



Review Article



Advances in Lipid Metabolism Reprogramming in Hepatocellular Carcinoma

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Abstract

Lipid metabolism reprogramming drives malignant proliferation and invasiveness in hepatocellular carcinoma (HCC). Beyond supplying energy and membrane components, lipids function as signaling molecules that modulate tumor cell epigenetics and the microenvironment. Accumulating research has clarified the implications of these metabolic alterations in HCC, providing a rationale for targeted therapies. This review summarizes key alterations in lipid metabolism within HCC and explores their mechanistic contributions to tumor progression. It further examines how lipid metabolic shifts in immune and stromal cells of the tumor microenvironment promote HCC advancement. Finally, we discuss the therapeutic potential of targeting lipid metabolism in liver cancer treatment.

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Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer globally, constituting 75%–85% of primary liver cancers. In China, HCC incidence is the fifth highest, with both mortality rate and absolute death toll ranking second.¹ Over recent years, the global incidence of hepatitis B virus (HBV)-related HCC has declined, whereas the proportion of HCC attributable to metabolic factors, including obesity and diabetes, has doubled over the past two decades. It is projected that by 2030, the incidence of metabolic-associated HCC in China will rise by at least 80%. Additionally, age-standardized death rates for non-alcoholic steatohepatitis-

related HCC are increasing across the Americas, the Eastern Mediterranean, the Western Pacific, and Europe. These trends underscore the critical importance of investigating metabolic-related HCC for future prevention and therapeutic strategies.^{2–4} Altered lipid metabolism is a pivotal driver in obesity-related HCC pathogenesis and progression. HCC cells fuel their growth primarily by upregulating key metabolic pathways: lipid uptake, de novo lipogenesis (DNL), and fatty acid oxidation (FAO).^{5,6} Beyond serving as an energy reservoir, lipids function as essential membrane components and signaling mediators during this metabolic reprogramming. Specific lipid species, such as palmitic acid (PA), can further regulate HCC progression via epigenetic mechanisms. Moreover, the lipophagy pathway has emerged as a key regulator of HCC invasion, metastasis, and drug resistance by controlling lipid droplet (LD) turnover.

Lipid metabolism alterations fuel HCC progression not only by directly affecting tumor cells but also by remodeling the tumor microenvironment (TME). This is achieved through the modulation of immune and stromal cell recruitment and function. Specifically, HCC cells secrete lipid-associated metabolites and signaling molecules that reprogram the activity of cancer-associated fibroblasts (CAFs) and diverse immune populations. Moreover, the intrinsic metabolic rewiring within the TME drives lipid accumulation and enhanced FAO, which collectively foster an immunosuppressive niche.

Most HCC patients are diagnosed at advanced stages, necessitating systemic therapy to delay disease progression.^{7,8} However, accumulating evidence has identified altered lipid metabolism as a key determinant of antitumor treatment efficacy in HCC. Lipid metabolism-related gene signatures enable the prediction of HCC patient responses to immunotherapy.⁹ Furthermore, inhibition of lipid synthesis has been shown to enhance therapeutic efficacy against HCC.^{10,11} Consequently, elucidating the role of lipid metabolism in HCC is critical for advancing antitumor strategies, underscoring its substantial research potential and broad implications for therapy development. In this review, we focus on lipid metabolism reprogramming in HCC and its impact on the TME. Finally, we discuss potential therapeutic strategies for HCC targeting lipid metabolism.

Lipid metabolism reprogramming in HCC

Most lipid molecules ingested daily by the organism are hy-

Keywords: Hepatocellular carcinoma; Lipid metabolism; Lipogenesis; Lipid droplets; Cholesterol esters; Fatty acids; Autophagy; Tumor microenvironment; Immunomodulation; Immunotherapy; Molecular targeted therapy; Neoplasm drug resistance.

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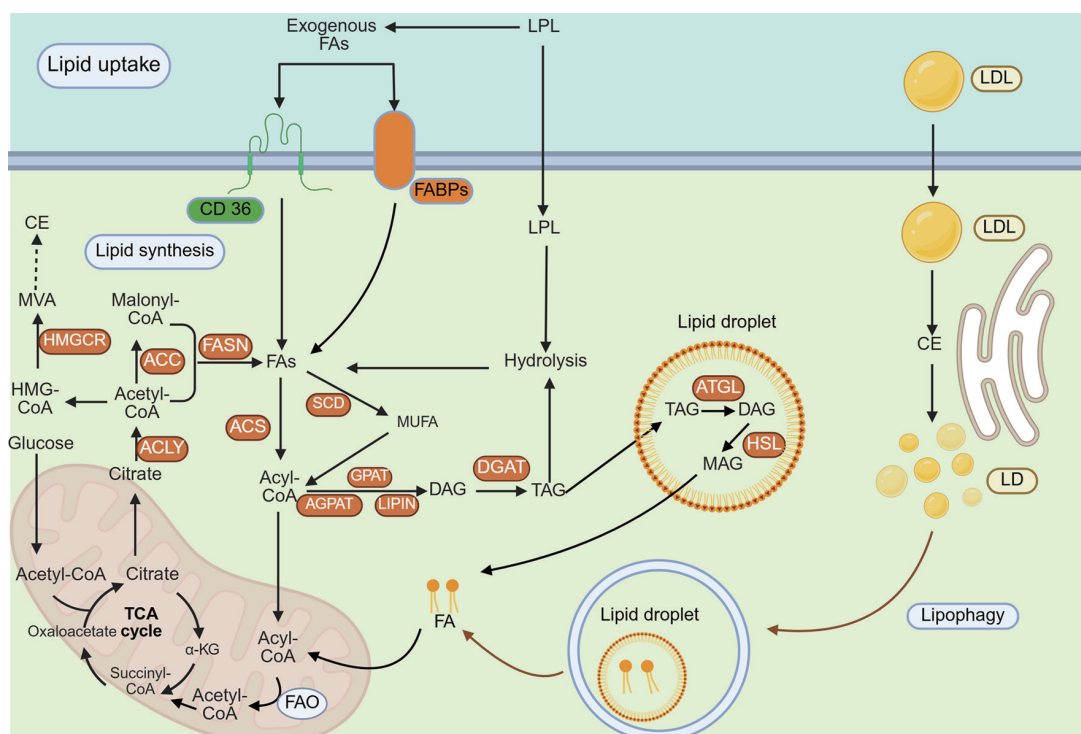


Fig. 1. Lipid metabolic pathways in HCC. HCC accrues lipids through two primary pathways: exogenous uptake and endogenous synthesis. Exogenous uptake is enhanced via the upregulation of transport proteins like CD36 and FABP during tumor progression. Meanwhile, endogenous synthesis is driven by key enzymes such as FASN and SCD, which catalyze the conversion of metabolites including citrate, glutamine, lactate, and acetate into saturated fatty acids and cholesterol. Excess intracellular lipids are stored primarily as CE and TAG within LDs, a storage form that confers protection against lipid peroxidation. The turnover of these LDs is regulated by lipophagy, a selective autophagy process that modulates HCC progression. CE, cholesteryl ester; CoA, coenzyme A; DAG, diacylglycerol; FA/FAs, fatty acid/fatty acids; HCC, hepatocellular carcinoma; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LD, lipid droplet; LDL, low-density lipoprotein; MAG, monoacylglycerol; MUFA, monounsaturated fatty acid; MVA, mevalonate; TAG, triacylglycerol; TCA cycle, tricarboxylic acid cycle; α -KG, α -ketoglutarate; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ACLY, ATP citrate lyase; ACS, acyl-CoA synthetase; SCD, stearoyl-CoA desaturase; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; DGAT, diacylglycerol acyltransferase; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase.

drolyzed into glycerol and fatty acids via lipid metabolism. Upon conversion, glycerol participates in glucose metabolism-related pathways. On the one hand, fatty acids act as biosynthetic substrates and energy sources, influencing HCC proliferation; on the other hand, fatty acids also function as membrane-associated components, maintaining cellular homeostasis within the body. In HCC, pathways governing lipid uptake, synthesis, and lipophagy frequently display heterogeneity, which directly influences disease progression. To this end, the following section systematically details the mechanisms of lipid metabolism reprogramming in HCC across three interconnected aspects: exogenous lipid uptake, endogenous lipid synthesis, and lipophagy (Fig. 1).

Lipid uptake during metabolic reprogramming

In HCC, fatty acid uptake is governed by specific transport proteins. Recent studies have revealed that lipid uptake mediated by cluster of differentiation 36 (CD36) and fatty acid-binding proteins 4 (FABP4), along with metabolic remodeling, contributes to the progression of liver diseases in animal models.^{12,13}

CD36 and FABPs represent the most pivotal transporters in the uptake of free fatty acids (FFAs). CD36 regulates the uptake of long-chain fatty acids (LCFAs) and FFAs, and numerous studies have demonstrated elevated CD36 expression on HCC cell membranes.^{14,15} Studies have shown that CD36 activates sarcoma tyrosine kinase (Src) and engages the downstream phosphatidylinositol 3-kinase (PI3K)/pro-

tein kinase B (Akt)/mechanistic target of rapamycin (mTOR) pathway. In HCC models, CD36 overexpression enhances signaling through this axis, promotes tumor growth, and facilitates distant metastasis. The CD36-high group also showed a higher incidence of tumor formation than the control group. RNA interference-mediated suppression of CD36 markedly inhibits downstream Src/PI3K/Akt signal transduction and attenuates tumor growth *in vivo*.¹⁶ Notably, in high-fat diet-induced HCC, CD36 selectively promotes monounsaturated fatty acid (MUFA) uptake. This maintains lipid homeostasis and alleviates saturated fatty acid (SFA)-induced endoplasmic reticulum (ER) stress and cell death, thereby supporting tumor progression.¹⁷ Additional studies reveal that CD36 augments exogenous fatty acid uptake by upregulating aldo-keto reductase family 1 member C2 expression, thereby driving HCC advancement. In murine HCC models, suppression of CD36-mediated fatty acid uptake effectively attenuates tumor growth and metastasis.^{18,19} CD36 is a key mediator of lipid uptake in HCC cells, where it regulates fatty acid uptake and downstream signaling. Beyond tumor cells, studies in the TME have also shown that CD36-driven lipid accumulation alters immune and stromal cell function. These changes are associated with the establishment of an immunosuppressive microenvironment.^{20,21}

The FABP family comprises small-molecule lipid chaperone proteins, with numerous studies demonstrating elevated FABP5 expression in HCC, primarily governing the intracellular trafficking and uptake of LCFAs and FFAs.²² FABP5-

mediated uptake of FFAs activates the hypoxia-inducible factor-1 (HIF-1) pathway. Under hypoxia, FABP5 enhances HIF-1 α translation, suppresses FIH-dependent hydroxylation, and facilitates p300 recruitment, collectively increasing HIF-1 α transcriptional activity. This axis upregulates lipid storage genes including acyl-CoA synthetase long-chain family member 1, glycerol-3-phosphate acyltransferase, LIPIN1, and diacylglycerol O-acyltransferase 2, while concurrently suppressing β -oxidation and lipolytic enzymes. These metabolic shifts drive LD accumulation, ultimately promoting HCC proliferation and conferring resistance to reactive oxygen species (ROS)-mediated toxicity.^{23,24} In murine HCC models, FABP5 inhibition or knockdown renders HCC cells more susceptible to lipid peroxidation and ferroptosis, thereby suppressing HCC development.^{25,26}

Lipid synthesis and metabolism reprogramming

In HCC, DNL is a key metabolic pathway; through enhancing lipid synthesis and accumulation, it provides the biosynthetic raw materials and energy required by tumor cells. Across multiple HCC cohorts, high expression of genes and regulatory factors involved in DNL shows a significant association with poorer overall survival. Enhanced DNL may therefore represent a prominent molecular hallmark associated with poor prognosis in HCC.^{27–29} DNL in HCC promotes lipid synthesis by upregulating core enzymes such as acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), fatty acid synthase (FASN), and stearoyl-CoA desaturase 1 (SCD1), leading to lipid accumulation. SCD1 mainly regulates the conversion of SFAs to MUFAs. In HCC, SCD1 overexpression increases the MUFA/SFA ratio, thereby enhancing membrane fluidity and promoting HCC invasion and metastasis.³⁰ In both *in vitro* and *in vivo* models, inhibition of lipogenesis mediated by SCD1 and FASN reduced lipid synthesis, HCC cell proliferation, and migration. It also markedly delayed tumor growth and metastatic progression.^{10,31} ACLY and acyl-CoA synthetase short-chain family (ACSS) mainly catalyze the generation of acetyl-CoA in DNL. In multiple metabolic dysfunction-associated steatohepatitis-HCC mouse models, ACLY inhibition significantly reduced tumor number. It also enhanced antitumor immunity and improved the therapeutic efficacy of lenvatinib.³² Acyl-CoA synthetase short-chain family member 2 (ACSS2) can mediate epigenetic modifications on histone H3 (H3K9, H3K27, H3K56), promoting the transcription of HCC lipid synthesis-related genes and oncogenes.^{33,34} Emerging evidence reveals that among HCC patients, those with high ACSS2 expression exhibit enhanced acetate uptake and active lipid synthesis yet display lower tumor malignancy. Conversely, the ACSS2-low subgroup shows reduced anabolic activity, increased glycolysis and hypoxia, and poorer clinical outcomes. These findings indicate that ACSS2-mediated acetate utilization supports lipogenesis independently of glucose availability and is associated with lower malignant potential in HCC.³⁵ Studies in pancreatic cancer and glioblastoma have associated ACSS2 with tumor progression under nutrient-deprived conditions.^{36,37} Its role in HCC appears to differ, possibly reflecting the unique metabolic environment of the liver. This dual and seemingly contradictory function warrants further investigation. Meanwhile, enhanced DNL leads to the abnormal accumulation of metabolites such as phospholipids, PA, and cholesterol. This accumulation subsequently impacts HCC cells by altering energy supply, activating growth signals, disrupting redox balance, and promoting immunosuppression.

Phosphatidylcholine (PC) constitutes a major component of the plasma membrane in most eukaryotic cells and is essential for preserving membrane integrity. Elevated PC synthesis

is recognized as a hallmark of malignant tumors.³⁸ In many HCC cases, activation of the PC biosynthetic pathway, primarily driven by upregulation of choline kinase α , promotes the production of phosphocholine—the essential precursor for PC synthesis. One study reported significantly higher PC levels in HCC tissues than in adjacent non-tumorous tissues, with an increase of approximately 1.5- to 2.0-fold. PC levels also showed a positive correlation with inflammatory markers. These findings suggest a role for dysregulated PC metabolism in regulating tumor-associated inflammatory responses.^{39,40} PC further drives HCC progression through plasma membrane remodeling. Overexpression of lysophosphatidylcholine acyltransferase 1, for instance, alters membrane composition by increasing saturated PC content, leading to sustained tyrosine receptor activation and enhanced HCC cell proliferation.⁴¹ Among PC derivatives, MUFA-containing PC (hereinafter referred to as MUFA-PC) is also elevated during liver regeneration and HCC progression.⁴² Augmented MUFA uptake induces increases in MUFA-PC and phosphatidylethanolamine within HCC cells, culminating in suppressed lipid peroxidation and ferroptosis. In HCC cell lines and mouse xenograft models, inhibition of this pathway increased sensitivity to sorafenib and reduced tumor cell viability by approximately 40%. It also significantly increased lipid peroxidation and upregulated the expression of ferroptosis-related molecules.⁴³ Multiple studies indicate a role for PC metabolic reprogramming in promoting HCC proliferation and metastasis through multiple pathways, and its complex regulatory mechanisms warrant further investigation.

PA is a key SFA among DNL metabolites. In hepatocytes, PA accumulation activates ER stress pathways, inducing oxidative stress and ROS generation, impairing mitochondrial function, and suppressing β -oxidation.^{44,45} Concurrently, PA, serving as a palmitoyl-CoA substrate, primarily exerts regulatory functions via post-translational palmitoylation of proteins. Palmitoylation represents a reversible post-translational modification involving the covalent attachment of fatty acids to proteins.⁴⁶ Palmitoylated oncogenic Akt activates the PI3K-Akt pathway, thereby promoting HCC development.⁴⁷ Furthermore, numerous studies demonstrate that the zinc finger DHHC-containing (ZDHC) protein family constitutes critical regulators of palmitoylation. ZDHC12 facilitates HCC progression by mediating palmitoylation of oncogenic histone deacetylase 8, thereby inhibiting its lysosomal degradation.⁴⁸ Studies have shown that, in *in vivo* models, a small-molecule inhibitor targeting ZDHC8 attenuated ZDHC8-mediated palmitoylation of glutathione peroxidase 4. It also significantly increased intratumoral CD8⁺ T-cell infiltration and enhanced HCC sensitivity to ferroptosis.⁴⁹ FASN, a pivotal enzyme in PA biosynthesis, is palmitoylated by ZDHC20. This modification competitively inhibits ubiquitination and degradation of FASN mediated by the SNX8-TRIM28 E3 ubiquitin ligase complex. Consequently, a FASN-ZDHC20 positive feedback loop is established, which ultimately enhances PA synthesis.⁵⁰

Cholesteryl ester (CE) metabolism represents a prominent focus in current lipid metabolism research, and its intricate alterations remain under intensive investigation. Multi-omics studies have shown that cholesterol metabolic reprogramming in HCC is characterized mainly by enhanced cholesterol synthesis and esterification. In a quantitative proteomic analysis of 110 paired samples from HBV-related early HCC, 32.7% of cases were classified as the S-III subtype with dysregulated cholesterol homeostasis. High sterol O-acyltransferase 1 (SOAT1) expression was a defining feature of this subtype. In an independent validation cohort, a tissue microarray of 254 HCC cases showed higher SOAT1 expression in tumor tissues

than in adjacent non-tumorous tissues. In addition, all three CE species were elevated in tumor tissues in 25 paired samples. These findings indicate markedly enhanced cholesterol esterification activity in HCC.⁵¹ Concurrently, investigations in murine HCC models demonstrate that prolonged high-CE-containing diets elevate HCC risk.^{47,52,53} Furthermore, sterol regulatory element-binding protein 2 (SREBP2) acts as the master transcriptional regulator of cholesterol metabolism. Its activation upregulates key rate-limiting enzymes in this pathway, including 3-hydroxy-3-methylglutaryl-coenzyme A reductase, squalene epoxidase, and 24-dehydrocholesterol reductase.^{54–56} Additionally, the mature sterol regulatory element-binding protein 2 undergoes SREBP cleavage-activating protein-mediated translocation to the Golgi apparatus and subsequent activation under low-cholesterol conditions.^{57,58} In a mouse HCC model with FASN knockdown, CE levels were approximately 15% higher than in FASN-positive HCC tissues. Further analyses reveal that FASN depletion enhances SREBP2 nuclear localization and activation, thereby augmenting CE synthesis and promoting HCC progression.⁵⁴ In mouse HCC models, inhibition of SREBP2 nuclear localization and activation attenuated CE synthesis and showed a synergistic effect with sorafenib, enhancing its therapeutic efficacy.⁵⁹ Moreover, SOAT1 exhibits high expression in HCC, facilitating the conversion of free cholesterol to CEs for storage in LDs, thus mitigating free cholesterol cytotoxicity and providing reserves for rapid proliferation. In *in vivo* xenograft and pulmonary metastasis models, SOAT1 overexpression fosters LD and CE accumulation, accelerating tumor growth and metastasis. Furthermore, administration of SOAT1-targeted compounds not only directly suppresses cholesterol esterification but also impedes cholesterol synthesis and transport while promoting cholesterol catabolism, culminating in tumor growth inhibition.^{60,61} Current evidence indicates that CE metabolism predominantly promotes HCC progression. However, emerging studies show that inhibiting endogenous CE synthesis can paradoxically activate prostaglandin E synthase 2-mediated arachidonic acid metabolism, which in turn drives HCC progression under conditions of high fatty acid load.⁶² The intricate mechanisms underlying cholesterol metabolism and its prospective therapeutic targets warrant further elucidation.

Lipophagy pathway alterations during metabolic reprogramming

Lipophagy represents a selective form of autophagy primarily involving the degradation and reutilization of LDs. Under physiological conditions, lipophagy sustains lipid homeostasis in hepatocytes; its dysregulation leads to lipid accumulation, oxidative stress, and amplified inflammation. In *in vivo* models, activation of peroxisome proliferator-activated receptor α (PPAR α)-related metabolic pathways was associated with increased tumor growth, while inhibition of these pathways significantly reduced tumor burden. These findings indicate a potential tumor-promoting role of PPAR α -mediated lipophagy in advanced HCC.⁶³ Recent studies reveal that PPAR α deficiency suppresses lipophagy, leading to the accumulation of ether lipids and LDs in HCC. This lipid accumulation subsequently promotes tumor proliferation, migration, and invasion by driving cytoskeletal remodeling and related catabolic processes.^{64–66} Furthermore, inhibiting the lipophagy pathway promotes chemoresistance in tumor cells. This inhibition leads to LD accumulation, which protects HCC cells from sorafenib-induced mitochondrial lipotoxicity and thereby drives sorafenib resistance. Meanwhile, release from lipophagy suppression promotes LD degradation and redirects fatty acids into mitochondrial metabolism.

This change increases ROS levels and enhances apoptosis. During this process, sorafenib sensitivity is partially restored in resistant HCC cells.⁶⁷ Another study demonstrated that, under stress conditions such as glutamine deprivation, activated lipophagy promotes CE mobilization from LDs to the ER while suppressing SREBF2-driven cholesterol synthesis and downstream CE formation. This dual regulation helps preserve nicotinamide adenine dinucleotide phosphate/redox homeostasis.⁶⁸ In HCC cells, inhibition of the lipophagy pathway promotes tumor growth, proliferation, and chemoresistance by allowing LD accumulation. Under stress conditions, however, activation of this same pathway suppresses CE synthesis, enabling cellular adaptation.

Lipid metabolism reprogramming and the TME in HCC

Lipid metabolic reprogramming in HCC cells is closely associated with proliferation, invasion, and metastasis. It may contribute to tumor initiation and progression through multiple mechanisms, including modulation of energy homeostasis, lipid storage, and cellular stress responses. Concomitantly, as HCC advances, the TME undergoes its own lipid metabolic reprogramming. Metabolic products and signaling molecules secreted by HCC cells not only influence the overall metabolic features of the TME but also impact resident immune and stromal cells, thereby inducing remodeling of the immune microenvironment. Concurrently, alterations in lipid metabolism within immune and stromal cells impair global immune competence, thus promoting immune evasion by HCC cells. Interactions between HCC cells and the TME further drive HCC progression (Fig. 2).

Lipid metabolism reprogramming and T cells

T cells constitute a critical component of cellular immunity, with alterations in lipid metabolism within the TME primarily influencing T cells via two mechanisms: lipid accumulation resulting from enhanced lipid metabolism and FAO.

Regulatory T cells (Tregs) represent a subset of CD4⁺ T cells that attenuate antitumor responses through cytokine secretion and expression of cell surface inhibitory receptors.⁶⁹ In investigations of HBV-associated HCC high-risk cohorts, expression of genes linked to the dysregulation of fatty acid metabolism (FAM), including those involved in fatty acid degradation and lipid synthesis, strongly correlates with adverse patient outcomes. Concurrently, immune infiltration analyses reveal elevated Treg proportions in FAM-characterized HBV-associated HCC high-risk groups, contributing to poor prognosis.⁷⁰ Similarly, HCC cells competitively deplete linoleic acid, a resource also required by CD4⁺ T cells. This metabolic competition may trigger CD4⁺ T-cell apoptosis in the TME. In addition, dysregulated FAM may increase the Treg proportion. This change may suppress antitumor immune responses through disruption of the metabolic support and functional activity of CD8⁺ T cells.⁷¹ Existing studies indicate that lipid accumulation in the TME may promote the establishment of immune suppression through the C-C motif chemokine ligand 20 (CCL20)/C-C motif chemokine receptor 6 (CCR6) signaling axis. Under hypoxic conditions with LD accumulation, CCL20 expression is upregulated in the TME. This change enhances recruitment of CCR6⁺ Tregs into tumor tissues and weakens antitumor immunity.^{72,73} Likewise, inhibition of key enzymes in triglyceride and sphingolipid synthesis pathways markedly diminishes Treg recruitment, concomitant with reduced lipid accumulation, thereby suppressing tumor growth.^{72,74} Genetic ablation of CD36 in Tregs reduced their intratumoral abundance and functional activity. Targeted inhibition of CD36 in Tregs showed a synergistic ef-

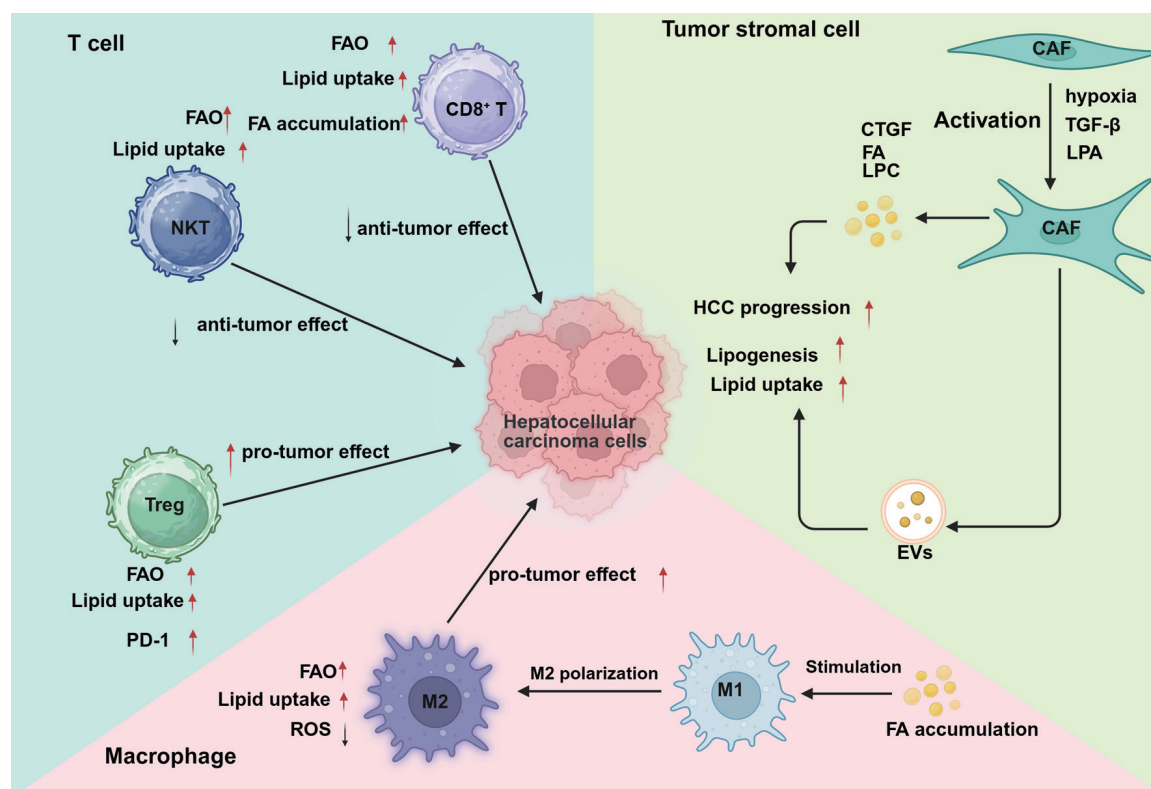


Fig. 2. Effects of TME lipid metabolism on immune and stromal cells. Reprogrammed lipid metabolism in HCC cells is a key driver of TME remodeling. Once activated by HCC-derived lipidic mediators, CAFs undergo intrinsic lipid metabolic rewiring, contributing to overall lipid accumulation within the TME. CAFs further propel HCC progression by secreting EVs laden with oncogenic cargo. Concurrently, immune cells in the TME, including CD8⁺ T cells and NK cell, also display altered lipid metabolism, often associated with functional dysfunction. The resulting lipid-rich milieu further skews immunity by recruiting Tregs and polarizing macrophages toward a pro-tumorigenic phenotype, collectively establishing an immunosuppressive niche. Thus, lipid metabolic alterations fuel a dynamic crosstalk between HCC cells and the TME, simultaneously accelerating tumor progression and reshaping TME function. ↑, increased; ↓, decreased; CAF, cancer-associated fibroblast; CD8⁺ T, CD8-positive T cell; CTGF, connective tissue growth factor; EVs, extracellular vesicles; FA, fatty acid; FAO, fatty acid oxidation; HCC, hepatocellular carcinoma; LPC, lysophosphatidylcholine; LPA, lysophosphatidic acid; M1, M1-like macrophage; M2, M2-like macrophage; NKT, natural killer T cell; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; Treg, regulatory T cell; TME, tumor microenvironment.

fect with anti-programmed cell death protein 1 (PD-1) therapy and improved the response to cancer immunotherapy.²¹

CD8⁺ T cells represent critical effectors in antitumor immunity. As HCC progresses, accumulated lipids activate multiple pathways, including c-Jun N-terminal kinase/signal transducer and activator of transcription (STAT), PI3K/Akt/mTOR, and STAT3, culminating in CD8⁺ T-cell exhaustion.^{75–77} Accumulation of lipids such as fatty acids, CE, and PA impacts CD8⁺ T-cell exhaustion through diverse mechanisms. Specifically, accrued PA/C16:0 promotes STAT3 activation via enhanced palmitoylation in T cells, thereby inducing CD8⁺ T-cell exhaustion.⁷⁸ Several studies have demonstrated that accumulation of LCFAs, CE, secondary bile acids, and oxysterols in HCC drives CD8⁺ T-cell exhaustion.^{79–81} Concurrently, CD36-mediated lipid uptake constitutes a key process influencing lipid accumulation within CD8⁺ T cells. In CD8⁺ tumor-infiltrating lymphocytes (TILs), CD36 expression is upregulated, concomitant with augmented lipid uptake and FAO. Profiling the lipid composition of tumor interstitial fluid identified elevated CD36 expression within dysfunctional PD-1⁺T-cell immunoglobulin and mucin domain-containing protein 3⁺ TIL subsets. This CD36 enrichment correlated with reduced antitumor cytokine production, including interferon-γ and tumor necrosis factor.⁸² Recent studies demonstrate that CD36-mediated lipid uptake induces ferroptosis in CD8⁺ T cells. This cell death occurs through mechanisms involving

the p38 mitogen-activated protein kinase-CCAAT/enhancer-binding protein β (CEBPB)-transferrin receptor 1 axis and/or lipid peroxidation, ultimately leading to CD8⁺ T-cell dysfunction.^{20,83} Furthermore, to acclimate to hypoxia, nutrient deprivation, and lipid accumulation in the TME, CD8⁺ T cells reprogram their metabolism from glycolysis toward FAO, sustaining viability and antitumor effector functions.^{75,84,85} Emerging evidence indicates that blockade of mitochondrial FAO compromises T-cell survival and proliferative capacity. Immunohistochemical analysis of tissue microarrays from 118 patients with HCC showed that high intratumoral infiltration of FABP5⁺ CD8⁺ T cells was significantly associated with prolonged overall survival and recurrence-free survival.⁸⁶ Upon activation of PPAR and STAT3 signaling, FAO is amplified in CD8⁺ T cells, augmenting CD8⁺ T-cell abundance and enhancing responsiveness to anti-PD-1 therapy.^{87,88} Separately, research shows that excessive FAO impairs the antitumor capacity of CD8⁺ T cells by activating STAT3 signaling.⁸⁹

Natural killer (NK) cells represent a specialized lymphocyte population primarily eliminating virus-infected cells or tumor cells through the secretion of perforin and granzymes. As natural killer T (NKT) cells predominantly recognize lipid antigens via the major histocompatibility complex class I-like molecule CD1d, alterations in lipid metabolism can modify these antigens, potentially impacting their immunoregulatory functions.⁹⁰ Lipidomic analysis of HCC tissues reveals

significant accumulation of long-chain acylcarnitines (LCACs) alongside broader lipid metabolic dysregulation. Experimentally, this exogenous LCAC accumulation directly suppresses NKT cell proliferation and promotes cellular senescence.⁹¹ In NKT cells, excessive CE accumulation promotes lipid peroxidation. This oxidative damage directly impairs NKT cell effector functions, ultimately compromising antitumor immunosurveillance in nonalcoholic fatty liver disease-associated HCC.⁹² Limited studies have shown that elevated serum CE levels enhance NK-cell antitumor activity. In Hepa1-6 tumor-bearing mice, adoptive transfer of NK cells from mice fed a high-cholesterol diet reduced tumor volume and increased the number of tumor-infiltrating NK cells compared with the control group.⁹³ Another study reported that invariant natural killer T (iNKT) cells may exacerbate liver injury and hepatocarcinogenesis in a diet-induced fibrotic and steatotic microenvironment. This effect may involve enhanced lipid accumulation and fibrosis. In advanced HCC, reinfusion of *ex vivo*-expanded autologous iNKT cells reduced serum alpha-fetoprotein levels. Prolonged overall survival and progression-free survival (PFS) were also observed in some patients. These findings indicate that iNKT cells may restore antitumor immunity under specific conditions.⁹⁴ Thus, the multifaceted roles of NK cells in HCC warrant further rigorous investigation.

Lipid metabolism reprogramming and tumor-associated macrophages (TAMs)

Macrophages represent key constituents of the mononuclear phagocyte system, ubiquitously distributed within the organism, and are pivotal in orchestrating innate immunity while facilitating the activation of adaptive immunity. Stimulated by elements such as chemokines, lipids, growth factors, and hypoxia within the TME, macrophages differentiate into TAMs and adopt two polarization phenotypes: pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages.^{95,96} Numerous investigations have revealed that alterations in lipid metabolism can promote the M1-to-M2 polarization shift in TAMs, which is intimately linked to HCC progression.^{97,98}

Lipid accumulation within the TME constitutes a major mechanism by which lipid metabolism reprogramming influences TAMs. This accumulation provides metabolic fuel for TAMs, supporting their survival and function in the lipid-rich HCC microenvironment.⁹⁹ The lipid-abundant milieu also promotes excessive fatty acid uptake by TAMs, leading to intracellular storage as LDs.¹⁰⁰ Such lipid accumulation drives TAMs toward an M2-polarized state by modulating PPAR-related signaling pathways.^{101,102} In HCC, accumulated oxidized low-density lipoprotein (oxLDL) and CE polarize triggering receptor expressed on myeloid cells 2-positive TAMs via the triggering receptor expressed on myeloid cells 2-spleen tyrosine kinase-CEBP α axis. These TAMs subsequently promote cancer cell invasion, resistance to effector cytokines, and CD8⁺ T-cell dysfunction.^{103,104} Pharmacological inhibition of CE synthesis by cinobufotalin via the adenosine monophosphate-activated protein kinase/SREBP1/FASN axis suppresses TAM M2 polarization, thereby delaying HCC progression.¹⁰⁵ Key transporters mediating lipid uptake include CD36 and FABPs. CD36 is predominantly expressed on metastasis-associated macrophages (MAMs) within metastatic liver tumor niches, and its inhibition attenuates M2 polarization of MAMs.¹⁰⁶ CD36 facilitates M2 polarization primarily through PPAR-related pathways. Mechanistically, CD36 mediates downstream p110 γ signaling via the CCL2/CCR2/p110 γ axis, thereby promoting TAM infiltration and stimulating tumor metastasis.¹⁰⁷ CD36-mediated oxLDL uptake and subsequent accumulation in TAMs can also promote

M2 polarization by affecting PPAR-related signaling. FABPs serve as another critical regulator of lipid uptake, precisely orchestrating the transport and distribution of specific fatty acids. Recent work shows that HIF-1 α -induced upregulation of FABP7 in hepatic macrophages drives LD accumulation within the pre-metastatic niche and enhances diacylglycerol O-acyltransferase 1 activity in macrophages.¹⁰⁸ Moreover, multiple studies indicate that FABP5 promotes TAM M2 polarization via PPAR-related pathways. FABP5-laden TAMs acquire immunosuppressive properties through PPAR γ activation. Consistently, in a mouse HCC xenograft model, exosomal FABP5 was shown to directly induce M2-related gene expression and immunosuppressive function involving PPAR γ activation.¹⁰⁹ Beyond inducing immunosuppressive M2 polarization, FABP5 can also augment IL-10 secretion from monocytes by inhibiting the PPAR α pathway, which in turn promotes programmed death ligand-1 (PD-L1) expression on Tregs.¹¹⁰

In a lipid-rich TME, metabolic reprogramming in TAMs is closely associated with their polarization state. M1 TAMs are characterized by enhanced glycolysis, whereas M2 TAMs exhibit increased FAO activity and depend on FAO to maintain their immunosuppressive phenotype.¹¹¹ FAO generates adenosine triphosphate and nicotinamide adenine dinucleotide phosphate, thereby contributing to lipid overload and LD accumulation within TAMs. This LD accumulation drives a significant increase in PD-L1 expression. The upregulated PD-L1 not only suppresses CD8⁺ T-cell activation and proliferation but also enhances the secretion of immunosuppressive factors, including interleukin-10 (IL-10) and transforming growth factor- β .^{25,72} Notably, HCC-derived 27-hydroxycholesterol potentially induces M2 polarization in TAMs. These M2 TAMs maintain their immunosuppressive function through upregulation of FAO-related metabolic pathways and are also associated with increased invasive and metastatic potential in HCC. These findings indicate a role for M2 TAMs in the establishment of a protumor regulatory loop.¹¹² In addition, enhanced FAO promotes induction of the M2 phenotype mainly through regulation of PPAR signaling pathways. These pathways control mitochondrial oxidative phosphorylation and ROS production. For instance, receptor-interacting protein kinase 3 downregulation in TAMs reduces ROS production and inhibits PPAR cleavage, thus enhancing the FAO pathway and reinforcing M2 polarization.¹¹³ Consistently, PPAR α activation regulates TAM M2 polarization via FAO metabolism.¹¹⁴ Collectively, inhibiting FAO emerges as a promising strategy to steer TAMs toward an antitumor phenotype.

Lipid metabolism reprogramming and CAFs

CAFs are a major stromal cell population in the TME. They regulate tumor cell proliferation and growth through promotion of extracellular matrix (ECM) deposition and remodeling, increased matrix stiffness, and activation of relevant signaling pathways.¹¹⁵ These cells are predominantly activated by transforming growth factor- β and lysophosphatidic acid (LPA) signaling in the TME. Upon activation, CAFs orchestrate multiple tumor-promoting programs such as facilitating tumor cell proliferation and metastasis, angiogenesis, immune modulation, and chemotherapy resistance. These functions are mediated primarily through extensive deposition of ECM.^{116,117} In addition, CAFs secrete a broad range of cytokines, chemokines, and growth factors. The levels of these mediators are significantly elevated in tumor tissues and show a positive correlation with infiltration of immunosuppressive cells and increased tumor growth. These findings indicate that CAFs may contribute to tumor microenvironmental regulation through paracrine signaling.¹¹⁸

Pro-tumorigenic CAFs exhibit upregulation of key lipid metabolism enzymes, including FASN, ACC, and SCD1, concomitant with altered lipid metabolism. This upregulation activates the IL-8/Akt signaling axis and enhances DNL in CAFs. Lipid metabolites released by CAFs are then taken up by tumor cells and promote tumor growth and migration through lipid metabolic programs.¹¹⁹ In CAFs, increased expression of ACC- and FASN-associated lipogenic genes correlates with lipid accumulation and histone acetylation, processes that collectively promote HCC progression.^{120,121} Under hypoxia, SCD1 interacts with HIF-1 α to elevate intracellular LD abundance in CAFs, driving a pro-tumorigenic phenotype.¹²² In addition, oleic acid secreted by metastasis-associated CAFs enhances SCD1 activity in tumor cells. This change promotes MUFA synthesis and maintains metabolic adaptation. Functional assays also showed upregulated expression of tumor cell stemness markers during this process, indicating an important role in driving malignant tumor phenotypes.¹²³ Beyond augmenting lipid synthesis, CAFs also enhance exogenous lipid uptake. Single-cell RNA sequencing of human and murine HCC tumors identified a CD36⁺ CAF subset originating from hepatic stellate cells. These CAFs display heightened lipid metabolism and express macrophage migration inhibitory factor (MIF). Mechanistically, the lipid peroxidation/p38 mitogen-activated protein kinase/CEBPs axis in CD36⁺ CAFs mediates oxLDL uptake-dependent MIF expression. CAF-derived MIF promotes myeloid-derived suppressor cells expansion and suppresses T-cell-mediated antitumor immunity. It may also be closely involved in maintenance of cancer stem cell properties.¹²⁴

Beyond regulating key lipid-metabolizing enzymes, CAFs fuel HCC progression through the secretion of bioactive lipid molecules and extracellular vesicles (EVs). Under hypoxic and nutrient-deprived conditions, CAF-secreted lysophosphatidylcholine is taken up by cancer cells and converted to PC to maintain membrane integrity.¹²⁵ Following its uptake, lysophosphatidylcholine can be hydrolyzed by autotaxin to LPA. LPA then promotes the transformation of peritumoral fibroblasts (PTFs) into CAF-like myofibroblasts via Akt pathway activation, enhancing HCC cell proliferation, migration, and invasion.^{126,127} Exposure to LPA also upregulates connective tissue growth factor secretion by CAFs in the TME, orchestrating pro-tumorigenic signaling.¹²⁸ Furthermore, HCC cells themselves can secrete LPA to induce a CAF phenotype in PTFs, thereby driving tumor cell proliferation, migration, and invasion.¹²⁹ EVs function as critical mediators of lipid metabolic crosstalk within the TME, contributing to the conversion of fibroblasts into CAFs. CAF-derived exosomes enhance cancer cell proliferation, metastasis, resistance to ferroptosis, and drug tolerance. These effects are mediated through multiple mechanisms: the exosomes target key oncogenes involved in proliferation and differentiation, activate signaling pathways such as cyclic adenosine monophosphate/protein kinase A, and concurrently induce lipophagy.^{130–132} For instance, the exosomal cargo nucleolar protein 16 reprograms CAF lipid metabolism by phosphorylating ACLY, leading to increased C-X-C motif chemokine ligand 5 expression and secretion, which enhances tumor metastasis.¹³³ Similarly, exosomal miR-522 suppresses ferroptosis in cancer cells by targeting arachidonate 15-lipoxygenase and inhibiting lipid peroxidation.¹³¹ Collectively, these findings underscore the significant potential of targeting CAF-derived EVs in HCC therapy.

Drug development targeting lipid metabolic reprogramming in HCC

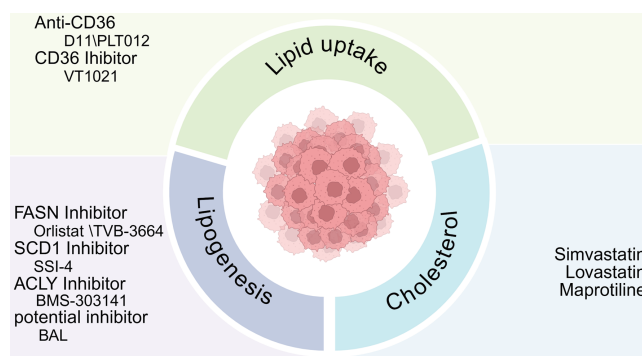


Fig. 3. Therapeutic targets for lipid metabolism. Altered lipid metabolism propels HCC progression and concurrently reshapes the function of the TME. These interconnected changes collectively undermine the efficacy of anti-tumor therapies. We have detailed key metabolic pathways involved in lipid uptake, DNL, and CE metabolism, and has discussed the potential therapeutic strategies that target these processes. BAL, baicalin; CE, cholesteryl ester; DNL, de novo lipogenesis; HCC, hepatocellular carcinoma; TME, tumor microenvironment.

Reprogramming of lipid metabolism in HCC cells not only serves as a hallmark of HCC progression but also offers novel therapeutic targets and strategies for antitumor therapy in HCC. Familiarity with the underlying mechanisms of lipid metabolic alterations in HCC cells enables researchers to develop novel and effective targeted therapeutics. Concurrently, this approach holds potential to overcome long-standing drug resistance issues, thereby improving patient prognosis. However, owing to the plasticity of lipid metabolism, perturbations in metabolic pathways activate compensatory routes, thereby constraining the antitumor efficacy of monotherapy. As research on lipid metabolism in liver cancer advances, combination therapies targeting lipid metabolism alongside conventional antitumor treatments have been developed.^{134,135} Such combinatorial regimens augment the cytotoxicity of antitumor agents against HCC cells and may resensitize resistant cells to these drugs, yielding overall efficacy substantially superior to that of single-agent therapy (Fig. 3). Furthermore, recent clinical trials in HCC have increasingly focused on lipid metabolism, with studies investigating its potential as tumor biomarkers, therapeutic targets, and prognostic indicators.^{136–138}

Targeting lipid uptake, particularly through the key transporter CD36, has shown therapeutic promise. Recent studies describe a human anti-CD36 single-chain variable fragment, D11. Upon binding membrane-bound CD36 on HCC cells, D11 inhibits CD36-mediated lipid uptake, curtailing tumor growth. In macrophage-like THP-1 cells, D11 blunts oxLDL-induced foam cell formation, reducing LD content and the expression of lipid metabolism genes. In HepG2 cells, it diminishes lipid accumulation and counteracts PA-stimulated clonogenicity.¹³⁹ Furthermore, a humanized anti-CD36 antibody, PLT012, blocks CD36-mediated metabolic reprogramming in both Tregs and CD8⁺ TILs within HCC models, leading to tumor growth inhibition.¹⁴⁰ Additionally, VT1021, another agent targeting CD36, has advanced into clinical trials.¹⁴¹

Therapeutic strategies targeting DNL center on inhibiting key lipogenic enzymes, including FASN, SCD1, and ACLY. FASN inhibition, for instance, elevates major histocompatibility complex class I expression on HCC cells. This enhances their elimination by CD8⁺ TILs and synergizes with immune checkpoint inhibitors.¹⁴² Preclinically, the FASN inhibitor orlistat resensitizes sorafenib-resistant HCC to therapy.¹⁴³ Furthermore, another FASN inhibitor, TVB-3664, demonstrates

synergistic activity with tyrosine kinase inhibitors (TKIs) in mouse models.¹⁴⁴ Targeting SCD1, another crucial lipogenic enzyme, also shows promise. The SCD1 inhibitor SSI-4 exhibits strong synergy with the TKIs lenvatinib and cabozantinib in HCC models without inducing the resistance observed with single-agent TKI treatment.¹⁴⁵ Both the ACLY inhibitor BMS-303141 and the small-molecule inhibitor EVT0185 suppress HCC cell proliferation, migration, and invasion.^{32,146} The ACC inhibitor ND-654, which mimics ACC phosphorylation, suppresses hepatic DNL and HCC development, improving survival in HCC-bearing rats either as monotherapy or in combination with sorafenib.¹¹ Additionally, the hepatoprotective agent baicalein holds potential for HCC therapy by down-regulating key lipogenic factors, including FASN and SCD1, via reducing nuclear expression of mature sterol regulatory element-binding protein 1c and carbohydrate-responsive element-binding protein.¹⁴⁷

Beyond direct enzyme targeting, CE metabolism is also under therapeutic investigation. Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase that lower cellular CE levels and are standard therapy for hyperlipidemia, show promise in oncology. Clinical studies in HCC patients indicate that combining statins with antitumor agents significantly reduces HCC-related outcomes.¹⁴⁸ For instance, simvastatin inhibits the HIF-1 α /PPAR- γ /PKM2 axis, suppressing proliferation, promoting apoptosis, and resensitizing HCC cells to sorafenib.¹⁴⁹ Recent advances utilizing nanomaterial-based delivery of simvastatin further enhance its efficacy against HCC progression and drug resistance.^{150,151} In addition to statins, maprotiline—a tetracyclic antidepressant approved by the U.S. Food and Drug Administration (hereinafter referred to as FDA)—inhibits HCC progression by directly targeting cellular retinoic acid-binding protein 1, thereby suppressing CE biosynthesis.¹⁵²

Clinical trials targeting lipid metabolism in HCC

PLT012 is the first anti-CD36 monoclonal antibody advanced into clinical evaluation. Preclinical studies showed that blockade of CD36-mediated lipid uptake remodels the immunosuppressive microenvironment in HCC and liver metastases and acts synergistically with PD-1/PD-L1 inhibitors.¹⁵³ PLT012 is currently being evaluated in a first-in-human phase I trial (NCT07337525), an open-label dose-escalation study in patients with advanced solid tumors. HCC is a major focus of its clinical development, and its potential in combination with atezolizumab in HCC is under further evaluation. The program received FDA Fast Track designation for HCC in February 2026 and has since entered active enrollment. Sufficient efficacy data have not yet been reported. Several issues also remain unresolved, including the optimal biomarker for efficacy assessment in HCC, the best combination strategy with current immune checkpoint inhibitor or anti-vascular endothelial growth factor regimens, and the risk of systemic metabolic toxicity after CD36 blockade. Overall, continued development of PLT012 in HCC will require more systematic clinical trials to define the patient populations most likely to benefit, the optimal combination patterns, and the safety profile. Such efforts may support a more precise combination strategy for HCC characterized by high CD36 expression and lipid metabolism dependence. Further in-depth studies are still needed to establish a comprehensive precision treatment framework for patients with HCC in whom high CD36 expression drives lipid metabolic reprogramming.

VT1021 is an agent that modulates a CD36-associated pathway. Its antitumor effects are mediated primarily through the thrombospondin-1/CD36/CD47 axis and involve TME re-

modeling. A published phase I dose-escalation study showed no dose-limiting toxicities in 38 patients with advanced solid tumors. The RP2D was 11.8 mg/kg. Among 28 evaluable patients, the disease control rate was 42.9%, and one patient with thymoma achieved a partial response.¹⁵⁴ A subsequent expansion cohort study reported a disease control rate of 45% with VT1021 monotherapy in 22 patients with recurrent glioblastoma (NCT03364400). The agent has since advanced to the GBM AGILE platform trial. No published or registered clinical trial of VT1021 in HCC is currently available. Therefore, its translational potential in HCC still requires further validation through high-quality studies and clinical trials.

In HCC, statins were among the earliest strategies targeting lipid metabolism to undergo clinical evaluation. An early open-label randomized study enrolled 83 patients with advanced HCC. After transarterial embolization and oral 5-fluorouracil treatment, patients were randomized to receive additional pravastatin. Median overall survival increased from 9 months to 18 months in the pravastatin group compared with the control group.¹⁵⁵ A subsequent prospective cohort study of 183 patients reported a median overall survival of 20.9 months with transarterial chemoembolization plus pravastatin, compared with 12.0 months with transarterial chemoembolization alone.¹⁵⁶ However, other clinical trials yielded less consistent results. The PRODIGE-11 randomized controlled trial showed no overall survival benefit with sorafenib plus pravastatin.¹⁵⁷ The ESTAHEP study of sorafenib plus pravastatin also reported longer radiologic time to progression (TTP) in the combination group than in the control group (9.9 months versus 3.2 months), while overall survival was similar between the two groups (12.4 months versus 11.6 months).¹⁵⁸ In addition, the more recent phase I SMASH study showed that the triplet regimen of sorafenib, atorvastatin, and metformin had acceptable safety and may reduce sorafenib-related adverse events. However, each dose cohort included only about 10 patients, and larger cohorts are needed for more generalizable results.¹⁵⁹

Limitations

In HCC, clinical trials of statins have mainly focused on combination strategies with existing antitumor agents. Although some studies reported prolonged overall survival and TTP, major limitations remain, particularly small sample sizes and heterogeneity of the study populations.

Beyond HCC, the clinical development of statin-based combination therapy has been more extensive. In lung cancer, a randomized phase II trial of gefitinib plus simvastatin showed no clear benefit in the overall unselected population; however, signals of higher response rates and longer PFS were observed in the non-adenocarcinoma subgroup with wild-type epidermal growth factor receptor.¹⁶⁰ In pancreatic cancer, a randomized double-blind phase II trial of gemcitabine plus simvastatin did not improve TTP or survival.¹⁶¹ In previously untreated advanced gastric cancer, simvastatin combined with the capecitabine plus cisplatin regimen did not improve PFS. Investigators further noted that, in an unselected population, a 40 mg dose of simvastatin might be insufficient to achieve concentrations required for cancer cell inhibition.¹⁶² The SPECTRE study in prostate cancer suggested that atorvastatin combined with androgen deprivation therapy may induce early biological effects and signals of disease stabilization; however, the trial was later terminated because fewer than two patients achieved a >50% decline in prostate-specific antigen. Investigators noted that future studies would require larger cohorts and longer statin exposure to fully evaluate long-term anticancer effects.¹⁶³ Overall, the main strengths

of statin-based combination therapy include well-established long-term safety, low cost, and easy integration into existing treatment regimens. However, several limitations also require attention: statins have broad biological effects, effective intratumoral exposure remains unclear, and patient populations most likely to benefit have not been prospectively enriched. Taken together, current evidence suggests that statins may hold therapeutic promise in oncology, particularly in combination strategies. Larger clinical trials with more refined designs are still needed, focusing on precise selection of relevant patient populations, identification of optimal dosing, and careful evaluation of safety and tolerability.

Overall, among CD36-targeted strategies, PLT012 represents a novel immunometabolic approach that more closely reflects the biological features of HCC. It remains at a critical transition from strong preclinical evidence to early clinical evidence. VT1021 provides preliminary support for pharmacologic modulation of CD36-associated pathways in humans and for their potential antitumor activity. Statins, by contrast, benefit from broad clinical use and well-defined pharmacologic properties, supporting their feasibility and safety in HCC-directed antitumor studies. Although clinical trials of statins in HCC have reported improvements in selected endpoints, further studies are still needed to validate the feasibility of statin-based combination strategies for HCC.

Conclusions

Tumor progression is frequently accompanied by alterations in lipid metabolism, primarily involving enhanced pathways such as lipid uptake, synthesis, and FAO. These upregulated pathways support HCC through dual mechanisms. First, they supply the energy and metabolic building blocks required for rapid proliferation. Second, the resulting metabolite overaccumulation further modulates tumor behavior, driving proliferation, metastasis, and invasion through mechanisms such as plasma membrane remodeling, epigenetic reprogramming, and disruption of redox homeostasis. As investigations into HCC deepen, it has become evident that lipid metabolic reprogramming not only propels intrinsic tumor progression but also modulates stromal and immune cells within the TME. Excessive lipid accrual and augmented FAO foster an immunosuppressive microenvironment by impairing T-cell antitumor effector functions, promoting M2 macrophage polarization, and activating CAFs, thereby facilitating HCC immune evasion. Consequently, targeting lipid metabolism to suppress HCC progression represents a promising avenue of research. In recent years, studies on lipid metabolism have proliferated, with interventions targeting lipid metabolism demonstrating favorable therapeutic outcomes in HCC. Several relevant targets have been identified. In studies combining these targets with antitumor agents, they show potential to inhibit tumor progression and overcome chemoresistance. Inhibitors of CE synthesis, such as statins, along with suppressors of key lipid biosynthetic enzymes, exhibit synergistic effects with concomitant antitumor drugs and can even resensitize HCC cells to certain chemotherapeutics. Nevertheless, given the intricate metabolic milieu of HCC, direct perturbation of metabolic pathways may elicit compensatory mechanisms and compromise the metabolic integrity of associated immune cells. Thus, substantial challenges persist in the development of targeted therapeutics directed at metabolic pathways. While clinically approved metabolism-targeted therapies are still limited, the rapidly evolving understanding of lipid metabolism and tumor immunometabolic crosstalk holds significant promise. This knowledge is poised to identify novel therapeutic targets with high specificity and

favorable toxicity profiles. Clinical trials targeting lipid metabolism in cancer remain exploratory, likely because of the complexity of lipid metabolic regulatory networks. More high-quality studies are needed to further elucidate the regulatory network of lipid metabolism in HCC. Building on current clinical evidence, future studies may require larger and more precisely selected patient populations closely associated with lipid metabolic alterations, together with more rigorous trial designs. Preclinical studies of lipid metabolism in HCC have shown considerable promise; however, many challenges still need to be addressed before these advances can translate into broad clinical benefit for most patients.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (YP, LL), manuscript writing (WD), critical revision (QJ), and acquisition of data (BS, HY, YD). The authors have approved the final version and publication of the manuscript.

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