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REVIEW

Lipid Metabolism as a Potential Target of Liver Cancer

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Abstract: Hepatocellular carcinoma (HCC) stands as a severe malignant tumor with a profound impact on overall health, often accompanied by an unfavorable prognosis. Despite some advancements in the diagnosis and treatment of this disease, improving the prognosis of HCC remains a formidable challenge. It is noteworthy that lipid metabolism plays a pivotal role in the onset, development, and progression of tumor cells. Existing research indicates the potential application of targeting lipid metabolism in the treatment of HCC. This review aims to thoroughly explore the alterations in lipid metabolism in HCC, offering a detailed account of the potential advantages associated with innovative therapeutic strategies targeting lipid metabolism. Targeting lipid metabolism holds promise for potentially enhancing the prognosis of HCC.

Keywords: cholesterol, fatty acid, hepatocellular carcinoma, lipid uptake, lipid catabolism, lipid synthesis

Introduction

Liver cancer significantly impacts human health, ranking as the sixth most common malignant tumor and the third leading cause of cancer-related deaths globally. Hepatocellular carcinoma (HCC) constitutes roughly 75%-85% of liver cancer cases. Multiple factors contribute to the development of HCC, including aflatoxin exposure, alcohol consumption, hepatitis B, hepatitis C, obesity, and other related elements. In high-risk regions like China, Korea, and sub-Saharan Africa, chronic HBV infection and aflatoxin exposure are predominant causes.[1]

Over time, primary risk factors for HCC have shifted. In several regions, the proportion of HCC cases linked to obesity and diabetes has progressively risen.[2] Western countries are witnessing an increase in HCC incidence due to non-alcoholic fatty liver disease, particularly non-alcoholic steatohepatitis (NASH), associated with metabolic syndrome or diabetes.[3] While advancements have been made in comprehending the pathophysiology of HCC, it remains a formidable disease.[3] Typically diagnosed at advanced stages, HCC often presents a poor prognosis.

In the United States, HCC patients have alarming survival rates. The average one-year survival rate is less than 50%, and the average five-year survival rate is less than 10%.[4] This underlines the urgency to enhance early detection and more effective treatments to improve the outlook for individuals diagnosed with HCC.

Numerous conventional treatments are available for HCC, selected according to the patient's health status. Early-stage HCC patients are typically recommended for resection, transplantation, or local ablation. Intermediate-stage patients often opt for transarterial chemoembolization (TACE), while those in the advanced stage generally receive systemic treatment as the primary approach.[5–7] Currently, surgical intervention remains the primary treatment for HCC.[5,8] However, a notable challenge post-surgery is the high recurrence rate, which can be as high as 70% even in patients with a single tumor of 2cm or less.[9]

In the last decade, sorafenib has stood out as a classic systemic drug with therapeutic effectiveness against HCC.[10] Advanced understanding of HCC development mechanisms has led to the establishment of anti-PD-L1 antibody atezolizumab and anti-vascular endothelial growth factor antibody bevacizumab as standard treatments for untreated advanced HCC, demonstrating superior effectiveness to sorafenib.[11,12] Yet, current treatments have limitations, stimulating researchers to actively search for new therapeutic targets. Among these, lipid metabolism has emerged as a notably promising focus of interest.[13–17]

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The liver, a vital organ, performs various physiological functions, including the intricate processing of lipids.[18] Lipids, comprising fats and lipoids, are diverse nutrients widely distributed in cellular organelles and serve as fundamental components of cellular membranes.[19] Central to the synthesis, storage, and breakdown of lipids, the liver plays a critical role in maintaining lipid balance within the body.

One notable trait of cancer metabolism involves the promotion of de novo lipid synthesis, a pivotal pathway responsible for the generation of fatty acids (FAs).[20] This metabolic shift is essential for rapidly dividing tumor cells to acquire necessary lipids, crucial for membrane construction, energy supply, and post-translational modifications.[21] Relevant studies on lipid metabolism in HCC have already been published. Studies indicate that non-coding RNA can influence the progression of HCC by modulating the reprogramming of FAs metabolism.[22,23] It has been reported that selective splicing of RNA can regulate lipid metabolism, thereby preventing the onset of HCC.[24] Additionally, research has identified lipid metabolism-related gene markers that can be utilized to predict the prognosis of HCC.[25] Given the significance of lipid metabolism in malignant tumors, a comprehensive understanding of how lipid metabolism is reprogrammed in HCC could provide valuable insights into targeting metabolic networks within HCC.

This review aims to summarize and analyze the influence of lipid metabolism on the genesis and advancement of HCC, introducing potential targets for therapeutic strategies based on lipid metabolism in the context of HCC.

Alteration of FAs Metabolism in HCC

In the physiological milieu of individuals with HCC, alterations in lipid metabolism manifest due to the heightened metabolic requirements of the tumor cells. Studies indicate that lipid biosynthesis and desaturation play crucial roles in the onset, sustenance, and advancement of HCC (Figure 1).[26–28]

There remain unexplored facets of lipid metabolism in HCC that warrant further investigation in current research.

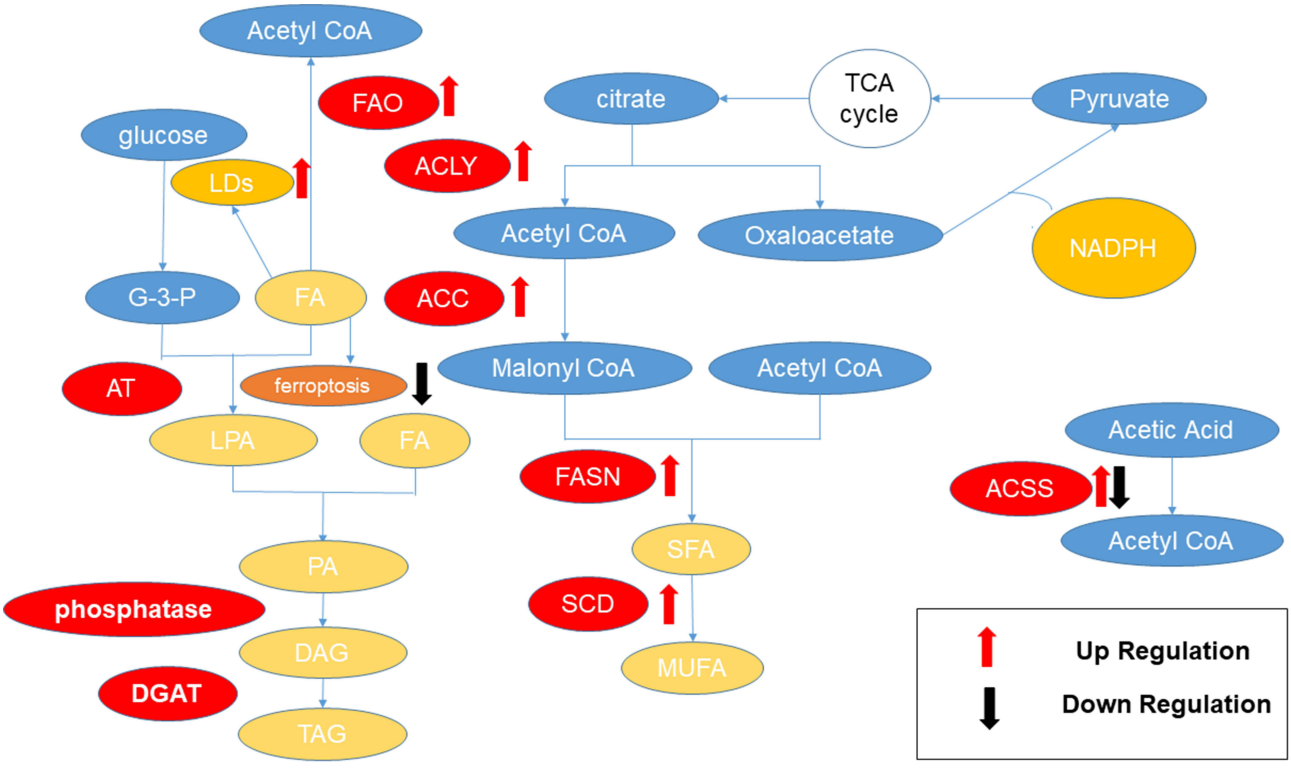

Figure 1 Aberrant FAs metabolism in HCC. In HCC, enzymes associated with fatty acid synthesis, such as ACLY, ACC, FASN, and SCD, are typically upregulated, and their increased expression is linked to a poor prognosis in HCC. However, ACSS stands out as relatively unique, as both upregulation and downregulation of its expression may be associated with adverse outcomes in HCC. In the FAs catabolism of HCC, there is typically an observed enhancement in FAO and LDs, while ferroptosis induced by FAs peroxidation tends to decrease. This is often associated with a poor prognosis in HCC.

Abbreviations: TCA, Tricarboxylic acid; FAs, fatty acids; ACLY, ATP-citrate lyase; CoA, coenzyme A; ACC, acetyl-CoA carboxylase; AT, acyltransferase; LPA, lysophosphatidic acid;ACSS, acetyl-CoA synthetase; FASN, fatty acid synthase, SCD, Stearoyl-Coenzyme A Desaturase-1; PA, phosphatidic acid; DAG, diacylglycerol; DGAT, DAG acyltransferase; TAG, triacylglycerol; SFA, saturated fatty acid; MUFA, monounsaturated FA; FAO, fatty acid oxidation; LDS, lipid droplets.

Aberrant FAs Uptake

Cells have the capacity to absorb FAs and cholesterol from their external surroundings.[29] This uptake of FA necessitates the involvement of diverse membrane-associated transport proteins, such as fatty acid transport proteins (FATPs), fatty acid translocase (CD36), and FA-binding proteins (FABPs) (Figure 2).[30]

CD36, a complete transmembrane glycoprotein, is expressed in various tissues, functioning as a scavenger receptor involved in immune recognition, inflammation, molecular adhesion, apoptosis, and lipid uptake.[31–33] Research has revealed its pivotal role in regulating proliferation, metastasis, and angiogenesis in various tumor types.[34–36] For instance, in esophageal squamous cell carcinoma, high CD36 expression significantly influences the reliance on FAs as a primary energy source, making it a critical regulator in this particular cancer.[34] Additionally, studies indicate a positive correlation between baseline CD36 expression levels and migration, invasion, as well as the expression of epithelial-mesenchymal transition (EMT) markers in gastric cancer cell lines. Furthermore, research has demonstrated that in gastric cancer, CD36 promotes migration by activating serine/threonine kinase phosphorylation and inhibiting glycogen synthase kinase 3/β-catenin degradation, thereby facilitating the EMT.[35] Intriguingly, in pancreatic cancer, low CD36 expression is associated with tumor growth and reduced survival rates.[37]

In the context of HCC, CD36's role is intricately linked to the tumor microenvironment, where it functions in mediating the progression of HCC by reprogramming tumor metabolism. Experimental evidence indicates that the upregulation of CD36 in HCC significantly enhances both proliferation and metastatic potential, both in in vitro and in vivo settings.[38] CD36, as a receptor for FAs, when deficient, leads to a reduction in FAs uptake across various human and mouse tissues.[39] Studies have revealed that the absence of CD36 notably decreases phospholipids, triglycerides, and neutral lipids in HCC cells. This deficiency also impacts the expression of key enzymes involved in lipid metabolism, such as fatty acid synthase (FASN), acetyl-coenzyme A(CoA) carboxylase1 (ACC1), and FABP5. Furthermore, research has shown that CD36 plays a role in regulating the proliferation and migration of HCC cells by influencing their FAs uptake.[38] Given these findings, CD36 emerges as a potential target for therapeutic intervention in HCC.

De Novo FAs Synthesis

In addition to the uptake of esters, de novo lipid synthesis in the body stands as a vital source of lipids. Primarily, de novo FAs synthesis takes place within the cytoplasm of liver cells or adipocytes, commencing with glucose conversion to pyruvate via

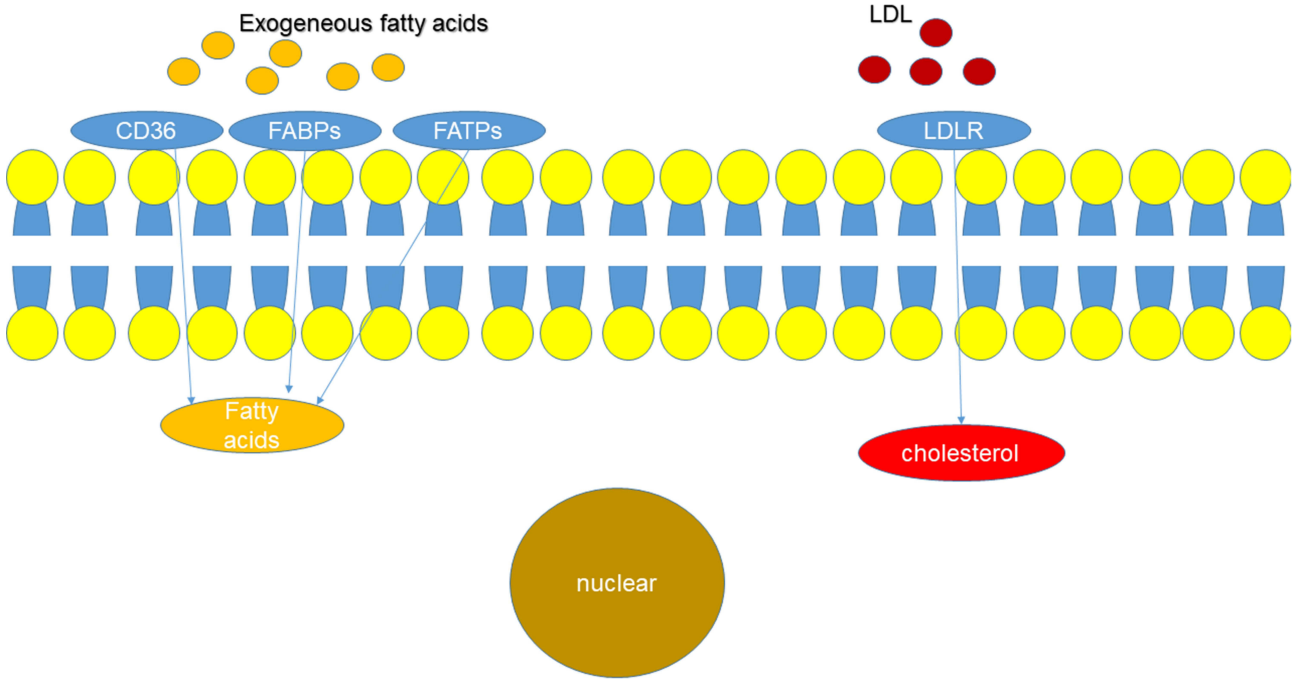

Figure 2 Lipid uptake. Cells uptake exogenous fatty acids through CD36, FABPs, and FATPs, and cholesterol transported by LDL is taken up through LDLR.
Abbreviations: CD36, Fatty acid translocase; FABPs, FA-binding proteins; FATPs, fatty acid transport proteins; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor.

glycolysis.[40] Pyruvate then enters the mitochondria, transforming into citrate through the citric acid cycle. Exiting the mitochondria, citrate, catalyzed by ATP-citrate lyase (ACLY), converts into acetyl-CoA and oxaloacetate. Acetyl-CoA, further broken down into pyruvate and NADPH, along with previously generated acetyl-CoA, enters the fatty acid synthesis pathway.[41] Acetyl-CoA is converted to malonyl-CoA by ACC. Malonyl-CoA, in conjunction with FASN, facilitates the formation of saturated fatty acids (SFAs) like palmitoyl-CoA and stearoyl-CoA.[42] Stearoyl-CoA Desaturase-1 (SCD) catalyzes the conversion of saturated FAs to monounsaturated FA (MUFA) palmitoyl-CoA and oleoyl-CoA (Figure 3).[43]

Once FAs are produced, the liver begins to store them. Glucose, in the liver, is transformed into glycerol-3-phosphate (G3P) via glycolysis. G3P, combined with activated FAs by acyltransferase (AT), generates lysophosphatidic acid (LPA). AT further adds another activated FA to LPA, forming phosphatidic acid, which is then converted into diacylglycerol (DAG) by phosphatase. DAG acyltransferase (DGAT) then converts DAG into triacylglycerol (TAG).[42] Moreover, acetate can be converted into acetyl-CoA via acetyl-CoA synthetase (ACSS) (Figure 3).[44]

Enzymes of Producing Acetyl-CoA in HCC

ACLY is an enzyme responsible for catalyzing the conversion of citrate and coenzyme A into acetyl-coenzyme A and oxaloacetate.[45] The upregulation of ACLY is notably observed in various cancer cells. For instance, in breast cancer, research indicates that in HER2+/PIK3CAmut cells, mTORC2 stimulates the phosphorylation of ACLY, promoting the production of acetyl-CoA and enhancing de novo FAs synthesis, thereby facilitating tumor growth. Conversely, reduced ACLY exerts inhibitory effects on the growth of breast cancer cells.[46] Immunohistochemical (IHC) analyses of gastric cancer patients have revealed a significant increase in ACLY in tumor tissues compared to surrounding normal tissues. Elevated ACLY levels are also positively associated with late-stage lymph node metastasis and shorter survival times in cancer.[47]

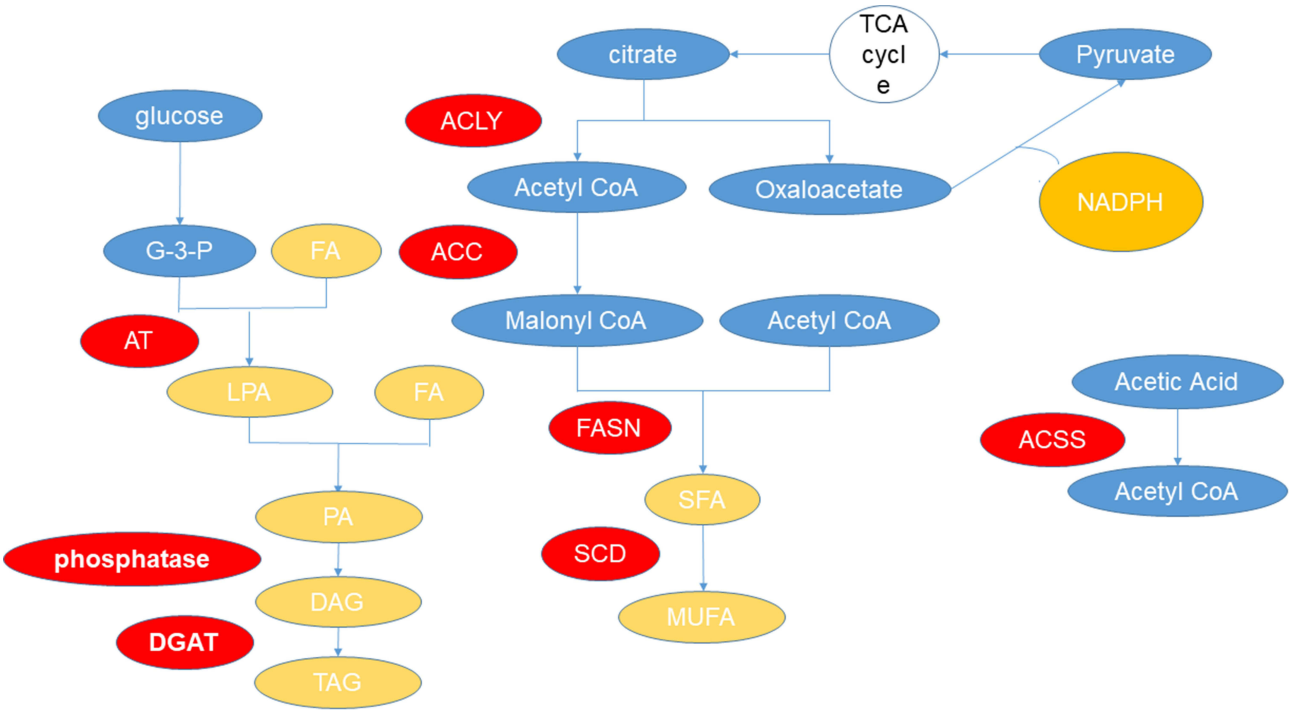

Figure 3 FAs synthesis. The citrate produced in the tricarboxylic acid cycle generates acetyl-CoA through ACLY. Acetyl-CoA is then converted to malonyl-CoA by ACC. Malonyl-CoA and acetyl-CoA combine through FASN to aid in the formation of SFA. Under the catalysis of SCD, SFAs are transformed into MUFA. G-3-P combines with activated fatty acids through AT to form LPA, which further converts to DAG. Subsequently, DGAT transforms DAG into TAG. Additionally, acetate can also be converted to acetyl-CoA through ACSS.

Abbreviations: TCA, Tricarboxylic acid; FAs, fatty acids; ACLY, ATP-citrate lyase; CoA, coenzyme A; ACC, acetyl-CoA carboxylase; AT, acyltransferase; LPA, lysophosphatidic acid; ACSS, acetyl-CoA synthetase; FASN, fatty acid synthase; SCD, Stearoyl-Coenzyme A Desaturase-1; PA, phosphatidic acid; DAG, diacylglycerol; DGAT, DAG acyltransferase; TAG, triacylglycerol; SFA, saturated fatty acid; MUFA, monounsaturated FA; G-3-P, Glycerol-3-phosphate.

In the context of HCC, ACLY plays a crucial role in disease occurrence and development.[48,49] Studies have shown that downregulating ACLY can reduce lipid synthesis, inflammation, and the incidence of HCC. ACLY's role in promotingHCC has been elucidated by research.[49]

Some studies report that HCA, an ACLY inhibitor, can redirect the flow of acetyl-L-carnitine towards lipids while decreasing glucose flux towards lipids. This redirection suggests that in HepG2 HCC cells, acetyl-L-carnitine bypasses the citric acid cycle and utilizes cytoplasmic acetyl-CoA.[50]

Ning and colleagues' research has identified that USP22 deubiquitinates and stabilizes Peroxisome Proliferator-Activated Receptor-γ (PPARγ), consequently upregulating ACLY expression, promoting lipid accumulation, and fostering tumor development in HCC cells.[51]

As ACLY mediates acetyl-CoA production, which is pivotal in tumor development, targeting ACLY could be an effective approach in cancer treatment.

The ACSS enzyme family, including ACSS1, ACSS2, and ACSS3, is involved in acetyl-CoA synthesis. In conditions of hypoxia and lipid depletion, ACSS2 is upregulated to produce acetyl-CoA.[52–54] ACSS1, a mitochondrial protein, plays a crucial role in the growth of low glycolytic phenotype HCC cells, with inhibiting ACSS1 reducing acetate uptake and cell viability in this cell line.[55]

ACSS3, found in both the cytoplasm and nucleus, can be utilized for subtyping HCC.[53,54,56] ACSS2, transcriptionally upregulated by sterol regulatory element-binding proteins (SREBPs), is identified through functional genomics as critical for cancer cell survival in hypoxic or low serum conditions.[52] Inhibiting ACSS2 can suppress tumor growth, potentially linked to increased acetate consumption during tumor growth.[57–59]

In HCC, ACSS2 contributes acetyl groups for the acetylation of hypoxia-inducible factor (HIF)-2α. Under hypoxic conditions, silencing ACSS2 leads to decreased acetylation of HIF-2α, enhancing HIF-2α activity, increasing invasion, migration capabilities of HCC cells, and promoting EMT. Reduced expression of ACSS2 in a cohort of HCC patients is associated with advanced stages and poorer overall survival and disease-free survival rates, suggesting potential implications for the prognosis of HCC by targeting ACSS.[60]

FA Biosynthesis Enzymes in HCC

ACC serves as the rate-limiting enzyme in fatty acid biosynthesis[61,62] and exists in two isoforms in humans: cytosolic ACC1, involved in metabolism, and outer mitochondrial membrane-anchored ACC2, responsible for regulating FAs beta-oxidation.[62] Current research highlights that ACC gene expression is regulated by various transcription factors including SREBP1a, SREBP1c and carbohydrate-responsive element-binding protein (ChREBP).[63]

In various human cancer cells, ACC1 is notably highly expressed, showing relevance to cancer growth.[64–66] In HCC, studies have identified ND-654, a liver-specific ACC inhibitor that mimics ACC phosphorylation, effectively inhibiting hepatic de novo lipogenesis and suppressing HCC development. Dysregulation of de novo lipogenesis and AMP-activated protein kinase (AMPK)-mediated ACC phosphorylation play pivotal roles in accelerating HCC.[67]

Zinc fingers and homeoboxes protein 2 (ZHX2) have been found to inhibit HCC tumor growth by significantly inhibiting de novo lipogenesis in HCC cells and reducing ACC1 expression.[68] Serine/threonine protein kinase 25 (STK25), highly expressed in HCC patients, promotes HCC progression through the STRN/AMPK/ACC1 pathway.[69]

In laryngeal cancer, ACC2 exhibits high expression positively correlated with clinical tumor staging and negatively correlated with the 5-year survival rate of patients.[70] miRNA-122's role in mediating nonalcoholic fatty liver disease (NAFLD) development involves reducing ACC2 expression.[71]

However, research on ACC2's role in HCC and its potential as a therapeutic target is still limited, requiring further investigation to expand our understanding in this area.

FASN is pivotal in de novo FAs synthesis, catalyzing the production of palmitate from acetyl-CoA, malonyl-CoA, and NADPH. Palmitate is crucial in more complex FA synthesis, contributes to cell membrane structure, and plays a significant role in post-translational protein acylation.[44] Tumor-associated FASN is commonly regulated by SREBP1.[72] Research across various cancers, including breast, prostate, and lung cancers, has consistently linked heightened FASN activity and overexpression to poor prognosis.[44]

In HCC, investigations have revealed intriguing findings. ZHX2 significantly reduces FASN expression, resulting in decreased de novo lipid synthesis in HCC cells, thereby inhibiting HCC development.[68] Moreover, Wu and colleagues' research highlighted that mitochondrial fission can elevate the acetylation level of SREBP1, subsequently upregulating FASN, promoting proliferation and metastasis in HCC.[73]

Additionally, upregulation of FASN has been associated with counteracting ferroptosis mediated by SLC7A11, leading to enhanced resistance to sorafenib. Combining FASN inhibitors with sorafenib has demonstrated synergistic anti-tumor effects in both in vitro and in vivo experiments, improving resistance to sorafenib in HCC.[74]

Studies have identified that ACAT1 can inhibit FASN degradation, promoting lipid synthesis and thereby stimulating HCC growth.[75]

SCD is an integral membrane protein situated in the endoplasmic reticulum. Its primary function involves catalyzing the production of MUFA, such as oleic acid and palmitoleic acid. SCD's activity is regulated by SREBP. In animals, the SCD gene presents five genotypes, whereas in humans, the predominant genotypes are SCD1 and SCD5.[44] SCD1 is notably overexpressed in various cancers, including pancreatic cancer.[76–78] It has been observed to protect ovarian cancer cells from ferroptosis, and combining SCD1 inhibitors with ferroptosis inducers significantly reduces ovarian tumor volume in mouse models.[44,79]

In the context of HCC, Ma and colleagues found upregulation of SCD1 in HCC-initiating cells and sorafenib-resistant cells. Their research highlights that SCD1 regulates endoplasmic reticulum stress, inhibiting tumor self-renewal, migration, invasion, and resistance to sorafenib.[80]

A study by Liu and colleagues demonstrated that SCD1 reprograms the lipid metabolism of HCC cells, altering the cell's lipid composition and impairing cytoplasmic membrane fluidity, consequently inhibiting invasion and metastasis of HCC cells. It was suggested that the damage to cytoplasmic membrane fluidity by SCD1 may be due to reduced levels of its primary product, oleic acid.[81] Furthermore, research has shown that miR-4310 inhibits HCC cell proliferation, migration, and invasion in vitro and suppresses HCC growth and metastasis in vivo by targeting SCD1 and thereby inhibiting lipid synthesis.[82] SCD5's role in HCC remains less explored, warranting further research.

Collectively, ACC, FASN, and SCD pathways have shown significance in HCC. Investigating these pathways further offers potential therapeutic avenues for HCC treatment.

Abnormal FAs Catabolism

Fatty Acid Oxidation

Fatty acid oxidation (FAO), also known as β-oxidation, is the mitochondrial process that breaks down long-chain FAs into acetyl-CoA, NADH, and FADH2.[83] The sequence of reactions in FAO involves multiple steps, starting with the activation of FAs catalyzed by fatty acyl-CoA synthetase. This step produces fatty acyl-CoA.

Further in the process, on the outer mitochondrial membrane, carnitine palmitoyltransferase 1 (CPT1), consisting of subtypes CPT1A, CPT1B, and CPT1C, converts fatty acyl-CoA to acylcarnitine. Subsequently, acylcarnitine is transported into the mitochondrial matrix by the carnitine-acylcarnitine translocase (CACT). Once in the matrix, CPT2 converts acylcarnitine back to fatty acyl-CoA. The fatty acyl-CoA undergoes a cyclic series of four steps inside the mitochondria, leading to the generation of acetyl-CoA. The resulting acetyl-CoA is further utilized in the tricarboxylic acid cycle to produce ATP.[44,84]

Research indicates that FAO is linked to various aspects of cancer, including tumor growth, metastasis, immune evasion, and chemotherapy resistance.[85–88]

In different cancers, such as breast cancer,[85] glioblastoma,[86] and acute myeloid leukemia,[87] components of the FAO pathway have been associated with cancer development and progression.

In breast cancer, blocking CPT1B, a component of the FAO process, by inhibiting the JAK/STAT3 pathway has shown potential in suppressing tumor stem cells and resensitizing cancer cells to chemotherapy.[85] Similarly, in glioblastoma, FAO has been suggested to facilitate immune evasion through CD47, contributing to invasive growth and radioresistance.[86]

In HCC, FAO has been shown to enhance chemoresistance by providing ATP for cell proliferation.[89] Inhibition of FAO can reverse immune-suppressive activities in tumor-associated macrophages and inhibit HCC tumor progression. Additionally, overexpression of FAO-related genes in HCC cells with CTNNB1 mutations suggests a role in the progression of this cancer.[90]

The involvement of FAO in cancer development and progression highlights its potential as a therapeutic target. Further investigation and research on FAO might offer promising pathways for novel treatments in HCC.

Lipid Peroxidation and Cell Death

Lipids, particularly polyunsaturated fatty acids (PUFAs), are highly susceptible to lipid peroxidation. This process can be categorized into non-enzymatic and enzymatic-mediated forms.[44,91] Non-enzymatic lipid peroxidation, also known as autoxidation of lipids, is a chain reaction triggered by reactive oxygen species (ROS), initiating the oxidation of PUFAs.[44] Meanwhile, enzymatic lipid peroxidation is driven by the lipoxygenase (LOX) family, catalyzing the deoxygenation of free and esterified PUFAs, leading to the creation of various lipid peroxidation products.[44]

Ferroptosis, an iron-dependent form of cell death, has garnered significant attention in the realm of cancer.[92] This non-apoptotic process can be activated via both exogenous and endogenous pathways. The exogenous pathway involves modulating transport proteins, such as inhibiting the amino acid reverse transport system xc− or activating iron transport proteins transferrin and lactotransferrin. Conversely, the endogenous pathway primarily triggers ferroptosis by hindering intracellular antioxidant enzymes, such as glutathione peroxidase 4 (GPX4). Moreover, various stressors, including extreme temperatures, hypoxia, and radiation, can also induce ferroptotic cell death.[93]

Many traditional cancer treatment methods induce ferroptosis, and augmenting the induction of this process through these methods can enhance their therapeutic efficacy.[94] Research indicates that under the influence of radiation therapy, cancer cells adapt by upregulating the expression of SLC7A11 or GPX4 to counteract ferroptosis triggered by radiation therapy.[95] In pancreatic cancer, the chemotherapy drug gemcitabine's effect of inducing GPX4 expression and activity might contribute to cancer cells developing resistance to chemotherapy.[96]

In liver cancer, it has been observed that cu and copper metabolism murr1 domain 10 (COMMD10) can effectively boost ferroptosis both in laboratory settings and in live subjects, thus enhancing sensitivity to radiotherapy.[97] Likewise, investigations have revealed that the suppressor of cytokine signaling 2 (SOCS2) can trigger the ubiquitination degradation of SLC7A11, promoting ferroptosis and increasing radio sensitivity in HCC.[98] Concurrently, a study found that reducing LCN2, an iron-consuming factor, amplified sorafenib-induced ferroptosis and its anticancer impact on xenograft tumors in liver cancer patients exhibiting low LIFR expression and high LCN2 expression.[99]

Sorafenib, a common treatment for HCC, has shown resistance in specific cases. Research demonstrates that the transcription factors YAP/TAZ impede sorafenib-induced ferroptosis, leading to resistance to sorafenib in HCC.[100] Lipid peroxidation has been identified as a contributing factor to various types of cell death, such as apoptosis, necrosis, ferroptosis, and alkaliptosis.[44] Focusing on these cell death pathways associated with lipid peroxidation might offer innovative targets for the treatment of liver cancer.

Lipid Droplets

Lipid droplets (LDs) are composed of TAG and cholesteryl esters (CE), acting as storage organelles for lipid and energy homeostasis.[101] Within tumors, intracellular LDs are often mobilized and increased, correlating with tumor invasiveness and resistance to treatment.[102] For instance, in ovarian cancer, studies have demonstrated that impeding the assembly and accumulation of LDs can work in conjunction with bevacizumab to hinder tumor growth and proliferation.[103] In the context of glioblastoma, researchers have shown that LDs accumulate in glioblastoma cells under hypoxic conditions. Inhibiting LD generation reduced cell survival during in vitro hypoxia reoxygenation and significantly hampered tumor development in vivo.[104]

Studies in HCC have revealed that BNIP3, a mitochondrial cargo receptor, can impede the growth of HCC by accelerating the turnover of LDs in lysosomes.[105] Additionally, ACSL4 has been implicated in promoting the buildup of cellular LDs, furthering the progression of HCC.[106]

There remains a need for expanded research on LDs in the context of HCC. Given the synergistic effects of LDs in other tumors, investigating this aspect might present a promising area to explore in the treatment of HCC as well.

Alteration of Cholesterol Metabolism in HCC

In HCC, changes occur in cholesterol metabolism, including uptake, synthesis, and catabolism, which, in turn, impact the prognosis of HCC (Figure 4).

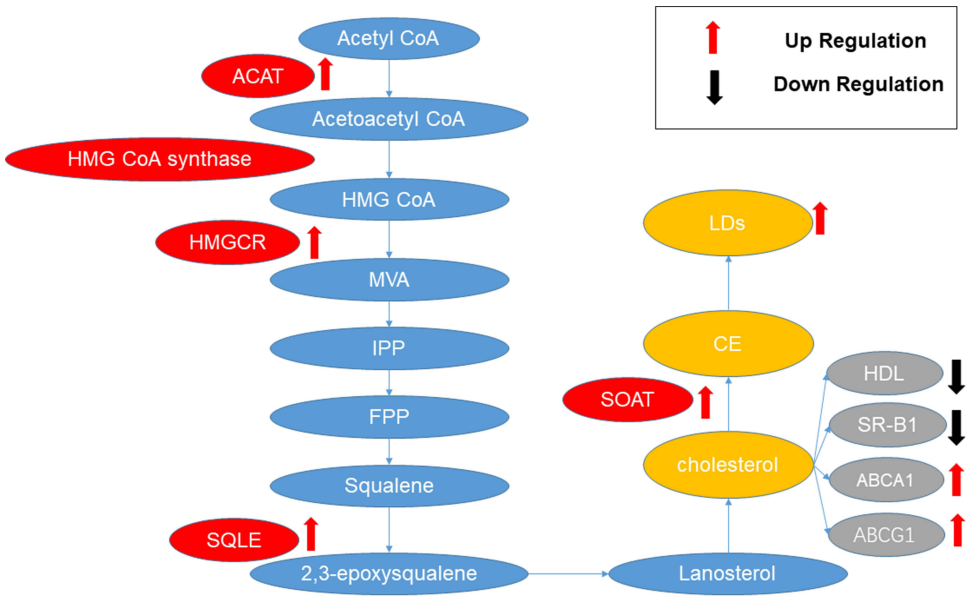

Figure 4 Aberrant cholesterol metabolism in HCC. In HCC, enzymes related to cholesterol synthesis, such as ACAT, HMGCR, SQLE, and SOAT, are typically upregulated, and their increased expression is associated with the occurrence and development of HCC. In the cholesterol catabolism of HCC, an observed enhancement in LDs is typically noted. The cholesterol efflux is characterized by a reduction in HDL and SR-B1, along with an increase in ABCA1 and ABCG1. This is associated with a poor prognosis in hepatocellular carcinoma (HCC).

Abbreviations: ACAT, Acetyl-CoA acetyltransferase; HMG-CoA, 3-hydroxy-3-methyl glutaryl CoA; HMGCR, HMG-CoA reductase; MVA, mevalonate; IPP, isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; SQLE, squalene monooxygenase; LDs, lipid droplets; HDL, high-density lipoprotein; ABCA1, ATP-binding cassette transporters A1; ABCG1ATP-binding cassette transporter G1.

Aberrant Cholesterol Uptake

Cholesterol plays a critical role in preserving membrane integrity, fluidity, and the creation of membrane microstructures.[107] Cells produce cholesterol through de novo biosynthesis or by absorbing cholesterol transported by low-density lipoprotein (LDL) (Figure 2).[108] Intracellular cholesterol balance is upheld through biosynthesis, uptake, excretion, and esterification processes.[109,110] Several studies have highlighted dysregulated cholesterol metabolism in cancer cells.[111–113] For instance, elevated levels of cholesterol, particularly 27-hydroxycholesterol (27HC), have been implicated as a significant risk factor for breast cancer incidence and recurrence. 27HC's action on bone marrow cells, including macrophages, in a liver X receptor (LXR)-dependent manner hampers T-cell proliferation and cytotoxic function.[111]

In the context of HCC, research indicates that mice with high cholesterol exhibit fewer and smaller tumors when injected with HCC cells or exposed to carcinogens. Cholesterol accumulation in natural killer (NK) cells activates their effector functions against HCC cells.[114] Studies by Chen and colleagues have unveiled that the downregulation of the LDL receptor (LDLR) is often linked to a poorer prognosis in HCC. Despite reducing LDL uptake, LDLR can partially stimulate cholesterol synthesis in HCC by activating the MEK/ERK pathway, thereby accelerating HCC proliferation and metastasis.[115]

While the specific mechanisms linking LDLR to HCC initiation, development, and prognosis are not yet fully understood, targeting LDLR remains a valuable avenue for research and potential intervention in HCC.

De Novo Cholesterol Synthesis

Cholesterol synthesis begins with acetyl-CoA. Two molecules of acetyl-CoA react with acetyl-CoA acetyltransferase (ACAT) to produce acetoacetyl-CoA. Under the catalysis of 3-hydroxy-3-methyl glutaryl CoA (HMG-CoA) synthase (HMGCS), acetoacetyl-CoA and another molecule of acetyl-CoA combine to produce HMG-CoA. HMG-CoA reductase (HMGCR), the major rate-limiting enzyme, catalyzes the reduction of HMG-CoA to mevalonate (MVA) while consuming two molecules of NADPH. MVA undergoes a three-step enzyme-catalyzed reaction to generate isopentenyl pyrophosphate (IPP), which further converts into farnesyl pyrophosphate (FPP) via a series of cytoplasmic enzymatic reactions. Condensation of two FPP molecules with pyrophosphate, under the action of squalene synthase, produces squalene. This squalene is oxidized to 2,3-oxidosqualene by squalene monooxygenase (SQLE), leading to cyclization in the endoplasmic reticulum, forming lanosterol. Lanosterol undergoes

a complex series of reactions to synthesize cholesterol. Newly synthesized cholesterol in the endoplasmic reticulum is transported directly to the cell membrane or indirectly via the Golgi apparatus (Figure 5).[116]

In contrast to normal physiological responses, cancer cells activate lipid synthesis even in the presence of abundant exogenous lipids.[117,118]

Enzymes of Producing Acetyl-CoA in HCC

Acetyl-CoA is a pivotal node in both FAs and cholesterol synthesis, making it a critical factor in lipid metabolism. Cancer cells can upregulate acetyl-CoA synthesis through various pathways. For example, under conditions of hypoxia and lipid depletion, ACSS2 is upregulated to produce acetyl-CoA.[52]

ACLY and ACSS play a role in regulating cholesterol metabolism by modulating the production of acetyl-CoA. It has been reported that ACLY promotes cholesterol synthesis in patients with HCC. Meanwhile, researchers have discovered that the combined blockade of ACLY and immune checkpoints may potentially enhance the prognosis of HCC.[119]

ACSS is classified into three phenotypes: ACSS1, ACSS2, and ACSS3. In gastric cancer, knocking out ACSS3 can reduce cholesterol synthesis and improve the prognosis of gastric cancer.[120] In HCC, ACSS1 has been found to be significantly upregulated in HCC tumors and is associated with tumor growth.[121] The upregulation of ACSS promotes cholesterol production.

Cholesterol and Cholesterol Ester Biosynthesis Enzymes in HCC

ACAT, also known as acetoacetyl-CoA thiolase, primarily participates in the synthesis of acetoacetyl-CoA. ACAT has two isoforms: ACAT1 and ACAT2. Studies suggest that ACAT2 is downregulated in clear cell renal cell carcinoma, and this downregulation might correlate with a poorer prognosis in this type of cancer.[122]

In the context of HCC, Gu et al 's research unveiled that ACAT1 stabilizes the structure of GNPAT by acetylating the K128 site, consequently impeding the degradation of GNPAT. This stabilization suppresses TRIM21-mediated FASN degradation, ultimately promoting lipid synthesis. Simultaneously, it enhances xenograft tumor growth and exacerbates DEN/CCl4-induced mouse liver cancer development. The combined application of an ACAT1 inhibitor and sorafenib has demonstrated the capability to suppress DEN/CCl4-induced mouse HCC.[75]

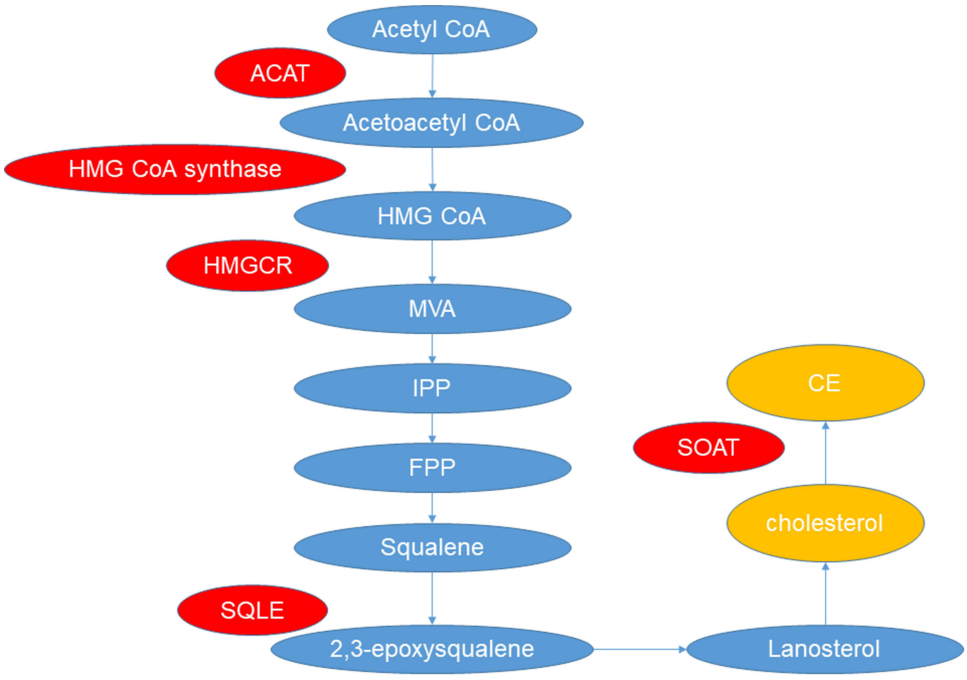

Figure 5 Cholesterol synthesis. Acetyl-CoA forms acetoacetyl-CoA catalyzed by ACAT, which then, through HMG CoA synthase, generates HMG-CoA. HMG-CoA, catalyzed by HMGCR, forms MVA, leading to the production of squalene. Squalene is oxidized by SQLE to 2,3-epoxysqualene, ultimately synthesizing cholesterol. Cholesterol, with the assistance of SOAT, is converted into CEs.

Abbreviations: ACAT, Acetyl-CoA acetyltransferase; HMG-CoA, 3-hydroxy-3-methyl glutaryl CoA; HMGCR, HMG-CoA reductase; MVA, mevalonate; IPP, isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; SQLE, squalene monooxygenase; Ces, cholesteryl esters.

HMGCR serves as the rate-limiting enzyme in the cholesterol synthesis pathway.[116] Statins, known as competitive inhibitors of HMGCR, are widely employed to lower cholesterol levels.[123] Existing research has highlighted the upregulation of HMGCR in various cancers.[44] Additionally, studies have demonstrated that statin drugs inhibit cell proliferation and induce apoptosis.[123]

In gastric cancer, HMGCR expression is heightened in gastric cancer tissues. Its overexpression promotes the growth and migration of gastric cancer cells. Conversely, downregulation of HMGCR expression can inhibit the growth, migration, and tumorigenesis of gastric cancer cells.[124]

In HCC, HMGCR expression is also increased.[125] A meta-analysis discovered that users of statin drugs have a reduced likelihood of developing HCC compared to non-users. Furthermore, the use of statin drugs is associated with a decreased risk of HCC.[126] Reports suggest that ASPP2, a p53-activating factor, can restrain the activity of enzymes, including HMGCR, thus inhibiting tumor growth. Patients displaying high ASPP2 and low HMGCR tend to exhibit a better prognosis.[127]

Therefore, HMGCR stands as a highly promising target for therapeutic intervention.

SQLE is an essential enzyme in the cholesterol synthesis pathway responsible for converting squalene to 2.3-epoxysqualene. Research indicates the pivotal role of SQLE in various cancers, including colorectal, pancreatic, and prostate cancers, among others.[128–131]

In colorectal cancer, cholesterol accumulation leads to reduced SQLE levels, contributing to the progression of the disease.[128] Conversely, in prostate cancer, SQLE is typically overexpressed, correlating with poorer survival rates. Inhibition of SQLE effectively impedes the growth of mouse orthotopic tumors.[131]

Regarding HCC, SQLE is often overexpressed in patients with NAFLD-HCC, linking this overexpression to a poorer prognosis. Inhibiting SQLE, particularly with terbinafine, significantly suppresses the growth of NAFLD-HCC and HCC cells. Increased SQLE levels in mice have been shown to promote CE biosynthesis, inducing NAFLD-HCC growth. Terbinafine inhibition of SQLE also mitigates tumor development in xenograft models and SQLE transgenic mice.[132] However, some studies suggest that terbinafine's anti-tumor effects may be unrelated to SQLE.[133] Additionally, overexpression of SQLE in HCC promotes its growth, EMT, and metastasis in both in vitro and in vivo settings. Inhibiting SQLE exhibits potential in suppressing the growth and development of HCC.[134]

The exact role of SQLE in the onset, progression, and prognosis of HCC is currently ambiguous. Nonetheless, the available data suggest that targeting SQLE might hold promise in aiding drug development and treatment strategies for HCC.

Sterol O-acyltransferase (SOAT), also recognized as acyl-CoA cholesterol acyltransferase, belongs to the membrane-bound O-acyltransferase (MBOAT) family, primarily facilitating the transfer of acyl groups from acyl-CoA to cholesterol, generating CE on the endoplasmic reticulum (ER) membrane. In mammals, two primary subtypes exist: SOAT1 and SOAT2.[44]

SOAT1 is broadly expressed in most cells and has shown some tumor-suppressive effects when targeted in pancreatic cancer,[135] prostate cancer,[136] and glioblastoma.[137] In HCC, research highlights significantly increased SOAT1 protein expression in tumor tissues compared to adjacent ones. Additionally, specific SOAT1 gene variants are associated with HCC susceptibility.[138] High SOAT1 expression in liver cancers contributes to altered cellular cholesterol distribution, effectively inhibiting HCC proliferation and migration. In mouse models, SOAT1 inhibitors significantly reduce tumor size when SOAT1 expression is high.[139]

Furthermore, studies indicate that in HCC patients with p53 deficiency, knocking down SOAT1 significantly reduces cholesterol esterification and the incidence of HCC.[140] SOAT2 is primarily distributed in hepatocytes and intestinal epithelial cells, participating in intracellular cholesterol storage and lipoprotein assembly.[141] In the context of leptin-induced breast cancer cells, silencing SOAT2 significantly diminishes cancer cell proliferation, migration, and invasion.[142] In HCC, inhibiting SOAT2 leads to the accumulation of non-esterified oxidized sterols intracellularly and suppresses the growth of HCC cell lines and their xenograft tumors.[143]

However, the specific mechanisms of SOAT in HCC necessitate further exploration.

Abnormal Cholesterol Catabolism

Lipid Droplets

For lipid and energy homeostasis, LDs act as storage organelles and are composed of TAG and CE.[101] Within tumors, intracellular LDs are often mobilized and increased, correlating with tumor invasiveness and resistance to treatment.[102] It is reported that

elevated cholesterol levels lead to the formation of cholesterol crystals on the membrane of LDs, subsequently inducing the development of NASH, and may potentially contribute to HCC.[144]

Cholesterol Efflux

Cholesterol is excreted through four primary pathways: 1) Passive diffusion into mature high-density lipoprotein (HDL) particles. 2) Facilitated diffusion mediated by scavenger receptor class B type 1 (SR-B1). 3) Excretion through ATP-binding cassette transporter A1 (ABCA1) into lipid-poor apolipoprotein A1. 4) Excretion into lipid-rich mature HDL mediated by ATP-binding cassette transporter G1 (ABCG1).[145]

HDL exhibits anti-tumor activity and has demonstrated inhibitory effects on ovarian, colon, breast, and metastatic lung cancers in preclinical models.[146] SR-B1 is notably overexpressed in various cancers, including breast,[147] prostate,[148] and nasopharyngeal cancers.[149] In breast cancer, researchers have observed a correlation between SR-B1 overexpression and poor prognosis.[150]

ABCA1 is considered an anticancer protein. Loss of function, mutations, or abnormal expression of ABCA1 may contribute to cancer development.[145] Some studies show a negative correlation between ABCA1 expression and breast cancer invasiveness.[151] Conversely, the loss of ABCA1 function in colorectal cancer has been associated with increased cancer survival rates.[152] However, certain studies have found that overexpression of ABCA1 in colorectal cancer enhances tumor migration and invasion capabilities.[153]

ABCG1 has been suggested to be associated with lower survival rates in a study on non-small cell lung cancer.[154] Research indicates its enhanced expression in prostate cancer, showing a negative correlation with overall survival.[155]

In HCC, researchers have discovered that the HDL-binding protein is clinically linked to tumor metastasis. In vitro and in vivo experiments have demonstrated that the downregulation and overexpression of HDL-binding proteins significantly hinder and enhance the migration, invasion, and epithelial-mesenchymal transition of liver cancer cells, respectively.[156]

There has been a reported upregulation of ABCA1 in tumor monocytes/macrophages in HCC, resulting in an increased production of immature and immunosuppressive macrophages. The rise in ABCA1+ macrophages within HCC tumors is associated with a poorer prognosis.[157]

Furthermore, in HCC, researchers found that saracatinib might cause an overexpression of the gene encoding ABCG1, leading to oxaliplatin resistance. Interfering with ABCG1 expression can reverse oxaliplatin resistance in HCC patients.[158]

The presence of abnormal cholesterol efflux in HCC indicates that targeting cholesterol efflux might be beneficial for the treatment of this disease.

Transcriptional Regulation of Lipid Metabolism

SREBPs

SREBPs comprise a transcription factor family, which includes SREBP1a and SREBP1c encoded by the SREBF1 gene, as well as SREBP2 encoded by the SREBF2 gene. SREBP1 mainly governs genes related to fatty acid synthesis and the expression of LDL receptor (LDLR), while SREBP2 primarily regulates genes involved in cholesterol biosynthesis.[159] These SREBPs are often activated in cancer cells.[44]

In HCC, studies have uncovered that ZHX2 can impede tumor growth. These studies demonstrated an inverse relationship between ZHX2 and the master regulator of de novo lipogenesis, SREBP1c, in HCC cell lines and human specimens.[68] Additionally, research by Cheng et al unveiled that the knockdown of SLC25A47 modulates hepatic lipid metabolism via the AMPKα-SREBPs signaling pathway, promoting lipid synthesis and contributing to the onset and progression of HCC.[160]

Researchers have also observed in hepatic cells that SREBP2 can induce excessive cholesterol production, leading to the accumulation of lipid peroxides and functional impairment of natural killer T cells. This impairment further diminishes the immune system's tumor surveillance function, thereby promoting the development of HCC.[161]

Furthermore, researchers have uncovered the pivotal role of SREBP2-mediated cholesterol biosynthesis in enhancing liver cancer stem cells (CSCs). The proliferation of CSCs, in turn, gives rise to drug resistance in tumor cells. Targeting SREBP2 may thus represent a potential strategy to overcome this drug resistance.[162]

LXRs

The LXRs are a class of nuclear receptors crucial for the transcriptional regulation of lipid metabolism, encompassing LXRα and LXRβ. These receptors govern fatty acid metabolism by controlling SREBP1c and are involved in various aspects of cholesterol function, including absorption, transport, efflux, and excretion through their capacity to regulate pertinent genes.[163]

In ovarian cancer, LXR ligands have been observed to induce the expression of P27, contributing to apoptosis in cancer cells.[164] Studies have identified increased LXRs in pancreatic cancer.[165] However, an alternate study reported significantly reduced LXR expression in tumor tissues compared to adjacent normal tissue in human pancreatic cancer patients.[166]

Regarding liver cancer, research has highlighted the capacity of LXRα to induce lipotoxicity and inhibit HCC.[167] It has been noted that LXRα agonists can potentially reverse resistance to sorafenib treatment in sorafenib-resistant cells.[168]

Targeting LXR might hold promise in improving the prognosis of HCC.

PPARs

PPAR is a ligand-activated transcription factor belonging to the nuclear receptor superfamily, playing a crucial role in the transcriptional regulation of lipid metabolism.[169] This family encompasses three subtypes: PPARα, primarily expressed in liver, heart, and kidneys, closely associated with FAO and energy metabolism;[170] PPARβ/δ, mainly expressed in skeletal muscles with lesser expression in adipose tissue and skin, influencing FAO metabolism and energy uncoupling processes;[171] and PPARγ, highly expressed in adipose tissue, regulating fat cell differentiation and energy storage in adipocytes.[172] PPARγ is also found in the liver, kidneys, lungs, and colon, and its overexpression can lead to lipid accumulation in these tissues.[173–177]

It is reported that CD147 has been identified as downregulating PPARα, inhibiting FAs β-oxidation, and promoting the proliferation and metastasis of HCC cells.[178]

Research indicates a significant upregulation of PPARβ/δ in HCC tissues and cell lines, correlating with unfavorable clinical staging and prognosis in HCC.[179]

In HCC, tumor cells have been observed to evade immune checkpoint-targeted therapy through PPARγ/VEGF-A-mediated immune suppression in the tumor microenvironment (TME). Targeting PPARγ is suggested as a potential strategy to overcome immunotherapy resistance in HCC.[180]

As previously mentioned, the study by Ning et al highlights that USP22 stabilizes PPARγ through deubiquitination, leading to the upregulation of ACLY expression and promoting lipid accumulation in HCC cells, contributing to tumor development.[51]

Overall, PPAR emerges as a highly promising target for addressing HCC.

Therapeutically Exploring Lipid Metabolism in HCC Treatment

Targeting FA Synthesis

Although there is substantial evidence indicating the potential effectiveness of targeting FAs synthesis for treating HCC, there is a lack of clinical trials focusing on this area at present (Table 1). Specifically, there is a scarcity of studies exploring the anticancer effects of ACLY and SCD. In contrast, for FASN, a FASN inhibitor known as TVB-2640 has entered clinical trials.[181]

The ongoing studies have primarily investigated the anticancer effects of FASN inhibition in glioblastoma, colon cancer, non-small cell lung cancer, and prostate cancer.[190–193] However, there is currently no research focused on its effects specifically in HCC. On a related note, clinical trials are evaluating its role in NASH,[182,183] which is a form of NAFLD considered a leading cause of HCC in many regions.[194]

Furthermore, a Phase II clinical trial aiming at FASN is currently recruiting participants for HCC. Researchers are using epigallocatechin gallate as an intervention to assess its effectiveness and safety in preventing the occurrence of HCC in patients with cirrhosis.[184]

Targeting Cholesterol Synthesis

Targeting cholesterol has emerged as a promising therapeutic approach in various cancers. Presently, there is a focus on targeting HMGCR, an enzyme involved in cholesterol production. Ongoing clinical research indicates promising results,

Table 1 Clinical Trials Targeting Lipid Metabolism

NCT Number	Main Target	Inhibitors/Drugs	Types	Reference
NCT03938246	FASN	TVB-2640	NASH	[182]
NCT04906421	FASN	TVB-2640	NASH	[183]
NCT06015022	FASN	Epigallocatechin Gallate	HCC	[184]
NCT02968810	HMGCR	Simvastatin	HCC	[185]
NCT05028829	HMGCR	Atorvastatin	HCC	[186]
NCT03024684	HMGCR	Atorvastatin	HCC	[187]
NCT02304289	Ferroptosis	Artesunate	HCC	[188]
NCT02432651	SREBPs	Xanthohumol	Oxidative DNA Damage	[189]

demonstrating that the use of statins in metastatic prostate cancer patients receiving first-line chemotherapy is associated with improved overall survival.[195]

In the context of HCC, there is an ongoing Phase II clinical trial examining the efficacy of simvastatin in preventing HCC in patients with liver cirrhosis, with an expected completion this year.[185] Simultaneously, another prospective, randomized, multicenter, double-blind, placebo-controlled trial is actively recruiting participants. This trial aims to evaluate the potential chemopreventive effect of atorvastatin in high-risk individuals with liver cirrhosis and fibrosis against the development of HCC.[186] Furthermore, a multicenter, double-blind, randomized, placebo-controlled trial is recruiting patients to explore the preventive effects of atorvastatin on the risk of HCC recurrence after treatment (Table 1).[187]

Targeting Lipid Catabolism

Lipid catabolism plays a crucial role in providing energy for cancer cell survival and growth, making the targeting of lipid metabolism a critical focus in cancer treatment. Ferroptosis, an iron-dependent form of lipid peroxidation, characterizes a non-apoptotic type of cell death.[92]

In an attempt to explore new treatments for advanced HCC, a single-center Phase I dose escalation study aimed to evaluate the safety and pharmacokinetics of oral Artemisinin (Table 1).[188] Unfortunately, the study was canceled due to slow patient recruitment. Despite this setback, further research is eagerly anticipated to confirm the clinical significance of lipid metabolism in the context of HCC.

Targeting Transcriptional Regulators of Lipid Metabolism

FA and cholesterol synthesis, which depend on gene transcription, are regulated by the membrane-bound transcription factor SREBPs. This makes SREBPs a potential target for cancer therapy.[44] Xanthohumol, an SREBPs inactivator, reduces the re-synthesis of FAs and cholesterol, potentially offering benefits in conditions such as obesity and fatty liver.[196] Xanthohumol has been clinically studied to showcase its ability to prevent DNA oxidative damage, potentially slowing down or impeding processes that can lead to cancer (Table 1).

Unfortunately, there are currently no published clinical studies on its effects specifically related to HCC. Further research in this area is eagerly anticipated to unveil its potential impact on HCC.

Conclusions

Undoubtedly, lipid metabolism significantly influences the development and prognosis of HCC. Changes in FAs and cholesterol intake have been correlated with the prognosis of HCC. Both FAs and cholesterol synthesis are key pathways, and their enhancement in HCC has been associated with its prognosis. Similarly, lipid catabolism, a crucial aspect of lipid metabolism, also contributes to the adverse prognosis of HCC. Current preclinical studies have demonstrated the benefits

of targeting lipid metabolism in improving the prognosis of HCC, reducing the occurrence and progression of HCC, showcasing substantial potential.

Lipid metabolism is a complex network involving triglyceride intake, synthesis, breakdown, and regulatory factors, all impacting HCC growth. Current research predominantly concentrates on FAs and cholesterol synthesis and iron-induced cell death via lipid peroxidation. However, further studies investigating lipid intake, oxidation, and cholesterol excretion are needed. While existing clinical trials in HCC have not yet provided ideal outcomes, foundational research in related fields underscores the potential of targeting lipid metabolism as a promising avenue.

Currently, targets such as FASN, HMGCR, SREBPs, have been incorporated into clinical trials. These studies emphasize the de novo synthesis pathways of FAs and cholesterol, which may soon find successful applications in a clinical setting. Conversely, pathways related to lipid catabolism have not been extensively studied. However, it is evident that lipid catabolism significantly influences the treatment of HCC. Targeting lipid catabolism might lead to new and promising outcomes.

In summary, lipid metabolism is involved in the entire process of HCC occurrence and development. Targeting lipid metabolism is beneficial for preventing the occurrence of HCC and improving the prognosis. Therefore, targeting lipid metabolism provides a novel approach for the treatment of HCC. Further research in this field may open up new avenues for more effective treatment strategies for HCC.

Abbreviations

27HC, 27-hydroxycholesterol; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ACAT1, acetyl-CoA acetyltransferase 1; ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ACSS, acetyl-CoA synthetase; AMPK, AMP-activated protein kinase; AT, acyltransferase; CACT, carnitine-acylcarnitine translocase; CD36, fatty acid translocase; CEs, cholesteryl esters; ChREBP, carbohydrate-responsive element-binding protein; COA, coenzyme A; COMMD10, cu and copper metabolism murr1 domain 10; CPT, carnitine palmitoyltransferase; DAG, diacylglycerol; DGAT, DAG acyltransferase; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; FABPs, FA-binding proteins; FAO, Fatty acid oxidation; FAs, fatty acids; FASN, fatty acid synthase; FATPs, fatty acid transport proteins; FPP, farnesyl pyrophosphate; G-3-P, glycerol-3-phosphate; GPX4, glutathione peroxidase 4; HCC, Hepatocellular carcinoma; HDL, high-density lipoprotein; HIF, Hypoxia-Inducible Factor; HMG-CoA, 3-hydroxy-3-methyl glutaryl CoA; HMGCR, HMG-CoA reductase; HMGCS, HMG-CoA synthase; IHC, Immunohistochemical; IPP, isopentenyl pyrophosphate; LDL, low-density lipoprotein; LDLR, LDL receptor; LDs, Lipid droplets; LOX, lipoxygenase; LPA, lysophosphatidic acid; LXR, liver X receptor; MBOAT, membrane-bound O-acyltransferase; MUFA, monounsaturated fatty acids; MVA, mevalonate; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NK, natural killer; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SCD, Stearoyl-Coenzyme A Desaturase; SFAs, saturated fatty acids; SOAT, Sterol O-acyltransferase; SOCS2, suppressor of cytokine signaling 2; SQLE, squalene monooxygenase; SR-B1, scavenger receptor class B type 1; SREBPs, sterol regulatory element-binding proteins; STK25, Serine/threonine protein kinase 25; TACE, transarterial chemoembolization; TAG, triacylglycerol; TCA, tricarboxylic acid; TME, tumor microenvironment.

Disclosure

The authors report no conflicts of interest in this work.

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