

Mechanistic Research on the Crosstalk Between Macrophage Polarization and Energy Metabolic Reprogramming in Hepatocellular Carcinoma

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Abstract: Liver cancer is ranked as the sixth most prevalent and the third deadliest cancer worldwide. Macrophages play a crucial role in cancer resistance mechanisms, and the regulation of their polarization state can alter their anti-tumor activity. Additionally, alterations in liver cancer pathways can shift the polarization of macrophages. Inflammatory agents and medications have the potential to alter macrophage polarization, favoring M1 differentiation and enhancing their anti-tumor activity. This review explores metabolic alterations in liver cancer, macrophage polarization processes, and their interconnections in hepatic oncogenesis. It further elaborates on the prospects and challenges of investigating targeted macrophage metabolism for liver cancer treatment. Modulating macrophage metabolic pathways represents a promising therapeutic approach for hepatic carcinoma.

Keywords: liver cancer, macrophage polarization, metabolic reprogramming

Introduction

Liver cancer is ranked as the sixth most prevalent cancer and is responsible for the third highest number of cancer-related fatalities worldwide.¹ Approximately 830,000 deaths occur annually due to liver cancer. Hepatocellular carcinoma is characterized by a complex pathogenesis and genetic mutations in proto-oncogenes, often resulting from external factors such as viral infections, excessive alcohol consumption, obesity, and exposure to aflatoxins.² Hepatocellular carcinoma is characterized by high heterogeneity, which affects tumor progression, invasiveness, and response to anti-tumor drugs.^{3,4} Treatment for advanced liver cancer primarily employs targeted agents and immunotherapeutics.^{5,6} Sorafenib has been the only systemic first-line treatment drug approved by the US Food and Drug Administration (FDA) for 10 years.⁷ Nevertheless, sorafenib exhibits drawbacks when utilized for HCC therapy.⁸ Consequently, additional research is needed to develop effective therapeutic strategies to improve outcomes for individuals with hepatic malignancies.

In recent years, with the extensive research on tumor immunology and cellular metabolism, the role of macrophage polarization in tumor initiation and progression has become an emerging area of focus. As a crucial component of the immune system, macrophages exhibit significant plasticity and heterogeneity,⁹ and can polarize into distinct phenotypes with various functions within the tumor microenvironment. Tumor-associated macrophages (TAMs) play a central role in hepatocellular carcinoma, acting as key players within the tumor microenvironment (TME). These critical cells play a pivotal role in tumor formation and progression, influencing angiogenesis, promoting immunosuppression, and facilitating drug resistance and cancer metastasis.¹⁰ Among these, M1 macrophages exhibit anti-tumor activity and can

eliminate tumor cells through cytokine secretion and immune cell activation, whereas M2 macrophages display pro-tumor effects, promoting neoplastic cell growth, dissemination, infiltration, and immunosuppression.^{11,12} Increasing evidence suggests that TAMs predominantly exhibit an M2 polarization state, which is strongly associated with the unfavorable prognosis of liver cancer. A comprehensive understanding of the biological characteristics and regulatory mechanisms of TAMs is expected to facilitate the development of more effective treatment strategies for HCC.

Although the M1/M2 dichotomy is a widely used framework for describing macrophage polarization in tumor immunity research, recent studies have increasingly suggested that this framework is overly simplistic and does not fully capture the complex role of macrophages within the tumor microenvironment. Particularly in the immune microenvironment of tumors like liver cancer, macrophages exhibit dynamic states and high spatial heterogeneity, with changes in their phenotypes and functions influenced by the local environment and metabolic conditions.

Meanwhile, energy metabolism reprogramming, a key feature of malignant cells, provides the energy and material foundation necessary for the rapid proliferation and sustained growth of cancer cells.^{13,14} Hepatocellular carcinoma cells satisfy their aberrant metabolic demands by reprogramming metabolic pathways, including those involved in glucose, lipid, and amino acid metabolism.¹⁵ Studies have demonstrated a close association between macrophage polarization and metabolic reprogramming in cancer cells. These factors interact and regulate each other to drive the progression of liver cancer.¹⁶ Moreover, several signaling pathways play a crucial role in regulating macrophage polarization and reprogramming energy metabolism in liver cancer, with notable examples including the PI3K/AKT, MAPK, and NF- κ B pathways.^{17–19} Their aberrant regulation is associated with the onset, progression, metastasis, and therapeutic resistance of liver cancer. However, the roles of fatty acid oxidation (FAO) and amino acid metabolism in macrophage polarization have not been fully elucidated, and these metabolic pathways exhibit distinct functions across different tumor microenvironments. Although numerous studies have explored the impact of tumor metabolism on macrophage reprogramming, the causal relationship between metabolic changes and macrophage polarization remains unclear. Metabolic reprogramming may serve as a driving factor in altering the polarization state of macrophages, or it may be a consequence of complex signaling within the tumor microenvironment. Furthermore, the effects of metabolic changes may be contingent upon the specific conditions of the microenvironment, manifesting as context-dependent feedback loops.

This review thoroughly examines the relationship between macrophage metabolic reprogramming and immune regulation within the HCC TME, with particular emphasis on the roles of glucose metabolism, FAO, and amino acid metabolism in macrophage polarization. It is proposed that targeting macrophage metabolism—particularly glucose and lipid metabolism—in conjunction with immunotherapy, may significantly enhance anti-tumor immune responses, offering new therapeutic strategies for liver cancer treatment. Furthermore, clinical trial data are incorporated to highlight the potential of combining metabolic regulation with immune checkpoint inhibitors, which have shown promising results, particularly in the treatment of liver cancer and other cancers, thereby providing novel perspectives and directions for clinical applications.

Basic Characteristics of Macrophages

The Concept and Methods of Macrophage Polarization

Monocytes are a subset of white blood cells derived from the bone marrow, comprising approximately 5%-10% of the total white blood cell count in peripheral blood. Among the sources of tissue macrophages, monocytes serve as the primary precursor cells, with the majority of macrophages originating from monocyte differentiation. In terms of their life cycle, circulating monocytes have a relatively short lifespan, lasting only about two days. However, when influenced by chemotactic signals, they migrate to the tissue microenvironment and differentiate into macrophages, leading to a significant extension of their survival time to several months. This “lifespan extension” enables macrophages to continuously perform vital functions, including phagocytosis, clearance, and immune regulation.²⁰ As a central component of the immune system, macrophages play a crucial role in initiating and executing immune responses, thereby forming a key defense barrier that protects the host from microbial invasion. However, studies have demonstrated that the functions of these cells extend beyond the realm of anti-infection. In pathological conditions where immune homeostasis is disrupted, macrophages are closely implicated in the onset and progression of autoimmune diseases, as well as in the proliferation and invasion of malignant tumors, serving as a critical regulatory link between immune defense and pathological damage.²¹

Macrophage polarization refers to the activation of macrophages in response to pathogenic microorganisms, inflammatory signals, cytokines, or specific physical and chemical factors, leading to their differentiation into distinct phenotypes based on the state and changes within the microenvironment.²² Macrophage polarization appears to serve as an intermediate process during both the onset and regression of diseases. It is activated by specific signals, leading to the generation of distinct phenotypes, which exert regulatory effects by modulating multiple signal transduction pathways.²³

Exogenous polarization is the primary mechanism of macrophage polarization, mediated by cytokines secreted by other cells, such as CD4⁺ Th1 or Th2 cells. In addition to the classic cytokine-mediated regulatory pathways, macrophage polarization is also influenced by various non-cytokine exogenous factors. Among these, the hypoxic microenvironment and the abnormal accumulation of lactic acid in the tumor microenvironment are two key inducing factors. These factors can specifically drive macrophages to polarize into the M2 phenotype through mechanisms such as the regulation of cellular metabolism and the activation of specific signaling pathways, thereby contributing to the modulation of the local immune microenvironment and disease progression.²⁴ The classically activated M1 phenotype and the alternatively activated M2 phenotype are distinguished by distinct surface receptor expressions, secretion profiles, and functional roles.²⁵ Due to the plasticity of macrophages, their polarization state is dynamic. The two primary phenotypes are the classically activated M1 type and the alternatively activated M2 type.²⁶ However, with advancing research, the academic community has recognized that the polarization state of macrophages is not confined to the dichotomy between M1 and M2 types, but exists along a continuous spectrum, dynamically regulated by factors such as local signals within the tumor microenvironment, metabolic status, and spatial location. Recent advancements in single-cell technology have revealed the spatial heterogeneity of macrophage phenotypes. Macrophages within the same tumor can display distinct functional characteristics across different regions. These findings indicate that the polarization and function of macrophages are not solely defined by the classic M1/M2 model, but result from the combined action of multiple factors, exhibiting both reversibility and diversity, which contribute to the complex regulation of the tumor immune microenvironment. For example, studies have demonstrated that M2-type macrophages are predominant in mouse models; however, their specific roles in human liver cancer may differ,²⁷ potentially influenced by various factors within the tumor microenvironment.

M1 Macrophage

Classically activated macrophages, or M1 macrophages, are the most well-documented subset of these immune cells. Typically stimulated by lipopolysaccharide (LPS) and interferon- γ (IFN- γ), they initiate a robust inflammatory response by releasing a range of pro-inflammatory cytokines, including tumor necrosis factor (TNF- α), interleukins (IL-1, IL-6), and inducible nitric oxide synthase (iNOS), effectively signaling the presence of potential threats.²⁸ In the tumor microenvironment, M1 macrophages initiate Th1 immune responses by releasing cytokines such as IL-1, IL-6, IL-12, TNF, and CXCL9, thereby promoting robust anti-tumor immune reactions.²⁹ In addition, as key effector cells in the body's anti-tumor and anti-infectious immunity, M1-type macrophages can also directly interact with CD8⁺ T cells (cytotoxic T cells) through specific receptors expressed on their surface, thereby precisely regulating the activation, proliferation, killing function, and other activity states of CD8⁺ T cells. In-depth studies have shown that such intercellular interactions do not occur randomly but are highly dependent on the mediation of co-stimulatory molecules. The molecular interaction between M1 macrophages and CD8⁺ T cells relies on the upregulation of co-stimulatory molecules such as CD40, CD80, and CD86 on the macrophage surface, which subsequently initiate signaling cascades in T cells upon receptor binding. These interactions are essential for the precise modulation of CD8⁺ T cell function.³⁰

IFN- γ was the first macrophage-activating factor identified in 1970. It is a soluble cytokine produced by activated CD4⁺ helper T cells (Th1), CD8⁺ cytotoxic T cells, and NK cells. It can induce the transformation of resting macrophages into activated cells and enhances their antigen-presenting ability, increases the synthesis of pro-inflammatory mediators and pathogenic substances, and promotes complement-mediated cellular consumption.³¹ The activation of early macrophages is referred to as the classical pathway. Stimulated by Th1 cells, also known as cytotoxic T cells, these classically activated macrophages are now termed M1 macrophages. In contrast, M1 macrophages promote Th1 and cytotoxic T-cell activation, inducing the production of IFN- γ , which reinforces M1 polarization through positive feedback regulation.³² M1 macrophages release numerous pro-inflammatory cytokines, including IL-1 β , IL-6, IL-12, IL-23, IFN- β , and TNF- α . (Figure 1). These factors simultaneously drive the Th1 response.³³

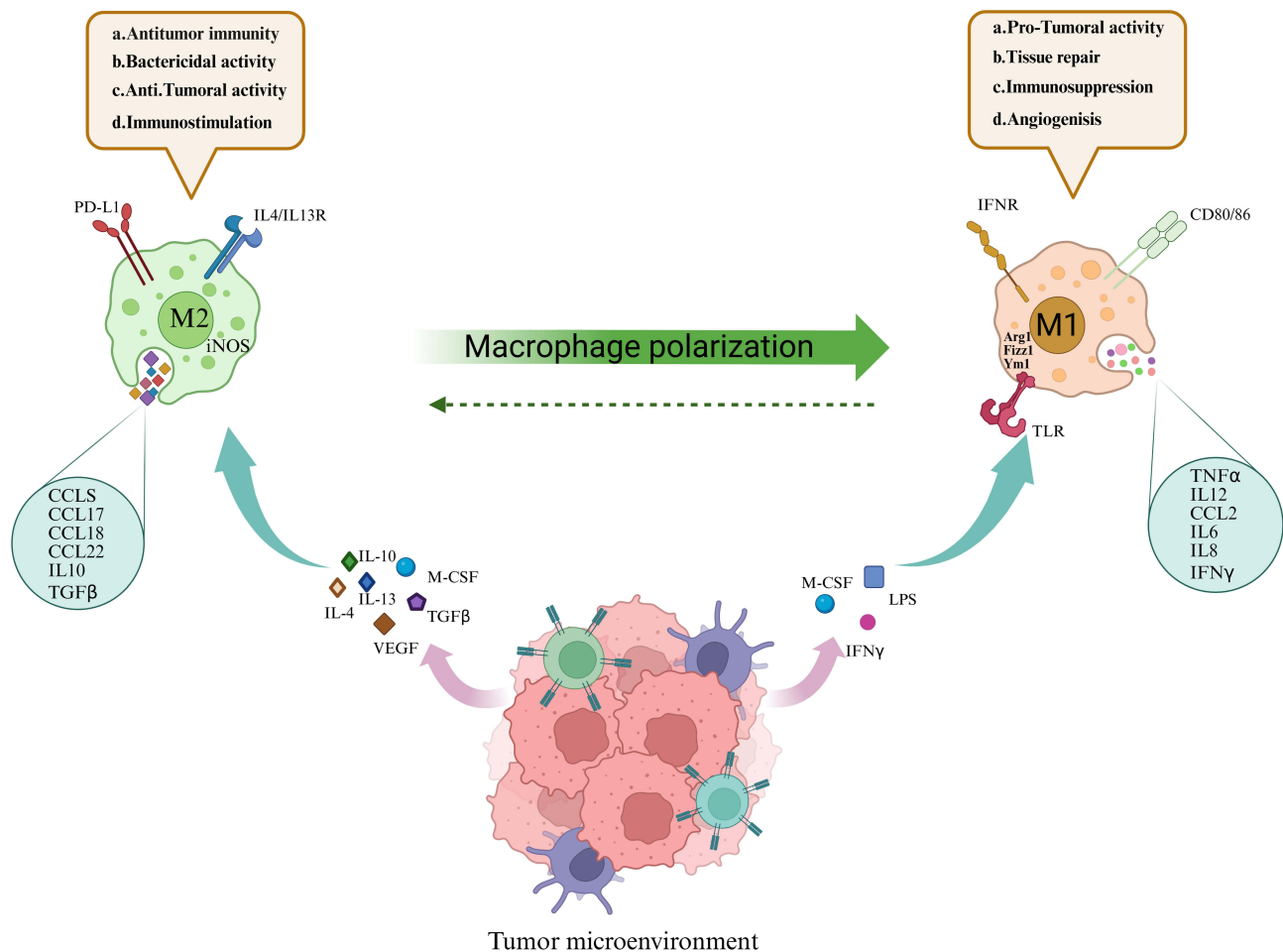


Figure 1 M1 and M2 can transform into each other under different stimulating factors and secrete cytokines, producing different effects. M1 macrophages promote anti-tumor immune responses by releasing IL1, IL6, IL12, and TNF- α under the action of interferon and lipopolysaccharide; while M2 macrophages achieve tissue repair and immune tolerance by releasing CCL chemokines under the influence of interleukins and tumor necrosis factors, and have anti-inflammatory and tumor-promoting properties.

M2 Macrophage

M2 macrophages were first identified in cases of worm infections, where they are distinguished from monocyte progenitor cells that are influenced by IL-4 and IL-13, and exhibit a pronounced Th2 polarization response. Although the recruitment of M2-type macrophages is strongly influenced by Th2-type cytokines, these cells do not solely function as passively recruited effector cells. They can also actively secrete various cytokines to reversely participate in the regulation of immune responses. On the one hand, they can further mediate and amplify Th2-type immune responses, thereby promoting the activation and functional maintenance of Th2 cells. Alternatively, they precisely modulate the severity and extent of regional inflammatory responses by secreting anti-inflammatory cytokines such as IL-10 and TGF- β . This results in the formation of a bidirectional regulatory loop, where Th2 cytokines recruit M2 macrophages, and M2 macrophages regulate Th2 responses and inflammation.³⁴ M2-type activation results from IL-4, IL-10, IL-34, IL-13, vitamin D3, TGF- β , prostaglandin E2 (PGE2), VEGF, EGF, glucocorticoids, and M-CSF.³⁵ M2 macrophages are classified into distinct subsets—IL-4/13-triggered M2a, immune complex-stimulated M2b, IL-10-inhibited M2c, and IL-6/M-CSF-mediated M2d—based on stimulation by various cytokines.³⁶

M2 macrophages primarily contribute to tissue healing and immune tolerance, exhibiting both anti-inflammatory and pro-tumor characteristics, in contrast to the roles of M1 macrophages. In the TME, TAMs in advanced tumors are predominant and serve as key regulators of the TME. Numerous studies have confirmed that, in various cancers, M2-like macrophages constitute a larger proportion of TAMs, and this characteristic is significantly associated with an unfavorable prognosis for patients (Figure 2).

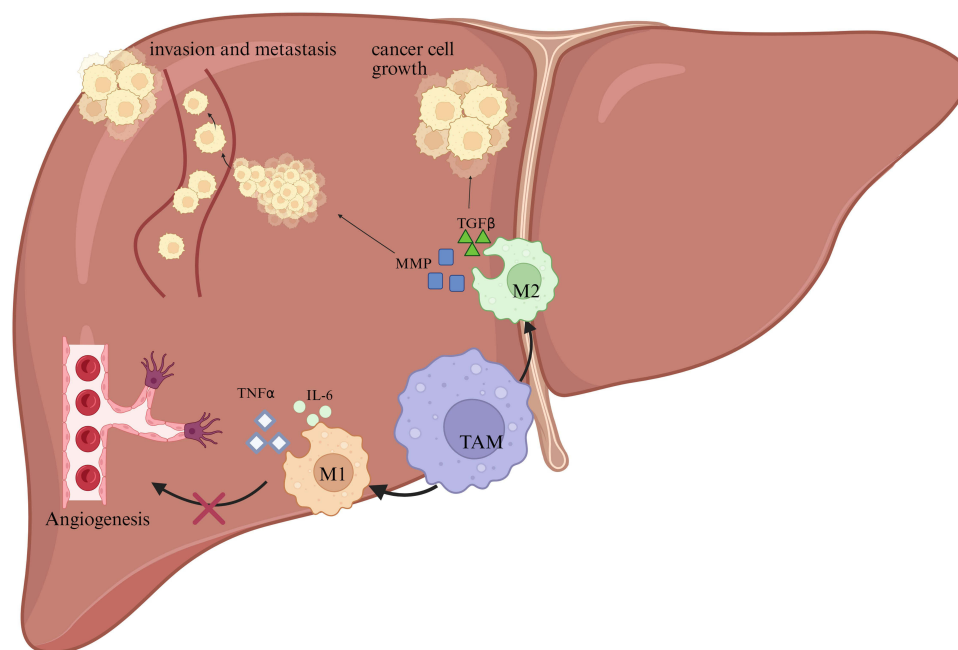


Figure 2 The role of TAMs in liver cancer progression. M1 macrophages secrete pro-inflammatory cytokines such as TNF α and interleukin-6 (IL-6), which inhibit angiogenesis and thereby suppress tumor growth. In contrast, M2 macrophages promote cancer cell proliferation and invasion through the secretion of TGF β and matrix metalloproteinases (MMPs). These factors contribute to the remodeling of the extracellular matrix and facilitate the metastatic spread of cancer cells.

M2 macrophages act as key drivers of tumor progression through multiple mechanisms, with epidermal growth factor (EGF) released by M2-simulating tumor-associated macrophages directly promoting cancer cell growth and metastasis.³⁷ The transition from M1-like to M2-like macrophage phenotypes reduces NO and iNOS production in TAMs, leading to the loss of the direct tumor cell-killing effect of M1.³⁸ VEGF secreted by M2-like TAMs promotes angiogenesis at the tumor site. M2 macrophages play a crucial role in suppressing NK cell activity through the secretion of inhibitory factors and direct cell-to-cell interactions.³⁹

In summary, M1-like TAMs exhibit anti-cancer properties by initiating inflammatory responses against tumor cells, whereas M2-like TAMs promote tumor growth through anti-inflammatory activities.

Energy Metabolism of Macrophages

Glycometabolism of Macrophages

TME plays a pivotal role in HCC cell proliferation, infiltration, and spread.⁴⁰ Immune cells are an important component of the TME. Increased infiltration of T cells and NK cells is considered a favorable prognostic indicator, also reflecting the efficacy of immunotherapy in the management of hepatocellular carcinoma.⁴¹ Concurrently, accumulating evidence suggests that the metabolic activity of TME cells, including immune cells, plays a crucial role in regulating cancer development.⁴² In the tumor microenvironment, a competitive struggle often arises between cancerous cells and immune cells, resulting in a metabolic conflict. This intense competition not only promotes tumor progression but also depletes immune cells of essential nutrients, thereby compromising their ability to mount an effective defense against the malignancy.⁴³

Regarding macrophage energy metabolism, M1-type macrophages primarily rely on glycolysis to support their pro-inflammatory functions, whereas M2-type macrophages depend more on fatty acid oxidation and oxidative phosphorylation to sustain their immunosuppressive functions. Although these mechanisms are supported by numerous studies, the specific manifestations and underlying processes of macrophage metabolic reprogramming may differ across tumor types or under varying experimental conditions. Therefore, additional experimental data are required to confirm their generalizability.⁴⁴

Cellular glucose metabolism primarily relies on three central processes: glycolysis, the pentose phosphate pathway, and the citric acid cycle. Glycolysis, a key metabolic pathway, occurs in the cytoplasm. In the presence of oxygen, glucose is metabolized into pyruvate, which then enters the mitochondria to participate in the tricarboxylic acid (TCA)

cycle. However, under conditions of limited oxygen, glucose bypasses the mitochondria and is converted directly into lactic acid, with adenosine triphosphate (ATP) produced as a byproduct.⁴⁵ Pyruvate, resulting from standard glycolysis, undergoes OXPHOS to produce additional ATP.

Nevertheless, when tumor cells are in oxygen-rich conditions, they bypass the TCA cycle entirely, instead favoring glycolysis. This metabolic shift leads to significant glucose depletion within the tumor microenvironment, while simultaneously producing lactic acid as a byproduct. Consequently, these altered metabolic conditions substantially reshape the function of immune cells within the same microenvironment.^{46,47} Glycolysis provides energy to macrophages and other cells at a much faster rate than OXPHOS, while simultaneously supplying essential intermediate metabolites needed for the synthesis of biological macromolecules. Under physiological conditions, unactivated naive M0 macrophages primarily rely on OXPHOS, an efficient energy metabolism pathway, to generate energy. Upon polarization, macrophages dynamically select an appropriate metabolic mode to support functional activity, based on the specific conditions of the TME, as well as their energy requirements and metabolic characteristics.⁴⁸

Metabolic changes in the tumor microenvironment, such as hypoxia and lactic acid accumulation, can subsequently influence the polarization state of macrophages. TAM is the immune cell population with the highest proportion in TME. It consistently exerts an immunosuppressive effect throughout tumor initiation and progression, thereby creating conditions conducive to tumor growth. Conversely, cancer cells exhibit a pronounced reliance on glucose for their energy metabolism. To satisfy the high energy demands required for rapid proliferation, tumor cells competitively consume glucose within the TME and undergo energy conversion via aerobic glycolysis, an efficient energy-producing pathway.⁴⁹ Therefore, the metabolic characteristics of TAMs undergo adaptive changes, shifting to OXPHOS and FAO as the primary metabolic pathways. Their functions subsequently resemble those of M2 macrophages in a low-glucose TME, ultimately resulting in a pronounced immunosuppressive effect.⁵⁰ Even slight variations in environmental cues can lead to significant disparities in macrophage profiles and metabolic characteristics. Under identical stimuli, macrophages may display varying reactivity.⁵¹ TAMs exhibit increased glucose uptake and enhanced glycolytic activity, similar to M1 macrophages, thereby supporting their cytokine profile and functional efficacy.⁵² Proteomic profiling research reveals that macrophages activated with breast cancer patient-derived tumor extracts show enhanced glycosylase expression, particularly of hexokinase 2 (HK2), as indicated in S2. Simultaneously, the export of lactic acid produced through glycolysis in malignant cells into the tumor microenvironment enhances HIF-1 α expression in tumor-associated macrophages, which subsequently increases glycolysis and drives these immune cells toward an M2-like phenotype.⁵³ Additionally, macrophage polarization remains fluid across physiological and bodily pathological conditions. Macrophages can not only reverse their polarization from the M2 to the M1 phenotype, but also co-express characteristics of both M1 and M2 polarization after the tumor reaches a specific stage, resulting in a “mixed polarization state” that exhibits attributes of both phenotypes.⁵⁴ Researchers have identified a novel subset of CD19+ tumor-associated macrophages in hepatocellular carcinoma, with evidence suggesting that glycolysis may be an intrinsic feature driving tumor progression. Notably, a glucose-rich environment can induce macrophage polarization, directing them toward an M2-like phenotype.⁵⁵ Studies have shown that O-GlcNAc modification in TAMs activates the HBP, enhances glucose metabolic flux, and promotes M2 macrophage polarization, thereby accelerating tumor progression and facilitating immune escape.⁵⁶ Tumor cells are more reliant on glucose than immune cells to support their rapid proliferation. This competition for glucose between these cell populations within the tumor microenvironment may, in fact, inhibit cancer progression.⁵⁷ In conclusion, a glucose-rich environment promotes the polarization of macrophages toward the M1 subtype and exerts a tumor-suppressive effect through M1 macrophages.

Macrophages in different polarization states exhibit distinct glucose metabolism patterns. Macrophages activated by IFN- γ and Toll-like receptors (TLRs) generate energy through anaerobic glycolysis. During this process, 6-phosphofructo-2-kinase (PFK2) transitions from the liver-type PFK2 (L-PFK2) to the ubiquitous PFK2 (uPFK2), which subsequently increases PFK2 production, thereby promoting the progression of the reaction. However, the glucose metabolism process of macrophages stimulated by IL-4 is the opposite.⁵⁸ This difference may be attributed to the distinct functions of cells: M1-type macrophages are typically directly involved in combating infections. These cells require rapid bactericidal activity, and the microenvironment at the site of tissue injury is typically hypoxic.⁵⁹ Therefore, anaerobic glycolysis is the most direct and optimal choice to meet the energy needs of M1-type macrophages. M2 polarization links with the

processes of tissue reorganization, restoration, and injury resolution. These activities require a continuous supply of intracellular energy, so aerobic glycolysis is more suitable for meeting the needs of M2 macrophages.⁶⁰ Macrophages contribute to tumor advancement and treatment resistance by supplying nutrients to cancerous cells.⁶¹ Glycolysis in cancerous cells yields lactic acid as an end product. It is essential in signal transduction and facilitates M2-like TAM polarization.⁶² In HCC, the elevated concentration of lactic acid in the tumor microenvironment can promote the development of a pro-tumor macrophage phenotype through the activation of the AKT signaling pathway.^{63,64} Conversely, research confirms M1-type macrophages promote glycolysis while suppressing mitochondrial respiration via the AKT/mTOR/HIF-1 α pathway.⁶⁵ The findings emphasize AKT pathway significance in macrophage M1/M2 transition within HCC.

Metabolic pathways are not only driving factors for macrophage polarization but also potential feedback mechanisms for tumor signals. For example, tumor cells affect macrophage metabolism through lactic acid secretion and HIF-1 α . The accumulation of lactic acid promotes macrophage polarization toward the M2 phenotype, which in turn enhances tumor cell growth and immune escape. This metabolic polarization of macrophages establishes a context-dependent feedback loop that operates within the metabolism-polarization-tumor progression cycle in the tumor microenvironment.⁶⁶

Lipid Metabolism of Macrophages

Under physiological conditions, tumor cells display distinct characteristics of metabolic reprogramming, with fatty acid synthesis and associated metabolic pathways exhibiting abnormal activity. Specifically, the expression levels of key regulatory biocatalysts, such as sterol regulatory element-binding protein (SREBP) and fatty acid synthase (FAS), are significantly upregulated, redirecting cellular metabolism toward de novo fatty acid synthesis to support the energy demands and membrane biosynthesis required for rapid tumor proliferation. It is worth noting that fatty acid metabolites synthesized by tumor cells are released into the TME. These metabolites can reshape the metabolic phenotype of immune cells through various pathways, thereby affecting their functional status and contributing to the formation of the tumor immunosuppressive microenvironment.⁶⁷ Tumor fatty acid metabolites exhibit significant differences in their regulatory effects on macrophages in different polarization states. As M1-polarized macrophages with inflammatory functions, the M1 subtype exhibits a distinct response pattern in this regulatory process. When M1 macrophages uptake excessive unsaturated fatty acids, their intracellular signaling pathways are activated, subsequently stimulating the synthesis and secretion of interleukin-1 α (IL-1 α). As a key pro-inflammatory cytokine, IL-1 α not only directly exacerbates local inflammatory responses but also inversely regulates the metabolic phenotype of M1 macrophages through paracrine or autocrine pathways. This regulation promotes the activation of intracellular fatty acid synthesis pathways, and the enhanced synthesis of fatty acids provides essential support for M1 macrophages to maintain inflammatory functions, such as facilitating inflammatory protein production and preserving cellular membrane integrity, thereby ensuring the effective execution of M1 macrophages' pro-inflammatory actions.⁶⁸ Conversely, the fatty acid metabolism pattern of M2 macrophages differs from that of the M1 subtype. M2 macrophages primarily absorb triglycerides via the CD36 fatty acid receptor on their cellular surfaces. Triglycerides entering the cells are initially broken down by lysosomal acid lipase, and their subsequent metabolism depends on a high level of carnitine palmitoyltransferase 1 α (CPT1 α). CPT1 α , as a key enzyme, facilitates the translocation of fatty acids across mitochondrial membranes and regulates the balance between respiratory and oxidative pathways. This metabolic process also reduces the production of inflammatory cytokines while enhancing fatty acid metabolism to support M2 macrophage function.⁶⁹

Although M1 macrophages predominantly rely on glycolysis for their metabolic processes, intracellular fatty acid levels significantly influence their function. Research has shown that M1 macrophage inflammatory activity requires the involvement of the fatty acid synthesis pathway.⁷⁰ Upon exposure to inflammatory stimuli like LPS and cytokines, M1 macrophages activate and amplify fatty acid synthesis pathways.⁷¹ M2 macrophages specifically mediate immunosuppression through two primary mechanisms: first, by expressing active arginase; and second, by performing S-nitrosylation modifications on the surface proteins of infiltrating T cells.⁷² M2 macrophages exhibit distinct metabolic profiles compared to M1 macrophages. Among these processes, those involved in triggering the glycolysis switch in M1 macrophages are downregulated in M2 macrophages, enabling M2 macrophages to exhibit higher FAO activity. Additionally, their mitochondrial respiratory rate is significantly elevated.⁷³ Reduction of OXPHOS levels significantly

inhibits the polarization of macrophages toward the M2 phenotype, as evidenced by a decrease in the secretion of anti-inflammatory cytokines and a marked reduction in the expression of M2 activation markers.⁷⁴ CPT1 is anchored to the outer mitochondrial membrane, where it plays a crucial role in facilitating the transport of fatty acids across the membrane. It functions as a critical gatekeeper enzyme in the β -oxidation of fatty acids, with its activity ultimately determining the rate of this metabolic process.⁷⁵ In macrophage cell lines, the upregulation of CPT1 α expression not only effectively promotes the FAO process but also significantly reduces the production of inflammatory cytokines.^{76,77} This effect is mediated by two key molecules, STAT6 and PGC-1 β .⁷⁸ Studies have shown that CPT1 deficiency does not affect M2 macrophage polarization, although it inhibits FAO.⁷⁹ In summary, it can be concluded that during M2 macrophage polarization, CPT1, in addition to its well-established role in mediating fatty acid transport, exerts other biological effects through complex mechanisms. Previous studies have confirmed that M2-type macrophages uptake triacylglycerol (TG) substrates via the scavenger receptor CD36, thereby activating the lipolysis process mediated by lysosomal acid lipase (LAL). This research breakthrough has revealed a novel finding: lysosomal lipolysis, occurring within the cell, plays a crucial role in activating M2-type macrophages. This discovery reveals a critical mechanism that activates M2 macrophages, akin to uncovering a hidden lever that triggers a crucial switch. It provides new empirical evidence, offering insights into the complex metabolic processes underlying M2 macrophage activation.⁸⁰

Amino Acid Metabolism of Macrophages

M2-like tumor-associated macrophages display heightened utilization of glutamine and fatty acids, aligning with glycolytic traits.⁸¹ Research indicates GLUL facilitates macrophage M2 polarization through glutamate-to-glutamine conversion.⁸² Therefore, the inhibitory effect on GLUL facilitates the polarization of M2-like macrophages toward the M1-like phenotype. This process is concurrently characterized by increased glycolytic throughput and enhanced succinate availability.⁸³ This phenomenon suggests a metabolic interaction between glucose and glutamine metabolism in the functional regulation of TAMs.⁸⁴ Furthermore, limited availability of α -ketoglutarate inhibits M2 polarization by depleting glutamine during epigenetic reprogramming.⁸⁵

Studies have shown that in environments with high levels of histidine metabolites, the population of macrophages with anti-tumor capabilities—including those associated with heat shock proteins (LA-APO⁺) and those linked to inflammatory responses (Inflam-AREG⁺)—is significantly reduced. In stark contrast, the population of macrophages lacking anti-tumor capabilities or exhibiting immunosuppressive characteristics—such as LA-APO⁺ and tissue-resident RTM-MARCO⁺ macrophages—dramatically increases.⁸⁶ Enhanced histidine catabolic function increases the transcription of genes associated with various metabolic pathways in macrophages. Simultaneously, the anti-tumor activity of macrophages is inhibited, as evidenced by regulatory changes in functional processes, including cellular signaling, signal propagation, growth, cytokine synthesis, and cytokine receptor-mediated responses. The specific metabolic mechanisms of macrophage capabilities such as (Figure 3).

Research on targeting macrophage metabolism for cancer treatment is developing rapidly and showing great application prospects and potential. Macrophages play an important role in the tumor microenvironment; they not only participate in immune surveillance but also play a key role in tumor immune escape, metastasis, and the development of drug resistance. In recent years, relevant clinical trials have been conducted (Table 1), which have demonstrated that targeting the metabolic pathways of macrophages can alter their immune response to tumors and enhance the efficacy of tumor immunotherapy.

Metabolism of Liver Cancer Cells

Hepatocellular carcinoma cells aggressively spread and grow by relying on their aberrantly remodeled metabolic pathways. Compared to normal hepatocytes, hepatocellular carcinoma cells primarily rely on the “Warburg effect” to favor glycolysis for energy production, utilize glutamine catabolism to maintain redox balance, and increase lipid synthesis to meet the demands of membrane expansion.⁸⁷ This “metabolic addiction” not only provides a survival advantage but also represents a key target for intervention. In recent years, the inhibition of energy supply through the targeting of metabolic enzymes has emerged as a prominent area of research (Table 2). The shift in focus from “attacking cellular structures” to “disrupting metabolic homeostasis” in intervention strategies targeting the metabolic vulnerabilities

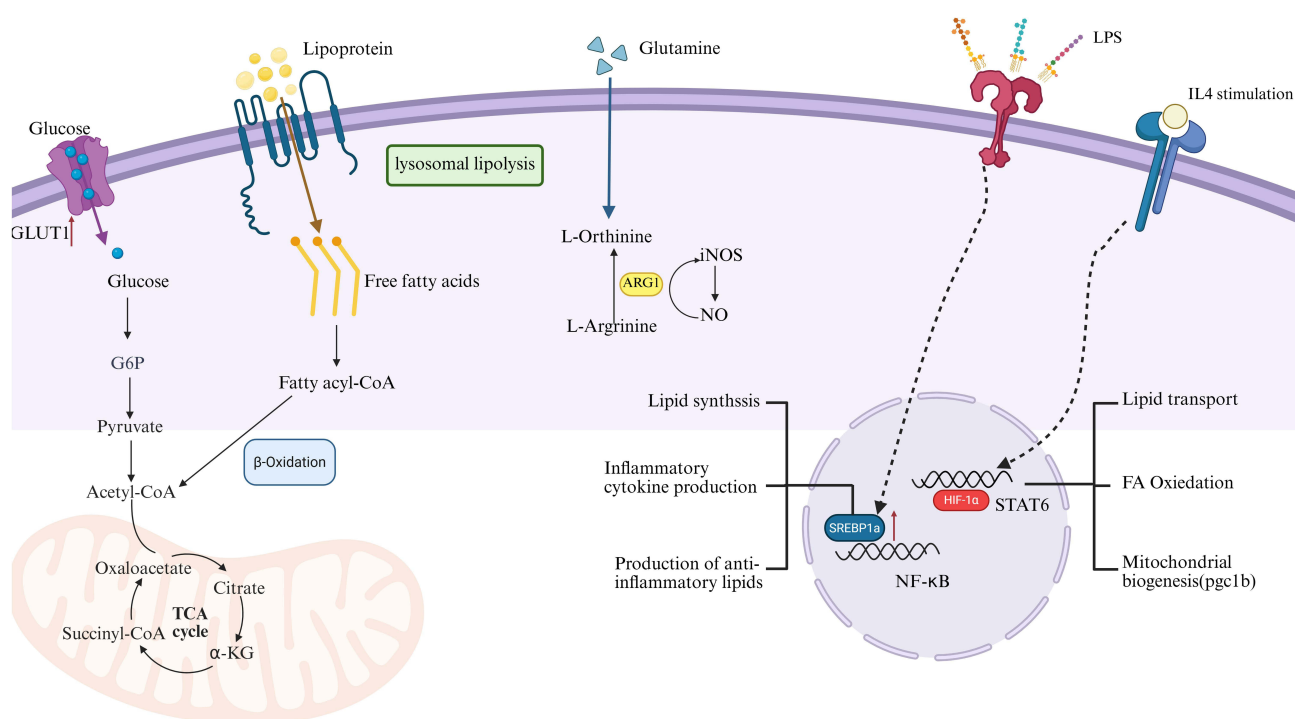


Figure 3 This figure illustrates the key pathways of macrophage metabolism and functional regulation, covering two major dimensions: nutrient metabolism and signal pathway activation. The left side shows the process where glucose, after being transported by GLUT1, participates in glycolysis and the TCA cycle. Meanwhile, lipoproteins generate free fatty acids through lysosomal lipolysis, which then participate in β -oxidation. Glutamine metabolism produces L-ornithine and L-arginine; the latter, catalyzed by ARG1 or iNOS, respectively participates in related metabolism or generates NO. The right side shows that under LPS stimulation and IL4 induction, signaling molecules such as SREBP1, NF- κ B, STAT6, and PPAR- γ are activated, regulating lipid synthesis, pro-inflammatory cytokine production, anti-inflammatory lipid generation, as well as lipid transport, fatty acid oxidation, mitochondrial biogenesis (mediated by pgc1b, for example) and other processes, ultimately affecting the metabolic phenotype and functional polarization of macrophages. The arrows and symbols in the figure represent different metabolic reactions and signaling pathways.

of liver cancer provides a more precise direction for treatment. It also fosters the deeper integration of anti-tumor research, from molecular targeting to metabolic regulation.

The metabolic characteristics of tumor cells, including lactate accumulation and glucose uptake, not only support their growth but also influence the function of immune cells by modifying the metabolic conditions of the tumor microenvironment. Lactate accumulation specifically regulates the metabolic state of macrophages through the GPR81 receptor and HIF-1 α pathway, promoting their polarization toward the M2 phenotype, thereby enhancing the immune escape capacity of tumors. Additionally, competition for metabolic resources occurs between tumor cells and immune cells. Tumor cells preferentially consume glucose and oxygen, resulting in alterations to the metabolism of immune cells and promoting the development of an immunosuppressive microenvironment.⁴²

Glycometabolism of Hepatocellular Carcinoma Cells

During the progression of liver cancer, the typical metabolic functions of hepatocytes, including gluconeogenesis, bile acid (BA) metabolism, detoxification, and urea production (related to ammonia metabolism), gradually diminish. Furthermore, the decline in these functions correlates with the progression of malignant tumors.^{98,99} The stress adaptation and unlimited proliferation of tumor cells are usually highly dependent on the reprogrammed metabolic state. In contrast to typical cells, which primarily rely on OXPHOS for energy, tumor cells preferentially utilize glycolysis for energy production, even under oxygen-rich conditions. This characteristic is known as the “Warburg effect”.¹⁰⁰ Despite the significantly lower energy conversion rate of aerobic glycolysis compared to OXPHOS, its ATP production rate is markedly higher, providing a more efficient energy supply to support the abnormal proliferation of tumor cells.¹⁰¹ Conversely, excess lactic acid produced during aerobic glycolysis can serve as an energy source for surrounding oxygenated cells, thereby fostering a metabolic symbiosis between glycolytic and oxidative metabolism.¹⁰² In addition to glucose metabolism, other key metabolic pathways in the TME

Table 1 Clinical Trials Targeting Macrophage Metabolism for Cancer Treatment and Their Targets

Metabolic Pathway	Targets and Mechanisms	Treatment Methods	Types of Cancer	Clinical Trial Number	Results and Conclusions
Glycolysis	Regulation of macrophage glycolysis through the AMPK/mTOR pathway promotes M1 polarization and enhances anti-tumor immune responses.	Metformin combined with immune checkpoint inhibitors (nivolumab)	Lung cancer, Melanoma	NCT02989153	Preliminary results suggest that metformin modulates macrophage glucose metabolism to enhance anti-tumor immune responses, showing promising efficacy particularly in melanoma and lung cancer, potentially offering an adjunctive treatment option for immunotherapy.
Glycolysis	Inhibition of LDH reduces glycolysis and lactate accumulation, thereby promoting M1 macrophage polarization and enhancing immune responses.	LDH inhibitors combined with immune checkpoint inhibitors (pembrolizumab)	NSCLC, Gastric cancer	NCT04441657	Preliminary data indicate that LDH inhibitors can regulate macrophage glucose metabolism, improve immune function within the tumor microenvironment, and enhance the efficacy of immune checkpoint inhibitors.
Lipid metabolism	Modulation of the FAO pathway alters macrophage polarization, promoting the generation of M1 macrophages and enhancing the anti-tumor activity of the immune system.	FAO inhibitors combined with immunotherapy (nivolumab or pembrolizumab)	Breast cancer, Colorectal cancer	NCT04125666	Preliminary results show that FAO inhibitors significantly alter the metabolic state of macrophages, enhancing the functionality of M1 macrophages. When combined with immunotherapy, they markedly improve anti-tumor immune responses and inhibit tumor growth.
Amino acid metabolism	Inhibition of tryptophan metabolism (via KMO inhibitors) alters macrophage function and enhances anti-tumor immune responses.	KMO inhibitors combined with immunotherapy (pembrolizumab)	Melanoma NSCLC	NCT03990025	Preliminary data suggest that KMO inhibitors regulate macrophage amino acid metabolism to promote immune responses, and when combined with immune checkpoint inhibitors, significantly enhance therapeutic efficacy.
Glycolysis, Lipid metabolism	By combinatorially targeting glycolysis and fatty acid metabolism, the metabolic state of macrophages is modulated, promoting enhanced immune function.	Glycolysis inhibitors + FAO inhibitors combined with immunotherapy (nivolumab)	Liver cancer, Lung cancer	NCT03817133	This study demonstrates that combined inhibition of glycolysis and fatty acid metabolism significantly alters macrophage polarization, enhances M1 function, and improves the anti-tumor efficacy of immunotherapy.

Table 2 Overview of Influencing the Progression of Liver Cancer by Targeting Energy Metabolism

Gene Symbol	Target Gene	Metabolic Type	Mechanism Pathway	Result	References
SRSF10	SRSF10	Glycolysis	SRSF10/MYB/ Glycolysis Axis	(+)	[88]
LINC01554	PKM2	Glycolysis	AKT/mTOR	(-)	[89]
CD36	CD36	Glycolysis	Src/PI3K/AKT/mTOR	(+)	[90]
Orexin A	GLUT1	Glycolysis	PI3K/AKT/mTOR	(+)	[91]
TMEM147	TMEM147	Lipid metabolism	TMEM147/STAT2/DHCR7/27HC Axis	(+)	[92]
RIPK3	RIPK3	Lipid metabolism	ROS-Caspase1-PPAR	(-)	[93,94]
ACADM	SREBP1	Lipid metabolism	CAVI/SREBP1/ACADM Axis	(-)	[95]
SLC6A8	SLC6A8	Amino acid metabolism	JAK-STAT1	(-)	[96]
BUD23	Histidine	Amino acid metabolism	/	(+)	[86]
TFAP2A	NEIL3	Amino acid metabolism	TFAP2A/NEIL3 Axis	(+)	[97]

Notes: (+) indicates oncogenic activity; (-) indicates tumor suppressive activity.

are frequently reprogrammed, triggering a series of changes, including imbalanced nutrient consumption, accumulation of oncometabolites, and dysregulated signaling pathways.^{103,104}

A hallmark of cancerous metabolism is the tendency towards enhanced aerobic glycolysis. Research indicates that the disruption of the AKT/mTOR signaling cascade leads to a significant reduction in aerobic glycolysis within hepatocellular carcinoma cells, thereby effectively inhibiting their proliferation.¹⁰⁵ The development of liver cancer is frequently driven by the activation of the AKT/mTOR signaling pathway, accompanied by increased glycolytic activity during tumor progression. These findings suggest that inhibiting AKT/mTORC1 could be a potential strategy to prevent HCC progression.¹⁰⁶ HCC cell lines exhibit an enhanced Warburg effect, which correlates with increased glucose consumption. Notably, miR-873 activates the AKT/mTOR pathway by suppressing NDFIP1, upregulates glycolytic protein expression, and promotes liver cancer progression and metastasis.¹⁰⁷ The laminin subunit Lamc1 inhibits the expression of PKM2 and reduces the concentrations of GLUT1 and LDHA, thereby suppressing glucose transport and inhibiting the growth of HCC cells. This confirms that the AKT pathway can promote HCC progression by remodeling glucose metabolism.¹⁰⁸ Additionally, as a key downstream molecule of AKT, mTOR activation promotes eIF4E-mediated protein translation by inhibiting eIF4E-binding protein (4EBP1). Consequently, enhancing the integration of GLUT1 into membranes and the function of HK2, thereby reinforcing glucose absorption and metabolic pathways.¹⁰⁹ According to researchers Cui et al, pharmacological agents targeting the AKT and mTOR pathways effectively reduce the migratory capabilities of liver cancer cells, while simultaneously decreasing glucose uptake and lactic acid secretion. Moreover, these compounds have been shown to suppress HK2 expression, strongly suggesting that interrupting the AKT/mTOR signaling cascade impedes cellular motility by effectively inhibiting glycolytic processes.¹¹⁰ Reduced AKT activity induces cell cycle arrest, inhibits glycolytic and TCA cycle metabolism, and consequently suppresses tumor progression.¹¹¹

Glucose metabolism occurs via two concurrent routes: glycolysis and the pentose phosphate pathway (PPP),¹¹² and the metabolic flux of glycolysis can be shunted to the PPP.¹¹³ As a metabolic pathway branching from G-6-P, the first step of glycolysis, the PPP plays a critical role in cancer cell proliferation. Its key enzyme, G6PD, has been shown to be involved in tumorigenesis,¹¹⁴ while activation of the PI3K/AKT signaling pathway enhances G6PD activity, increases cellular metabolic activity, and promotes cancer cell growth.¹¹⁵ Studies have shown that overexpression of G6PD can promote the proliferation of normal hepatocytes,¹¹⁶ while targeted inhibition of G6PD can reduce the growth and survival of HCC cells. Cheng et al demonstrated that the PI3K/AKT signaling pathway interacts closely with PPP metabolism. AKT activation stabilizes G6PD by inhibiting the E3 ligase TRIM21, thereby promoting PPP metabolism. Metabolites from the PPP, in turn, reinforce AKT activation by suppressing its inhibitor PHLDA3, thereby facilitating cancer metabolic reprogramming.¹¹⁷ Furthermore, the extracellular matrix protein Versican V1 enhances the Warburg effect in HCC cells via the EGFR-PI3K-AKT pathway, thereby promoting cell proliferation and metastasis.¹¹⁸ The transmembrane glycoprotein CD36 also promotes mTOR-mediated oncogenic glycolysis by activating the PI3K/AKT signaling axis.⁸⁹

Lipid Metabolism in Hepatocellular Carcinoma Cells

Fatty acids (FAs) serve as key energy sources for cells and also support cell growth and proliferation. In cancer, elevated levels of lipogenesis have emerged as a distinct metabolic characteristic. This is because lipogenesis can work in synergy with lipolysis to jointly promote the growth, proliferation, and survival of tumors.¹¹⁹ Liver cancer is characterized by two significant metabolic features: regulation of the Warburg effect and upregulation of lipid catabolism.¹²⁰ Alterations in lipid metabolism significantly contribute to the development of liver cancer, with excessive lipid accumulation not only promoting obesity but also increasing the risk of HCC. Acetyl-CoA is a central metabolic compound intersecting numerous biochemical pathways and processes. This substance plays a dual role in cellular processes: it serves as a building block for essential macromolecules while actively participating in both the breakdown and synthesis of biochemical compounds. Specifically, it is involved in the synthesis of fatty acids, steroids, and various non-steroidal compounds essential for proper cellular function.^{121,122} Acetyl-CoA is derived from multiple sources and can be generated through various metabolic reactions within cells, including those involving glucose, fatty acids, and amino acids. As a key metabolic molecule, its importance is primarily reflected in its diverse functional roles in various cellular processes.¹²³ Firstly, it participates in mitochondrial TCA cycle activity to facilitate energy production; secondly, it acts as a key cellular component in the cytoplasm, contributing to the synthesis of macromolecules such as FA and sterols; third, it functions as an essential nucleocytoplasmic molecule involved in histone acetylation, thereby activating gene expression.¹²⁴ Acetyl-CoA traverses mitochondrial and cytosolic compartments utilizing carnitine as a carrier.⁷⁶ The sources of mitochondrial acetyl-CoA (mAc-CoA) include pyruvate, FAO, and acetic acid, while cytosolic acetyl-CoA (cAc-CoA) is generated from acetic acid, citric acid, and ketone bodies.^{125,126}

Lipid metabolism plays a crucial role in tumorigenesis by serving as an essential energy source, supporting cellular proliferation, and providing metabolic precursors for tumor cell anabolism.¹²⁷ Lipids and sterols fuel tumor development as membrane building blocks.¹²⁸ The liver plays a critical role in energy metabolism, lipid biogenesis, and lipid distribution. Abnormal lipid metabolism is observed in liver cancer cells when activated forms of AKT and Nras are introduced into mouse hepatocytes using a transposon system and hydrodynamic injection.¹²⁹ LncRNA transcribes the micropeptide SMIM30, which is located in the membranes of the endoplasmic reticulum and mitochondria, while LncRNA LINC00998 promotes liver cancer cell growth and motility.¹³⁰ Following the activation of the AKT/mTOR signaling cascade triggered by the CD147 transmembrane glycoprotein, a series of events is initiated that leads to the transcription of key genes involved in fatty acid production, such as fatty acid synthase and acetyl-CoA carboxylase. This sequence of actions ultimately facilitates an increase in fatty acid synthesis within hepatocellular carcinoma cells.^{131,132} The AKT/mTOR/SREBP-1 signaling pathway plays a critical role in the regulation of lipid metabolism in hepatocytes.¹³³ In the HepG2 liver cancer cell line, targeted inhibition of adipogenesis can be achieved by inhibiting AKT.¹³⁴ The promotion of adipogenesis is mediated by the AKT/mTORC1/S6 pathway through both transcriptional and post-transcriptional mechanisms. These mechanisms involve the inhibition of fatty acid synthase ubiquitination by the USP2a deubiquitinase and the disruption of the degradation complexes of SREBP1 and SREBP2.¹³⁵

In addition, the inhibition of ATP-citrate lyase, acetyl-CoA carboxylase, fatty acid synthase, stearoyl-CoA desaturase 1, or SREBP-1, all of which are involved in adipogenesis, reduces proliferation and survival, as well as AKT-dependent cell proliferation.¹³⁶ Celecoxib, a steroidal anti-inflammatory, modulates the COX-2/AKT pathway. By targeting this pathway, it inhibits adipogenesis and effectively suppresses the progression of HCC.¹³⁷ In the oxygen-deprived tumor microenvironment, the AKT/mTOR signaling pathway becomes hyperactivated, leading to abnormal fat production and lipid storage as liver cancer progresses. This process also drives uncontrolled cell proliferation, enhanced cancer cell vitality, and increased angiogenesis.¹³⁸ In quiescent, non-dividing liver cells, the NRF2 transcription factor initiates the expression of growth factor genes, specifically those encoding the platelet-derived growth factor receptor C and EGFR ligands such as transforming growth factor alpha and amphiregulin. These growth factors enhance AKT phosphorylation through paracrine signaling, thereby modulating liver glycogen and lipid metabolism.^{139,140}

Amino Acid Metabolism in Hepatocellular Carcinoma Cells

Glutamine is one of the most abundant amino acids in the human body. Immune and rapidly proliferating cancer cells have significantly higher glutamine demands.¹⁴¹ To sustain bioenergetic metabolism and anabolic processes, cancer cells enhance the metabolic pathways of glucose and glutamine. Significant external carbon sources are directed toward specific metabolic pathways, facilitating the synthesis of key molecules, including DNA, proteins, and lipids, essential for the proliferation of cancer cells.¹⁴² Cells promote tumor growth by utilizing glutamine to activate the PI3K/AKT signaling pathway.¹³¹ Glutamine activates mTORC1 through the mTOR signaling pathway, which can occur via either a Rag GTPase-dependent mechanism or an independent mechanism.¹⁴³ Liver cancer's reliance on glutamine metabolism presents a viable therapeutic target for its treatment.¹⁴⁴

GLS1, a key enzyme in glutamine catabolism, is highly expressed in HCC compared to normal liver tissue. Furthermore, GLS1 correlates with clinical and pathological characteristics as well as poor outcomes in individuals with HCC. The underlying mechanism likely involves the activation of the AKT signaling cascade by GLS1, which promotes HCC cell proliferation.¹⁴⁵ In hepatocellular carcinoma tumorigenesis, glutamine metabolism promotes the activation of the positive feedback loop in the mTORC2/AKT/C-Myc axis. As a result, the expression of glutamine synthetase (GS) increases, and mTORC1 signaling is enhanced. This series of changes ultimately leads to the release of the effect of sirtuin 4 (SIRT4) on glutamate dehydrogenase (GDH).¹⁴⁶ In tumor cells, the PI3K/AKT pathway mediates the N-Myc downstream-regulated gene (NDRG2)-dependent inhibition of c-Myc, which subsequently suppresses the process of glutaminolysis.¹⁴⁷

Saha et al found in their study that tumors presenting elevated basal PI3K/AKT activity would likely respond favorably to amino acid deficiency.¹⁴⁸ Under amino acid deprivation conditions, normal cells are induced to enter a quiescent state, a process that enhances the sensitivity of proliferating cancer cells to tumor-targeted therapies. Meanwhile, the utilization of glutamine is crucial; when glutamine concentration is elevated, it may promote the production of other metabolites, including liver growth-promoting amino acids.¹⁴⁹ Furthermore, following the knockout of NAD(P)H dehydrogenase 1 (Nqo1), the activated PI3K/AKT pathway not only downregulates the expression of glutaminolysis-related genes but also drives hepatocytes to adapt their metabolic processes. Conversely, Nqo1 upregulation hyperactivates PI3K/AKT signaling, thereby accelerating metabolic adaptation.¹⁵⁰ The specific metabolic mechanism of liver cancer cells is shown in the [Figure 4](#).

The Role of Macrophage Polarization and Changes in Energy Metabolism in Anti-Hepatocellular Carcinoma

The liver, long thought of as immune-privileged, houses a vast majority of the body's macrophages 90% to be exact. This diverse group includes liver-specific macrophages, as well as a variety of infiltrating cells, such as the persistent Kupffer cells and transient macrophages that are recruited as needed.^{151,152} Kupffer cells, typically found lining the sinusoidal blood vessels of the liver, originate from two distinct sources: specialized progenitor cells derived from the yolk sac, which establish themselves in the liver during embryonic development, and monocytes from the bone marrow, which are recruited and transformed to maintain the Kupffer cell population.^{153,154}

In the normal liver, Kupffer cells are the predominant component of liver macrophages, comprising a significant proportion of this population and playing a central role. They primarily maintain liver homeostasis by regulating various physiological processes.¹⁵⁵ When external factors invade the liver and induce pathological changes, Kupffer cells are the first to detect these signals and initiate phenotypic differentiation, producing either pro-inflammatory or anti-inflammatory factors. Simultaneously, a wide range of additional macrophages are recruited to the liver. These macrophages exhibit versatility and multifaceted roles similar to those of Kupffer cells, playing a critical role in liver disease pathogenesis.¹⁵⁶

The Role of Glucose Metabolism Between Macrophages and Liver Cancer Cells

Metabolic pathways in TAMs serve as a mechanism for modulating macrophage polarization, with M1 utilizing glycolysis and M2 primarily depending on OXPHOS.^{131,157} Enhancing glucose absorption and redirecting metabolic

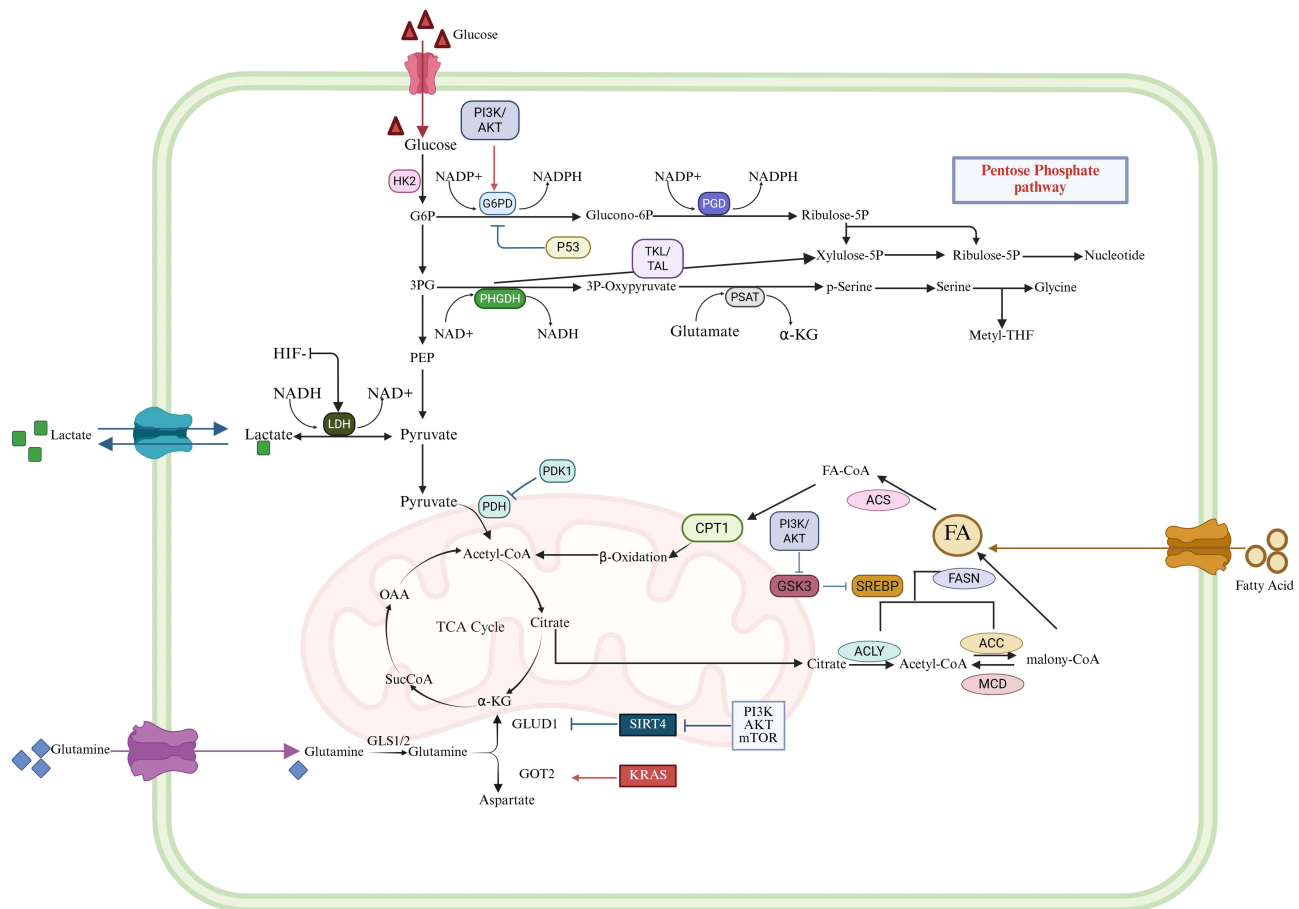


Figure 4 Energy metabolism network of hepatocellular carcinoma cells and their regulatory mechanisms: After glucose enters the cell, part of it undergoes glycolysis to generate pyruvate. Under the regulation of HIF-1 and other factors, pyruvate can be converted into lactic acid by the action of LDH and then excreted from the cell; another part enters the pentose phosphate pathway to generate NADPH and other substances, which provide reducing power and raw materials for biosynthesis and also participate in the synthesis of nucleotides and the like. Glutamine, through the action of glutaminase (GLS1/2) and other enzymes, participates in processes related to the tricarboxylic acid cycle, providing intermediates such as α -ketoglutarate (α -KG) for the TCA cycle, and can also generate aspartic acid and the like. In addition, fatty acids can generate Acetyl - CoA through β -oxidation to enter the TCA cycle, and can also undergo anabolic metabolism under the action of a series of enzymes (such as FASN, etc.). Multiple signaling pathways such as PI3K/AKT and mTOR are involved in regulating these metabolic processes. Meanwhile, molecules like p53, SIRT4, and KRAS also play a role in metabolic regulation, collectively maintaining cellular metabolic homeostasis. These metabolic processes are closely related to physiological functions such as cell growth and proliferation, and they also hold significant importance in metabolic reprogramming in diseases like tumors. The arrows in the figure indicate the transformation and flow direction between metabolites, while the symbols represent different enzymes, pathways, and regulatory factors. Red arrows represent pro-tumorigenic pathways, while blue arrows indicate anti-tumorigenic pathways.

pathways from oxidative phosphorylation to glycolysis effectively reverses macrophage polarization. Research indicates ACCS modifies immune function via macrophages¹⁵⁸ and can also affect biological functions related to metabolism.¹⁵⁹

Under normal physiological conditions, macrophages use OXPHOS as their main metabolic pathway to meet energy demands.¹⁶⁰ However, when macrophages are stimulated by external pathogens, cytokines (such as LPS, IFN- γ , TNF- α , IL-1, IL-4, IL-10), and tumor metabolites, polarization and metabolic reprogramming occur.¹⁶¹ The metabolic profile of M1 macrophages undergoes a shift from glucose-fueled oxidative phosphorylation to glycolysis. This transition is accompanied by increased lactic acid secretion, reduced oxygen consumption, and enhanced glutaminolysis pathways.⁷⁰ In pro-inflammatory macrophages, TCA cycle impairment results in succinate and citrate buildup.¹⁶² The accumulation of these substances effectively inhibits prolyl hydroxylase, a key enzyme that not only regulates HIF-1 α but also promotes IL-1 β production. This cascade subsequently accelerates glycolytic metabolism, further amplifying the inflammatory response.¹⁶³

The metabolic profiles of M2 and M1 macrophages exhibit distinct differences; they have a complete TCA cycle. Activated M2 macrophages not only show a significant increase in oxygen consumption but also primarily rely on oxidative phosphorylation and fatty acid oxidation for metabolic energy production.⁷² M2 macrophage differentiation

similarly relies on glutamine. Glutamine plays a multifaceted role in cellular metabolism, serving not only as an intermediate in the TCA cycle but also as a precursor for lipid biosynthesis. Furthermore, this versatile amino acid serves as a primary nitrogen donor for the synthesis of non-essential amino acids and nucleic acids when required by the cell.¹⁶⁴ T Macrophages undergo metabolic reprogramming, with the core trigger being changes in the TME. Additionally, M1 and M2 macrophages can undergo bidirectional conversion through the regulation of lactic acid and specific cytokines. Within the TME, a competition occurs between liver cancer cells and macrophages, both competing for a limited supply of glucose. To avoid the consequences of this intense competition, M2-like macrophages reduce their glucose metabolism, which results in elevated glucose levels within the TME.¹⁶⁵ Hence, cancerous cells exponentially increase glucose uptake for enhanced energy and proliferation.

Lactic acid, produced by glycolysis, plays a crucial role in signaling within the tumor microenvironment. It induces the polarization of TAMs, promoting the expression of VEGF and driving their differentiation into an M2-like phenotype, thereby influencing cancer progression.¹⁶⁶

In studies on the source of VEGF, Folkman's pioneering work has confirmed the decisive significance of neovascularization for tumor growth. The traditional view generally holds that, in growing tumors, hypoxic cancer cells are the primary source of VEGF. However, research by Oscar et al presents a new perspective: in certain tumor contexts, tumor-associated cells, particularly macrophages, are the primary producers of VEGF.¹⁶⁷ In addition, TAM can also participate in the homeostasis of the tumor microenvironment by regulating nitrogen metabolism: on the one hand, the expression levels of all urea cycle-related enzymes in TAM are higher than those in other tumor cells; on the other hand, the expression levels of its transaminase GPT and GLU1 are also significantly higher, and these two types of enzymes together promote the nitrogen metabolism process.¹⁶⁸

The Role of Lipid Metabolism Between Macrophages and Hepatocellular Carcinoma Cells

Under oxygen-rich conditions, FAO generates more ATP through the TCA cycle than glucose oxidation, making it a critical energy source for cellular growth and function.¹⁶⁹ Cellular lipid accumulation significantly enhances liver cancer cell proliferation, thereby accelerating the progression of HCC. Notably, enzymes involved in the FAO pathway exhibit tumor-suppressive properties in HCC.¹⁷⁰ Enhancing β -oxidation reduces free fatty acid levels in HCC cells, offering a novel therapeutic approach for HCC. M2-like macrophages have different metabolic characteristics from M1-like macrophages. Upon activation by M2-like inducers, such as IL-4, IL-10, and IL-13, macrophages exhibit a marked increase in FAO and OXPHOS, accompanied by a reduced glycolysis rate.¹⁷¹ The PGC1 β signaling pathway regulates these metabolic alterations.¹⁷² In contrast, FAO is significantly reduced in the M1-like macrophage phenotype. Furthermore, nuclear receptors such as PPAR and LXR regulate lipid metabolic pathways,¹⁷³ thereby influencing macrophage polarization. In general, M2-like macrophages exhibit reduced glycolysis, increased fatty acid oxidation, and enhanced oxidative phosphorylation.

Furthermore, previous studies have shown that SIRT4 is involved in lipid metabolic processes. When SIRT4 is knocked out, the expression of FAO-related genes, including peroxisome proliferator-activated receptor δ (PPAR δ), is upregulated in TAMs.¹⁷⁴ When SIRT4 is knocked down in TAMs, the expression of p-STAT3 protein is significantly increased, a change that is critical for the polarization of the M2 phenotype.¹⁷⁵ PPAR δ and PPAR δ -STAT3 axis drive M2-like macrophage differentiation. Conversely, inhibition of PPAR δ reverses the SIRT4 knockdown-induced M2-like polarization.¹⁷⁶ Upon SIRT4 knockdown, the apoptosis of M1-type TAMs is enhanced, resulting in an increased M2-to-M1 ratio in TAMs. Consequently, SIRT4 suppression in macrophages drives M2-like phenotype polarization. The FAO/PPAR/STAT3 pathway elevates the M2/M1 ratio, facilitating HCC advancement. The complex metabolic functions of hepatic macrophages play a critical role in HCC progression and immune modulation. Targeting macrophage metabolism to counteract immunosuppression holds significant potential as a therapeutic strategy for HCC.

OXCT1 serves as a pivotal enzyme in the ketolysis pathway, and its expression level in mature hepatocytes is low. OXCT1 plays a pivotal role in hepatocellular carcinoma cells, particularly under nutrient-limited conditions. The upregulation of this expression enhances the survival of cancer cells, enabling them to withstand stress and continue

proliferating.¹⁷⁷ Studies have demonstrated that the ketogenic gene OXCT1 is highly expressed in tumor-associated macrophages. This elevated expression promotes tumor growth by regulating the reprogramming of these macrophages. For TAMs, both strategic drug interventions and the reduction of OXCT1 gene expression can effectively enhance anti-tumor immunity, inhibit tumor growth, and slow its progression.¹⁷⁸

Elevated TMEM147 expression at both mRNA and protein levels in hepatocellular carcinoma correlates with diminished patient survival.^{91,179} This protein interacts with DHCR7, disrupting cholesterol equilibrium in cells and increasing 27HC concentrations outside HCC cells. Additionally, TMEM147 promotes DHCR7 expression by enhancing the activity of signal transducers and activators of transcription.⁹² Studies have demonstrated that upregulation of 27HC expression in HCC induces an increase in the expression of glutathione peroxidase 4, thereby conferring resistance to ferroptosis and promoting the proliferation of cancer cells.¹⁸⁰ When 27HC produced by liver cancer cells accumulates, it enhances the lipid-processing capabilities of macrophages, activates the peroxisome proliferator-activated receptor γ (PPAR γ) signaling pathway, which subsequently drives macrophages toward the M2 phenotype, thereby enhancing the ability of hepatocellular carcinoma cells to invade and metastasize.¹⁸¹ TMEM147 enables cells to acquire resistance to ferroptosis and promotes M2 macrophage polarization. Cancer progression and metastasis largely depend on the body's ability to maintain cellular cholesterol balance and increase the production of 27HC, thereby creating a favorable environment for tumor development.¹⁸²

Research has confirmed the critical role of RIPK3 in the necroptotic process. Its expression is significantly reduced in liver cancer-associated macrophages, where this modification not only drives cancer progression but also promotes the accumulation and polarization of M2-type TAMs.¹⁸³ From a molecular mechanism perspective, the deficiency of RIPK3 in TAMs leads to a reduction in reactive oxygen species (ROS) and significantly inhibits the caspase-1-mediated cleavage of PPARs.⁹⁴ These outcomes trigger the activation of PPARs, promote fatty acid metabolism, and subsequently induce M2 macrophage polarization within the TME. Additionally, increased RIPK3 expression or inhibited FAO can counteract TAM-mediated immunosuppression and inhibit the progression of HCC. RIPK3 expression is decreased in TAMs from both mouse and human HCC samples. In the absence of RIPK3, the ROS-Caspase-1-PPAR axis enhances FAO in TAMs, promoting their polarization toward the M2 phenotype.¹⁸⁴ Co-culturing TAMs with H22 cells induces RIPK3 knockout, leading to increased lipid droplet accumulation in TAMs. RIPK3 initiates the E3 ligase activity within the pyruvate dehydrogenase complex, thereby increasing anaerobic glycolysis,¹⁸⁵ indicating that RIPK3 influences glucose processing. As the activation of M1 macrophages primarily depends on aerobic glycolysis, RIPK3 may promote glycolysis in macrophages, thereby facilitating M1 polarization and enhancing inflammation. However, most TAMs are of the M2 phenotype, which experience hypoxia and nutrient deficiency (particularly glucose deficiency) in the TME. As a result, they are compelled to adjust their metabolism by enhancing FAO and glutaminolysis to meet their energy demands.^{186,187} This suggests that the deficiency of RIPK3 in TAMs simultaneously promotes fatty acid metabolism and the M2-type activation of macrophages through the ROS-caspase1-PPAR pathway. In summary, the deletion of RIPK3 in TAMs reprograms fatty acid metabolism through the ROS-caspase1-PPAR pathway. This signaling pathway plays a crucial role in regulating the accumulation and differentiation of TAMs into M2 macrophages within the TME, thereby promoting the progression of HCC.¹⁸⁸

The Role of Amino Acid Metabolism Between Macrophages and Liver Cancer Cells

Histidine metabolism plays a critical role in tumor biology. In liver cancer, dysregulated histidine metabolism likely contributes to oncogenesis and facilitates immune evasion.⁸⁵ Histidine metabolism primarily occurs through two pathways: in one, histidine is decarboxylated by histidine decarboxylase to produce histamine, which is subsequently metabolized into imidazole acetic acid; in the other, histidine undergoes transamination to form glutamic acid, which plays a role in energy metabolism.¹⁸⁹

Histidine metabolites, especially histamine, play a critical role in modulating immune responses and the tumor microenvironment. Liver cancer is known to induce alterations in the immune microenvironment. Histamine influences immune cell activities through its various receptors, including H1, H2, H3, and H4. This modulation affects key immune players, such as T cells, B cells, macrophages, and dendritic cells, ultimately shaping the tumor's immune landscape.^{190–192} Furthermore, when histidine is metabolized into byproducts such as uric acid, glutamic acid, and cis-uric acid, these compounds interfere with the immune system, suppressing anti-tumor immunity and allowing cancer cells to proliferate

unchecked.¹⁹³ Histidine metabolism also regulates oxidative stress through metabolites that affect redox conditions, thereby maintaining cellular antioxidant balance.^{194–196} Hepatocellular carcinoma cells often experience high levels of oxidative stress, a condition that promotes tumor cell viability and growth.^{197–200} Thus, targeting histidine metabolism or oxidative stress pathways may provide a promising therapeutic strategy for liver cancer management. Histidine metabolism is closely linked to the energy demands of hepatic cancer cells. By producing glutamic acid, it supports the TCA cycle, thereby regulating hepatic cellular energy metabolism.^{201,202} In liver cancer, metabolic reprogramming increases cellular energy demand,^{203,204} and histidine metabolic processes influence cancer cell growth and lifespan by modulating energy metabolic pathways.

Liu et al demonstrated that in a high histidine metabolome, the number of hepatocytes is significantly increased, whereas the number of immune cells and stromal cells remains relatively low. Additionally, histidine metabolism-related genes are highly expressed in hepatocytes, moderately expressed in macrophages, and minimally expressed in lymphocytes and stromal cells. These findings suggest that the elevation in histidine metabolism is not only associated with the expansion of liver cancer cells but also correlates with a reduced infiltration of immune cells and stromal cells within the TME.⁸⁵

In recent years, single-cell RNA sequencing technology (scRNA-seq) has been widely used to depict the heterogeneity of macrophages in the tumor microenvironment. scRNA-seq analysis has identified macrophage subsets with different functional and metabolic states in non-small cell lung cancer (NSCLC), showing the high diversity and regional differences of TAMs in tumor tissues.²⁰⁵ Similarly, in gastric cancer, researchers characterized tens of thousands of single cells and identified multiple macrophage subsets with different functional characteristics, further confirming the phenotypic diversity of macrophages in different locations within tumors.²⁰⁶ In addition, studies have found that the heterogeneity of TAMs is closely related to their specific localization in the microenvironment, suggesting that spatial factors play an important role in shaping their phenotypes.²⁰⁷

Conclusion

Based on the analysis of macrophage polarization and energy metabolism reprogramming in liver cancer, macrophages play a key role in the progression of liver cancer by altering energy metabolism and activating signaling pathways. Specifically, M1-type macrophages are associated with inhibiting the metabolism and signaling pathways of cancer cells, thereby exerting an anti-tumor effect, while M2-type macrophages promote tumor growth by facilitating energy metabolism pathways. Several potential therapeutic targets mentioned in the article include specific markers on the surface of M2 macrophages, as well as key signaling pathway molecules. For example, the polarization of M2-type macrophages is closely related to the FAO pathway. Nuclear receptors such as PPAR- γ and STAT3 regulate lipid metabolism pathways, and these receptors can serve as targets for intervention. Furthermore, the study also pointed out that interventions targeting the SIRT4, RIPK3, and AKT/mTOR signaling pathways can effectively regulate the polarization state of macrophages, improve the immunosuppressive environment of liver cancer, and inhibit tumor progression. Despite notable advances in this research area, several challenges persist. For instance, interspecies variations in immune system function may compromise the efficacy of targeted therapies. The distinct metabolic profiles and functional characteristics of macrophages across species pose significant limitations to the translational applicability of experimental models. Current metabolic detection techniques, such as mass spectrometry and nuclear magnetic resonance (NMR), are hindered by issues related to sensitivity and quantitative precision, making it difficult to capture the subtle metabolic alterations of macrophages within the complex TME. Furthermore, the metabolic state of macrophages is profoundly influenced by the TME, with significant variability across tumor types and individual patients. This variability introduces considerable challenges for personalized therapeutic strategies, particularly when addressing the intricacies and dynamic nature of metabolic pathways within the TME. Clinical translation is further complicated by issues such as drug targeting and the sustainability of therapeutic interventions. The highly dynamic nature of macrophage metabolism necessitates that therapeutic approaches be both highly adaptable and precisely controllable to achieve optimal efficacy. Future research should combine single-cell technology to explore the functional heterogeneity of macrophages in different tumor regions, investigate the dynamic relationship between metabolic and polarization states, provide new directions for immunotherapy of liver cancer, achieve significant breakthroughs in liver cancer treatment, and bring new hope to the majority of liver cancer patients.

Data Sharing Statement

All data analyzed in this study are included in this paper. All data are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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