleic acid upregulates miR21, which promotes steatosis, G1/S

**Table 2. Ability of various lipids to promote or inhibit tumour growth in HCC and CCA.**

| Lipid | Impact | Mechanism | Ref |
|---|---|---|---|
| **Fatty acids** | | | |
| SFA | Telomere shortening in obesity | Increase DNA methylation in TERT promoter | [123,165] |
| Oleic acid | Promote HCC | deregulate p53 signalling via miR21-HBP1 axis | [132,168] |
| Palmitoleic acid (16:1) | Promote HCC | Rising lipolysis and increased oxidative stress via mitochondrial beta oxidation, as well as increases insulin sensitivity, Wnt and TGFβ activation | [117,118] |
| Linoleic acid (18:2) | Promote NAFLD-HCC | Linoleic acid upregulates CPT1 to induce CD4(+) T cell apoptosis, hence mitochondrial function disruption along with increased FADS2 expression in tumours | [96,97,118] |
| Vaccenic and erucic acid | Promote NAFLD-HCC | Upregulation of SCD and ELOVL6 causes upregulation of these fatty acids | [117] |
| n-3 PUFA | Inhibit CCA | n-3 PUFAs suppressed c-Myc and inhibits CCA tumour growth | [171] |
| EPA, DHA | Inhibit HCC | Simultaneous inhibition of COX-2 and beta-catenin | [313] |
| **Glycerophospho-lipids** | | | |
| Cardiolipin | Promote HCC | mTORC2 promotes cardiolipin synthesis, leading to accumulation in liver and then tumorigenesis, most probably via enhanced oxidative phosphorylation | [124] |
| **Phospholipids** | | | |
| LPA (16:0) | Promote HCC | LPCs are metabolized by phospholipase D to produce LPAs that are potent mitogens, mediating their tumorigenic effect by the PI3K/AKT/mTOR signalling pathway or p38 MAPK signalling pathway | [175–177,314] |
| LPC (20:4) | Inhibit HCC | Low LPC indicate inflammatory and oxidative stress, through apoptosis induction through the death ligands (Fas and/or TNF-alpha) pathway | [135,178] |
| MUFA-PC | Promote HCC | Increased lipogenesis, fatty acyl desaturation, de novo synthesis of PC, and PC remodeling and decreased β-oxidation | [134] |
| **Sphingolipids** | | | |
| S1P | Promote HCC and CCA | S1P activates YAP, PI3K/AKT and TFG-β1 production in HCC cells | [125–128] |
| Glucosylceramide | Promote HCC | mTORC2 promotes glucosylceramide accumulation which increases tumorigenesis | [124] |
| (SM) 18:2/24:1 | Promote HCC | Enrichment might be due to a specific diet; more studies are needed | [123,135] |
| C16 | Promote HCC | Long-chain ceramides may have proliferative effects for HCC, RAS activation, regulatory ligand of p53 | [123,135,172] |
| C12:0, 16:0, 18:1 and 24:1 ceramides | Promote HCC | Associated with cannabinoid receptor activation and SCD downregulation | [132] |
| **Sterols** | | | |
| Cholesteryl ester | Promote NAFLD-HCC | PTEN/PI3K/AKT/mTOR signalling pathway is responsible for cholesteryl ester accumulation which then leads to tumorigenesis | [249] |
| Cholesterol | Promote HCC | Upregulation of TAZ to promote fibrotic NASH | [114,249] |

CCA, cholangiocarcinoma; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HCC, hepatocellular carcinoma; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; MUFA, monounsaturated fatty acid; NASH, non-alcoholic steatohepatitis; PC, phosphatidylcholine; PUFA, polyunsaturated fatty acid; S1P, sphingosine-1-phosphate; SM, sphingomyelin.

transition and proliferation through the miR21-HMG-box transcription factor 1 (HBP1)-p53 axis.[168] In ALD, hepatic FAs suppress the LAMP-2 (lysosome-associated membrane protein 2) autophagy flux pathway through ER stress signalling and increase hepatic injury[169] (Table 2). Furthermore, palmitic acid treatment leads to transcriptional upregulation of Wnt and transforming growth factor-β (TGF-β) signalling, activating EMT.[170] In CCA, it has been demonstrated in vitro that n-3 PUFAs may inhibit c-myc expression.[171]

Among sphingolipids, Cer16 has been shown to be an important activator of the p53 pathway.[172] Cer16 binds the DNA-binding domain of p53 and disrupts its complex with MDM2 (mouse double minute 2), leading to p53 accumulation and transcriptional activation, contributing to the apoptotic process and hepatic liver injury.[123] Indeed, Cer16 is significantly upregulated in serum[123] and tumour tissues obtained from patients with HCC.[173] Moreover, Cer activates KSR1 (kinase suppressor of Ras 1), acting as a positive regulator of the RAS-RAF-MAPK pathway,[174] which is frequently deregulated in liver cancers (Table 2).

Phospholipids can act as signal transductors as well as directly bind to G-protein-coupled receptors, with both oncogenic and tumour suppressive roles. Lysophosphatidic acid (16:0) is a potent regulator of the PI3K/Akt, mTOR (mammalian target of rapamycin), and p38 MAPK signalling pathways, increasing HCC cell migration, invasion, and adhesion.[175–177] Conversely, LPC (20:4) was shown to induce Fas and tumour necrosis factor-α pathways, resulting in apoptosis and thus playing a tumour suppressive role[178] (Table 2).

Sterol lipids, particularly cholesterol, may play important roles in liver cancer. Increased cholesterol in hepatocytes upregulates the transcriptional regulator TAZ (WWTR1), and thus promotes NASH.[114] Elevated TAZ activity leads to the synthesis and secretion of IHH (Indian hedgehog)[179] and activation of HSCs.[179] Currently, no association has been shown between TAZ and CCA (Table 2).

Collectively, these studies suggest that prominent lipidomic rearrangements occur before carcinogenesis and continue to play a role during liver cancer progression. Several types of lipids have been shown to interact with oncogenes, altering the signalling activity of many pathways, and likely contributing to tumour formation through these interactions. This emphasises possible opportunities for future preventative treatments.

### Molecular alterations in liver cancer promote lipid remodelling

Metabolic stress contributes to increased reactive oxygen species levels that may result in mutational processes, with the accumulation of somatic mutations in chronic liver disease eventually leading to cancer. A recent study in patients with ALD and NAFLD showed that 3 master regulators of lipid processing and storage – FOXO1 (forkhead box protein O1), CIDEB (cell death inducing DFFA like effector B) and GPAM (glycerol-3-phosphate acyltransferase, mitochondrial) – are frequent targets of convergent somatic mutations.[167] Recurrent mutations in RAS, TP53, MYC, and CTNNB1 have also been shown to alter the lipidome of liver tumours (Fig. 2).

Mutations in the RAS-RAF pathway are frequent in HCC[167] and CCA,[180] and lead to transcriptional activation of fatty acid synthase (FASN), which promotes lipogenesis.[181] Furthermore, increased Wnt and Myc activities intensify FA desaturation and

elevate unsaturated fatty acyl groups in phospholipids in a RAS-dependent manner. Through this metabolic reprogramming, stearoyl-CoA desaturase (SCD) was identified as a putative therapeutic target.[182]

Mutated TP53 is a dominant driver-gene in many cancers, including HCC[167] and CCA,[180] regulating cellular metabolism (reviewed in[183]). On the one hand, wild-type p53 is a potent repressor of sterol regulatory element-binding proteins (SREBP-1/2) that regulate DNL and cholesterol synthesis, respectively.[184,185] On the other hand, wild-type p53 promotes FAO through expression of lipin 1, sirtuin 1, and CPT, maintaining lipid homeostasis in the liver.[186,187]

The role of the Wnt pathway in reprograming cancer metabolism has been extensively studied and reviewed elsewhere.[188] Many of the recurrent mutations in this pathway are not druggable (though it has received significant attention in the area of small molecule development). However, exploiting the lipidomic changes inflicted by the mutations in Wnt could present an indirect therapeutic strategy. Overall, there is a convincing rationale to target the Wnt/β-catenin pathway in liver cancers[189]; however, the effect on lipid metabolism has received less attention. The activation of the Wnt pathway leads to the release of β-catenin, its translocation to the nucleus and consequently to increased expression of peroxisome proliferator-activated receptor-α (Pparα)[190] resulting in increased FAO in this subset of HCC. Moreover, inhibition of Wnt/β-catenin may lead to downregulation of DNL and FA desaturation, which is frequently upregulated in liver cancer. Thus, further studies to investigate the effects of lipid-targeted therapies are warranted.

### Transcriptionally deregulated lipid metabolism pathways

PPARs, SREBPs, and liver X receptors (LXRs) are key hepatic transcriptional regulators of enzymes involved in lipid metabolism (reviewed in[191]). As cofactors, lipids can bind directly to transcription factors, modulating the expression of lipid metabolism in a feedback loop. As such, PUFAs and 4-phenyl butyric acid have been shown to directly bind to PPARs,[22,192] which can contribute to the development of HCC. It has been implied that the PPARα-SCD1 axis is important to maintain the stemness of HCC cells by promoting the nuclear accumulation of β-catenin.[193] Furthermore, LXRs are activated by oxysterols and their activation can trigger lipotoxicity in liver cancer,[194] while their inactivation leads to NAFLD-HCC development.[195] As such, the transcriptomic landscape of lipid metabolism is significantly deregulated in liver cancer[196–198] (Fig. 3).

### FA uptake and transport

FAs are required for tumour cell proliferation to provide new phospholipids for plasma membranes. Their availability in serum is dependent on the dietary supply and TG lipolysis by lipoprotein lipase.[199,200] FAs are intracellularly translocated through CD36[170,201] and/or FA transporters of the SLC27 family.[202] SLC27A1 and lipoprotein lipase are upregulated in CCA tumour tissue compared to the adjacent normal liver parenchyma, which suggests an increased demand and dependency on exogenous FAs in tumour tissue.[203] In HCC, high CD36 expression is associated with diminished overall survival (TCGA KMplotter, $p = 0.047$). Furthermore, CD36-mediated uptake and trafficking via fatty acid-binding proteins (FABP1 and FABP4) correlate with increased EMT and activation of the Wnt/β-catenin and TGF-β signalling pathways[170] (Fig. 3).
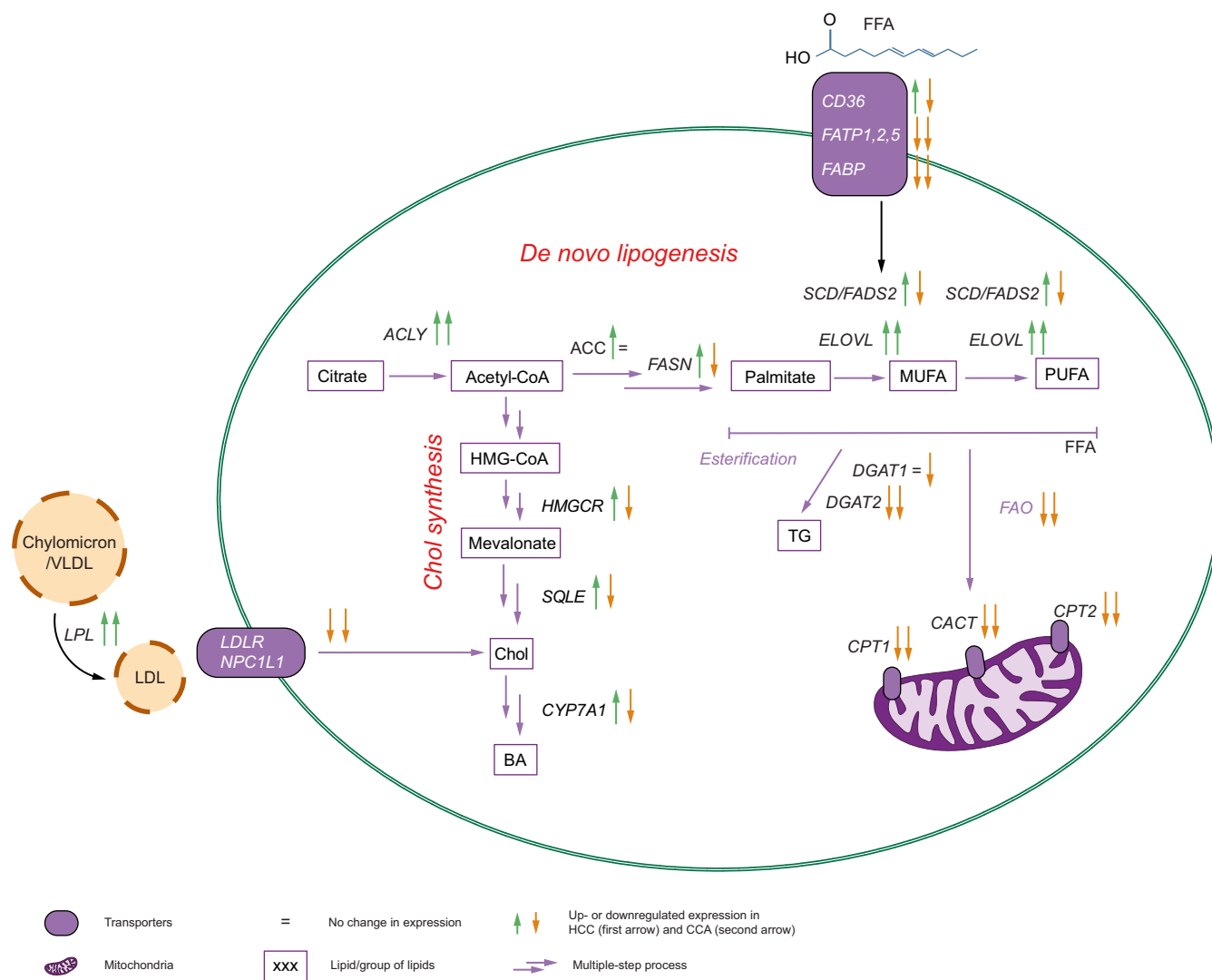
**Fig. 3. Transcriptionally deregulated lipidomic processes are different in HCC compared to CCA.** The alteration in gene expression profiles of tumour *vs.* surrounding tissue in HCC (first arrow) and CCA (second arrow). The upregulated genes are marked with red ↑, and downregulated with ↓. ACLY, acetyl-CoA by ATP citrate lyase; ACC, acetyl-CoA carboxylase; BA, bile acids; CCA, cholangiocarcinoma; Chol, cholesterol; DGAT1/2, diglyceride acyltransferase 1 and 2; DNL, *de novo* lipogenesis; ELOVLs, elongation of very-long-chain fatty acids; FADS2, fatty acid desaturase 2; FAO, fatty acid oxidation; FASN, fatty acid synthase; FATPs, fatty acid transport proteins; FFA, free fatty acids; HCC, hepatocellular carcinoma; HMGCR, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase; LPL, lipoprotein lipase; MUFA, monounsaturated FA; PUFA, polyunsaturated FA; SCD, stearoyl-CoA desaturase; SQLE, squalene epoxidase; TG, triglyceride.

## De novo lipogenesis and triglyceride synthesis

DNL is significantly upregulated in the proliferative class of HCC[204,205] and it is predictive of patient prognosis.[206] Therefore, rate-limiting genes of DNL, such as ATP citrate lyase (ACLY),[207] acetyl-CoA carboxylase (ACC),[208–210] and FASN,[17,210–213] are frequently upregulated in HCCs compared to the normal adjacent liver tissue. Interestingly, in CCA, tumour cells show lower dependency on DNL and instead a higher addiction to exogenous FAs.[203] Thus, DNL as a process, and rate-limiting genes in particular, may present an attractive therapeutic option for obesity, NAFLD and HCC, but not CCA (Table 2). Furthermore, it has been suggested that, in HCC, DNL is glucose-derived[209] and thus, restricting HCC cells access to glucose results in diminished DNL activity.[214] However, a recent study implicated fructose and sucrose, rather than glucose, as substrates in DNL[215] in the healthy liver. Thus, in HCC, the substrates driving DNL require

comprehensive studies. Indeed, several HCC studies have focused on DNL inhibition as a therapeutic option, but such work remains in its infancy.[206,208,216]

ACLY is the first step in DNL and has been shown to promote HCC transcriptionally by interacting with NONO (non-POU domain-containing octamer binding protein).[217] Overall, ACLY was shown to regulate stemness, migration, and invasion of HCC cells via the Wnt/β-catenin signalling pathway.[207] In CCA, the expression of ACLY is higher in tumour tissues compared to the surrounding tissue,[218] however, its role remains unknown.

Parts of acetyl-CoA are carboxylated to malonyl-CoA by ACC, which is the primary rate-limiting enzyme in this process. Either inhibition of ACC itself or deletion of AMPK-targeted ACC phosphorylation sites lead to a significant decreased tumour burden and attenuated DNL in diethylnitrosamine-induced HCC.[208] Also, *in vitro,* these modifications result in decreased proliferation and

viability of HCC cells.[17] Accordingly, several inhibitors designed to block ACC activity and reduce lipogenesis have led to significant reductions in the accumulation of hepatic TG and activation of HSCs.[219,220] Still, liver-specific ACC knockout in mice with diethylnitrosamine-induced HCC led to a significant increase in the tumour burden and altered redox regulation.[206] Additionally, complete deletion of ACC1 and ACC2 abrogates acetogenic lipogenesis but fails to protect murine livers from increased lipid accumulation, likely due to inhibition of FAO as the compensatory mechanism.[221] Taken together, these data suggest that ACC inhibition, but not deletion, could be a beneficial treatment option for patients with HCC.

The next step in DNL is palmitate synthesis, which is catalysed from malonyl-CoA by FASN. The role of FASN in HCC is dependent on the model. First, overexpression of FASN alone or in combination with either N-Ras, c-Met, or SCD1 is not sufficient to promote HCC.[222] However, FASN expression is essential in the development of HCC in both the AKT[222] and AKT/Ras[203] models and FASN inhibition delays Pten/c-Met-driven HCC.[216] As such, stabilisation of FASN by glyceronephosphate O-acyltransferase promotes DNL and formation of liver tumours in mice.[212] Interestingly, FASN expression is dispensable for CCA formation in AKT/Notch intracellular domain 1- and AKT/Ras-driven models,[203] and KDM5C-mediated repression of FASN was shown to correlate with reduced CCA cell proliferation and invasion.[223]

Finally, palmitate, which is the end-product of DNL, can undergo a series of desaturation and elongation reactions that are catalysed by SCD, FADS2, and elongation of very-long-chain fatty acids (ELOVL1-6), respectively. In HCC, upregulation of SCD has been comprehensively described in mice, rats, tumour cells, and patients.[134,198,224,225] SCD has been shown to be crucial for proliferation of HCC cells,[134,224] for development of HCC in mice,[198,225] and is present at higher levels in more aggressive HCCs in patients.[198] Additionally, a subset of HCC cell lines is metabolically flexible since they upregulate FADS2 and utilise this as an alternative desaturation pathway when SCD is inhibited,[226] suggesting that targeting both desaturation pathways would be necessary to impair HCC growth. Furthermore, suppression of ELOVL6 in HCC cells led to reduced proliferation, tighter cell-cell junctions, and increased lipid accumulation,[227] as well as reduced HCC tumour growth *in vivo* and increased survival.[227]

The role of TG synthesis in liver cancer development and progression remains elusive. It is implied that TG synthesis is downregulated in HCC.[228] The formation of TG from acetyl-CoA and diacylglycerol is catalysed by evolutionarily unrelated enzymes (diglyceride acyltransferase [DGAT]1 and DGAT2) that are downregulated in HCC compared with matched normal tissues.[228] Higher expression of DGAT2 results in longer overall survival.[228] These data were corroborated *in vitro* and *in vivo*, demonstrating that overexpression of DGAT2 curbs cell proliferation and diminishes tumour growth.[228] While comprehensive studies linking TG synthesis to HCC development and progression are lacking, overexpression of DGAT1 and DGAT2 in hepatocytes[229,230] leads to steatosis and lipid accumulation,[231] which is one of the key long-term causes of hepatocarcinogenesis. However, DGAT1 is important for the maintenance of HCC *in vitro*, silencing it reverts HCC cells to a dedifferentiated and stem cell-like phenotype.[232] Interestingly, *in vitro,* if DGAT1 is silenced in HCC cells, the cells compensate by upregulating DGAT2.[233] Hence, inhibition of DGAT2 *in vivo*[234] ameliorated liver steatosis. Another less studied enzyme in the TG synthesis pathway is monoacylglycerol O-acyltransferase, which catalyses the synthesis of TGs, may contribute to hepatic steatosis *in vivo*[235,236] and could be an important therapeutic target for the treatment of NAFLD.[237]

### Fatty acid oxidation
CPT1 and CPT2 deliver long-chain FAs to the mitochondria for oxidation and thereby generate ATP and NADPH.[238] In both HCC and CCA, the expression levels of CPT1 and CPT2 are downregulated (TCGA,[239,240] www.firebrowse.org). In fact, downregulation of CPT2 was shown to protect against lipotoxicity[241] in an E2F2-dependant manner in HCC.[242] Furthermore, downregulation of acylcarnitine translocase (SLC25A20) in the mitochondrial matrix is observed in both HCC and CCA (TCGA, www.firebrowse.org) and was shown to suppress FAO and promote HCC proliferation as well as metastasis.[243] Furthermore, enzymes in the FAO process, such as medium-chain acyl-CoA dehydrogenase[244] and long-chain acyl-CoA dehydrogenase,[245] have potential tumour suppressor roles in HCC.[244,245] Therefore, FA utilisation for structural and messenger molecules, rather than storage or energy sources, supports HCC development and progression.

### Cholesterol and BA synthesis
In addition to FA synthesis, other lipogenesis pathways have also been demonstrated to be deregulated during HCC development. The rate-limiting enzyme of cholesterol synthesis (and target of statins) 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) is upregulated in HCC[246] and CCA[247] and thus, the use of statins is associated with reduced risk of liver cancer development.[143,248] Furthermore, increased expression of squalene epoxidase[249] has been implicated in the development of NAFLD-HCC. Interestingly, a decreased ability to utilise circulating cholesterol was associated with increased HCC proliferation and metastasis.[250] Furthermore, cholesterol synthesis was shown to support HCC growth in the absence of FASN,[216] which indicates crosstalk between DNL and cholesterol synthesis. Similarly, increased cholesterol and BA synthesis, through PPARα activation, cause cholestasis, liver damage, and finally CCA development.[251]

## Diagnostic potential of circulating lipids
Most lipids detected in human serum or plasma remain stable and are well correlated with the liver lipidome.[86] Therefore, the lipidome in circulation is an attractive source of biomarkers.[16,107]

Several studies exploited serum FA as a diagnostic tool.[88,252] Recently, it has been shown that a combination of several FAs and PC (18:2) can robustly distinguish patients with NAFLD-HCC from those with HCC of other aetiologies and non-cancerous controls,[88] providing a potential tool for non-invasive surveillance.

The increased serum/plasma levels of TGs are a well-known biomarker of liver dysfunction in cholestasis, ALD, NAFLD, and HBV-,[87,88,103,253–255] but not HCV-associated hepatitis.[256] Similarly, increased TG levels have been identified as risk factors for CCA.[147,257] Furthermore, diminished levels of circulating TG in patients with HCC are associated with worse overall survival.[258] However, due to the unspecific nature of these changes, they remain a generic biomarker of liver dysfunction. On the other hand, the changes in specific TG species may be more useful. The major differences observed with the development of NAFLD and its progression to NASH are increasing serum levels of saturated and monounsaturated TGs,[87,103] many of which progressively
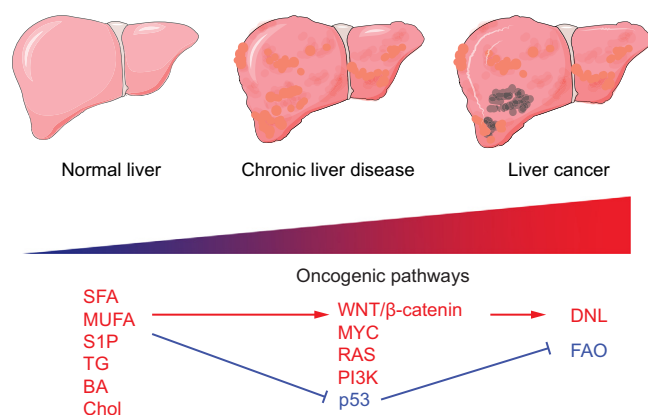
**Fig. 4. Outline of the lipidomic alterations in liver cancer progression.** Progression from the normal liver through chronic liver disease (hepatic steatosis to NASH) and into primary liver cancers. Oncogenic pathways activated by a change in different metabolic classes (SFA; MUFA; S1P; TG; BA; Chol) during neoplastic onset. Activation of DNL and p53-mediated inactivation of FAO. BA, bile acid; Chol, cholesterol; DNL, *de novo* lipogenesis; FAO, fatty acid oxidation; MUFA, monounsaturated fatty acid; NASH, non-alcoholic steatohepatitis; S1P, sphingosine-1-phosphate; SFA, saturated fatty acid; TG, triglyceride.

increase with the onset of HCC,[88,258] particularly in the absence of cirrhosis. Conversely, the depletion of cholesterol esters, another energy storage class of lipids, has diagnostic potential in HCC[18,59] and CCA.[59]

Differences in the abundance of structural lipids have also been exploited, with specific sphingolipids having biomarker potential. As an example, following increased levels of C16-ceramides, S1P has been shown to distinguish patients with HCC from those with cirrhosis.[18,259] The depletion of serum SMs in HCC could distinguish patients with HCC from healthy controls, while SMs were significantly altered between HCC and CCA and could thus distinguish between these malignancies.[59] Furthermore, several LPCs have shown diagnostic value in CCA[260] and HCC.[18,75,259]

The increase in lipidomic studies in liver cancer has led to an abundance of novel biomarkers, many of which show significantly higher diagnostic potential than alpha-fetoprotein or carbohydrate antigen 19-9. However, most of these studies lack external validation cohorts. Furthermore, most of these studies lack absolute quantification of metabolites, their reference ranges, and the cut-off values that could be considered as diagnostic. As a result, they have limited clinical value and require further development before clinical use.

## Therapeutic opportunities
For decades, lipid metabolism has been an attractive target for the development of new therapies that could alleviate the burden of chronic liver diseases and hence reduce the risk of cancer. Furthermore, similar genes orchestrating lipid metabolism in chronic liver diseases have recently been investigated as therapeutic targets in cancer treatment (Table S1).

### Treatment of underlying diseases to prevent liver cancer
Several inhibitors of DNL, FAO, or cholesterol synthesis have reached clinical trials and use (Table S1). In DNL, drugs that target ACC have progressed significantly. The ACC inhibitor

firsocostat is the most prominent, having shown promising results in mice,[261] as well as significantly reducing steatosis in patients with NAFLD in phase II clinical trials.[262–264] The FASN inhibitor TVB-2640 has also shown promise in humans[211,265] as has the inhibitor cerulenin in mice.[213] A PPAR inhibitor targeting the intracellular transport of FAs (lobeglitazone) has reached phase VI clinical trials in NAFLD,[266] where it reduced intrahepatic fat content and improved glycaemic and lipid profiles in 38 patients with NAFLD and type 2 diabetes. Other PPAR inhibitors such as pioglitazone,[267] IVA337 (lanifibranor)[268] and elafibranor[269] have also shown promise, but are at the earlier phases of clinical trials. Perhaps the most noteworthy inhibitors in NAFLD and PSC treatment are LXR and FXR agonists such as oltipraz,[270] obeticholic acid,[271,272] Px-104,[273] and MET409.[274] Interestingly, the FXR agonist obeticholic acid has shown promise as a therapeutic target in both NAFLD[271] and PSC.[272] Another noteworthy pathway is the cholesterol biosynthesis pathway; statins, which suppress HMGCR, have been studied in both NAFLD and PSC (Table S1) and successfully lowered LDL cholesterol in NASH.[275] As far as sphingolipid metabolism is concerned, there have been no clinical studies yet, but the SK2 inhibitor K145[276] and the S1P1R inhibitor fingolimid[277] have ameliorated NAFLD in mouse models.

### Targeting lipid metabolism in liver cancer treatment
Since lipids partake in liver cancer development and progression through various pathways and there is some progress targeting these in the pre-malignant liver, it is not surprising that there is considerable interest in exploiting lipid metabolism pathways in liver cancer treatment. Many pre-clinical studies have focused on DNL: the ACC inhibitor AICAR showed an anti-cancer growth effect *in vitro*,[278] and ND-654 improved survival of HCC tumour-bearing rats.[208] The FASN inhibitor orlistat has also displayed antitumor activity *in vitro*[279,280] and in murine models, along with the inhibitors C75,[281] triclosan[21,282] and EGCG[283] showing promise *in vitro*. The SCD inhibitor CAY10566 has also been successful in ameliorating HCC *in vitro*[224,284] and *in vivo*[285] and the DGAT inhibitor tussilagone reduced TG synthesis *in vitro*.[286] Interestingly, sorafenib, which is an inhibitor of tyrosine kinases in HCC,[287] targets liver cancer cells by acting on the SCD1 pathway *in vitro*[288] and in human liver tumours[289] and, in return, SCD inhibition sensitises the tumour to sorafenib treatment.[289] Targeting FAO by CPT1 inhibition with etomoxir is another pathway that has successfully reduced HCC occurrence *in vivo*,[190,290–292] however these studies are limited to the pre-clinical setting (Table S1). Furthermore, the SREBP inhibitor betulin,[293] the FXR agonist INT-767[294] and simvastatin[295] (a HMGCR and PPAR inhibitor) significantly ameliorate HCC in a pre-clinical setting. Several statins are under investigation in combination therapy for HCC (Table S1). Atorvastatin is in phase IV clinical trials for HCC but it is still at the recruiting phase (NCT03024684), while pravastatin in combination with sorafenib failed to improve patient outcomes.[296]

In CCA treatment, targeting sphingolipid metabolism or more specifically the enzyme sphingosine kinase 2 (encoded by the gene SPHK2) with the inhibitor ABC294640 has shown promise *in vitro*,[297,298] *in vivo*[299] and in a clinical trial setting.[136] In addition, the ASBT inhibitor Bamet-UD2[300] has shown significant anticancer effects in a pre-clinical setting, while the role of statins in CCA has not been investigated in a controlled clinical setting. Furthermore, obeticholic acid, which has shown promise

in ameliorating NAFLD and PSC, managed to decrease proliferation of CCA cells *in vitro*.[301]

### Dietary intervention as preventative and therapeutic strategy
In addition to drugs, dietary combination strategies may also be helpful.[302] n-3 PUFAs have been implicated as a way to reduce hepatic steatosis and inflammation in ALD,[109] NAFLD,[303,304] and NASH.[305] The supplementation of n-3 PUFAs has been shown in a meta-analysis to reduce HCC risk by up to 51%,[306] results that have been mimicked *in vitro*[307] and in mice.[308] In fact, reducing the ratio (n-6:n-3) FAs in the diet has been shown to impair liver steatosis *in vivo*.[309,310] Therefore, we can speculate that patients with HCC, particularly patients with underlying NAFLD or NASH aetiologies, may benefit from a dietary supplement in combination with their pharmacological therapy.

### Conclusion and future perspectives
Despite the increasing interest in the investigation of lipidomic rearrangements in liver cancer, targeting lipid metabolism in a therapeutic setting has not been successful. The dynamic nature of the lipidome and lack of mechanistic insights into the role(s) of individual lipids in the development of liver cancer significantly hinder the development of new therapies. Our current knowledge allows us to exploit the human lipidome as a non-invasive diagnostic and prognostic tool; however, dissecting the mechanism of lipid metabolism and homeostasis in liver cancer development and progression is necessary. This review highlights the fact that while we are making great strides to unravel the role of lipids in the development and progression of liver cancer, directed mechanistic studies to understand lipids are necessary (Fig. 4).

### Abbreviations
ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ALD, alcohol-related liver disease; BAs, bile acids; CCA, cholangiocarcinoma; Cer, ceramide(s); CPT, carnitine palmitoyltransferase; DNL, *de novo* lipogenesis; ELOV1-6, elongation of very-long-chain fatty acids; FA, fatty acid; FABP, fatty acid-binding protein; FADS2, fatty acid desaturase 2; FAO, fatty acid oxidation; FASN, fatty acid synthase; FXR, farnesoid X receptor; HCC, hepatocellular carcinoma; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; HSCs, hepatic stellate cells; LA, linoleic acid; LPC, lysophosphatidylcholine; LXR, liver X receptor; MUFA, monounsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PC, phosphatidylcholine; PPARs, peroxisome proliferator-activated receptors; PSC, primary sclerosing cholangitis; PUFA, polyunsaturated fatty acid; S1P, sphingosine-1-phosphate; SCD, stearoyl-CoA desaturase; SE, sterol esters; SFA, saturated fatty acid; SM, sphingomyelin; SREBP, sterol regulatory element-binding protein; TERT, telomerase reverse transcriptase; TG, triglycerides; TLR, Toll-like receptor.

### Conflict of Interest
Authors declare no conflicts of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions
B.P. and M.L. researched data for the article; B.P., M.L, and J.B.A wrote and edited the manuscript before submission.

### Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100479.

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