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COMMENTARY

SOAT1 as a metabolic immune checkpoint: Reprogramming lipid metabolism to inflame hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is characterized by profound metabolic reprogramming and immune evasion, yet the mechanisms by which lipid metabolism intersects with antitumor immunity remain incompletely understood. Recent work by Ma *et al.* identifies sterol O-acyltransferase 1 (SOAT1) as a metabolic immune checkpoint in HCC. Beyond its canonical role in cholesterol esterification, SOAT1 inhibition disrupts lipid homeostasis, triggering lipotoxic stress, reactive oxygen species production, and endoplasmic reticulum stress that converge on NF-κB activation. This metabolic-inflammatory cascade drives chemokine secretion, recruits antigen-presenting cells and cytotoxic T cells, and converts immunologically "cold" tumors into inflamed ones. Importantly, pharmacological SOAT1 inhibition synergizes with PD-1 blockade, highlighting a tractable strategy to reprogram the tumor microenvironment and enhance immunotherapy efficacy in hepatocellular carcinoma.

Keywords: Sterol O-acyltransferase 1; Lipid metabolic reprogramming; Tumor immune microenvironment; NF-κB signaling; Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer.[1,2] The management of HCC poses significant clinical challenges, primarily due to the tumor's aggressive nature characterized by rapid progression, a high propensity for recurrence and metastasis, as well as inherent resistance to standard treatments.[3-5]

These factors collectively contribute to the limited efficacy often observed with conventional systemic therapies and cytotoxic drugs.

Research in recent years has established that metabolic reprogramming and immune evasion are two central hallmarks of HCC pathogenesis.[6,7] To support rapid proliferation and survival, tumors rewire their metabolic pathways while concurrently developing mechanisms to evade immune surveillance. The tumor microenvironment (TME) serves as a critical interface for this metabolic-immune interplay, and its well-defined role in HCC provides a compelling rationale for targeting the dynamic crosstalk between hepatocytes and immune cells as a therapeutic strategy.[8] Within the TME, tumor cells actively remodel their surroundings by secreting metabolites and lipid-related signaling molecules, which drive pathological changes such as acidosis and lipid accumulation. Notably, lipid metabolism and signaling have emerged as key regulators of tumor cell motility and progression, and their capacity to modulate the immunosuppressive TME is being actively investigated.[9-12] Recent studies further highlight that specific alterations in long-chain fatty acid distribution and novel lipid mediators are intricately involved in HCC progression and immune modulation.[13,14] While these discoveries broaden the scope of metabolic-immune interactions, they also point to the need to identify central regulatory nodes that can be therapeutically targeted. Among the various facets of lipid reprogramming, alterations in cholesterol and fatty acid metabolism not only supply energy and biosynthetic precursors to cancer cells but also actively sculpt the tumor's immune landscape.

In this context, sterol O-acyltransferase 1 (SOAT1) stands out due to its position at a decisive metabolic junction and its direct link to a defined immune-activating pathway. SOAT1, localized on the endoplasmic reticulum (ER), performs catalytic functions as dimers or tetramers and could esterify cholesterol to cholesterol ester,[15] playing a vital role in cellular cholesterol homeostasis by catalyzing the esterification of free cholesterol. Increasing evidence indicates that the suppression of SOAT1 blocks tumor growth in various cancers, such as gastric cancer, colon cancer, and pancreatic cancer.[16-18]

However, its detailed mechanistic contributions, particularly in linking lipid metabolic alterations to immune regulation, and its full therapeutic utility remain to be fully elucidated. The precise molecular pathways through which SOAT1 influences the crosstalk between tumor cells and immune components within the TME are a critical area of investigation.

Given the critical roles of metabolic reprogramming and immune evasion in cancer progression, targeting lipid metabolism-related pathways and the TME offers new therapeutic opportunities for cancer, particularly HCC, a malignancy notorious for its therapeutic resistance and immunosuppressive TME. Ma *et al.* recently reported a study published in *Hepatology*, entitled "Targeting sterol O-acyltransferase 1 rewires fatty acid metabolism and uncovers immune vulnerability in hepatocellular carcinoma," presenting a compelling narrative that positions SOAT1 as a critical metabolic vulnerability and a novel immune regulator in HCC.[19] Their work provided a multi-layered mechanistic dissection that extends far beyond SOAT1's canonical role in cholesterol esterification (Figure 1).

Ma *et al.*'s work[19] represents a major conceptual advance by formally establishing SOAT1 as a *bona fide* metabolic immune checkpoint. This definition is functionally critical. In contrast to many metabolic enzymes whose immunomodulatory effects are often secondary or incidental, SOAT1 acts as a dominant regulatory node. It directly links inhibition of cholesterol esterification to the coordinated induction of a pro-inflammatory and immune-recruiting transcriptional program. By establishing a mechanistic and causal connection from a single enzymatic activity to a specific anti-tumor immune phenotype, this work provides new insight into how lipid metabolic pathways regulate immune suppression in hepatocellular carcinoma.

The study began with a multi-step screening strategy that effectively bridges the gap between *in vitro* discovery and clinical relevance. By sequentially applying a metabolic compound library screen on HCC cell lines, validating hits in patient-derived organoids (PDOs), and finally assessing immune modulation through a monocyte migration assay, the authors systematically identify SOAT1 as a top candidate. This approach prioritized targets that not only impair tumor cell viability but also alter the immune landscape, a crucial consideration for modern oncology drug development. The subsequent clinical validation, demonstrating SOAT1 upregulation in multiple independent HCC cohorts and its association with poor prognosis, firmly establishes its pathological significance. This aligns with prior proteomic studies that have identified SOAT1 as a potential therapeutic target in early-stage HCC.

The most significant contribution of this research lies in its detailed elucidation of the mechanism linking SOAT1 inhibition to immune activation. The authors demonstrated that genetic or pharmacological inhibition of SOAT1 disrupts lipid homeostasis, leading to a marked accumulation of saturated long-chain fatty acids (LCFAs) like palmitate (C16:0) and stearate (C18:0). Reconstitution

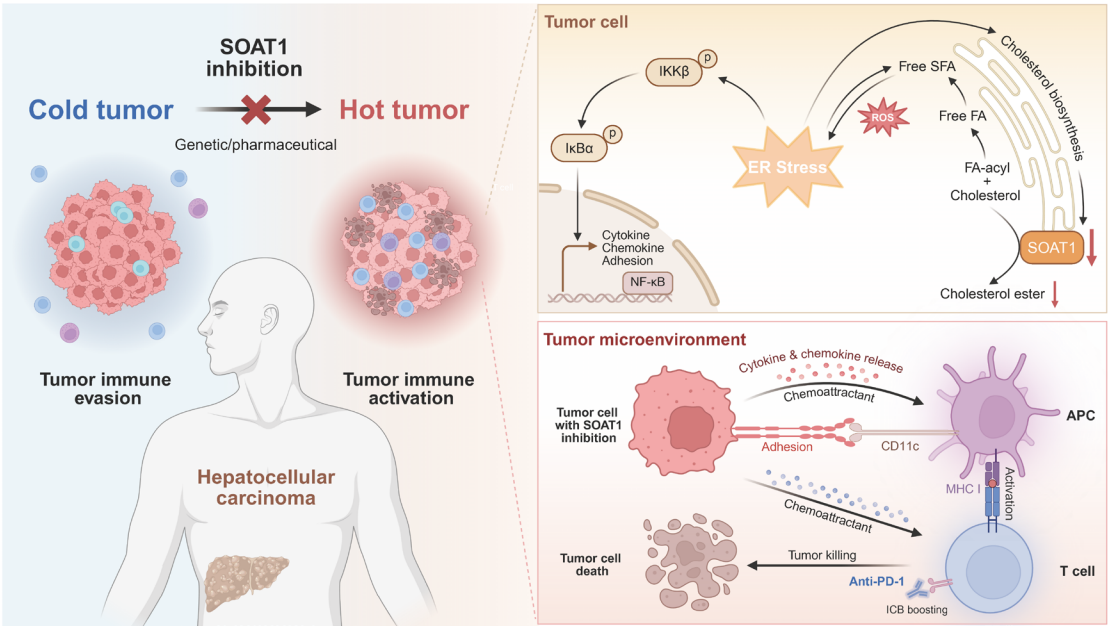


Figure 1. SOAT1 inhibition triggers a metabolic–inflammatory cascade that primes HCC for immunotherapy. This study delineates a coordinated mechanism through which SOAT1 inhibition remodels the immunosuppressive HCC microenvironment. Genetic or pharmacological SOAT1 blockade disrupts cholesterol esterification, leading to toxic accumulation of long-chain fatty acids that induce lipotoxic stress, ROS production, and ER stress. This metabolic crisis converges on the activation of the canonical NF-κB signaling pathway, driving tumor cells to secrete key cytokines and chemokines. Consequently, this secretory profile recruits $CD11c^+$ antigen-presenting cells and cytotoxic $CD8^+$ T cells into tumors, converting immunologically "cold" HCC into "hot" tumors. This SOAT1-ablation-induced inflammation synergizes with anti-PD-1 therapy, providing a mechanistic rationale for metabolic-immunotherapy combinations. Created in BioRender. Chen, M. (2026). https://BioRender.com/ge8j6tr
Abbreviations: APC: Antigen-presenting cell; ER: Endoplasmic reticulum; HCC: Hepatocellular carcinoma; ICB: Immune checkpoint blockade; NF-κB: Nuclear factor kappa B; ROS: Reactive oxygen species; SFA: Saturated fatty acid; SOAT1: Sterol O-acyltransferase 1.

experiments with wild-type SOAT1, but not a catalytically inactive mutant (rH460N), confirmed that this lipidomic shift is a direct consequence of SOAT1 loss of function. This lipidomic shift precipitates a cascade of cellular stress responses, including increased reactive oxygen species (ROS) and ER stress, which ultimately converge on the activation of the nuclear factor kappa B (NF-κB) signaling pathway. Critically, the authors provided evidence that ER stress is functionally linked to NF-κB activation, as reconstitution with wild-type SOAT1 reversed this signaling, whereas the catalytically inactive mutant did not. This connection between lipid-induced lipotoxicity and inflammatory signaling is a critical insight. It provided a mechanistic explanation for how intracellular metabolic alterations can be translated into extracellular signals that reshape the TME.

The authors further confirmed that this NF-κB activation is functionally crucial, as its co-depletion with IKKβ abrogated the downstream effects. It drives the transcription and secretion of a specific set of cytokines and chemokines, including CXC motif chemokine ligand 16 (CXCL16), CXCL12, and CX3CL1, which in turn recruit cytotoxic T cells and antigen-presenting cells. Conditioned media experiments and spatial transcriptomics supported that these chemokines are primarily tumor cell–derived. Collectively, these findings establish a definitive mechanistic bridge between SOAT1-mediated lipid metabolism and NF-κB-driven immune activation, providing a novel paradigm for how intracellular metabolic perturbations can extrinsically orchestrate anti-tumor immunity.

Building on these mechanistic insights, the study provided extensive evidence from both immunodeficient and immunocompetent mouse models to show that SOAT1 ablation does not merely stunt tumor growth autonomously but also actively converts the TME from an immune-deserted ("cold") state to an inflamed ("hot") one. The attenuated effect in immunodeficient models underscores the essential role of adaptive immunity. The observed influx of $CD11c^+$ antigen-presenting cells and $CD8^+$ T cells is a hallmark of productive anti-tumor immunity. Particularly noteworthy is the demonstration that $CD8^+$ T cells exhibited enhanced cytotoxicity against SOAT1-deficient HCC cells *in vitro*. This finding moves beyond correlation to establish a direct functional link between a tumor cell-intrinsic metabolic perturbation

and its susceptibility to immune-mediated killing. While enhanced antigen release from stressed or dying tumor cells may contribute to immune activation, the specific upregulation of NF-κB-dependent chemokines (e.g., CXCL10, CXCL16) argues for a program of immune recruitment and microenvironment reprogramming.

Finally, the translational potential of these findings was unequivocally demonstrated by the synergistic antitumor effect observed when the SOAT1 inhibitor avasimibe is combined with anti-PD-1 therapy in a mouse model of HCC. This combination strategy effectively addresses a significant limitation of current immunotherapies: the inability to jump-start an immune response in immunologically ignorant tumors or resistant tumors. By targeting SOAT1, the authors proposed a strategy to fundamentally remodel the TME, making it more permissive to pre-existing or therapy-induced immune cells. The repurposing of avasimibe, a drug with a well-established safety profile, could accelerate its path to clinical testing.

In conclusion, the study by Ma *et al.* masterfully connected the dots from a cholesterol- and fatty acid–metabolizing enzyme to a potent modulator of anti-tumor immunity, broadening the canonical understanding of other lipid-metabolizing enzymes, such as phosphoinositide kinases in metabolism, immune responses, and tumorigenesis.[11,20-27] It provided a clear mechanistic framework in which SOAT1 inhibition disrupts lipid metabolism, triggers stress-induced NF-κB signaling, and secretes a cocktail of cytokines that recruit and activate a potent immune attack against HCC cells. This work not only deepens our understanding of HCC pathogenesis but also opens a promising new avenue for combination therapy.

Several important questions and future directions emerge from this work by Ma *et al.* First, while their study compellingly links SOAT1 inhibition in tumor cells to TME remodeling, its potential direct effects on the metabolism and function of immune cells, such as T cells and dendritic cells, remain to be fully elucidated. Second, the efficacy of SOAT1 inhibition in models of established PD-1 resistance and its ability to overcome specific resistance mechanisms warrant in-depth investigation. Third, given SOAT1's critical role in systemic lipid homeostasis, potential on-target toxicities, and the influence of patient metabolic status (*e.g.*, metabolic dysfunction–associated steatotic liver disease [MASLD]) on therapeutic responses, these represent key translational considerations. To address these challenges, identifying reliable biomarkers, such as tumoral SOAT1 expression or a tumor-specific saturated fatty acid signature, will be essential for effective patient stratification in future clinical trials.

Future studies should prioritize the development of combination therapies that concurrently target SOAT1 and other immunosuppressive pathways, such as immune checkpoints, to overcome therapeutic resistance potentially. It is also crucial to determine whether the SOAT1-mediated metabolic–inflammatory axis is conserved across other solid tumors, thereby significantly broadening the therapeutic relevance of their findings. Ultimately, translating these compelling preclinical insights into meaningful clinical impact will require dedicated clinical trials to validate SOAT1-targeted strategies in patients with HCC, which hold considerable promise for enhancing the efficacy of existing immunotherapies and improving clinical outcomes.

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Conflict of interest

The authors declare no competing interests.

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Ethics approval and consent to participate

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Consent for publication

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