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RECEIVED 13 March 2025
ACCEPTED 07 April 2025
PUBLISHED 30 April 2025

CITATION
Gao B, Lu Y, Lai X, Xu X, Gou S, Yang Z, Gong Y and Yang H (2025) Metabolic reprogramming in hepatocellular carcinoma: mechanisms of immune evasion and therapeutic implications.
Front. Immunol. 16:1592837.
doi: 10.3389/fimmu.2025.1592837

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Metabolic reprogramming in hepatocellular carcinoma: mechanisms of immune evasion and therapeutic implications

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide, with limited treatment options for advanced stages. Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to adapt to the harsh tumor microenvironment (TME) and evade immune surveillance. This review involves the role of metabolic reprogramming in HCC, focusing on the dysregulation of glucose, lipid, and amino acid metabolism, and its impact on immune evasion. Key metabolic pathways, such as the Warburg effect, fatty acid synthesis, and glutaminolysis, are discussed, along with their influence on tumor-associated macrophages (TAMs) and immune cell function. Targeting these metabolic alterations presents a promising therapeutic approach to enhance immunotherapy efficacy and improve HCC patient outcomes.

KEYWORDS

hepatocellular carcinoma, metabolic reprogramming, immune evasion, tumor microenvironment, TME, tumor-associated macrophages (TAMs), immunotherapy

1 Introduction

Hepatocellular carcinoma (HCC) demonstrates limited therapeutic responsiveness, with objective response rates remaining at approximately 20% in clinical settings (1, 2). While immunotherapy has emerged as a potential therapeutic strategy for advanced HCC (3), its clinical efficacy remains constrained by tumor immune evasion mechanisms operating within the immunosuppressive tumor microenvironment (TME) (4–6). Metabolic reprogramming drives both tumorigenesis and disease progression through profound alterations in core metabolic pathways including glycolysis, fatty acid synthesis, and glutamine metabolism (7–9). These adaptations not only fulfill the biosynthetic and bioenergetic demands of rapidly proliferating tumor cells but also actively shape an immunosuppressive TME. Critically, the metabolic crosstalk between malignant cells and immune cell populations within the TME facilitates immune evasion mechanisms and confers resistance to immunotherapeutic interventions (10). The liver's

immunosuppressive nature and the TME's enrichment with regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and TAMs drive HCC progression and limit immunotherapy efficacy (11, 12).

During HCC development, malignant cells continuously adapt their metabolic patterns to acquire sufficient nutrients for self-renewal and proliferation in the hypoxic and nutrient-deprived TME (13). These metabolic alterations not only induce phenotypic and functional changes in TAMs but also lead to their metabolic reprogramming, enabling them to exert immunosuppressive functions and promote tumor progression and metastasis (14). Recent advances in HCC metabolism research have provided significant insights. However, current immunotherapies, including checkpoint inhibitors targeting the PD-1/PD-L1 or CTLA-4 pathways, face substantial challenges in HCC due to the profoundly immunosuppressive metabolic landscape (15). This review explores metabolic reprogramming in HCC, focusing on dysregulated enzymes and pathways in glucose, lipid, amino acid, and nucleotide metabolism, and discusses how effectively targeting dysregulated metabolic pathways can synergize with existing immunotherapies, thereby potentially overcoming immune evasion and improving clinical outcomes.

2 Glucose metabolism in HCC

2.1 Glucose metabolic reprogramming: key enzymes and pathways

Glucose metabolic reprogramming is one of cancer cells' most prominent metabolic features. HCC cells upregulate the expression of glucose transporters 1 and 2 (GLUT1 and GLUT2) to increase glucose uptake, and the downregulation of GLUT1 and GLUT2 significantly inhibits HCC cell growth and proliferation (16, 17). Once inside the cell, glucose is phosphorylated by hexokinase (HK) to form glucose-6-phosphate (G6P). Among these, HK2 is overexpressed in various cancers, including HCC, and its high expression is associated with poor prognosis in HCC patients (18). Inhibition of HK2 expression has been shown to enhance the therapeutic efficacy of sorafenib in HCC (19). M1-like macrophages consume large amounts of glucose for glycolysis, upregulating anabolic pathways to provide substrates and rapid energy production. Studies have demonstrated that the glycolysis inhibitor 2-deoxy-D-glucose (2-DG) significantly reduces ATP levels in HCC M1-like macrophages, inhibiting glycolysis (20). Additionally, glycolysis fuels the pentose phosphate pathway (PPP), generating NADPH to produce reactive oxygen species (ROS), which is crucial for the phagocytic activity of M1-like macrophages (21). Another key enzyme in glycolysis, pyruvate kinase (PK), catalyzes the conversion of phosphoenolpyruvate to pyruvate. PK has two isoforms, PKM1 and PKM2, with PKM2 being highly expressed in HCC and associated with poor patient prognosis (22). Finally, pyruvate is converted to lactate by lactate dehydrogenase (LDH) (23), and elevated LDH levels in HCC tissues and plasma are significantly correlated with poor prognosis (24).

The upregulation of key glycolytic enzymes in HCC cells is closely linked to the activation of oncogenes and pro-tumor signaling pathways. Hypoxia-inducible factor 1 α (HIF-1 α) plays a critical role in regulating glycolysis in HCC cells by transcriptionally upregulating several glycolytic enzymes, including GLUT1 and HK2 (25). HIF-1 α is a key transcription factor that enables cells to adapt to low oxygen levels and is essential for glycolysis in TAMs. Studies have shown that LPS induces the phosphorylation of PKM2, promoting the formation of a nuclear PKM2/HIF-1 α complex that binds to the HIF-1 α promoter, driving its expression and enhancing glycolysis in TAMs in HCC (26). Inhibition of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway plays a significant role in tumorigenesis and progression (27). The PI3K/Akt/mTOR signaling pathway, which plays a significant role in tumor progression, has also been implicated in promoting glycolysis in HCC cells by regulating GLUT4 and HK2 (28, 29).

2.2 Impact of glucose metabolism on immune evasion

The inefficient delivery of nutrients and oxygen, along with the poor clearance of metabolic waste in tumors, creates a hypoxic and acidic TME, which significantly impairs anti-tumor immune responses (30–32). HCC cells enhance glycolysis, producing large amounts of lactate, which acidifies the TME and suppresses immune cell function. In HCC patients, serum HIF-1 α levels are negatively correlated with prognosis, as HIF-1 α recruits macrophages to hypoxic regions of the TME via chemokines such as CCL-2 and endothelin (31, 33). Accumulated HIF-1 α promotes the release of IL-1 β by TAMs through the TLR4/TRIF/NF- κ B signaling pathway, facilitating immune evasion (34). Tumor cells enhance lactate dehydrogenase A (LDH-A) activity to convert pyruvate into lactate, which is then exported out of the cell via monocarboxylate transporter 4 (MCT4), further acidifying the TME. This acidic environment inhibits the anti-tumor functions of cytotoxic T lymphocytes, natural killer (NK) cells, and dendritic cells (DCs) while promoting the immunosuppressive functions of Tregs and MDSCs (35).

Lactate also plays a pivotal role in stabilizing HIF-1 α , which in turn upregulates the expression of arginase-1 and VEGF. These factors drive the polarization of macrophages toward the M2 phenotype, an alteration that promotes tumor growth and metastasis (36). The M2 macrophages, characterized by their pro-tumorigenic properties, further secrete factors that enhance angiogenesis and tissue remodeling, creating a feedback loop that perpetuates tumor progression and immune suppression (37). In summary, the hypoxic and acidic conditions within the HCC TME, driven by enhanced glycolysis and lactate production, create a hostile environment for anti-tumor immunity. This environment not only impairs the function of key immune cells but also promotes the recruitment and polarization of immunosuppressive cells, thereby facilitating tumor immune evasion and progression.

Previous evidence underscores the direct immunomodulatory role of the pyruvate kinase M2 (PKM2)/HIF-1 α axis in macrophages, T cells, and NK cells. PKM2 can translocate to the nucleus and serve as a coactivator for HIF-1 α , driving transcription of glycolytic enzymes and immunosuppressive mediators (38, 39). This heightened glycolytic state not only fuels tumor metabolism but also skews macrophage polarization toward an M2-like phenotype, suppresses T cell effector function through local lactate accumulation, and hampers NK cell cytotoxicity (39, 40). Consequently, interventions targeting PKM2's nuclear function or inhibiting the PKM2/HIF-1 α complex can disrupt key immunosuppressive circuits in the TME and restore anti-tumor immune responses. In addition to tumor cells, non-tumor stromal cells also undergo glycolytic shifts that contribute to this immunosuppressive milieu. For example, cancer-associated fibroblasts (CAFs) may increase glucose consumption and release lactate, fueling adjacent HCC cells while simultaneously creating an acidic TME that hampers T cell and NK cell function (41). This reciprocal metabolic interplay between tumor and stromal cells magnifies immune evasion by shaping an environment that favors HCC survival and progression.

3 Dysregulation and immune modulation functions of lipid metabolism in HCC

3.1 Lipid metabolic reprogramming in HCC

Lipid metabolic reprogramming in HCC is characterized by enhanced fatty acid uptake and *de novo* synthesis, increased cholesterol synthesis, and reduced fatty acid oxidation. These alterations are closely associated with HCC development and progression. HCC cells promote growth and proliferation by increasing the uptake of exogenous fatty acids (42). CD36, a fatty acid transporter, facilitates the uptake of long-chain fatty acids (LCFAs) and oxidized low-density lipoprotein (Ox-LDL), playing a crucial role in lipid metabolism and serving as a significant tumor marker (43). Studies have shown that tumor cells utilize CD36 on their cell surface to uptake fatty acids, and CD36 is overexpressed in HCC cells. CD36 promotes HCC progression by activating Wnt and TGF- β signaling pathways and inducing epithelial-mesenchymal transition (EMT) (44–46). These findings suggest that CD36 may be a novel target for enhancing HCC immunotherapy through metabolic pathways.

De novo fatty acid synthesis (*de novo* FAS) is a critical pathway for tumor cells to acquire lipids. HCC cells exhibit heightened *de novo* FAS activity (47). Key enzymes involved in *de novo* FAS, such as ATP citrate lyase (ACLY) and fatty acid synthase (FASN), are overexpressed in HCC, and their upregulation is associated with poor prognosis (48). Several transcription factors and signaling pathways regulate *de novo* FAS in HCC cells. Sorafenib disrupts monounsaturated fatty acid synthesis mediated by stearoyl-CoA desaturase-1 (SCD1) through the ATP-AMPK-mTOR-SREBP1 signaling pathway, leading to HCC cell death (49). Dysregulated

cholesterol synthesis is another hallmark of lipid metabolic reprogramming in HCC. HMG-CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis, is upregulated in HCC and is the target of statins, which regulate plasma cholesterol levels (50). Increased mitochondrial cholesterol content in HCC cells reduces mitochondrial membrane permeability, inhibiting cytochrome c release and conferring resistance to chemotherapy (50). Recent studies have highlighted the importance of fatty acid β -oxidation (FAO) in tumor progression. SIRT4, a member of the Sirtuin family, functions as an ADP-ribosyl transferase and regulates FAO and mitochondrial gene expression in liver and muscle cells (51). Loss of SIRT4 enhances the expression of FAO-related genes such as pyruvate dehydrogenase kinase 4 (PDK4) and carnitine palmitoyl transferase 1 (CPT1), as well as mitochondrial genes such as cytochrome c (CytC) and isocitrate dehydrogenase 3 α (IDH3 α) in TAMs. SIRT4 deficiency also promotes M2 polarization of TAMs through the PPAR δ -STAT3 signaling pathway, driving HCC progression (52).

3.2 Role of lipid metabolism in immune evasion and tumor progression

Liver fatty acid-binding protein (L-FABP) is highly expressed in HCC tissues and has been shown to regulate lipid metabolism and inflammation in host cells (53). TAMs derived from HCC highly express L-FABP and promote NK cell recruitment through the production of IFN- β , mediating anti-tumor effects (54). However, TAMs also produce prostaglandin E2 (PGE2), which suppresses anti-tumor immunity. In HCC, TAMs upregulate cyclooxygenase-2 (COX2) and prostaglandin E synthase 1 (PGES1) to produce high levels of PGE2, which inhibits IFN- γ production and NK cell cytotoxicity (55). HCC cells enhance FAO, promoting M2 polarization of TAMs and suppressing immune cell function (56). The FAO inhibitor etomoxir blocks FAO activity in TAMs, inhibiting their pro-tumor functions (57, 58). Consequently, targeting FAO in TAMs may not only impede tumor progression but also enhance the efficacy of immune checkpoint inhibitors and other immunotherapies by restoring anti-tumor immune responses within the TME (59, 60).

4 Amino acid metabolism and immune suppression in HCC

4.1 Amino acid metabolic reprogramming

Amino acid metabolism in HCC is characterized by increased glutaminolysis (61). The alanine-serine-cysteine transporter 2 (ASCT2) is the primary transporter of glutamine in cells (62). ASCT2 is overexpressed in HCC and is associated with poor prognosis (63). Glutamine serves as a major energy source for HCC cells, being catabolized by glutaminase (GLS) into glutamate, which enters the tricarboxylic acid (TCA) cycle to generate energy. Glutamine synthetase (GS) converts ammonia and glutamate into

glutamine. Targeting GS with small-molecule inhibitors can reprogram TAMs into antigen-presenting cells, exerting anti-tumor effects. GLS has two isoforms, GLS1 and GLS2. GLS1 promotes tumor cell growth in various cancers (64), while GLS2 suppresses cancer cell proliferation and migration (65). In HCC, GLS1 is overexpressed and promotes cell proliferation via the AKT/GSK3 β /CyclinD1 pathway (66). High GLS1 expression is positively correlated with stemness in HCC cells, and targeting GLS1 reduces stemness by increasing mitochondrial ROS and suppressing the Wnt/ β -catenin pathway (67). In contrast, GLS2 is downregulated in HCC and inhibits tumor growth by negatively regulating the PI3K/AKT signaling pathway (68–71). However, despite these well-established roles, there are also contradictory or context-dependent findings concerning GLS1 and GLS2 in HCC (72). These conflicting observations underscore the complexity of glutamine metabolism in HCC and highlight the importance of studying tumor-stage specific expression and activity of these isoforms. Further investigation into the interplay between GLS1/GLS2 and other metabolic or signaling pathways will be crucial for designing precision therapies targeting glutaminolysis in HCC.

M2-like TAMs highly express arginase-1, which hydrolyzes arginine into ornithine and urea. Ornithine serves as a precursor for polyamines and collagen, contributing to extracellular matrix formation and tissue repair. Ornithine is further metabolized by ornithine decarboxylase into polyamines, promoting M2

polarization of macrophages and tumor cell growth (73). Additionally, serine metabolism plays a crucial role in HCC progression. Studies have confirmed that under conditions of glucose or glutamine starvation, the serine biosynthesis pathway in HCC cells is significantly enhanced. c-Myc promotes the production of glutathione, progression of the cell cycle, and synthesis of nucleic acids by upregulating the expression of various SSP enzymes, thereby facilitating the survival and proliferation of HCC cells (74–76).

4.2 Amino acid metabolism influences immune cell function in HCC

Amino acid metabolism in HCC significantly influences the immune response of various cells, playing a crucial role in tumor progression. TAMs exhibit increased activity of indoleamine 2,3-dioxygenase 1 (IDO1), which converts tryptophan into kynurenine. Kynurenine induces T cell death, reduces the number of pro-inflammatory T lymphocytes, and diminishes T cell anti-tumor activity (77). CHEN et al. (78) demonstrated that early-activated CD69⁺ T cells enhance IDO activity in TAMs, accelerating tryptophan metabolism. This metabolic shift not only promotes T cell proliferation and cytokine production but also activates Tregs, thereby facilitating HCC cell proliferation and metastasis. Excessive

TABLE 1 Key metabolic pathways in HCC and their roles in immune evasion.

Metabolic Pathway	Key Enzymes/Transporters	Regulatory Mechanisms	Impact on Immune Evasion
Glucose Metabolism	GLUT1/2, HK2, PKM2, LDH-A	HIF-1 α , PI3K/Akt/mTOR signaling	Acidic TME (via lactate) inhibits CTLs/NK cells; M2 polarization of TAMs via HIF-1 α /IL-1 β
Lipid Metabolism	CD36, FASN, ACLY, SCD1	Wnt/TGF- β signaling, SREBP1	FAO promotes M2 TAMs; PGE2 suppresses NK cells; L-FABP recruits NK cells
Amino Acid Metabolism	ASCT2, GLS1, IDO1, Arg-1	AKT/GSK3 β /CyclinD1, TLR4/NF- κ B	Tryptophan depletion by IDO1 induces T cell death; arginine depletion impairs NK function
Cholesterol Metabolism	HMGCR, SIRT4	PPAR δ -STAT3 signaling	Mitochondrial cholesterol confers chemotherapy resistance

TABLE 2 Therapeutic strategies targeting HCC metabolism.

Target	Drug/Intervention	Mechanism	Stage (Preclinical/Clinical)
Glucose Transport	Aspirin	Inhibits GLUT1, reduces glucose uptake	Preclinical
Glycolysis	2-DG, Celastrol	Inhibits HK2/LDHA, shifts TAM metabolism	Preclinical
Fatty Acid Synthesis	Sorafenib + SSI-4	Inhibits SCD1, induces cell death	Preclinical
Glutaminolysis	GLS1 inhibitors (e.g., CB-839)	Reduces glutamine dependency, suppresses stemness	Clinical trials
PD-L1/PD-1 Pathway	Atezolizumab + Bevacizumab	Blocks immune checkpoint, enhances T cell activity	FDA-approved (HCC)
IDO1	Epacadostat	Restores tryptophan, reverses T cell suppression	Phase II trials

arginine consumption in HCC depletes arginine levels in the TME, impairing NK cell proliferation and IFN- γ production (79, 80). *In vitro* studies have shown that low arginine levels in the HCC microenvironment suppress the expression of NK cell activation receptors such as NKp46 and NKp30 (81, 82). Additionally, the acidic microenvironment resulting from high lactate levels inhibits NK cell cytotoxicity and cytokine production (83). Given the crucial role of amino acids in T cell activation and effector function, reducing IDO1-mediated tryptophan depletion or alleviating excessive arginine consumption could reverse T cell dysfunction and synergize with immunotherapies such as anti-PD-1/PD-L1 antibodies. Indeed, clinical trials evaluating IDO1 inhibitors in combination with checkpoint inhibitors in other cancer types suggest potential avenues for analogous therapeutic approaches in HCC (84).

Collectively, the interplay between metabolic reprogramming (glucose, lipid, and amino acid metabolism) and immune evasion is a pivotal driver of HCC progression. As summarized in Table 1, dysregulated enzymes and pathways in these metabolic networks not only sustain tumor cell proliferation but also actively suppress anti-tumor immunity by polarizing TAMs and acidifying the TME. Future combination therapies that simultaneously target metabolic checkpoints and enhance T cell functionality may thus open new pathways toward reversing immunosuppression and improving HCC patient outcomes.

5 Therapeutic targeting of metabolic pathways in HCC

Given the dysregulation of key enzymes and signaling pathways in glucose, lipid, amino acid, and nucleotide metabolism in HCC, targeting these metabolic abnormalities represents a promising therapeutic strategy. Aspirin has been shown to inhibit HCC by targeting the overexpression of GLUT1, reducing glucose uptake in HCC cells (85). Similarly, HK2 can be targeted by resveratrol (86), miRNAs (87, 88), and Ras-associated glycolysis inhibitors (89). Celastrol, a triterpenoid compound derived from the medicinal plant *Tripterygium wilfordii*, covalently modifies glycolytic enzymes like HK2 in M1 macrophages, shifting their metabolism from glycolysis to oxidative phosphorylation and promoting M2 polarization, thereby alleviating lipid accumulation, inflammation, and fibrosis in the liver (90). Additionally, the SCD1 inhibitor SSI-4, when combined with sorafenib, enhances anti-tumor efficacy, suggesting a novel therapeutic strategy for HCC (91).

Beyond targeting metabolic enzymes, dysregulated metabolic pathways in HCC are also potential therapeutic targets. TAM metabolism influences the expression of PD-L1 and PD-1, which mediate immune suppression. Clinical studies have shown that targeting the PD-L1/PD-1 pathway significantly improves clinical

outcomes in HCC patients (92). In HCC, PD-L1 is primarily produced by PD-L1⁺ macrophages (93). Inflammatory factors are pivotal in diseases' progression (94–97). A recent study found that fibronectin 1 derived from HCC interacts with Toll-like receptor 4, activating glycolysis in macrophages via the PKM2/HIF- α signaling pathway and promoting the secretion of pro-inflammatory cytokines IL-1 β and TNF- α , which enhance PD-L1 expression on macrophages, ultimately leading to immune evasion (98). These findings highlight the intricate link between metabolic reprogramming and immunosuppression in HCC, suggesting that interventions aimed at inhibiting glucose uptake, fatty acid synthesis, or glutaminolysis could potentiate the efficacy of immune checkpoint inhibitors. As combination therapies that pair PD-1/PD-L1 or CTLA-4 blockade with metabolic modulators continue to be explored, a personalized approach to targeting both tumor metabolism and immune evasion may emerge as a new standard for advanced HCC (Table 2).

6 Conclusion

Metabolic reprogramming, encompassing the dysregulation of glucose, lipid, and amino acid metabolism, directly fosters immune evasion and immunotherapy resistance in HCC. By creating a microenvironment characterized by hypoxia, nutrient depletion, and acidification, these metabolic changes blunt the activity of cytotoxic T cells, NK cells, and other effector populations while promoting the expansion of immunosuppressive cell subsets such as Tregs and M2-polarized TAMs. This reciprocal relationship between aberrant metabolism and immunosuppression underlies one of the most formidable challenges to effective HCC treatment, as it contributes to the suboptimal response rates to current immunotherapies. Targeting metabolic pathways offers promising therapeutic strategies to overcome immune evasion and improve HCC treatment outcomes. Future research should focus on developing metabolic inhibitors and combining them with existing immunotherapies to enhance their efficacy. In particular, early-phase clinical trials investigating combination regimens that integrate metabolic interference with anti-PD-1/PD-L1 therapies are poised to illuminate the feasibility and potential synergy of dual-targeting approaches in HCC.

Author contributions

BG: Writing – original draft. YL: Writing – original draft. XL: Writing – original draft. XX: Writing – original draft. SG: Writing – original draft. ZY: Writing – original draft, Writing – review & editing. YG: Writing – review & editing, Writing – original draft. HY: Writing – review & editing, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study is supported by the Natural Science Foundation of Sichuan Province (Grant No. 2023NSFSC1758).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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