The Role of Lipids in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma is the fastest growing cause of cancer-related mortality worldwide, with few treatment options and a 70% recurrence rate. This trend is driven largely by the recent surge in incidence of metabolic syndrome, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis. Given the central role of the liver in lipid homeostasis, altered hepatic lipid metabolism has been identified as a contributing factor to hepatocellular carcinoma. Neoplastic cells are highly dependent on lipid metabolism as a source of energy and to support rapid cell division, and fatty acid derivatives play key roles in cell signaling. Aberrant expression of liver fatty acid–binding protein and changes in the ratio of saturated to unsaturated triacylglycerols have been shown to be associated with disease severity and subtype. This chapter focuses on metabolic reprogramming and dysregulation of lipid metabolism as hallmarks of hepatocellular carcinoma.

Keywords: carcinogenesis; fatty acid metabolism; lipidomics; lipid metabolic reprogramming; non-alcoholic steatohepatitis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related mortality, with 840,000 new cases per year worldwide, nearly half of which are in China alone, due in part to the high (5.4%) incidence of chronic hepatitis B virus (HBV) infection (1–3). The incidence of HCC in the United States has tripled over the last four decades, resulting in more than 30,000 new cases and 20,000 deaths per year (1, 4, 5). HCC accounts for 75–85% of cases of primary liver cancer and is the sixth most common cause of cancer and the fourth most common cause of cancer-related death (3). A number of approaches have been developed to treat HCC, including liver resection, ablation, and transplantation. However, the disease is often asymptomatic at early stages and defies early detection. While the short-term prognosis for HCC has improved, the long-term prognosis remains poor, with a 5-year survival rate of 17% (6–8). Surgical resection provides the best chance for recovery, but the cancer is often detected too late for the treatment to be effective, and only about 15% of patients are eligible (9). Even in the case of successful resection, the 5-year rate of HCC recurrence remains about 70 % (10).

HCC is a complex disease with a number of known or suspected etiologies, including hepatitis B or C virus infection; non-alcoholic steatohepatitis (NASH); hemochromatosis; alcohol abuse; primary biliary cirrhosis; α-1 antitrypsin deficiency; Wilson's disease; and carcinogens such as aflatoxin B_1, thorotrast, polyvinyl chloride, and carbon tetrachloride (11, 12). However, inflammation associated with viral hepatitis and fatty liver disease is thought to be a common cross-etiological factor that drives the development of over 90% of liver tumors (13). HBV accounts for 85% of HCC cases in endemic regions such as Southeast Asia and sub-Saharan Africa, whereas HCV is the leading risk factor for HCC in Europe and North America. While HBV and HCV have traditionally driven the majority of HCC cases, the proportion of non-viral HCC cases, especially due to NASH, is expected to increase exponentially, and the overall number of HCC cases is expected to skyrocket over the next decade due to increasing incidence of obesity and diabetes (14). Estes et al. projected that by 2030, the number of NAFLD cases in the United States will increase by 21%, NASH cases by 63%, and HCC cases by 137% (14).

The incidence of fatty liver-associated HCC is increasing in many western countries due to the alarming increase in the number of adults and children with obesity, diabetes, and metabolic syndrome (15). Lipid metabolism is among the liver's most critical functions. Along with proteins, carbohydrates, and nucleic acids, lipids represent one of the four main classes of biomolecules. Starvation depletes fat reserves and causes muscle wasting, whereas excessive caloric intake accompanied by lack of physical activity can lead to obesity, in which fat accumulates in the liver and adipose tissue, disrupting lipid homeostasis and promoting insulin resistance. Altered lipid metabolism is thought to induce inflammation and promote fibrosis (16). Defined as having a body mass index (BMI) greater than 30 kg/m², obesity is one of the greatest public health challenges of this century, affecting 700 million people worldwide (17). Now classified as a disease in its own right, obesity is a leading preventable cause of death and is associated with increased risk of diabetes, cardiovascular disease, depression, and several types of cancer, including esophageal adenocarcinoma, leukemia, non-Hodgkin's
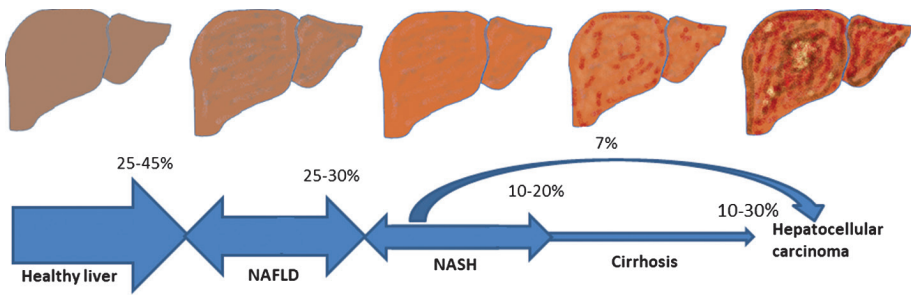
Figure 1 **Potential routes of progression from fatty liver to hepatocellular carcinoma.** Most steps are at least partially reversible with lifestyle changes, but a fraction of patients at each stage progresses to more severe liver inflammation and fibrosis until loss of hepatic function becomes mostly permanent. In some patients, HCC can develop on a more rapid course without cirrhosis.

lymphoma, multiple myeloma, malignant melanoma, and endometrial, colorectal, breast, prostate, thyroid, and renal cancers (18). Lipids play an intriguing role in the development of HCC, and factors associated with lipid and energy dysregulation, such as obesity (19), diabetes (20), and hepatic steatosis, are risk factors for HCC (21). Although the different viral, genetic, chemical, and metabolic etiologies of HCC vary with respect to early events leading to hepato-carcinogenesis, they increasingly converge on a set of shared biochemical pathways, of which lipid metabolism is a central player. For example, HBV infection, alcoholic liver disease, and NASH lead to increased lipogenesis and reduction of lysophosphatidylcholine (22, 23).

The pathophysiology of metabolic syndrome is complex and involves multiple organ systems, but in the liver the presence of excess fat promotes inflammation and can lead to cycles of liver cell injury and repair. Damage to the liver is often progressive and can result in fibrosis and eventually cirrhosis, but the process is often partially reversible at the early stages with changes in diet and lifestyle (Figure 1).

NAFLD, CIRRHOSIS, AND HCC

While the long-term progression from NAFLD to NASH to cirrhosis to HCC over a period of decades is frequently observed, there are exceptions. Being overweight increases the risk of HCC by 17%, and obesity increases the risk by 89% (24). In patients with chronic HCV or HBV infection, the presence of NAFLD has been shown to increase the risk of oncogenesis in a synergistic manner (25), suggesting that lipid dysregulation is an independent risk factor for HCC.

NAFLD is on track to become the leading cause of non-cirrhotic HCC, in which liver cancer develops independently of cirrhosis (26–29) and might contribute to cryptogenic cirrhosis, in which the otherwise non-symptomatic cirrhosis is discovered incidentally (30, 31). The mechanism underlying cryptogenic HCC is unclear but may involve progression from NAFLD-based steatosis to lipid catabolism such that the underlying steatosis is no longer observable (32, 33).

Some aspects of lipid dysregulation, such as attenuated lysophosphatidylcholine levels, have been found to be common in patients with NASH and cirrhosis (34), whereas levels of the non-essential amino acids such as valine and isoleucine were elevated in patients with cirrhosis (35, 36). Aside from its direct risks, cirrhosis is also the primary risk factor for HCC, and more than 90% of patients with HCC have cirrhosis (37). In a study of 34,932 patients with cirrhosis, 1,960 patients developed HCC (5.6%) within 1.3 years (37). Currently, NASH-related cirrhosis accounts for about 10% of liver transplantations (38).

HBV AND HCC

Several studies have reported changes in lipid metabolism associated with HBV infection and liver regeneration. Park et al. reported significant changes in phosphatidylcholine composition in HBV-infected mouse livers and found that expression of choline-phosphate cytidylyltransferase A (PCYT1A) was significantly delayed (39). Using an HBx transgenic mouse model, Teng et al. tracked changes in lipid profiles during HBV-induced HCC and observed a biphasic peak in triglyceride, cholesterol, and fatty acid levels in serum and liver tissue (40). The first peak was associated with non-specific pro-inflammatory responses to oxidative stress in mouse hepatocytes. Lipid profiles then transiently resolved at 6 months before peaking again at 12 months, representing a terminal metabolic shift and formation of fatty nodules. The peaks were associated with the upregulation of the following five lipid metabolism-related genes, which were subsequently validated in human HBV-related HCC tumors: arachidonate 5-lipoxygenase, lipoprotein lipase, fatty acid–binding protein (FABP) 4, 1-acylglycerol-3-phosphate O-acyltransferase 9, and apolipoprotein A-IV (40). These results suggest that HBV-mediated perturbation of lipid metabolism plays a role in the mechanism of hepatocarcinogenesis.

DE NOVO LIPOGENESIS IN HCC

Given the role of lipids as structural, signaling, and energy storage molecules, there are a number of ways that lipid dysregulation could contribute to hepatocarcinogenesis. Increased *de novo* lipogenesis and enforced glycolysis appear to be hallmarks of liver cancer (41). One reason for this is the severe metabolic stress experienced within the poorly vascularized tumor core during rapid proliferation causing a nutrient-poor, hypoxic microenvironment on the brink of necrosis or apoptosis. Fatty acid oxidation can continue to provide energy required for cellular metabolism after glycogen has been depleted and in the absence of glucose from the blood. Therefore, glycolysis is elevated, and lipid catabolism is strongly and characteristically upregulated in HCC and other cancers as a means of cell survival. In rapidly proliferating tumor cells, elevated lipid catabolism helps to satisfy the high energy demands of the cells via acetyl-CoA, NADH, and FADH and supplies glycerophospholipids for cell membrane formation (42).

LIPID METABOLIC REPROGRAMMING

Although not fully understood and not as well studied as changes in glucose or glutamine metabolism, lipid metabolic reprogramming appears to be an effective strategy to sustain cancer stem cells in a hypoxic environment (43, 44). Tumor cells harboring beneficial metabolic changes, including those that produce pro-oncogenic metabolic intermediates, may undergo clonal selection (45). For example, the Warburg effect is a well-known adaptive strategy in which tumor cells forsake normal oxidative phosphorylation in exchange for less-efficient aerobic glycolysis, even in the presence of oxygen (46). Similarly, glutaminolysis helps to sustain the Krebs cycle via increased production of citrate and α-ketoglutarate through elevated glutamine metabolism (47). Changes in fatty acid metabolism through metabolic reprogramming have also been found to play an important role in facilitating carcinogenesis (48). Generally, cells import fatty acids and other lipids from the blood, but HCC tumors upregulate genes involved in fatty acid biosynthesis, including SREBP-1-regulated genes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), FAS, SCD-1, and GPAT, in order to generate fatty acids *de novo* (48, 49). A number of key enzymes, including ACLY, ACC, and fatty acid synthase (FASN), catalyze biosynthesis of fatty acids from citrate and acetyl-CoA. ACC catalyzes a key initial step in fatty acid biosynthesis, the conversion of acetyl-CoA to malonyl-CoA (50), and helps to sustain HCC tumors experiencing metabolic stress (51). As a rate-limiting enzyme in lipogenesis, elevated expression of ACCα has been reported to be an independent predictor associated with poor HCC prognosis (51). Similarly, FASN is a multifunctional enzyme that catalyzes the synthesis of long-chain saturated fatty acids during one of the final stages of fatty acid biosynthesis. FASN is over expressed in HCC as well as in many other types of cancer (52), and genetic ablation and drug targeting studies of FASN have revealed suppressed development of HCC (41, 53, 54). Interestingly, aspirin has been shown to suppress abnormal lipid metabolism in hepatoma cells via NF-κB targeting by downregulating the expression of acyl-CoA synthetase long-chain family member 1 (ACSL1), which converts free fatty acids into fatty acyl-CoA esters, an early step in fatty acid degradation and important for lipid biosynthesis (55).

To exploit fatty acids as an efficient source of stored energy, β-oxidation has also been shown to be upregulated in HCC and other cancers (49, 56, 57). In particular, 2-oxoglutarate is upregulated in HCC, and the levels of pyruvate and lactic acid are elevated, whereas carnitine esters, citrate, glycerol-3-phosphate, and free fatty acid levels are reduced (36, 58–61). This lipid-rich state is also associated with obesity, as obese patients not only take in more dietary fatty acids than non-obese patients but also hydrolyze more stored fats from adipose tissue. As a result, the liver is exposed to very high fatty acid levels. The liver adjusts to this stress through adaptive metabolic changes (metabolic reprogramming), such as a shift to aerobic glycolysis and increased glutamine synthesis to provide α-ketoglutarate and citrate for the citric acid cycle, which collectively increase the risk of HCC (44). Obesity-mediated insulin resistance also promotes hyperinsulinemia, and oxidative and endoplasmic reticulum stress and changes in gut microbiota promote release of pro-inflammatory cytokines (62–68). The association between obesity and HCC suggests that

use of statins to treat obesity by inhibiting hepatic cholesterol biosynthesis and metformin to treat insulin resistance might offer some protection against HCC (odds ratios 0.74 and 0.38, respectively) (69, 70). FABPs, which regulate intracellular transport of fatty acids, are upregulated in a number of different cancers, including cancers of the bladder, breast, liver, lung, and prostate, and serve as biomarkers for cancer risk and aggressiveness (71). In a study of lipid-related HCC in a mouse model, Chiyonobu et al. showed that FABP4 was strongly upregulated in activated hepatic stellate cells (HSCs) resident within murine HCC tumors as well as in human metabolic-related HCC tumors but not in viral or alcohol-related HCCs, suggesting a mechanistic role of HSCs in NASH-related HCC (72).

LIPIDOMICS

Although a number of studies have examined changes in gene expression during HCC (73), fully understanding diseases as complex as NASH and HCC requires deep understanding of the internal state of individual cells. Single-cell transcriptomics is now possible; however, HCC tumor heterogeneity remains a challenge. A snapshot of the internal state can be partially reconstructed by assembling multiple complementary types of omics data. Lipidomics, first introduced in 2003, is the branch of metabolomics charged with characterizing the diversity of fatty acids and other lipid products within a cell, tissue, organ, or biofluid. Another goal of lipidomics is to uncover the enzymatic mechanisms and turnover kinetics responsible for changes in lipid metabolism (74). The lipidome is complex, diverse, and dynamic, representing tens to hundreds of thousands of molecular species in a constant state of flux (74). The following is an overview of how lipidomics can help elucidate the molecular mechanisms that contribute to HCC. The common lipidomics methods and selected lipidomics studies pertinent to HCC are summarized in Tables 1 and 2, respectively.

Several metabolomics and lipidomics studies involving HCC or NASH have been performed (Table 2). Puri et al. reported elevated levels of saturated and monounsaturated fatty acids (especially palmitoleic acid and oleic acid) and reduced levels of polyunsaturated fatty acids (e.g., linoleic acid) in patients with NAFLD or NASH compared to healthy controls (90). Patterson et al. compared plasma samples from HCC patients, healthy controls, and patients with cirrhosis or acute myeloid leukemia using ultra-performance liquid chromatography electrospray ionization-quadrupole mass spectrometry (UPLC-ESI-QTOFMS) and ultra-performance liquid chromatography-electrospray ionization-triple quadrupole mass spectrometry (UPLC-ESI-TQMS) (91). They reported that glycodeoxycholate, deoxycholate 3-sulfate, bilirubin, biliverdin, and several fetal bile acids were elevated in the plasma of patients with HCC, whereas lysophosphocholine levels were reduced. Notably, they found that two very long chain fatty acids (VLCFAs), lignoceric acid and nervonic acid, were largely undetectable in plasma from HCC patients compared to patients with cirrhosis. Due to their extended length (≥22 carbons), VLCFAs are synthesized through a multistep elongase-dependent pathway in the endoplasmic reticulum and must be metabolized in peroxisomes (92).

| | TABLE 1 | Common lipidomics methods and selected lipidomics studies involving HCC | |

Method	Description	HCC lipidomics studies
GC	Gas chromatography	(75) (76)
UPLC-MS	Ultra-high performance liquid chromatography mass spectrometry	(77)
MALDI-MS	Matrix-assisted laser desorption/ionization mass spectrometry	(78)
ESI–MS	Electrospray ionization tandem mass spectrometry	(79)
IMS	Imaging mass spectrometry	(80)
LC-MS	Liquid chromatography mass spectrometry	(60, 81–83)
Shotgun lipidomics	Electrospray ionization mass spectrometry	(82)
RPLC-MS	Reversed-phase liquid chromatography mass spectrometry	(84)
LC/IT-TOF MS	Liquid chromatography/ion trap time-of-flight mass spectrometry	(85)
HPLC-MS	High-performance liquid chromatography mass spectrometry	(76, 86)
DESI-MSI	Desorption electrospray ionization mass spectrometry imaging	(87)
LC-ESI–MS	Liquid chromatography electrospray ionization mass spectrometry	(88)
UPLC-ESI-QTOF MS	Ultra-high performance liquid chromatography-electronic spray ionization-QTOF mass spectrometry	(89)
MALDI-FTICR MS	Matrix-assisted laser desorption ionization-Fourier transform ion cyclotron resonance mass spectrometry	(89)
GC-MS	Gas chromatography mass spectrometry	(83)

Lignoceric and nervonic acid, in particular, are involved in the maintenance of myelin, but VLCFAs are known to perform a range of functions, including skin barrier formation, sperm maturation, retinal functions, and liver homeostasis (92). VLCFAs also serve as precursors of inflammation-resolving lipid mediators, with potential roles in HCC formation (92). In a large case-control study comparing matched blood samples from patients before and after HCC diagnosis relative to healthy controls, Fages et al. identified a set of 16 metabolites involved in lipid and amino acid metabolism and ammonium detoxification that served as predictive biomarkers that differed between pre-diagnostic HCC patients and healthy controls, reflecting a characteristically altered metabolic state prior to HCC development (93). Two studies in China also reported panels of serum amino acid and fatty acid biomarkers able to predict HCC with area under the curve (AUC) greater than 0.96 (61, 94). Lin et al. recently showed that a decrease in palmitic acyl-based glycerophospholipids, a key component of the cell membrane, was associated with metastatic HCC (86).

TABLE 2	Selected lipidomics studies

Study	Description
Muir et al. (75)	The authors reported an increased ratio of long chain n6-polyunsaturated fatty acids to n3-polyunsaturated fatty acids in NASH and HCC using a Pten-null mouse model.
Weylandt et al. (76)	Using a fat-1 transgenic mouse model, the authors showed that increased omega-3 polyunsaturated fatty acids suppress HCC tumorigenesis by reducing inflammation.
Passos-Castilho et al. (77)	Serum ultra-high performance liquid chromatography mass spectrometry (UPLC-MS) lipid profiles discriminated patients with HBV-related HCC from patients with chronic HBV.
Passos-Castilho et al. (78)	Matrix-assisted laser desorption/ionization mass spectrometry lipid profiles discriminated patients with HCV-related HCC from patients with chronic HCV.
Krautbauer et al. (79)	Ceramide levels were found to be notably reduced in HCC tissues.
Morita et al. (80)	Levels of phosphatidylcholine containing palmitoleic acid or oleic acid were found to be elevated in HCC using imaging mass spectrometry.
Lu et al. (81)	Lipid signatures varied between HCC and serum samples. Plasmalogens (36:4) and (40:6) are potential serum biomarkers for HCC.
Zhou et al. (60)	Using liquid chromatography-mass spectrometry of serum samples, higher levels of long-chain acylcarnitines and lower levels of free carnitine and medium and short-chain acylcarnitines were detected in HCC.
Lu et al. (83)	Mass spectroscopic analysis of matched tissue and serum samples from patients with HCC was used to evaluate the usefulness of acetylcarnitine as a biomarker.
Chen et al. (85)	Ultra-fast LC/IT-TOF MS serum lipidomics was used to compare lipid profiles for patients with HBV, cirrhosis, and HCC. 75 out of 96 lipids were downregulated in patients with HCC compared to healthy patients.
Lin et al. (86)	Lipid profiling of HCC cells revealed anomalies affecting 93 different lipids. Reduced palmitic acyl glycerophosholipids were associated with greater metastatic activity.
Li et al. (89)	The number of polyunsaturated triacylglycerols with >2 double bonds was found to be reduced based on lipid profiling using UPLC-ESI-QTOF MS and MALDI-FTICR MS.

THERAPEUTIC ADVANCES TARGETING LIPID METABOLISM

Despite a better understanding of lipid metabolism, drugs targeting key steps in lipogenesis in various types of cancer are still in the experimental stage (Table 3) (95, 96). Given the central regulatory role of SREBPs in lipid metabolism, SREBPs represent promising drug targets. SREBP-1 and SREBP-2 are upregulated in glioblastoma and prostate cancer, respectively, and SREBP ablation or blocking has

TABLE 3	Drugs targeting lipid metabolism in tumor cells			

Year	Compound	Target	Tumor Type	Model	Ref.
2019	Simvastatin	Lipid rafts	Human lung cancer	A549 cell	(101)
2018	Paclitaxel and vinblastine	Microtubule dynamics	Human osteosarcoma	U2OS cell	(102)
2017	Betulin	SREBPs	Human liver cancer	Diethylnitrosamine-injected mice model	(83)
2017	Cetuximab	Acetyl-CoA carboxylase (ACC)	Head and neck squamous cell carcinoma (HNSCC)	HN5, FaDu, Tu159, OSC19, MDA1986, UMSCC1, and Tu167)	(103)
2016	Nutlin-3 and actinomycin D	Ceramide synthase 6 (CerS6)	Human lung cancer	A549 cell	(104)
2015	TVB-2640	Fatty acid synthase (FASN)	-	Phase I	(105)
2014	Azoxymethane/dextran sodium sulfate	Sphingosine-1-phosphate (S1P) lyase (SPL)	Colitis-associated cancer (CAC)	CAC murine model	(106)
2012	C75	FASN	Prostate cancer (PC)	LNCaP cell	(107)
2010	PX-866	PI3K	Human glioblastoma	U251, U87, LN229, and LN18 cells	(108)
2010	NDNSAs	Unknown	Human breast cancer	MCF-7 cell	(109)
2009	LCL385	Acid ceramidase (AC)	PC	PPC-1 cell	(110)
2009	15-dPGJ2	PPARγ	Colorectal cancer	CT-26 s.c. tumor model and an HL-60 xenograft model	(111)

been shown to induce cancer cell death and suppression of tumor growth (95). However, development of drugs that directly target transcription factors is difficult, and efforts have instead focused on drugs such as betulin, fatostatin, xanthohumol, and PF-429242 that inhibit the translocation of SREBP to the Golgi apparatus (95). Li et al. examined whether inhibition of *de novo* lipid biosynthesis is protective against HCC by blocking SREBP cleavage-activating protein in hepatocytes using betulin in a diethylnitrosamine-induced HCC mouse model (97). They found that blocking or ablation of this key component of the SREBP pathway suppressed HCC. Drugs have also been developed targeting specific steps in lipid metabolism. The ACC inhibitor GS-0976 has been found to reduce the extent of liver steatosis and fibrosis in NASH patients (98, 99), and drug targeting

of FASN has been shown to suppress HCC development (41, 53, 54). Several existing drugs such as statins and metformin are thought to have a protective effect against HCC (69, 70). Statins, as lipid-lowering agents, have long been used for the treatment of heart disease. They have also been reported to have a protective effect against tumorigenesis. Some published evidence supports the use of statins in HCC prevention in patients with liver disease (100).

CONCLUSION

While much progress has been made in limiting viral and environmental causes of HCC, new cases of NASH-related HCC are currently increasing and are likely to continue to increase for the foreseeable future. Many cases of NASH-related HCC are preventable through changes in lifestyle, including exercise and reduced intake of fructose and high-fat foods, but such changes are difficult to maintain. Therefore, there is an important unmet need to develop biomarkers to monitor changes in hepatic lipid metabolism in NAFLD patients, so that it is possible to intervene as early as possible in patients with the highest risk of progressing to NASH and cirrhosis. Early detection of HCC offers the best chance of treatment, while few procedures significantly improve survival in the case of advanced HCC. It is essential to determine the key molecular events that trigger hepatocarcinogenesis in order to facilitate drug development to prevent or slow development of HCC. Lipidomics provides a valuable tool to assess the detailed metabolic changes that may lead to initiation of liver cancer.

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