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Research Progress on Anti-Hepatocellular Carcinoma Therapy Targeting Lipid Metabolism

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Abstract: Lipid metabolic reprogramming is a critical characteristic in hepatocellular carcinoma (HCC) development and progression. Hepatoma cells reshape their metabolic patterns and tumor microenvironment by dysregulating fatty acid synthesis, uptake, and cholesterol metabolism, thereby promoting malignant progression and modulating treatment response. In recent years, targeting lipid metabolism pathways has emerged as a significant research direction in HCC therapy. This review systematically outlines key mechanisms of lipid metabolic reprogramming in HCC, focusing on emerging therapeutic strategies targeting critical pathways including cholesterol metabolism (HMGCR, SCAP, ACLY inhibitors), fatty acid metabolism (FABP5, FASN, ACC, CD36, lipoxygenase inhibitors), and sphingolipid metabolism (SphK2 and SMS1 inhibitors). Additionally, it discusses the potential and challenges of lipid metabolism-targeting agents in monotherapy and combination regimens, and prospects their clinical translation potential to provide a theoretical foundation for precision metabolic intervention in HCC.

Keywords: Hepatocellular carcinoma; Lipid metabolic reprogramming; Targeted therapy; Cholesterol metabolism; Fatty acid metabolism; Sphingolipid metabolism; Combination therapeutic strategy

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1. Introduction

Hepatocellular carcinoma (HCC) remains one of the most prevalent and lethal malignancies worldwide[1]. Despite advances in surgical techniques and systemic treatments, prognosis for advanced HCC patients remains poor with limited options and frequent drug resistance. Multikinase inhibitors such as sorafenib and lenvatinib, as well as immune checkpoint inhibitors, have improved clinical outcomes[2]; however, response rates are variable and acquired resistance inevitably develops.

Metabolic reprogramming, particularly lipid metabolism dysregulation, is increasingly recognized as a hallmark of HCC[3]. Unlike normal hepatocytes that primarily obtain lipids from circulation, cancer cells undergo profound alterations including enhanced de novo fatty acid synthesis, increased lipid uptake, and dysregulated cholesterol homeostasis. These adaptations provide building blocks for membrane biosynthesis and energy production while generating bioactive lipid

signaling molecules that drive tumor growth, angiogenesis, metastasis, and immune evasion[4].

Consequently, targeting lipid metabolism pathways has emerged as a promising therapeutic strategy for HCC[5]. This approach offers several advantages: metabolic pathways are enzymatic and druggable; cancer cells exhibit metabolic dependencies providing therapeutic windows; and metabolic interventions may synergize with existing therapies. This review summarizes recent advances in therapeutic strategies targeting cholesterol, fatty acid, and sphingolipid metabolism in HCC.

2. Cholesterol Metabolism Targets

2.1. HMGCR Inhibitors

Statins, as inhibitors of HMGCR—the rate-limiting enzyme of the mevalonate pathway—exemplify drug repurposing in HCC therapy. The mevalonate pathway produces cholesterol and isoprenoid intermediates that are essential for the post-translational modification of small GTPases—molecules that regulate cell proliferation, survival, and migration[6]. By reducing cholesterol precursors and depleting isoprenoid pools, statins exert pleiotropic anti-tumor effects including cell cycle arrest, apoptosis induction, angiogenesis inhibition, and immune modulation.

Clinical studies demonstrate that long-term statin use reduces HCC incidence by approximately 33% in chronic liver disease patients[7]. Lipophilic statins confer more potent protective effects due to enhanced hepatic penetration. Beyond classical statins, novel HMGCR inhibitors targeting allosteric sites are being developed to overcome side effects while enhancing targeting efficiency[8]. Combination strategies with other metabolic inhibitors are under investigation to achieve comprehensive lipid synthesis blockade.

2.2. SCAP Inhibitors

SCAP serves as a master regulator of lipid metabolism reprogramming in HCC. Under low sterol conditions, SCAP escorts SREBPs from the endoplasmic reticulum to the Golgi, where proteolytic cleavage releases active transcription factors upregulating lipogenic genes including ACLY, ACC, and FASN[9]. In HCC, this pathway is constitutively activated by oncogenic signaling, hypoxia, and metabolic stress.

SCAP inhibitors specifically block SCAP activation or SREBP interaction, disrupting aberrant lipid synthesis at the upstream level. Compared to downstream inhibitors, SCAP inhibitors avoid compensatory metabolic activation and exhibit lower hepatotoxicity[10]. 125B11 (fatostatin), the most studied direct SCAP inhibitor, prevents SCAP-SREBP complex transport from the ER to the Golgi[11]. While showing efficacy in preclinical obesity, diabetes, and breast cancer models, 125B11 suffers from pharmaceutical limitations including poor water solubility and low oral bioavailability, requiring structural optimization or advanced delivery systems[12].

2.3. ACLY Inhibitors

ACLY connects mitochondrial metabolism with lipid biosynthesis by converting citrate to oxaloacetate and acetyl-CoA, the fundamental building block for fatty acid and cholesterol synthesis. ACLY is significantly upregulated in HCC, correlating with poor prognosis. ACLY drives excessive lipid synthesis while its product acetyl-CoA serves as substrate for histone acetylation, which regulates proliferation and metabolic genes[13]. Importantly, ACLY shapes the tumor immune microenvironment by promoting immunosuppressive mediator secretion and regulating immune cell function[14]. Thus, ACLY inhibition exerts dual antitumor effects: directly suppressing tumor growth through metabolic restriction and remodeling the immune microenvironment[15].

EVT0185 represents the first triple inhibitor to enter clinical trials, simultaneously targeting ACLY, ACSS2, and ACC. This multi-target approach achieves synergistic blockade and overcomes metabolic compensation[14]. Preclinical studies demonstrate significant tumor suppression in metabolism-associated HCC models with synergistic potential when combined with lenvatinib. Other ACLY inhibitors including Bempedoic acid are under investigation, with current research

focusing on combination strategies with chemotherapy, targeted therapy, and immune checkpoint inhibitors[16].

3. Fatty Acid Metabolism Targets

3.1. FABP5 Inhibitors

FABP5 mediates intracellular lipid transport and signaling, emerging as a novel HCC target. FABP5 facilitates fatty acid transport to mitochondria, endoplasmic reticulum, and nucleus, activating PPARγ and regulating genes involved in lipid metabolism, inflammation, and cell survival[17]. FABP5 is highly expressed in HCC tissues and tumor-associated macrophages, correlating with aggressive behavior. FABP5 in macrophages processes tumor-derived unsaturated fatty acids, shaping an immunosuppressive microenvironment by promoting M2 polarization characterized by IL-10 and TGF-β production. These FABP5-positive lipid-loaded macrophages suppress CD8+T cell function, leading to exhaustion and reduced immunotherapy efficacy[18].

FABP5 targeting exerts dual anti-tumor effects by blocking macrophage lipid metabolism to restore T cell function and inhibiting cancer cell lipid signaling. Preclinical studies combining FABP5-targeted nano-delivery with radiofrequency ablation significantly attenuate macrophage immunosuppression and enhance anti-tumor T cell responses, particularly in lipid metabolism-active HCC subtypes[19]. Specific small molecule inhibitors remain in early preclinical development.

3.2. FASN Inhibitors

FASN catalyzes palmitate production from acetyl-CoA and malonyl-CoA, representing the core rate-limiting enzyme in de novo fatty acid synthesis. While normal hepatocytes utilize dietary lipids, HCC cells become highly dependent on endogenous synthesis regardless of exogenous availability—termed "metabolic addiction."[20] FASN overexpression correlates with poor differentiation, vascular invasion, and reduced survival in HCC. Mechanistically, FASN provides membrane building blocks for proliferation, generates lipid second messengers activating PI3K/Akt/mTOR signaling, and modifies immune checkpoint molecules through palmitoylation enhancing their stability[20].

FASN inhibitors suppress palmitate synthesis through competitive enzyme binding. Combining FASN inhibitors with tyrosine kinase inhibitors (cabozantinib or sorafenib) demonstrates significant synergistic anti-tumor effects in FASN-dependent HCC models through concurrent blockade of angiogenic signaling and lipid synthesis[21]. However, no significant synergy was observed with anti-PD-1 agents, emphasizing the need for patient selection based on driver genes.

3.3. Lipoxygenase Inhibitors

5-Lipoxygenase (ALOX5) catalyzes arachidonic acid conversion to leukotrienes—bioactive lipid mediators that are not only pro-inflammatory but also potent signals promoting tumor progression. ALOX5 is significantly upregulated in HCC, correlating with aggressive features and poor prognosis[22]. Mechanistically, ALOX5 products activate NF-κB promoting survival and inflammation, Wnt/β-catenin driving proliferation, and PI3K/Akt enhancing metabolism[23]. ALOX5 activity shapes a chronic inflammatory microenvironment facilitating immune evasion while directly regulating cell cycle proteins and epithelial-mesenchymal transition.

Zileuton, the only clinically approved ALOX5 inhibitor indicated for asthma, has shown preclinical anti-tumor potential by disrupting lipid metabolism networks and inducing apoptosis[24]. Combining ALOX5 inhibitors with existing HCC therapies may represent a promising strategy to overcome resistance through simultaneous targeting of metabolic dependencies and inflammatory signaling.

3.4. ACC Inhibitors

ACC catalyzes acetyl-CoA carboxylation to malonyl-CoA—the first committed step in de novo fatty acid synthesis. Two isoforms exist: ACC1 regulates synthesis in cytosol while ACC2 produces malonyl-CoA regulating fatty acid oxidation at mitochondria[25]. ACC expression is significantly upregulated in HCC, correlating with tumor grade, metastasis, and poor

prognosis. ACC activity contributes to chemotherapy resistance through altered membrane lipid composition, enhanced detoxification via lipid droplets, and metabolic flexibility under therapeutic stress[26].

Several ACC inhibitors including Clesacostat (Pfizer) and Firsocostat (Gilead) have entered Phase II trials for NASH[27], accumulating valuable human safety data. Since NASH shares metabolic dysregulation features with HCC, these findings support ACC inhibitor potential in HCC prevention and treatment[27]. Combining ACC inhibitors with standard therapies represents a core direction, with preclinical studies showing enhanced efficacy when combined with sorafenib or immune checkpoint inhibitors.

3.5. CD36 Inhibitors

CD36 (fatty acid translocase) is a multifunctional scavenger receptor mediating long-chain fatty acid uptake. CD36 overexpression enables efficient lipid acquisition from microenvironment, providing energy substrates and biosynthetic precursors. In metastatic cells, CD36-mediated uptake confers metabolic advantages for distant colonization through PPARγ activation enhancing stemness and epithelial-mesenchymal transition[28, 29].

In HCC, CD36 upregulation correlates with aggressive features and sorafenib resistance by maintaining energy homeostasis under therapeutic stress. Therapeutic strategies focus on neutralizing antibodies, with humanized anti-CD36 monoclonal antibodies showing significant efficacy in preclinical models by disrupting tumor lipid supply[30]. PLT012 demonstrates particularly pronounced effects under high-fat diet conditions, reflecting increased exogenous lipid dependency. Current research emphasizes combination strategies with standard therapies and identification of CD36-dependent tumors through biomarker strategies[31].

4. Sphingolipid Metabolism Targets

4.1. SphK2 Inhibitors

Sphingosine kinases (SphK1 and SphK2) generate S1P from sphingosine. The balance between pro-apoptotic ceramide and pro-survival S1P—the "sphingolipid rheostat"—critically determines cell fate. SphK2 has emerged as particularly important in HCC[32]. SphK2 promotes HCC progression through multiple mechanisms: generating S1P that activates PI3K/AKT and ERK pathways; nuclear S1P inhibiting HDACs to drive c-Myc expression; promoting angiogenesis; and modulating immune function[33]. SphK2 overexpression correlates with poor prognosis and represents a key mechanism of acquired sorafenib resistance through compensatory upregulation maintaining survival signaling[34].

ABC294640 (opaganib), a selective oral SphK2 inhibitor, demonstrates significant anti-tumor activity in preclinical HCC models. Striking synergy with sorafenib in overcoming resistance arises from complementary mechanisms: while sorafenib inhibits RAF/MEK/ERK signaling, ABC294640 blocks compensatory SphK2 upregulation while reducing S1P and increasing ceramide[35, 36]. Based on robust preclinical evidence, ABC294640 has advanced to early clinical trials in advanced solid tumors.

4.2. SMS1 Inhibitors

Sphingomyelin synthases (SMS1 and SMS2) transfer phosphocholine to ceramide, generating sphingomyelin and diacylglycerol. SMS1, primarily Golgi-localized, regulates levels of bioactive lipids including pro-apoptotic ceramide and pro-survival diacylglycerol. SMS1 promotes HCC progression by consuming ceramide while generating diacylglycerol, shifting balance toward survival. SMS1-generated sphingomyelin serves as reservoir for S1P production and facilitates RAS membrane localization and signaling[37]. Activated RAS feedback-upregulates SMS1 expression, creating positive feedback sustaining oncogenic signaling.

SMS1 is upregulated in HCC, correlating with aggressive features and poor prognosis. SMS1 contributes to sorafenib resistance through compensatory upregulation maintaining sphingomyelin levels and RAS activity despite RAF/MEK/ERK inhibition. D609, a broad-spectrum SMS inhibitor, disrupts ceramide-sphingomyelin balance, promoting ceramide

accumulation while interfering with RAS membrane localization[38]. D609 restores sorafenib sensitivity in resistant models through synergistic growth inhibition. While D609 currently serves primarily as research tool due to pharmaceutical limitations, its defined mechanism drives development of next-generation selective SMS inhibitors with improved drug-like properties[39].

5. Conclusion and Perspectives

Targeting lipid metabolism represents a promising therapeutic paradigm for HCC. Cholesterol metabolism targeting through HMGCR, SCAP, and ACLY inhibitors demonstrates preclinical and clinical potential, with statins already showing preventive efficacy. Fatty acid metabolism inhibitors targeting FABP5, FASN, 5FLO, ACC, and CD36 offer diverse intervention points matched to specific tumor contexts. Sphingolipid metabolism targeting through SphK2 and SMS1 inhibitors provides opportunities particularly in overcoming acquired resistance.

Key challenges remain: improving drug-like properties of novel inhibitors through medicinal chemistry and advanced formulations; identifying predictive biomarkers for patient stratification through molecular profiling; and managing metabolic side effects through tumor-selective strategies. Combination strategies integrating lipid metabolism-targeting agents with tyrosine kinase inhibitors or immune checkpoint inhibitors hold particular promise for synergistic efficacy by addressing complementary vulnerabilities.

Future research should prioritize translational studies validating preclinical findings in clinical settings. Early-phase trials with careful biomarker analyses will provide proof-of-mechanism data, while subsequent randomized trials in molecularly defined subsets will establish clinical utility. As understanding of HCC metabolic heterogeneity advances, personalized metabolic intervention strategies may ultimately improve outcomes for this challenging malignancy.

Disclosure statement

The author declares no conflict of interest.

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