Chapter 4

# Lipid Metabolism in Liver Cancer

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Additional information is available at the end of the chapter

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**Abstract**

Hepatocellular carcinoma (HCC) represents 90% cases of liver cancer that is the second leading cause of cancer death in the world. With the pandemic of obesity and other metabolic syndromes in both adults and children, the incidences of fatty liver diseases and the derived HCC are on their upward track. Emerging metabolomic studies have revealed the perturbation of lipid profiles and other metabolites in fatty liver diseases and HCC. Two common metabolic features including enforced fatty acid oxidation and glycolysis could distinguish HCC from healthy liver and chronic non-tumor liver diseases. The potential translational impacts of fatty acid oxidation are gaining great interests, because many recent investigations have demonstrated that tumor cells were dependent on fatty acid oxidation for cell survival and tumor growth. Blockage of fatty acid oxidation could sensitize to metabolic stress-induced cell death and tumor growth inhibition. Thus, lipid catabolism, in terms of fatty oxidation, is tuned for tumor maintenance but vulnerable to pharmacological disruption. The therapeutic potentials of blocking fatty acid oxidation are yet to be further carefully examined.

**Keywords:** liver cancer, lipid metabolism, metabolomics, fatty liver diseases, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, cirrhosis

## 1. Introduction

Liver cancer is the second leading cause of cancer death worldwide [1]. Hepatocellular carcinoma (HCC) represents 90% of primary liver cancer. The incidence of HCC has been successfully improved in China and Southeast Asia, owing to several decades' endeavor in controlling viral hepatitis B and environmental toxicants, for example, aflatoxin in contaminated food and microcystin in pond water [1–3]. By contrast, HCC incidence has been increased in the United States and other Western countries in the last three decades. The fast-growing fraction of the

cases was reported to result from chronic fatty liver diseases: nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) [4].

Epidemiologic studies lend the credence to the importance of NAFLD as the most common cause of liver disease in the world [4]. The prevalence of NAFLD can reach as high as 25–45% [4–6], when image scanning is applied into diagnostic decision. This heavy disease burden of NAFLD may mirror the epidemic of obesity, diabetes, and other metabolic syndromes, which are still on their upward trend in the world [7]. These metabolic disorders are well characterized with the disruption of glucose and lipid homeostasis, accumulated deposition of systemic and hepatic fat, and insulin resistance. As a consequence, these metabolic alterations may predispose liver to chronic inflammation and fibrogenesis, and finally cancerous transformation into HCC, no matter whether liver cirrhosis ensues. Furthermore, the coexistence of NAFLD with viral hepatitis and environmental toxicants may drive the disease progression in a more complicated manner.

The emerging metabolomic technologies enable hepatologists and biologists to have a panorama view of a highly complex and dynamic flux of small metabolites in liver diseases [8]. This methodology includes high-throughput analytical mass spectrometry, nuclear magnetic resonance spectroscopy, and multivariate data analysis, permitting unbiased comparison of "global" profiles of hundreds to thousands of metabolites between samples from two or more liver disease status. As same as the other omics technologies, the metabolomic investigations have provided new insights into liver disease mechanisms and identified novel biomarkers involved in liver diseases and oncogenesis. Recent findings, comparing different phases of liver diseases from healthy liver to NAFLD/NASH, cirrhosis, and eventually HCC, revealed that both Warburg shift (from mitochondrial oxidative phosphorylation to enforced cytosolic glycolysis) and the up-regulation of lipid catabolism occurred as early as in NAFLD/NASH, and throughout the whole oncogenic processes [9].

Different from the well-studied lipogenesis and fat deposition in the liver, the emerging roles of lipid catabolism in cancer maintenance and progression have been unveiled recently [10]. Mechanically, lipid catabolism in terms of fatty acid oxidation and its upstream autophagy pathway may promote cancer cell survival and tumor growth, especially during stringent nutrient deprivation. The aforementioned nutrient deprivation and the metabolic stress ensued usually occur during rapid solid tumor development and during clinical embolization intervention. These recent findings brought to light the translational significance of lipid catabolism in cancer therapeutics.

## 2. Lipid metabolism in liver physiology: a brief introduction

Liver is the central organ for lipid metabolism and fat deposition in the body [11]. Through well-tuned coordination with adipose, muscle, and other tissues, liver plays an essential role in the maintenance of lipid homeostasis and energy balance. Whenever an excess of calories is ingested, fatty acids are synthesized primarily in the liver, and to a lesser extent in the adipose tissue [12]. Dietary carbohydrate, which is digested into two-carbon units acetyl-CoA, is the

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major source of carbon for the synthesis of fatty acids. The process is termed as lipogenesis. An excess of dietary protein also can promote lipogenesis through conversion to acetyl-CoA and other intermediates of tricarboxylic acid cycle (also known as citric acid cycle). After elongation and desaturation, three fatty acids join together by one glycerol molecule to form triacylglycerols. Subsequently, triacylglycerols are packaged into very long low-density lipoprotein (VLDL) particles with cholesterol, phospholipids, and proteins. VLDL particles are then released into blood and then transported to major organs including adipose tissues for storage in the form of triacylglycerols, and muscle for energy metabolism. The aforementioned process is briefly summarized in **Figure 1**.

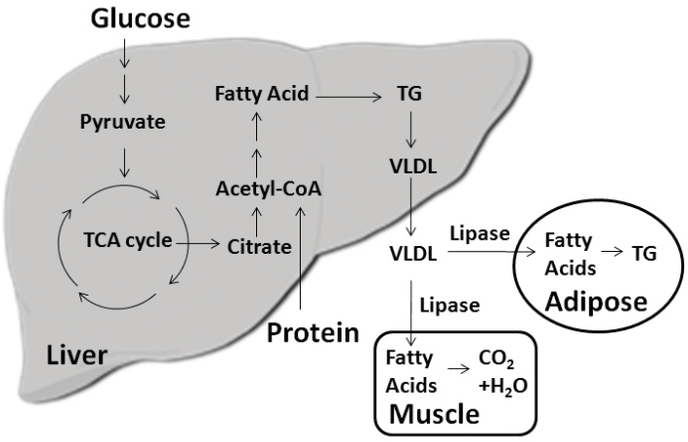


**Figure 1.** Schematic diagram of lipogenesis in the liver. Fatty acids are synthesized from glucose and excess protein in the liver after meals. After conversion into triacylglycerol, fatty acids are packaged in VLDL particles and then transported to adipose for storage and muscle for energy metabolism. TCA cycle: tricarboxylic acid cycle; TG: triacylglycerol; VLDL: very long low-density lipoprotein.

When the serum level of glucose runs low before next meal or during short-term fasting, the body can mobilize energy deposits sequentially from glycogen to triacylglycerols. This process is tightly regulated by hormones, in a coordination of decrease in insulin and increase in glucagon. The hormone-sensitive lipase breaks down triacylglycerols into glycerol and fatty acids, and the latter are released into the blood. The fatty acids are then transported to muscle and other tissues to meet immediate energy demands, where fatty acids are oxidized to $CO_2$ and water to produce energy. During extended fasting, the body mainly mobilizes lipids through fatty acid beta-oxidation, and even digests unnecessary protein and organelles through a catabolic process called autophagy.

Therefore, lipid metabolism is important for normal liver physiology. Triacylglycerols are the predominant form to store fat energy, mainly in adipose tissue and also in liver. However, unhealthy lifestyles of nutrition overload and physical inactivity may tilt the balance of lipid homeostasis and disrupt the body sensitivity to insulin [7]. In the long run, fat accumulates systemically in the adipose tissues and locally in the liver, contributing to inflammation and fibrogenesis, and consequently obesity and fatty liver diseases [12].

## 3. A heavy burden of fatty liver diseases for liver carcinogenesis

NAFLD is a well-recognized common liver disease in the world [4, 13, 14]. Most individuals with NAFLD are restricted to benign and dormant liver steatosis. Up to 25–30% NAFLD patients progress to NASH [14], an aggressive form of NAFLD with combined complications of steatosis, inflammation, and fibrosis. NAFLD is a growing etiological cause of HCC, especially in those regions with low incidence of viral hepatitis, for example, USA, UK, and other Western countries [13, 14]. The incidence of HCC has tripled from 1.5 to 4.9 per 100,000 individuals in the past three decades in the United States alone [15]. It has been suggested that NAFLD will become the leading cause of HCC in the coming decade [16, 17], due to not only the epidemics of obesity and type 2 diabetes but the successful control of risk factors including hepatitis B virus (HBV) by at-birth vaccination, hepatitis C virus (HCV) by novel antiviral treatments, aflatoxin contamination by food hygiene, and microcystin in pond water by the change of drinking water source.

NAFLD coincides with or occurs on the basis of preexisting metabolic conditions, accounting for up to 90% of obese patients [18, 19] and up to 70% of type 2 diabetic patients [20, 21], which were confirmed by large cohort studies based on examinations using ultrasound examination and liver biopsy. The high prevalence of NAFLD (25–45% for all ages and 10–20% for children) is not surprising [14, 22], if the pandemic background of overweight and obesity in the world is considered. The proportion of adults with overweight or obesity, whose BMI (body mass index) was more than 25 kg/m$^2$, increased between 1980 and 2013 from 28.8 to 36.9% in male and from 29.8 to 38.0% in female globally [7]. Note that there were 23.8% boys (younger than 20) and 22.6% girls suffering from overweight or obesity in 2013. In China, the biggest developing country in the world, the prevalence of adult overweight (30.1%, BMI between 25 and 30) and obesity (11.9%, BMI of >30) in 2012 was catching up with those of Western countries. Thus, obesity has become and will remain a major public health challenge in both developed and developing countries. Undoubtedly, the prevalence of NAFLD is also on its upward track in the foreseeable future.

Meta-analysis of large prospective population-based cohorts demonstrated that overweight or obese persons had relatively 17 or 89% higher risks, respectively, to develop HCC, compared to their normal-weight peers [23]. The risk in male was much higher than that in female. According to a large Swedish cohort study, obese males had 3.1-fold higher risk than the normal-weight control [24]. Another US study reported a 4.5-fold increase in HCC risks in overweight and obese males [25]. Similar trends have been found in diabetic patients. El-Serag and colleagues reported that the risk of males with type 2 diabetes to develop HCC was 2.5 times of those without, according to a systematic review and meta-analysis of case-control and cohort studies [26]. Although yet unproven in large cross-section populations, some case-control studies have shown that the active treatment of obesity (by Statins) and/or diabetes (by Metformin) may be beneficial for HCC reduction with odds ratio of 0.74 (95% confidence interval (CI): 0.64–0.87) and 0.38 (95% CI: 0.24–0.59), respectively [27, 28].

NAFLD may coexist with other chronic liver disease and synergistically promote liver oncogenesis [13, 14]. A large Taiwan cohort study observed that obesity and hepatitis C

combined had a higher HCC risk than obesity alone or obesity and hepatitis B combined (odds ratio 4.13 vs. 2.36 and vs. 1.36, respectively) [29]. Furthermore, according to another study based on 23,712 Taiwan residents, obesity and alcohol use had a synergistic effect in HCC incidence with an unadjusted odds ratio of 7.19 (95% CI: 3.69–14.00), compared to obesity alone (odds ratio 1.47, 95% CI: 0.95–2.30) and alcohol use alone (odds ratio 2.56, 95% CI: 1.96–3.35) [30]. After multivariate adjustment, the combined effect was still significant with an odds ratio of 3.82 (95% CI: 1.94–7.52). NAFLD may also contribute to cryptogenic cirrhosis, which represents 30–40% of HCC cases in developed countries [31]. The relationship between NAFLD and cryptogenic HCC could only be verified through medical history taking. Cryptogenic HCC may account for more advanced stage HCC through a complicated process from initial NAFLD/NASH-based hepatosteatosis to subsequent extensive lipid catabolism [32–34], so that the original steatosis was not observable at diagnosis. Although cirrhosis usually precedes HCC, increasing studies showed that NAFLD might induce HCC independent of cirrhosis [34–36]. It has been reported that NAFLD may account for 59% of non-cirrhotic HCC, compared to diabetes (36%) and chronic hepatitis C (22%), according to a recent study based on US health-care claims database [17].

It is worth noting that the risk of NAFLD to develop HCC may not be as high as those of hepatic virus and aflatoxin. The relative risk of NAFLD/NASH alone in the absence of cirrhosis for HCC mortality was found to be as weak as 0–3% for a follow-up period up to 20 years [37]. The cumulative incidence for NAFLD with cirrhosis increased to a range between 2.4 and 11.3%, which was yet comparatively lower than that of hepatitis C with cirrhosis (17–30% for a 5-year cumulative incidence) [34, 35, 38]. By contrast, the relative risks for HBV and HCV to develop HCC are 15–20 folds, according to large case-control and cross-sectional studies [3, 39, 40]. A nested case-control study of 18,000 male residents in Shanghai, China, found that exposure to HBV alone caused an increased HCC risk by 7.3, exposure to aflatoxin alone 3.4, and exposure to both remarkably 59.4 [41]. The public health impact of NAFLD on HCC development, however, could not be overlooked, if considering the higher prevalence of NAFLD than that of viral hepatitis (20–40% for NAFLD vs. 6.3% for viral hepatitis in the Western countries, and 15–30% for NAFLD vs. 11–14% for viral hepatitis in China) [3, 4, 13, 40].

The underlying molecular mechanisms involving how NAFLD promote HCC are yet unclear. Several hypotheses have been suggested. First, chronic inflammation, the increased release of adipokine, and insulin resistance may affect cell proliferation and responsiveness [42, 43]. Second, enhanced lipogenesis and fat deposition may induce extensive lipotoxicity, oxidative stress, and subsequent DNA damages [44, 45]. Third, oncogenic insulin-like growth factor (IGF)-1/PI3K/mTOR, tumor necrosis factor (TNF)-alpha/mitogen-activated protein kinase (MAPK), and/or interleukin (IL)-6/STAT3 pathways were actively involved in HCC [46, 47]. Fourth, hepatosteatosis may influence the hepatic stellate cells and alter microenvironment, causing irreversible fibrosis and cirrhosis [48]. Lastly, the alteration of gut microbiota may influence HCC through bacterial metabolites [49].

Taken together, the growing contribution of NAFLD to HCC development is acknowledged globally. Although the risk of NAFLD alone is comparatively low, the public health impact of

NAFLD and its synergistic effects with other chronic liver diseases on HCC development may pose a huge threat in the coming decades.

## 4. Lipid metabolism in liver oncogenesis: insights from metabolomic studies

Emerging metabolomic technologies represent a powerful platform to dissect global metabolite profiles in an unbiased manner and to discover novel biomarkers and pathways in liver oncogenesis [8]. This high-throughput strategy may complement the other omics technologies (genomics, proteomics, and others) to improve diagnosis, prognostication, and tumor therapy in HCC. Recent metabolomic investigations have shed light on the importance of lipid metabolism on the liver oncogenic processes.

Dr. Beyoglu and Idle in the University of Bern, Switzerland [9], recently well summarized the metabolomic findings conducted in chronic liver diseases and HCC, and proposed a three-stage biochemical progression from healthy liver to carcinoma through intermediate phases of chronic liver diseases including NAFLD/NASH and cirrhosis, according to the alterations of major metabolites and the involved metabolic pathways. A common alteration of "core metabolic phenotype [9]" was found between liver diseases and healthy liver. Deregulation of bile acid and phospholipid occurred in the early phase of NAFLD/NASH, and maintained in cirrhosis and HCC. In HCC, Warburg effect (enforced cytosolic glycolysis over mitochondrial oxygen respiration) and induction of lipid catabolism were commonly observed phenotypes, and could be detected as early as in a few NAFLD/NASH cases. The NAFLD-derived HCC also demonstrated the up-regulation of metabolites from triglycerides that were originally stored in adipose. These alterations observed in HCC (also termed as metabolic reprogramming), as summarized in **Figure 2**, were regarded as one of common hallmarks of tumor [50].

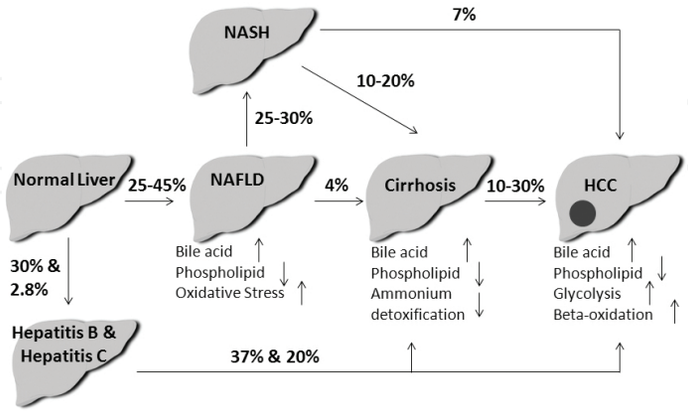


**Figure 2.** The metabolomic alterations during liver oncogenesis. Liver oncogenesis progresses from healthy liver to HCC through several intermediate chronic liver diseases including NAFLD/NASH, cirrhosis, and viral hepatitis. The percentages of early-stage or intermediate liver diseases progress to the next advanced stage were shown as indicated. The major metabolomic alterations were summarized.

Metabolomic investigations of NAFLD utilized serum and tissue specimens from animal models and human. As a manifestation of steatosis, the lipogenesis (triacylglycerols, diacylglycerol, and phospholipids) [51–53] and bile acid biosynthesis (cholesterol esters, choline, and bile acids) [54, 55] pathways were found to be up-regulated. The hepatic lipids were found to be rearranged and repartitioned from adipose to liver, rather than *de novo* lipogenesis and deposition in the liver, possibly through increased turnover of phosphatidylcholine and phosphatidylethanolamine [9]. This conclusion was supported by a mouse starvation experiment that TG(44:2) and TG(48:3), the most abundant triacylglycerols in adipose, were significantly deposited in the liver after 24-h starvation [52]. Similar increase in glycolysis was also demonstrated by the common elevation of lactate and reduction of glucose in mouse obesity models and human NAFLD specimens [56, 57], which is consistent with the inductive role of insulin resistance on pyruvate kinase M2 [58]. On the other hand, the sustained hyperactivation of hepatic lipid metabolism subsequently aroused extensive oxidative stress and competitively repressed antioxidant biochemical species such as glutathione and cysteine-glutathione disulfide [54, 56]. As an advanced stage of NAFLD, NASH has a similar demonstration of increased lipogenesis (triacylglycerols) and bile acid biosynthesis [53, 56], but differs in the decreased lysophosphatidylcholine [59]. The decrease of lysophosphatidylcholine and increase of bile acids were indicative of inflammation in NASH.

Cirrhosis is characterized by extensive liver fibrosis/regeneration and liver dysfunction, attributable directly to liver cell damages and indirectly to portal hypertension. It has been estimated that 10–20% of NASH cases eventually progressed to cirrhosis over a follow-up period of 10 years [4]. Metabolomic studies examined the alterations of metabolite profiles comparing serum or biopsies from healthy liver and from cirrhotic liver in human, but the results varied possibly due to the different etiologies. As same as NASH, the cirrhotic liver had attenuated lysophosphatidylcholine [60]. But cirrhosis differed from NASH in liver dysfunctions of several metabolic pathways. First, amino acids metabolism was impaired, as exemplified by the increase of serum nonessential amino acids and aromatic amino acids but the decrease of essential amino acids particularly branched-chain amino acids valine and isoleucine [61, 62]. Second, ammonium detoxication was found to be reduced, as evidenced by the increase of glutamate but the decrease of glutamine and glucose [63]. Therefore, these metabolic dysfunctions of amino acid metabolism and ammonium detoxification may collectively mirror the pathological damages in cirrhosis.

The metabolic reprogramming in HCC has been investigated by a greatest number of metabolomic studies. Accumulated data suggested that glycolysis and beta-oxidation were commonly elevated in HCC. On one hand, the enforced glycolysis over mitochondrial oxygen respiration (also called Warburg effect), although comparatively lower in reaction rates (fourfold increase) than the other types of tumor, was a common metabolic phenotype in tumor. This phonotype was evidenced by the following metabolic changes including the decrease in glucose, citrate, and glycerol 3-phosphate but the increase in lactic acid and pyruvate [64–69]. On the other hand, the common induction of beta-oxidation was exemplified by the elevation of 2-oxoglutarate and reduction of free fatty acids, carnitine and carnitine esters [61, 64, 66, 68, 70–73]. This theme will be further explored in the next section. As same

as the intermediate liver diseases, HCC maintained the aforementioned "core metabolic phenotype" of bile acid and phospholipid perturbation [66, 71, 73–75]. Some findings also demonstrated similar liver impairments of ammonium detoxication and amino acid metabolism in HCC as in cirrhosis [66, 72, 73, 76].

Other chronic liver diseases, for example, alcoholic liver disease and viral hepatitis, share some similar metabolic alterations to NASH, such as increased lipogenesis and reduction in lysophosphatidylcholine [77, 78]. Metabolomic profiling of a hepatitis B virus X (HBx) transgenic mouse model confirmed the involvement of lipid metabolism (triacylglycerol, cholesterol, saturated, and monounsaturated fatty acids) in HBV-induced liver oncogenesis [79]. This similarity indicated that chronic liver diseases may share some common biochemical and mechanical pathways particularly lipid metabolism, in spite of the differences in etiologies.

A recent nested case-control study from a large European prospective cohort compared serums collected before diagnosis in 114 HCC with 222 matched controls and carefully controlled possible confounders such as tobacco usage, alcohol consumption, and so on [80]. Sixteen metabolites involved in amino acid metabolism, choline metabolism, polyunsaturated lipid metabolism, and ammonium detoxication were selected for potential biomarkers. These metabolomic changes are actually reflective of the underlying precancer liver dysfunctions before HCC occurrence (as discussed above). And these data are pivotal for understanding the process of HCC oncogenesis. The results also demonstrated that the pre-diagnostic metabolic profiles between HCC cases and respective control were different, which was dependent on hepatitis infection status, liver function, and the length of time from blood collection to HCC diagnosis.

Many recent investigations applied metabolomics technologies in biomarker discovery to advance HCC diagnosis. One Chinese study using a panel of metabolic markers (formate, phytosphingosine, and $3\alpha,6\alpha,7\alpha,12\alpha$-tetrahydroxy-$5\beta$-cholan-24-oleic acid) achieved high accuracy (area under curve (AUC): 0.995–1.000, sensitivity: 100%, and specificity: 94.7–100%) in diagnosing HCC patients with low alpha-fetoprotein (a commonly accepted but mediocre biomarker to differentiate HCC from non-tumor liver at a cut-off value of 20 ng/ml) [73]. Another Chinese study, which used tryptophan, glutamine, and 2-hydroxybutyric acid as biomarkers in 183 human serum, also achieved high accuracy (AUC: 0.969–0.990) in both training and validation dataset [69]. Furthermore, the aforementioned European study [80] also demonstrated better diagnostic performance of metabolites than alpha-fetoprotein and liver enzymes.

Taken together, metabolomic investigations have suggested many useful biomarkers and potential biochemical pathways in chronic liver diseases and HCC. Some of them such as bile acid and lysophosphatidylcholine may belong to the "core metabolic phenotype" of background chronic liver diseases and are not necessarily indicative of the tumor status of HCC. Some other alterations, for example, those of ammonium detoxication or amino acid metabolism, may suggest the impaired liver functions. In HCC, there are common findings of enforced glycolysis and enhanced lipid catabolism. These two changes are consistent with the high

demand of energy and intermediate metabolites in HCC cells for protein and membrane synthesis during fast tumor growth.

## 5. Lipid catabolism in liver cancer: a potential therapeutic target

As same as the enforced glycolysis, hyperactivation of lipid catabolism is commonly observed in HCC and other types of cancer. In tumor cells, lipid catabolism and glycolysis may share a few common oncogenic functions. First, both of them are important energy resources physically and pathologically. Second, their metabolisms support cell survival and tumor growth during stringent metabolic stress. Third, they can donor essential metabolic intermediates for protein and membrane anabolic biosynthesis in the fast growing tumor.

The body stores two types of major energy resources: triacylglycerol and glycogen. After a meal, the liver synthesizes both triacylglycerol and glycogen. Comparatively, triacylglycerol can provide six times as much ATP as glycogen, so that triacylglycerol is the preferred resource for storage. Lipid catabolism in terms of fatty acid oxidation is physically performed in heart and skeletal muscle, the highest energy-demanding tissues in the body. But the high activity of fatty acid oxidation in HCC and other types of cancer tissues, as revealed above by metabolomic studies, may provide excess ATP generation when needed.

During fast proliferation, tumor cells, especially those in the core of solid tumor nodules, may experience limited nutrient and oxygen availability because of insufficient tumor neoangiogenesis. This type of nutrient deprivation and the metabolic stress ensued may drive the tumor cells to programmed cell death. However, active fatty acid oxidation in the resistant HCC cells can protect cells with necessary ATP generation even if the exogenous glucose is unavailable and the endogenous glycogen is depleted. The author recently confirmed this hypothesis by comparing the starvation-sensitive with -resistant HCC cells [81]. The results demonstrated that the sensitive HCC cells, lack of an important transcription factor C/EBPalpha, could not initiate fatty acid oxidation and died within 12 h during enforced glucose deprivation *in vitro*. By contrast, the resistant C/EBPalpha-expressing HCC cells could activate autophagy-mediated lipid catabolism and survive as long as 8 days. But blockage of autophagy and the downstream fatty acid beta-oxidation by either pharmacological inhibitors or genetic shRNA intervention could significantly abolish the protective effect. Furthermore, this phenotype could be reproduced *in vivo* in a mice xenograft experiment that the C/EBPalpha-silenced HCC cells failed to develop tumor nodules due to extensive necrosis within a few days after inoculation of the tumor cells into the flank of mice. More importantly, we observed an inverse association of the expression level of C/EBPalpha with tumor necrosis in human HCC tissues. The higher C/EBPalpha expressed in human HCC, the less tumor necrosis observed. Consistently, these results shed the light on the importance of fatty acid oxidation on cell survival and tumor maintenance.

The involvement of fatty acid oxidation in cell survival was also observed during cell detachment from tumor matrix. Cells derived from solid tumor are dependent on fatty acid oxidation to survive when the cell experiences loss of attachment (LOA) to the extracellular matrix [82].

Otherwise, the cell will die in anoikis, a specific form of apoptotic cell death induced by inadequate cell-matrix interactions. Accumulating data have shown that antioxidants and oncogenes (e.g., promyelocytic leukemic protein, carnitine palmitoyltransferase isoform 1C) could activate fatty acid oxidation to support cell survival during LOA and other types of metabolic stresses [82–84]. Promyelocytic leukemic protein was found to be overexpressed in a subset of aggressive breast cancer [83], while the brain-isoform carnitine palmitoyltransferase 1C was abnormally up-regulated in human lung cancer [84]. With the aid of fatty acid oxidation, the survived cancer cells could migrate to distant locations and settle down in possible metastatic sites. Second, during metabolic stress, fatty acid oxidation could sustain NADPH level and consequently counteract harmful oxidative stress. In glioma cells, inhibition of fatty acid oxidation caused significant reduction of NADPH, accumulation of redox oxygen species, and eventually cell death [85]. The involved mechanisms of NADPH production by fatty acid oxidation were later found to be mediated by LKB1-AMPK pathway [86, 87]. Lastly, one study demonstrated that leukemia progenitor cells required fatty acid oxidation to maintain stem cell property [88].

The translational impact of fatty acid oxidation on cell survival and tumor growth has been tested recently. Dr. Samuduio and colleagues initially showed that pharmacological inhibitors (etomoxir and ranolazine) of fatty acid beta-oxidation could sensitize leukemia cells to chemotherapeutic drugs-induced cell death *in vitro* [89]. Later, the antitumor effects of a novel inhibitor ST1326 were confirmed in patients-derived leukemia primary cells *in vitro* [90] and in an *in vivo* mice model of Burkitt's lymphoma [91]. Furthermore, the synergistic effects of fatty acid oxidation inhibitors (etomoxir or CVT-4325) were reproduced in L-asparaginase-treated childhood acute lymphoblastic leukemia cells [92] and in dexamethasone-treated lymphocytic leukemia cells [93], respectively. Recently, etomoxir was applied to MYC-overexpressing triple-negative breast cancer [94]. The results showed that the inhibition of fatty acid oxidation significantly abolished tumor growth in both an MYC-driven transgenic mice model of breast cancer and patient-derived xenografts.

Nutrient deprivation may occur not only in pathological solid tumor growth but during clinical intervention. Embolization treatment, especially transarterial chemoembolization, is applied to intermediate-stage HCC (BCLC B), which may account for 20% HCC patients [95]. By blocking the main arterial of blood supply to tumor nodules, this clinical intervention aims to starve and suffocate tumor cells. Whether fatty acid oxidation helps HCC cells escape cell death induced by embolization and whether this survival advantage contributes to HCC recurrence are yet to be determined. It will be also interesting to learn whether the addition of pharmacological inhibitors of fatty acid beta-oxidation is beneficial for the efficacy and safety of transarterial chemoembolization therapy.

Taken together, lipid catabolism (especially fatty acid oxidation) is important for tumor cell survival and tumor growth during nutrient deprivation-induced metabolic stress. Several investigations have confirmed the antitumor effects of the inhibitors of fatty acid oxidation *in vitro* and *in vivo*. The therapeutic potentials of this target need to be further explored.

## 6. Conclusion and perspective

Lipid metabolisms are essential for both healthy and diseased liver. It is apparent that with the pandemic of obesity, diabetes, and other metabolic syndromes, the incidence of NAFLD-, NASH-, and NAFLD-derived HCC will be on the upward trend in the foreseeable future. The *de novo* lipogenesis induced by nutrition overload dominates in the liver. Excess lipids deposit in the adipose and liver, causing lipotoxicity, oxidative stress, and inflammatory reactions. The metabolomic investigations have analyzed the perturbed metabolite profiles in the fatty liver diseases and identified several novel biomarkers and biochemical pathways. At this precancer stage, enhancement of lipid catabolism, together with dietary control, will be beneficial for the health. This goal can be achieved by regular physical exercises, medical intervention (e.g., administration of Statins or Metformin), and other preventive countermeasures. It has been reported that the consumption of coffee or tea could reduce HCC risks, according to large epidemiological studies [96]. Mechanically, the main components of coffee (caffeine) and tea (epigallocatechin-3-gallate) were found to promote autophagy and fatty acid oxidation [97, 98].

The induction of fatty acid beta-oxidation in HCC may reflect the high-energy demand for rapid tumor growth and cell survival. Accumulating metabolomic studies have confirmed this change. The oncogenic drivers for the metabolic reprogramming from the original net lipid gain in fatty liver diseases to the increased lipid loss in HCC, however, are yet to be unveiled. The translational impacts and therapeutic potentials of fatty acid oxidation are gaining growing interests. Oriented inhibition of fatty acid oxidation in the tumor cells may be useful for cancer treatment, especially if applied with the strictly localized application of transarterial chemoembolization. However, this hypothesis has not been carefully tested. It is of particular importance to examine the safety of systemic administration of fatty acid oxidation inhibitors in the non-tumor tissues.

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