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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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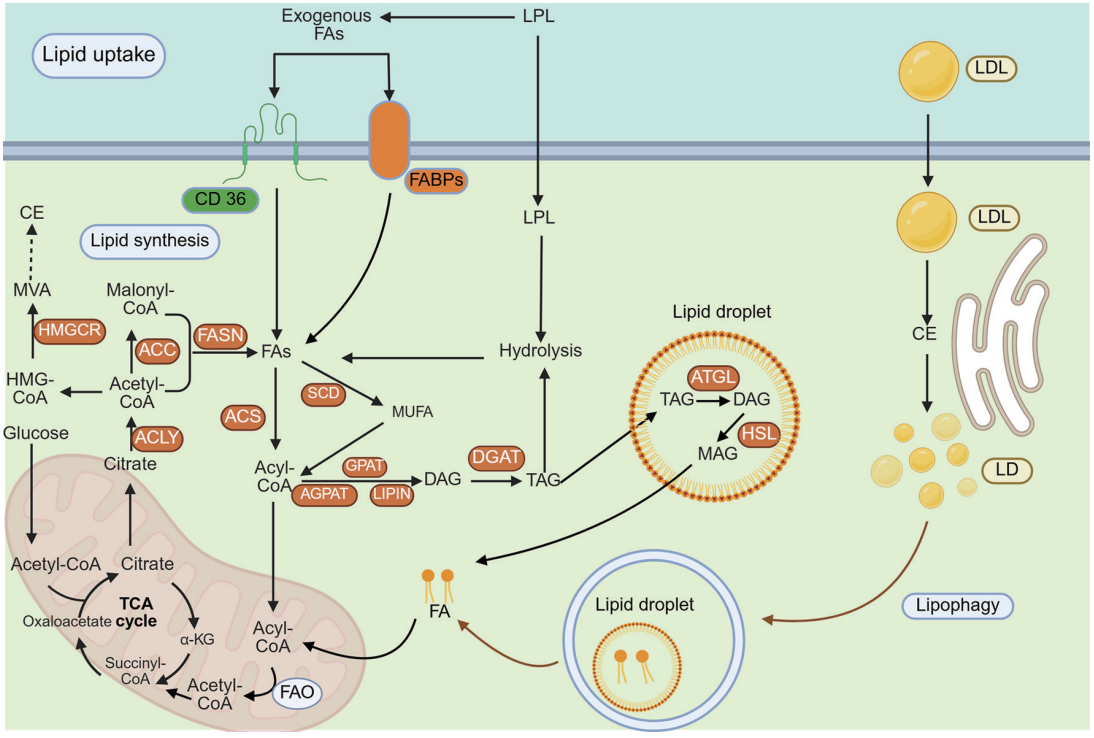

Fig. 1. Lipid metabolic pathways in HCC. HCC accrues lipids through two primary pathways: exogenous uptake and endogenous synthesis. Exogenous uptake is enhanced via the upregulation of transport proteins like CD36 and FABP during tumor progression. Meanwhile, endogenous synthesis is driven by key enzymes 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)/protein 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-1α translation, suppresses FIH-dependent hydroxylation, and facilitates p300 recruitment, collectively increasing HIF-1α 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] 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 (ZDHHC) protein family constitutes critical regulators of palmitoylation. ZDHHC12 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 ZDHHC8 attenuated ZDHHC8-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 ZDHHC20. This modification competitively inhibits ubiquitination and degradation of FASN mediated by the SNX8-TRIM28 E3 ubiquitin ligase complex. Consequently, a FASN–ZDHHC20 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 (PPARα)-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 PPARα-mediated lipophagy in advanced HCC.[63] Recent studies reveal that PPARα 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 effect with anti-programmed cell death protein 1 (PD-1) ther-

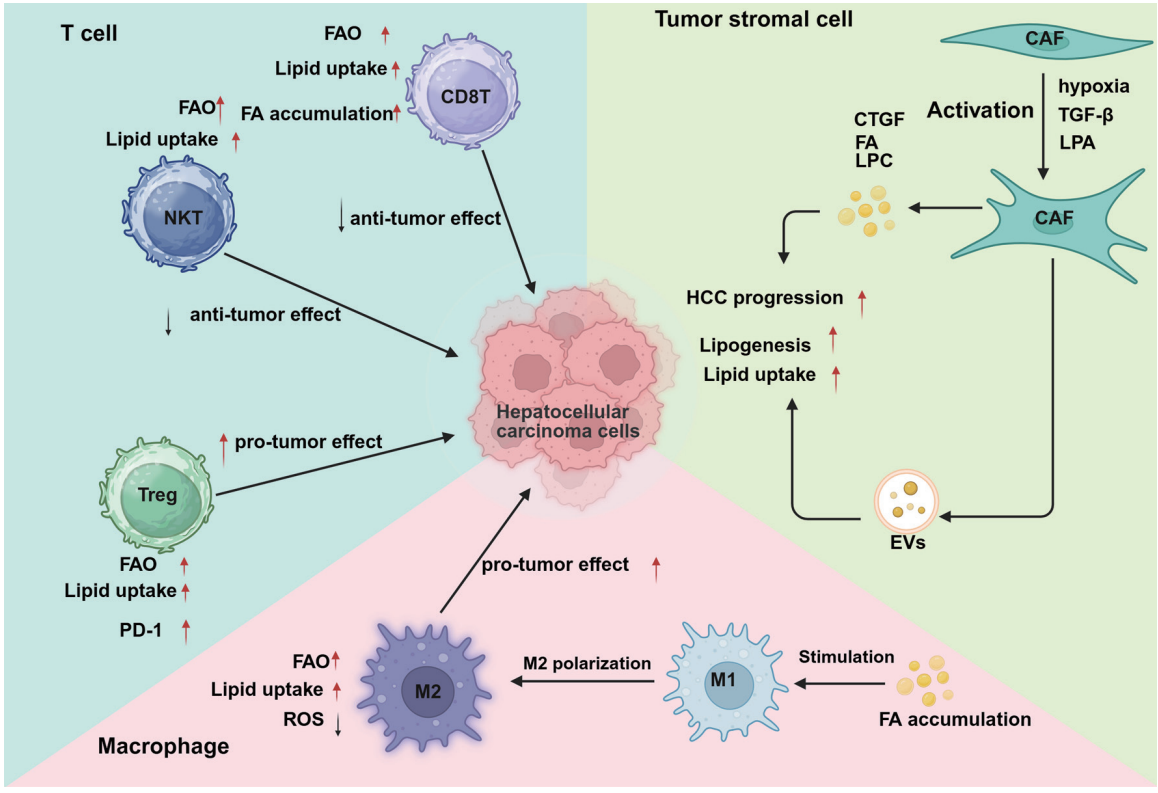

Fig. 2. Effects of TME lipid metabolism on immune and stromal cells. Reprogrammed lipid metabolism in HCC cells is a key driver of TME remodeling. Once activated by HCC-derived lipidic mediators, CAFs undergo intrinsic lipid metabolic rewiring, contributing to overall lipid accumulation within the TME. 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; CD8T, 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.

apy 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-CEBPα 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 p110γ signaling via the CCL2/CCR2/p110γ 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-1α-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 PPARγ activation. Consistently, in a mouse HCC xenograft model, exosomal FABP5 was shown to directly induce M2-related gene expression and immunosuppressive function involving PPARγ activation.[109] Beyond inducing immunosuppressive M2 polarization, FABP5 can also augment IL-10 secretion from monocytes by inhibiting the PPARα 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 potently 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, PPARα 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-1α 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

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]

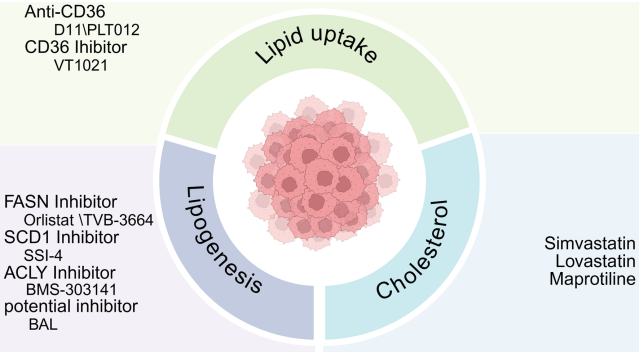

Fig. 3. Therapeutic targets for lipid metabolism. Altered lipid metabolism propels HCC progression and concurrently reshapes the function of the TME. These interconnected changes collectively undermine the efficacy of anti-tumor therapies. We have detailed key metabolic pathways involved in lipid uptake,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

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 downregulating 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-1α/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 remodeling. 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.

References

[1] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018; 391(10127):1301–1314. doi:10.1016/S0140-6736(18)30010-2, PMID:29307467.
[2] Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet 2022;400(10360):1345–1362. doi:10.1016/S0140-6736(22)01200-4, PMID:36084663.
[3] Mak LY, Liu K, Chirapongsathorn S, Yew KC, Tamaki N, Rajaram RB, *et al*. Liver diseases and hepatocellular carcinoma in the Asia-Pacific region: burden, trends, challenges and future directions. Nat Rev Gastroenterol Hepatol 2024;21:834–851. doi:10.1038/s41575-024-00967-4, PMID:39147893.
[4] Huang DQ, Singal AG, Kono Y, Tan DJH, El-Serag HB, Loomba R. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. Cell Metab 2022;34(7):969–977.e2. doi:10.1016/j.cmet.2022.05.003, PMID:35793659.
[5] Sangineto M, Villani R, Cavallone F, Romano A, Loizzi D, Serviddio G. Lipid Metabolism in Development and Progression of Hepatocellular Carcinoma. Cancers (Basel) 2020;12(6):1419. doi:10.3390/cancers12061419, PMID:32486341.
[6] Sun B, Ding P, Song Y, Zhou J, Chen X, Peng C, *et al*. FDX1 downregulation activates mitophagy and the PI3K/AKT signaling pathway to promote hepatocellular carcinoma progression by inducing ROS production. Redox Biol 2024;75:103302. doi:10.1016/j.redox.2024.103302, PMID:39128228.
[7] Cao LQ, Xie Y, Fleishman JS, Liu X, Chen ZS. Hepatocellular carcinoma and lipid metabolism: Novel targets and therapeutic strategies. Cancer Lett 2024;597:217061. doi:10.1016/j.canlet.2024.217061, PMID:38876384.
[8] Yang R, Lu C, Jian Q. HBV-driven expansion of CXCR6+-exhausted T cells and CXCL16+ macrophage interaction: Implications for immunotherapy in HCC. Innovation 2026;7(6):101274. doi:10.1016/j.xinn.2026.101274.

[9] He D, Cai L, Huang W, Weng Q, Lin X, You M, *et al*. Prognostic value of fatty acid metabolism-related genes in patients with hepatocellular carcinoma. Aging (Albany NY) 2021;13(13):17847–17863. doi:10.18632/aging.203288, PMID:34257161.

[10] Li G, Li X, Mahmud I, Ysaguirre J, Fekry B, Wang S, *et al*. Interfering with lipid metabolism through targeting CES1 sensitizes hepatocellular carcinoma for chemotherapy. JCI Insight 2023;8(2):e163624. doi:10.1172/jci.insight.163624, PMID:36472914.

[11] Lally JSV, Ghoshal S, DePeralta DK, Moaven O, Wei L, Masia R, *et al*. Inhibition of Acetyl-CoA Carboxylase by Phosphorylation or the Inhibitor ND-654 Suppresses Lipogenesis and Hepatocellular Carcinoma. Cell Metab 2019;29(1):174–182.e5. doi:10.1016/j.cmet.2018.08.020, PMID:30244972.

[12] Guan Y, Kim Y, Wang Y, Cho YE, Xiang X, Kim SJ, *et al*. Adipocyte death promotes hepatic infiltration of S100A8+ macrophages and steatotic liver disease progression in mice. J Clin Invest 2025;135(21):e190635. doi:10.1172/JCI190635, PMID:41178716.

[13] Leung CON, Gurung S, Chung KPS, Leung RWH, Lei MML, Chan MSM, *et al*. Adipocyte-derived FABP4 promotes metabolism-associated steatotic liver-induced hepatocellular carcinoma by driving ITGB1-mediated β-catenin activation. J Clin Invest 2025;135(24):e182322. doi:10.1172/JCI182322, PMID:41392988.

[14] Pepino MY, Kuda O, Samovski D, Abumrad NA. Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. Annu Rev Nutr 2014;34:281–303. doi:10.1146/annurev-nutr-071812-161220, PMID:24850384.

[15] Liu Y, Yin W. CD36 in liver diseases. Hepatol Commun 2025;9(1):e0623. doi:10.1097/HC9.0000000000000623, PMID:39774047.

[16] Luo X, Zheng E, Wei L, Zeng H, Qin H, Zhang X, *et al*. The fatty acid receptor CD36 promotes HCC progression through activating Src/PI3K/AKT axis-dependent aerobic glycolysis. Cell Death Dis 2021;12(4):328. doi:10.1038/s41419-021-03596-w, PMID:33771982.

[17] Terry AR, Nogueira V, Rho H, Ramakrishnan G, Li J, Kang S, *et al*. CD36 maintains lipid homeostasis via selective uptake of monounsaturated fatty acids during matrix detachment and tumor progression. Cell Metab 2023;35(11):2060–2076.e9. doi:10.1016/j.cmet.2023.09.012, PMID:37852255.

[18] Hong J, Liu J, Zhang Y, Ding L, Ye Q. MiR-3180 inhibits hepatocellular carcinoma growth and metastasis by targeting lipid synthesis and uptake. Cancer Cell Int 2023;23(1):66. doi:10.1186/s12935-023-02915-9, PMID:37041584.

[19] Tao L, Ding X, Yan L, Xu G, Zhang P, Ji A, *et al*. CD36 accelerates the progression of hepatocellular carcinoma by promoting FAs absorption. Med Oncol 2022;39(12):202. doi:10.1007/s12032-022-01808-7, PMID:36175596.

[20] Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, *et al*. CD36-mediated ferroptosis dampens intratumoral CD8(+) T cell effector function and impairs their antitumor ability. Cell Metab 2021;33(5):1001–1012.e5. doi:10.1016/j.cmet.2021.02.015, PMID:33691090.

[21] Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, *et al*. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. Nat Immunol 2020;21(3):298–308. doi:10.1038/s41590-019-0589-5, PMID:32066953.

[22] Li Y, Lee W, Zhao ZG, Liu Y, Cui H, Wang HY. Fatty acid binding protein 5 is a novel therapeutic target for hepatocellular carcinoma. World J Clin Oncol 2024;15(1):130–144. doi:10.5306/wjco.v15.i1.130, PMID:38292656.

[23] Seo J, Jeong DW, Park JW, Lee KW, Fukuda J, Chun YS. Fatty-acid-induced FABP5/HIF-1 reprograms lipid metabolism and enhances the proliferation of liver cancer cells. Commun Biol 2020;3(1):638. doi:10.1038/s42003-020-01367-5, PMID:33128030.

[24] Bensaad K, Favaro E, Lewis CA, Peck B, Lord S, Collins JM, *et al*. Fatty acid uptake and lipid storage induced by HIF-1α contribute to cell growth and survival after hypoxia-reoxygenation. Cell Rep 2014;9(1):349–365. doi:10.1016/j.celrep.2014.08.056, PMID:25263561.

[25] Yang X, Deng B, Zhao W, Guo Y, Wan Y, Wu Z, *et al*. FABP5(+) lipid-loaded macrophages process tumour-derived unsaturated fatty acid signal to suppress T-cell antitumour immunity. J Hepatol 2025;82(4):676–689. doi:10.1016/j.jhep.2024.09.029, PMID:39357545.

[26] Sun J, Esplugues E, Bort A, Cardelo MP, Ruz-Maldonado I, Fernández-Tussy P, *et al*. Fatty acid binding protein 5 suppression attenuates obesity-induced hepatocellular carcinoma by promoting ferroptosis and intratumoral immune rewiring. Nat Metab 2024;6(4):741–763. doi:10.1038/s42255-024-01019-6, PMID:38664583.

[27] Ning Z, Guo X, Liu X, Lu C, Wang A, Wang X, *et al*. USP22 regulates lipidome accumulation by stabilizing PPARγ in hepatocellular carcinoma. Nat Commun 2022;13(1):2187. doi:10.1038/s41467-022-29846-9, PMID:35449157.

[28] Yang Y, Luo J, Wang Z, Liu K, Feng K, Wang F, *et al*. Energy Stress-Induced circEPB41(2) Promotes Lipogenesis in Hepatocellular Carcinoma. Cancer Res 2025;85(4):723–738. doi:10.1158/0008-5472.CAN-24-1630, PMID:39636740.

[29] Zhou S, Zhang L, You Y, Yu K, Tie X, Gao Y, *et al*. eIF3f promotes tumour malignancy by remodelling fatty acid biosynthesis in hepatocellular carcinoma. J Hepatol 2025;83(3):712–728. doi:10.1016/j.jhep.2025.02.045, PMID:40154622.

[30] Liu HH, Xu Y, Li CJ, Hsu SJ, Lin XH, Zhang R, *et al*. An SCD1-dependent mechanoresponsive pathway promotes HCC invasion and metastasis through lipid metabolic reprogramming. Mol Ther 2022;30(7):2554–2567. doi:10.1016/j.ymthe.2022.03.015, PMID:35358687.

[31] Li H, Chen Z, Zhang Y, Yuan P, Liu J, Ding L, *et al*. MiR-4310 regulates hepatocellular carcinoma growth and metastasis through lipid synthesis. Cancer Lett 2021;519:161–171. doi:10.1016/j.canlet.2021.07.029, PMID:34303763.

[32] Gautam J, Wu J, Lally JSV, McNicol JD, Fayyazi R, Ahmadi E, *et al*. ACLY inhibition promotes tumour immunity and suppresses liver cancer. Nature 2025;645(8080):507–517. doi:10.1038/s41586-025-09297-0, PMID:40739358.

[33] Wang S, Niu Z, Zhang Y, Liu R, Zhu R, Sun Y, *et al*. ACSS2 coupled with KAT7 regulates histone β-hydroxybutyrylation to enhance transcription. Sci Adv 2025;11(33):eadv8448. doi:10.1126/sciadv.adv8448, PMID:40815653.

[34] Gao X, Lin SH, Ren F, Li JT, Chen JJ, Yao CB, *et al*. Acetate functions as an epigenetic metabolite to promote lipid synthesis under hypoxia. Nat Commun 2016;7:11960. doi:10.1038/ncomms11960, PMID:27357947.

[35] Jung KH, Lee S, Kim HS, Kim JM, Lee YJ, Park MS, *et al*. Acetyl-CoA synthetase 2 contributes to a better prognosis for liver cancer by switching acetate-glucose metabolism. Exp Mol Med 2024;56(3):721–733. doi:10.1038/s12276-024-01185-3, PMID:38528124.

[36] Li X, Yu W, Qian X, Xia Y, Zheng Y, Lee JH, *et al*. Nucleus-Translocated ACSS2 Promotes Gene Transcription for Lysosomal Biogenesis and Autophagy. Mol Cell 2017;66(5):684–697.e9. doi:10.1016/j.molcel.2017.04.026, PMID:28552616.

[37] Schug ZT, Peck B, Jones DT, Zhang Q, Grosskurth S, Alam IS, *et al*. Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. Cancer Cell 2015;27(1):57–71. doi:10.1016/j.ccell.2014.12.002, PMID:25584894.

[38] Kwee SA, Hernandez B, Chan O, Wong L. Choline kinase alpha and hexokinase-2 protein expression in hepatocellular carcinoma: association with survival. PLoS One 2012;7(10):e46591. doi:10.1371/journal.pone.0046591, PMID:23071593.

[39] Lacal JC, Zimmerman T, Campos JM. Choline Kinase: An Unexpected Journey for a Precision Medicine Strategy in Human Diseases. Pharmaceutics 2021;13(6):788. doi:10.3390/pharmaceutics13060788, PMID:34070409.

[40] Li X, Hu Z, Shi Q, Qiu W, Liu Y, Liu Y, *et al*. Elevated choline drives KLF5-dominated transcriptional reprogramming to facilitate liver cancer progression. Oncogene 2024;43(42):3121–3136. doi:10.1038/s41388-024-03150-w, PMID:39251845.

[41] Bi J, Ichu TA, Zanca C, Yang H, Zhang W, Gu Y, *et al*. Oncogene Amplification in Growth Factor Signaling Pathways Renders Cancers Dependent on Membrane Lipid Remodeling. Cell Metab 2019;30(3):525–538.e8. doi:10.1016/j.cmet.2019.06.014, PMID:31303424.

[42] Hall Z, Chiarugi D, Charidemou E, Leslie J, Scott E, Pellegrinet L, *et al*. Lipid Remodeling in Hepatocyte Proliferation and Hepatocellular Carcinoma. Hepatology 2021;73(3):1028–1044. doi:10.1002/hep.31391, PMID:32460431.

[43] Li Z, Liao X, Hu Y, Li M, Tang M, Zhang S, *et al*. SLC27A4-mediated selective uptake of mono-unsaturated fatty acids promotes ferroptosis defense in hepatocellular carcinoma. Free Radic Biol Med 2023;201:41–54. doi:10.1016/j.freeradbiomed.2023.03.013, PMID:36924851.

[44] Egnatchik RA, Leamy AK, Noguchi Y, Shiota M, Young JD. Palmitate-induced activation of mitochondrial metabolism promotes oxidative stress and apoptosis in H4IIEC3 rat hepatocytes. Metabolism 2014;63(2):283–295. doi:10.1016/j.metabol.2013.10.009, PMID:24286856.

[45] Huang CY, Chen HW, Lo CW, Wang YR, Li CC, Liu KL, *et al*. Luteolin ameliorates palmitate-induced lipotoxicity in hepatocytes by mediating endoplasmic reticulum stress and autophagy. Food Chem Toxicol 2023;171:113554. doi:10.1016/j.fct.2022.113554, PMID:36509263.

[46] S Mesquita F, Abrami L, Linder ME, Bamji SX, Dickinson BC, van der Goot FG. Mechanisms and functions of protein S-acylation. Nat Rev Mol Cell Biol 2024;25(6):488–509. doi:10.1038/s41580-024-00700-8, PMID:38355760.

[47] Bu L, Zhang Z, Chen J, Fan Y, Guo J, Su Y, *et al*. High-fat diet promotes liver tumorigenesis via palmitoylation and activation of AKT. Gut 2024;73(7):1156–1168. doi:10.1136/gutjnl-2023-330826, PMID:38191266.

[48] Jin X, Hong Y, Zhao Y, Shi W, Liu R, You X, *et al*. ZDHHC12 Palmitoylates HDAC8 to Promote the Progression of Hepatocellular Carcinoma Associated with a Diet High in Saturated Fatty Acids. Adv Sci (Weinh) 2025;12(40):e05702. doi:10.1002/advs.202505702, PMID:40787880.

[49] Zhou L, Lian G, Zhou T, Cai Z, Yang S, Li W, *et al*. Palmitoylation of GPX4 via the targetable ZDHHC8 determines ferroptosis sensitivity and antitumor immunity. Nat Cancer 2025;6(5):768–785. doi:10.1038/s43018-025-00937-y, PMID:40108413.

[50] Mo Y, Han Y, Chen Y, Fu C, Li Q, Liu Z, *et al*. ZDHHC20 mediated S-palmitoylation of fatty acid synthase (FASN) promotes hepatocarcinogenesis. Mol Cancer 2024;23(1):274. doi:10.1186/s12943-024-02195-5, PMID:39696259.

[51] Jiang Y, Sun A, Zhao Y, Ying W, Sun H, Yang X, *et al*. Proteomics identifies new therapeutic targets of early-stage hepatocellular carcinoma. Nature 2019;567(7747):257–261. doi:10.1038/s41586-019-0987-8, PMID:30814741.

[52] Tsuchida T, Lee YA, Fujiwara N, Ybanez M, Allen B, Martins S, *et al*. A simple diet- and chemical-induced murine NASH model with rapid progression of steatohepatitis, fibrosis and liver cancer. J Hepatol 2018;69(2):385–395. doi:10.1016/j.jhep.2018.03.011, PMID:29572095.

[53] Liang JQ, Teoh N, Xu L, Pok S, Li X, Chu ESH, *et al*. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. Nat Commun 2018;9(1):4490. doi:10.1038/s41467-018-06931-6, PMID:30367044.

[54] Che L, Chi W, Qiao Y, Zhang J, Song X, Liu Y, *et al*. Cholesterol biosynthesis supports the growth of hepatocarcinoma lesions depleted of fatty acid synthase in mice and humans. Gut 2020;69(1):177–186. doi:10.1136/gutjnl-2018-317581, PMID:30954949.

[55] Zhang Z, Wu W, Jiao H, Chen Y, Ji X, Cao J, *et al*. Squalene epoxidase

promotes hepatocellular carcinoma development by activating STRAP transcription and TGF-β/SMAD signalling. Br J Pharmacol 2023;180(12):1562–1581. doi:10.1111/bph.16024, PMID:36581319.
[56] Wu J, Guo L, Qiu X, Ren Y, Li F, Cui W, *et al*. Genkwadaphnin inhibits growth and invasion in hepatocellular carcinoma by blocking DHCR24-mediated cholesterol biosynthesis and lipid rafts formation. Br J Cancer 2020;123(11):1673–1685. doi:10.1038/s41416-020-01085-z, PMID:32958824.
[57] Xu M, Jiang SY, Tang S, Zhu M, Hu Y, Li J, *et al*. Nuclear SREBP2 condensates regulate the transcriptional activation of lipogenic genes and cholesterol homeostasis. Nat Metab 2025;7(5):1034–1051. doi:10.1038/s42255-025-01291-0, PMID:40394324.
[58] Fowler JWM, Boutagy NE, Zhang R, Horikami D, Whalen MB, Romanoski CE, *et al*. SREBP2 regulates the endothelial response to cytokines via direct transcriptional activation of KLF6. J Lipid Res 2023;64(8):100411. doi:10.1016/j.jlr.2023.100411, PMID:37437844.
[59] Mok EHK, Leung CON, Zhou L, Lei MML, Leung HW, Tong M, *et al*. Caspase-3-Induced Activation of SREBP2 Drives Drug Resistance via Promotion of Cholesterol Biosynthesis in Hepatocellular Carcinoma. Cancer Res 2022;82(17):3102–3115. doi:10.1158/0008-5472.CAN-21-2934, PMID:35767704.
[60] Wang Z, Wang M, Zhang M, Xu K, Zhang X, Xie Y, *et al*. High-affinity SOAT1 ligands remodeled cholesterol metabolism program to inhibit tumor growth. BMC Med 2022;20(1):292. doi:10.1186/s12916-022-02436-8, PMID:35941608.
[61] Fu R, Xue W, Liang J, Li X, Zheng J, Wang L, *et al*. SOAT1 regulates cholesterol metabolism to induce EMT in hepatocellular carcinoma. Cell Death Dis 2024;15(5):325. doi:10.1038/s41419-024-06711-9, PMID:38724499.
[62] Zhao Z, Liu X, Xiang Y, Hou Z, He K, Zhong G, *et al*. Inhibiting cholesterol de novo synthesis promotes hepatocellular carcinoma progression by upregulating prostaglandin E synthase 2-mediated arachidonic acid metabolism under high fatty acid conditions. Cancer Sci 2024;115(2):477–489. doi:10.1111/cas.16035, PMID:38081591.
[63] Tian Y, Yang B, Qiu W, Hao Y, Zhang Z, Yang B, *et al*. ER-residential Nogo-B accelerates NAFLD-associated HCC mediated by metabolic reprogramming of oxLDL lipophagy. Nat Commun 2019;10(1):3391. doi:10.1038/s41467-019-11274-x, PMID:31358770.
[64] Lin Y, Liang Z, Weng Z, Liu X, Zhang F, Chong Y. CRSP8-driven fatty acid metabolism reprogramming enhances hepatocellular carcinoma progression by inhibiting RAN-mediated PPARα nucleus-cytoplasm shuttling. J Exp Clin Cancer Res 2025;44(1):93. doi:10.1186/s13046-025-03329-3, PMID:40069732.
[65] Liao PY, Lin WJ, Shen PC, Yang CR, Yu YC, Yeh CC, *et al*. Ether-lipids accumulation promotes hepatocellular carcinoma progression linked to PPARα deficiency. J Biomed Sci 2025;32(1):89. doi:10.1186/s12929-025-01178-y, PMID:40936093.
[66] Lee JM, Wagner M, Xiao R, Kim KH, Feng D, Lazar MA, *et al*. Nutrient-sensing nuclear receptors coordinate autophagy. Nature 2014;516(7529):112–115. doi:10.1038/nature13961, PMID:25383539.
[67] Wu C, Dai C, Li X, Sun M, Chu H, Xuan Q, *et al*. AKR1C3-dependent lipid droplet formation confers hepatocellular carcinoma cell adaptability to targeted therapy. Theranostics 2022;12(18):7681–7698. doi:10.7150/thno.74974, PMID:36451864.
[68] Kong Y, Wu M, Wan X, Sun M, Zhang Y, Wu Z, *et al*. Lipophagy-mediated cholesterol synthesis inhibition is required for the survival of hepatocellular carcinoma under glutamine deprivation. Redox Biol 2023;63:102732. doi:10.1016/j.redox.2023.102732, PMID:37150151.
[69] Yan Y, Huang L, Liu Y, Yi M, Chu Q, Jiao D, *et al*. Metabolic profiles of regulatory T cells and their adaptations to the tumor microenvironment: implications for antitumor immunity. J Hematol Oncol 2022;15(1):104. doi:10.1186/s13045-022-01322-3, PMID:35948909.
[70] Yan P, Luo Y, Huang Z, Mou T, Yang H, Peng D, *et al*. Establishment of a prognostic signature based on fatty acid metabolism genes in HCC associated with hepatitis B. BMC Gastroenterol 2023;23(1):390. doi:10.1186/s12876-023-03026-5, PMID:37957550.
[71] Ma K, Chu J, Liu Y, Sun L, Zhou S, Li X, *et al*. Hepatocellular Carcinoma LINC01116 Outcompetes T Cells for Linoleic Acid and Accelerates Tumor Progression. Adv Sci (Weinh) 2024;11(21):e2400676. doi:10.1002/advs.202400676, PMID:38460179.
[72] Wang Y, Chen W, Qiao S, Zou H, Yu XJ, Yang Y, *et al*. Lipid droplet accumulation mediates macrophage survival and Treg recruitment via the CCL20/CCR6 axis in human hepatocellular carcinoma. Cell Mol Immunol 2024;21(10):1120–1130. doi:10.1038/s41423-024-01199-x, PMID:38942796.
[73] Wu Q, Zhou W, Yin S, Zhou Y, Chen T, Qian J, *et al*. Blocking Triggering Receptor Expressed on Myeloid Cells-1-Positive Tumor-Associated Macrophages Induced by Hypoxia Reverses Immunosuppression and Anti-Programmed Cell Death Ligand 1 Resistance in Liver Cancer. Hepatology 2019;70(1):198–214. doi:10.1002/hep.30593, PMID:30810243.
[74] Ma S, Sandhoff R, Luo X, Shang F, Shi Q, Li Z, *et al*. Serine enrichment in tumors promotes regulatory T cell accumulation through sphinganine-mediated regulation of c-Fos. Sci Immunol 2024;9(94):eadg8817. doi:10.1126/sciimmunol.adg8817, PMID:38640251.
[75] Tang Y, Chen Z, Zuo Q, Kang Y. Regulation of CD8+ T cells by lipid metabolism in cancer progression. Cell Mol Immunol 2024;21(11):1215–1230. doi:10.1038/s41423-024-01224-z, PMID:39402302.
[76] Jin HR, Wang J, Wang ZJ, Xi MJ, Xia BH, Deng K, *et al*. Lipid metabolic reprogramming in tumor microenvironment: from mechanisms to therapeutics. J Hematol Oncol 2023;16(1):103. doi:10.1186/s13045-023-01498-2, PMID:37700339.
[77] Wong TL, Kong Y, Ma S. Lipid metabolism in cancer cells: Its role in hepatocellular carcinoma progression and therapeutic resistance. Hepatol Commun 2025;9(11):e0837. doi:10.1097/HC9.0000000000000837, PMID:41118283.
[78] Liang J, Liao J, Chang R, Jia W, Li G, Chen Z, *et al*. Riplet promotes lipid metabolism changes associated with CD8 T cell exhaustion and anti-PD-1 resistance in hepatocellular carcinoma. Sci Immunol 2025;10(108):eado3485. doi:10.1126/sciimmunol.ado3485, PMID:40577442.
[79] Xie Y, Sun R, Gao L, Guan J, Wang J, Bell A, *et al*. Chronic Activation of LXRα Sensitizes Mice to Hepatocellular Carcinoma. Hepatol Commun 2022;6(5):1123–1139. doi:10.1002/hep4.1880, PMID:34981658.
[80] Manzo T, Prentice BM, Anderson KG, Raman A, Schalck A, Codreanu GS, *et al*. Accumulation of long-chain fatty acids in the tumor microenvironment drives dysfunction in intrapancreatic CD8+ T cells. J Exp Med 2020;217(8):e20191920. doi:10.1084/jem.20191920, PMID:32491160.
[81] Hu C, Qiao W, Li X, Ning ZK, Liu J, Dalangood S, *et al*. Tumor-secreted FGF21 acts as an immune suppressor by rewiring cholesterol metabolism of CD8(+)T cells. Cell Metab 2024;36(3):630–647.e8. doi:10.1016/j.cmet.2024.01.005, PMID:38309268.
[82] Xu S, Chaudhary O, Rodríguez-Morales P, Sun X, Chen D, Zappasodi R, *et al*. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8(+) T cells in tumors. Immunity 2021;54(7):1561–1577.e7. doi:10.1016/j.immuni.2021.05.003, PMID:34102100.
[83] Qin Y, Huo F, Feng Z, Hou J, Ding Y, Wang Q, *et al*. CD36 promotes iron accumulation and dysfunction in CD8+ T cells via the p38-CEBPB-TfR1 axis in early-stage hepatocellular carcinoma. Clin Mol Hepatol 2025;31(3):960–980. doi:10.3350/cmh.2024.0948, PMID:40037690.
[84] O'Sullivan D, van der Windt GJ, Huang SC, Curtis JD, Chang CH, Buck MD, *et al*. Memory CD8(+) T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development. Immunity 2014;41(1):75–88. doi:10.1016/j.immuni.2014.06.005, PMID:25001241.
[85] Barili V, Fisicaro P, Montanini B, Acerbi G, Filippi A, Forleo G, *et al*. Targeting p53 and histone methyltransferases restores exhausted CD8+ T cells in HCV infection. Nat Commun 2020;11(1):604. doi:10.1038/s41467-019-14137-7, PMID:32001678.
[86] Liu F, Liu W, Zhou S, Yang C, Tian M, Jia G, *et al*. Identification of FABP5 as an immunometabolic marker in human hepatocellular carcinoma. J Immunother Cancer 2020;8(2):e000501. doi:10.1136/jitc-2019-000501, PMID:32611686.
[87] Xiao L, Ma X, Ye L, Su P, Xiong W, Bi E, *et al*. IL-9/STAT3/fatty acid oxidation-mediated lipid peroxidation contributes to Tc9 cell longevity and enhanced antitumor activity. J Clin Invest 2022;132(7):e153247. doi:10.1172/JCI153247, PMID:35192544.
[88] Chowdhury PS, Chamoto K, Kumar A, Honjo T. PPAR-Induced Fatty Acid Oxidation in T Cells Increases the Number of Tumor-Reactive CD8(+) T Cells and Facilitates Anti-PD-1 Therapy. Cancer Immunol Res 2018;6(11):1375–1387. doi:10.1158/2326-6066.CIR-18-0095, PMID:30143538.
[89] Zhang C, Yue C, Herrmann A, Song J, Egelston C, Wang T, *et al*. STAT3 Activation-Induced Fatty Acid Oxidation in CD8(+) T Effector Cells Is Critical for Obesity-Promoted Breast Tumor Growth. Cell Metab 2020;31(1):148–161.e5. doi:10.1016/j.cmet.2019.10.013, PMID:31761565.
[90] Lee MS, Webb TJ. Novel lipid antigens for NKT cells in cancer. Front Immunol 2023;14:1173375. doi:10.3389/fimmu.2023.1173375, PMID:37908366.
[91] Cheng X, Tan X, Wang W, Zhang Z, Zhu R, Wu M, *et al*. Long-Chain Acylcarnitines Induce Senescence of Invariant Natural Killer T Cells in Hepatocellular Carcinoma. Cancer Res 2023;83(4):582–594. doi:10.1158/0008-5472.CAN-22-2273, PMID:36512635.
[92] Tang W, Zhou J, Yang W, Feng Y, Wu H, Mok MTS, *et al*. Aberrant cholesterol metabolic signaling impairs antitumor immunosurveillance through natural killer T cell dysfunction in obese liver. Cell Mol Immunol 2022;19(7):834–847. doi:10.1038/s41423-022-00872-3, PMID:35595819.
[93] Qin WH, Yang ZS, Li M, Chen Y, Zhao XF, Qin YY, *et al*. High Serum Levels of Cholesterol Increase Antitumor Functions of Nature Killer Cells and Reduce Growth of Liver Tumors in Mice. Gastroenterology 2020;158(6):1713–1727. doi:10.1053/j.gastro.2020.01.028, PMID:31972238.
[94] Papanastasatou M, Gioulbasani M, Nakou E, Galaras A, Rubio-Tomás T, Talianidis I, *et al*. Dual regulatory role of natural killer T cells during development of hepatocellular carcinoma. Commun Biol 2025;8(1):1478. doi:10.1038/s42003-025-08872-5, PMID:41116010.
[95] Yang Y, Ye YC, Chen Y, Zhao JL, Gao CC, Han H, *et al*. Crosstalk between hepatic tumor cells and macrophages via Wnt/β-catenin signaling promotes M2-like macrophage polarization and reinforces tumor malignant behaviors. Cell Death Dis 2018;9(8):793. doi:10.1038/s41419-018-0818-0, PMID:30022048.
[96] Liu Y, Xu R, Gu H, Zhang E, Qu J, Cao W, *et al*. Metabolic reprogramming in macrophage responses. Biomark Res 2021;9(1):1. doi:10.1186/s40364-020-00251-y, PMID:33407885.
[97] Zeng W, Li F, Jin S, Ho PC, Liu PS, Xie X. Functional polarization of tumor-associated macrophages dictated by metabolic reprogramming. J Exp Clin Cancer Res 2023;42(1):245. doi:10.1186/s13046-023-02832-9, PMID:37740232.
[98] Xie Q, Zeng Y, Zhang X, Yu F. The significance of lipid metabolism reprogramming of tumor-associated macrophages in hepatocellular carcinoma. Cancer Immunol Immunother 2024;73(9):171. doi:10.1007/s00262-024-03748-9, PMID:38954021.
[99] Su P, Wang Q, Bi E, Ma X, Liu L, Yang M, *et al*. Enhanced Lipid Accumulation and Metabolism Are Required for the Differentiation and Activation of Tumor-Associated Macrophages. Cancer Res 2020;80(7):1438–1450. doi:10.1158/0008-5472.CAN-19-2994, PMID:32015091.
[100] Petan T, Jarc E, Jusović M. Lipid Droplets in Cancer: Guardians of Fat in a Stressful World. Molecules 2018;23(8):1941. doi:10.3390/molecules23081941, PMID:30081476.

[101] Vassiliou E, Farias-Pereira R. Impact of Lipid Metabolism on Macrophage Polarization: Implications for Inflammation and Tumor Immunity. Int J Mol Sci 2023;24(15):12032. doi:10.3390/ijms241512032, PMID:37569407.
[102] Xu J, Ding L, Mei J, Hu Y, Kong X, Dai S, *et al*. Dual roles and therapeutic targeting of tumor-associated macrophages in tumor microenvironments. Signal Transduct Target Ther 2025;10(1):268. doi:10.1038/s41392-025-02325-5, PMID:40850976.
[103] Chu T, Zhu G, Tang Z, Qu W, Yang R, Pan H, *et al*. Metabolism archetype cancer cells induce protumor TREM2(+) macrophages via oxLDL-mediated metabolic interplay in hepatocellular carcinoma. Nat Commun 2025;16(1):6770. doi:10.1038/s41467-025-62132-y, PMID:40695827.
[104] Tan J, Fan W, Liu T, Zhu B, Liu Y, Wang S, *et al*. TREM2(+) macrophages suppress CD8(+) T-cell infiltration after transarterial chemoembolisation in hepatocellular carcinoma. J Hepatol 2023;79(1):126–140. doi:10.1016/j.jhep.2023.02.032, PMID:36889359.
[105] Wang M, Li Y, Li S, Wang T, Wang M, Wu H, *et al*. Cinobufacini injection delays hepatocellular carcinoma progression by regulating lipid metabolism via SREBP1 signaling pathway and affecting macrophage polarization. J Ethnopharmacol 2024;321:117472. doi:10.1016/j.jep.2023.117472, PMID:37995825.
[106] Yang P, Qin H, Li Y, Xiao A, Zheng E, Zeng H, *et al*. CD36-mediated metabolic crosstalk between tumor cells and macrophages affects liver metastasis. Nat Commun 2022;13(1):5782. doi:10.1038/s41467-022-33349-y, PMID:36184646.
[107] Qin H, Xiao A, Lu Q, Li Y, Luo X, Zheng E, *et al*. The fatty acid receptor CD36 promotes macrophage infiltration via p110γ signaling to stimulate metastasis. J Adv Res 2025;74:237–253. doi:10.1016/j.jare.2024.10.006, PMID:39419288.
[108] Xu S, Peng X, Wang Z, Le C, Wu X, Zeng Z, *et al*. FABP7-mediated lipid-laden macrophages drive the formation of pre-metastatic niche and liver metastasis. Int J Biol Sci 2025;21(10):4388–4409. doi:10.7150/ijbs.110750, PMID:40765822.
[109] Luo S, Tang R, Jiang L, Luo Q, Fu J, Wu B, *et al*. Exosomal FABP5 drives HCC progression via macrophage lipid metabolism and immune microenvironment remodeling. Front Immunol 2025;16:1644645. doi:10.3389/fimmu.2025.1644645, PMID:41035647.
[110] Liu J, Sun B, Guo K, Yang Z, Zhao Y, Gao M, *et al*. Lipid-related FABP5 activation of tumor-associated monocytes fosters immune privilege via PD-L1 expression on Treg cells in hepatocellular carcinoma. Cancer Gene Ther 2022;29(12):1951–1960. doi:10.1038/s41417-022-00510-0, PMID:35902729.
[111] Zhang S, Lv K, Liu Z, Zhao R, Li F. Fatty acid metabolism of immune cells: a new target of tumour immunotherapy. Cell Death Discov 2024;10(1):39. doi:10.1038/s41420-024-01807-9, PMID:38245525.
[112] Huang J, Pan H, Sun J, Wu J, Xuan Q, Wang J, *et al*. TMEM147 aggravates the progression of HCC by modulating cholesterol homeostasis, suppressing ferroptosis, and promoting the M2 polarization of tumor-associated macrophages. J Exp Clin Cancer Res 2023;42(1):286. doi:10.1186/s13046-023-02865-0, PMID:37891677.
[113] Wu L, Zhang X, Zheng L, Zhao H, Yan G, Zhang Q, *et al*. RIPK3 Orchestrates Fatty Acid Metabolism in Tumor-Associated Macrophages and Hepatocarcinogenesis. Cancer Immunol Res 2020;8(5):710–721. doi:10.1158/2326-6066.CIR-19-0261, PMID:32122992.
[114] Feng R, Cui Z, Yang L, Liu Z. Sphingosine 1-phosphate derived from tumor-educated hepatic stellate cells combining with S1PR4 promotes tumor associated macrophages differentiation through FAO modulation. Sci Rep 2025;15(1):20507. doi:10.1038/s41598-025-02588-6, PMID:40592997.
[115] Pan Y, Qiu Y, Zhou X, Mao W, Xu X. Cancer-associated fibroblasts: multidimensional players in liver cancer. Front Oncol 2025;15:1454546. doi:10.3389/fonc.2025.1454546, PMID:40248197.
[116] Ge J, Jiang H, Chen J, Chen X, Zhang Y, Shi L, *et al*. TGF-β signaling orchestrates cancer-associated fibroblasts in the tumor microenvironment of human hepatocellular carcinoma: unveiling insights and clinical significance. BMC Cancer 2025;25(1):113. doi:10.1186/s12885-025-13435-2, PMID:39838288.
[117] Radhakrishnan R, Ha JH, Jayaraman M, Liu J, Moxley KM, Isidoro C, *et al*. Ovarian cancer cell-derived lysophosphatidic acid induces glycolytic shift and cancer-associated fibroblast-phenotype in normal and peritumoral fibroblasts. Cancer Lett 2019;442:464–474. doi:10.1016/j.canlet.2018.11.023, PMID:30503552.
[118] Wu F, Yang J, Liu J, Wang Y, Mu J, Zeng Q, *et al*. Signaling pathways in cancer-associated fibroblasts and targeted therapy for cancer. Signal Transduct Target Ther 2021;6(1):218. doi:10.1038/s41392-021-00641-0, PMID:34108441.
[119] Liu P, Wang Y, Li X, Liu Z, Sun Y, Liu H, *et al*. Enhanced lipid biosynthesis in oral squamous cell carcinoma cancer-associated fibroblasts contributes to tumor progression: Role of IL8/AKT/p-ACLY axis. Cancer Sci 2024;115(5):1433–1445. doi:10.1111/cas.16111, PMID:38494608.
[120] Gong J, Lin Y, Zhang H, Liu C, Cheng Z, Yang X, *et al*. Reprogramming of lipid metabolism in cancer-associated fibroblasts potentiates migration of colorectal cancer cells. Cell Death Dis 2020;11(4):267. doi:10.1038/s41419-020-2434-z, PMID:32327627.
[121] Murthy D, Attri KS, Shukla SK, Thakur R, Chaika NV, He C, *et al*. Cancer-associated fibroblast-derived acetate promotes pancreatic cancer development by altering polyamine metabolism via the ACSS2-SP1-SAT1 axis. Nat Cell Biol 2024;26(4):613–627. doi:10.1038/s41556-024-01372-4, PMID:38429478.
[122] Zhang Y, Gu Z, Wan J, Lou X, Liu S, Wang Y, *et al*. Stearoyl-CoA Desaturase-1 dependent lipid droplets accumulation in cancer-associated fibroblasts facilitates the progression of lung cancer. Int J Biol Sci 2022;18(16):6114–6128. doi:10.7150/ijbs.74924, PMID:36439884.
[123] Hwang SH, Yang Y, Jung JH, Kim Y. Oleic acid from cancer-associated fibroblast promotes cancer cell stemness by stearoyl-CoA desaturase under glucose-deficient condition. Cancer Cell Int 2022;22(1):404. doi:10.1186/s12935-022-02824-3, PMID:36514170.
[124] Zhu GQ, Tang Z, Huang R, Qu WF, Fang Y, Yang R, *et al*. CD36(+) cancer-associated fibroblasts provide immunosuppressive microenvironment for hepatocellular carcinoma via secretion of macrophage migration inhibitory factor. Cell Discov 2023;9(1):25. doi:10.1038/s41421-023-00529-z, PMID:36878933.
[125] Han X, Burrows M, Kim LC, Xu JP, Vostrejs W, Van Le TN, *et al*. Cancer-associated fibroblasts maintain critical pancreatic cancer cell lipid homeostasis in the tumor microenvironment. Cell Rep 2024;43(11):114972. doi:10.1016/j.celrep.2024.114972, PMID:39535921.
[126] Salgado-Polo F, Borza R, Matsoukas MT, Marsais F, Jagerschmidt C, Waeckel L, *et al*. Autotaxin facilitates selective LPA receptor signaling. Cell Chem Biol 2023;30(1):69–84.e14. doi:10.1016/j.chembiol.2022.12.006, PMID:36640760.
[127] Mazzocca A, Dituri F, Lupo L, Quaranta M, Antonaci S, Giannelli G. Tumor-secreted lysophostatidic acid accelerates hepatocellular carcinoma progression by promoting differentiation of peritumoral fibroblasts in myofibroblasts. Hepatology 2011;54(3):920–930. doi:10.1002/hep.24485, PMID:21674557.
[128] Volat F, Medhi R, Maggs LZ, Deken MA, Price A, Andrews L, *et al*. Pancreatic CAF-Derived Autotaxin Drives Autocrine CTGF Expression to Modulate Protumorigenic Signaling. Mol Cancer Ther 2025;24(2):230–241. doi:10.1158/1535-7163.MCT-23-0522, PMID:39570650.
[129] Wang H, Liu F, Wu X, Zhu G, Tang Z, Qu W, *et al*. Cancer-associated fibroblasts contributed to hepatocellular carcinoma recurrence and metastasis via CD36-mediated fatty-acid metabolic reprogramming. Exp Cell Res 2024;435(2):113947. doi:10.1016/j.yexcr.2024.113947, PMID:38301989.
[130] Lin Z, Li G, Jiang K, Li Z, Liu T. Cancer therapy resistance mediated by cancer-associated fibroblast-derived extracellular vesicles: biological mechanisms to clinical significance and implications. Mol Cancer 2024;23(1):191. doi:10.1186/s12943-024-02106-8, PMID:39244548.
[131] Zhang H, Deng T, Liu R, Ning T, Yang H, Liu D, *et al*. CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. Mol Cancer 2020;19(1):43. doi:10.1186/s12943-020-01168-8, PMID:32106859.
[132] Tong T, Gao W, Jian H, Yang R, Zhang J, Li K, *et al*. The role and potential mechanisms of exosomes in the progression of hepatocellular carcinoma. Holist Integ Oncol 2025;4:36. doi:10.1007/s44178-025-00171-7.
[133] Zhang C, Wang XY, Zhang P, He TC, Han JH, Zhang R, *et al*. Cancer-derived exosomal HSPC111 promotes colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts. Cell Death Dis 2022;13(1):57. doi:10.1038/s41419-022-04506-4, PMID:35027547.
[134] Sun HC, Zhou J, Wang Z, Liu X, Xie Q, Jia W, *et al*. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). Hepatobiliary Surg Nutr 2022;11(2):227–252. doi:10.21037/hbsn-21-328, PMID:35464283.
[135] Liu S, Jiang J, Jian Q, Liu Y, Huang Z, Chen Y, *et al*. Chinese multicenter expert consensus on the diagnosis and treatment of hilar cholangiocarcinoma: 2025 edition. Biosci Trends 2025;19(4):379–403. doi:10.5582/bst.2025.01233, PMID:40803877.
[136] Shen X, Zhao D, Wang F, Li X, Sun K, Du H, *et al*. Dietary intervention reshapes gut microbiota and lipid metabolism to enhance anti-tumor immunity and prognosis in hepatocellular carcinoma: a randomized controlled trial. BMC Cancer 2026;26(1):42. doi:10.1186/s12885-025-15325-z, PMID:41491437.
[137] Lei Y, Xie C, Mo X, Zhuang B, Li Q, Liu C, *et al*. Preoperative plasma ceramide profiling coupled with machine learning accurately predicts recurrence of hepatocellular carcinoma after resection. Lipids Health Dis 2025;24(1):355. doi:10.1186/s12944-025-02749-6, PMID:41194075.
[138] Lin ZY, Lu D, Wu SD, Hu ZH, Yang XD, Liu P, *et al*. Body composition predicts prognosis of patients with hepatocellular carcinoma after liver transplantation: A multicenter study. Hepatobiliary Pancreat Dis Int 2025. doi:10.1016/j.hbpd.2025.11.002, PMID:41233280.
[139] Mata-Cruz C, Guerrero-Rodríguez SL, Gómez-Castellano K, Carballo-Uicab G, Almagro JC, Pérez-Tapia SM, *et al*. Discovery and in vitro characterization of a human anti-CD36 scFv. Front Immunol 2025;16:1531171. doi:10.3389/fimmu.2025.1531171, PMID:39967671.
[140] Yu YR, Tsai CH, Hsiao HW, Park J, Koni P, Chen H, *et al*. 1401 PLT012, a monoclonal antibody targeting CD36, unleashes anti-tumor immunity via metabolic reprogramming in tumor microenvironment. J Immunother Cancer 2023;11(Suppl 1):A1559. doi:10.1136/jitc-2023-SITC2023.1401.
[141] Mahalingam D, Harb W, Patnaik A. 374 A first-in-human Phase 1/2 open label trial evaluating the safety, pharmacology, and preliminary efficacy of VT1021 in subjects with advanced solid tumors. J Immunother Cancer 2020;8:A228. doi:10.1136/jitc-2020-SITC2020.0374.
[142] Huang J, Tsang WY, Fang XN, Zhang Y, Luo J, Gong LQ, *et al*. FASN Inhibition Decreases MHC-I Degradation and Synergizes with PD-L1 Checkpoint Blockade in Hepatocellular Carcinoma. Cancer Res 2024;84(6):855–871. doi:10.1158/0008-5472.CAN-23-0966, PMID:38486485.
[143] Li Y, Yang W, Zheng Y, Dai W, Ji J, Wu L, *et al*. Targeting fatty acid synthase modulates sensitivity of hepatocellular carcinoma to sorafenib via ferroptosis. J Exp Clin Cancer Res 2023;42(1):6. doi:10.1186/s13046-022-02567-z, PMID:36604718.
[144] Wang H, Zhou Y, Xu H, Wang X, Zhang Y, Shang R, *et al*. Therapeutic efficacy of FASN inhibition in preclinical models of HCC. Hepatology 2022;76(4):951–966. doi:10.1002/hep.32359, PMID:35076948.
[145] Gleba JJ, Alasonyalilar-Demirer A, Pawlush ML. Abstract 5489: Synergis-

tic activity of SCD1 blockade in combination with tyrosine kinase inhibitors lenvatinib and cabozantinib in hepatocellular carcinoma (HCC). Cancer Res 2023;83:5489. doi:10.1158/1538-7445.AM2023-5489.
[146] Zheng Y, Zhou Q, Zhao C, Li J, Yu Z, Zhu Q. ATP citrate lyase inhibitor triggers endoplasmic reticulum stress to induce hepatocellular carcinoma cell apoptosis via p-eIF2α/ATF4/CHOP axis. J Cell Mol Med 2021;25(3):1468–1479. doi:10.1111/jcmm.16235, PMID:33393219.
[147] Li P, Zhang R, Wang M, Chen Y, Chen Z, Ke X, *et al*. Baicalein Prevents Fructose-Induced Hepatic Steatosis in Rats: In the Regulation of Fatty Acid De Novo Synthesis, Fatty Acid Elongation and Fatty Acid Oxidation. Front Pharmacol 2022;13:917329. doi:10.3389/fphar.2022.917329, PMID:35847050.
[148] Vell MS, Loomba R, Krishnan A, Wangensteen KJ, Trebicka J, Creasy KT, *et al*. Association of Statin Use With Risk of Liver Disease, Hepatocellular Carcinoma, and Liver-Related Mortality. JAMA Netw Open 2023;6(6):e2320222. doi:10.1001/jamanetworkopen.2023.20222, PMID:37358849.
[149] Feng J, Dai W, Mao Y, Wu L, Li J, Chen K, *et al*. Simvastatin re-sensitizes hepatocellular carcinoma cells to sorafenib by inhibiting HIF-1α/PPAR-γ/PKM2-mediated glycolysis. J Exp Clin Cancer Res 2020;39(1):24. doi:10.1186/s13046-020-1528-x, PMID:32000827.
[150] Mahmoud K, Teaima M, Attia Y, El-Nabarawi M, Swidan S. Size-optimized simvastatin-loaded TPGS modified lipid nanocapsules for targeting epithelial-to-mesenchymal transition in hepatocellular carcinoma: Role of PTEN/AKT signaling. Expert Opin Drug Deliv 2023;20(5):703–719. doi:10.1080/17425247.2023.2216451, PMID:37208857.
[151] Harisa GI, Alzhrani RF, Alluhaidan AA, Alamri SM, Bakheit AH, Asiri HH, *et al*. Chitosan capped-NLCs enhanced codelivery of gefitinib and simvastatin into MDR HCC: impact of compositions on cell death, JNK3, and Telomerase. Oncol Res 2025;33(2):477–492. doi:10.32604/or.2024.053337, PMID:39866231.
[152] Zheng C, Zhu Y, Liu Q, Luo T, Xu W. Maprotiline Suppresses Cholesterol Biosynthesis and Hepatocellular Carcinoma Progression Through Direct Targeting of CRABP1. Front Pharmacol 2021;12:689767. doi:10.3389/fphar.2021.689767, PMID:34093212.
[153] Tzeng SF, Yu YR, Park J, von Renesse J, Hsiao HW, Hsu CH, *et al*. PLT012, a Humanized CD36-Blocking Antibody, Is Effective for Unleashing Antitumor Immunity Against Liver Cancer and Liver Metastasis. Cancer Discov 2025;15(8):1676–1696. doi:10.1158/2159-8290.CD-24-1409, PMID:40294022.
[154] Mahalingam D, Harb W, Patnaik A, Bullock A, Watnick RS, Vincent MY, *et al*. First-in-human phase I dose escalation trial of the first-in-class tumor microenvironment modulator VT1021 in advanced solid tumors. Commun Med (Lond) 2024;4(1):10. doi:10.1038/s43856-024-00433-x, PMID:38218979.
[155] Kawata S, Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, *et al*. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. Br J Cancer 2001;84(7):886–891. doi:10.1054/bjoc.2000.1716, PMID:11286466.
[156] Graf H, Jüngst C, Straub G, Dogan S, Hoffmann RT, Jakobs T, *et al*. Chemoembolization combined with pravastatin improves survival in patients with hepatocellular carcinoma. Digestion 2008;78(1):34–38. doi:10.1159/000156702, PMID:18797167.
[157] Jouve JL, Lecomte T, Bouché O, Barbier E, Khemissa Akouz F, Riachi G, *et al*. Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma. J Hepatol 2019;71(3):516–522. doi:10.1016/j.jhep.2019.04.021, PMID:31125576.
[158] Riaño I, Martín L, Varela M, Serrano T, Núñez O, Mínguez B, *et al*. Efficacy and Safety of the Combination of Pravastatin and Sorafenib for the Treatment of Advanced Hepatocellular Carcinoma (ESTAHEP Clinical Trial). Cancers (Basel) 2020;12(7):1900. doi:10.3390/cancers12071900, PMID:32674461.
[159] Ostwal V, Ramaswamy A, Gota V, Bhargava PG, Srinivas S, Shriyan B, *et al*. Phase I Study Evaluating Dose De-escalation of Sorafenib with Metformin and Atorvastatin in Hepatocellular Carcinoma (SMASH). Oncologist 2022;27(3):165–e222. doi:10.1093/oncolo/oyab008, PMID:35274724.
[160] Han JY, Lee SH, Yoo NJ, Hyung LS, Moon YJ, Yun T, *et al*. A randomized phase II study of gefitinib plus simvastatin versus gefitinib alone in previously treated patients with advanced non-small cell lung cancer. Clin Cancer Res 2011;17(6):1553–1560. doi:10.1158/1078-0432.CCR-10-2525, PMID:21411446.
[161] Hong JY, Nam EM, Lee J, Park JO, Lee SC, Song SY, *et al*. Randomized double-blinded, placebo-controlled phase II trial of simvastatin and gemcitabine in advanced pancreatic cancer patients. Cancer Chemother Pharmacol 2014;73(1):125–130. doi:10.1007/s00280-013-2328-1, PMID:24162380.
[162] Kim ST, Kang JH, Lee J, Park SH, Park JO, Park YS, *et al*. Simvastatin plus capecitabine-cisplatin versus placebo plus capecitabine-cisplatin in patients with previously untreated advanced gastric cancer: a double-blind randomised phase 3 study. Eur J Cancer 2014;50(16):2822–2830. doi:10.1016/j.ejca.2014.08.005, PMID:25218337.
[163] Rushworth LK, Loveridge C, Salji M, MacLeod M, Mui E, Sumpton D, *et al*. Phase II proof-of-concept study of atorvastatin in castration-resistant prostate cancer. BJU Int 2023;131(2):236–243. doi:10.1111/bju.15851, PMID:35844167.