Targeting lactylation in hepatocellular carcinoma: Mechanistic insights and therapeutic opportunities (Review)

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Abstract. Hepatocellular carcinoma (HCC) is a malignant tumor characterized by profound metabolic reprogramming and a pronounced Warburg effect, resulting in excessive lactate accumulation in the tumor microenvironment (TME). Traditionally regarded as a metabolic byproduct, lactate has recently been recognized as a substrate for lactylation, offering new insights into tumorigenesis and cancer progression. The present review systematically summarized the molecular basis of lactylation and delineated its regulatory network in HCC. It focused on how lactylation contributes to the malignant phenotype of HCC cells and reshapes the TME, highlighting its roles in tumor progression and metabolic-immune interactions. Based on current evidence, lactylation-related features show potential translational value in the diagnosis, treatment and prognosis of HCC. A deeper understanding of lactylation mechanisms may provide novel insights and strategies for precision therapy in HCC.

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Key words: lactylation, hepatocellular carcinoma, cancer metabolism, tumor microenvironment, clinical translation

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1. Introduction

According to epidemiological statistics from the World Health Organization, primary liver cancer presently claims the lives of ~700,000 individuals each year (1,2). Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75 to 90% of all cases. With a 5-year overall survival (OS) rate of ~18%, its prognosis is often dismal (3,4). Clinical data has shown that only 5-15% of patients with HCC meet the indications for surgical resection at the time of diagnosis, and most of them are early confirmed cases. In addition, <1/3 of patients benefit from current conventional therapies due to characteristics such as tumor heterogeneity and reduced liver regenerating ability (5). As a result, identifying more effective and precise therapeutic strategies has become a central priority in both scientific and clinical research.

Two major discoveries at the intersection of tumor metabolism and epigenetics have generated novel opportunities to elucidate the molecular processes behind HCC: Initially, Otto Warburg's early 20th-century identification of the Warburg effect revealed that tumor cells excessively absorb glucose, even in the presence of oxygen, preferentially converting it into lactate through glycolysis, thereby supplying the necessary materials and energy for accelerated tumor growth (6); subsequently, Zhang *et al*'s (7) pioneering 2019 study first demonstrated that lactate can function as an endogenous precursor for the lysine lactylation (Kla) modification of histones.

Previous studies have established that lactylation is crucial in liver cancer progression by modulating essential biological processes, including liver cancer cell proliferation, augmenting

tumor invasion and metastatic potential, and facilitating immune suppression within the tumor microenvironment (TME) (8-10). Nonetheless, current research demonstrates considerable limitations: On the one hand, research on the mechanisms through which lactylation influences HCC regulation is disjointed, lacking systematic integration from the molecular to the microenvironmental level, hence complicating the establishment of a full knowledge of the regulatory network. Conversely, clinical translational research regarding lactate modification as a diagnostic and prognostic biomarker for HCC, as well as the formulation of focused therapy regimens, is yet nascent, with its potential clinical uses not yet thoroughly clarified (9,11). The present review aimed at systematically clarifying the molecular basis of lactylation, its specific mechanisms in the development of HCC, and its potential applications in the clinical diagnosis and treatment of liver cancer, serving as a reference for future research and clinical translation.

2. Molecular basis of lactylation modification

Chemical nature and conditions for the occurrence of lactate modification. In physiological homeostasis, the liver functions as the principal organ for lactate clearance in the human body, sustaining lactate balance through the glucose-pyruvate-lactate metabolic cycle. In the development of HCC, liver cancer cells are often accompanied by the 'Warburg effect'. This metabolic pattern will significantly increase the production of lactic acid and reduce the clearance ability, leading to a large accumulation of lactic acid within the hepatic TME (9). The buildup of lactate furnishes the necessary substrate for the alteration of proteins by lactate, hence substantially enhancing the likelihood of these modifications taking place.

Lactylation is a recently identified important post-translational modification (PTM). In the context of tissue dynamic metabolic balance, some lactate generated by cells is involved in energy metabolism, while another fraction aids in epigenetic changes and non-histone lactylation processes (12). Specifically, lactylation is a chemical process induced by increased lactate concentrations in the TME, during which lactate groups are preferentially appended to lysine residues on proteins. It has been identified as a fundamental method for HCC cells to acclimatize to metabolic stress and modulate the tumor immunological microenvironment (13).

Key regulatory factors of lactylation. In the process of enzyme-dependent protein acylation modification, there is usually a classic regulatory mode of 'write-recognition-erase': The 'writers' are responsible for transferring the acyl group in acyl-CoA to the side chain of amino acid residues such as lysine, glycine, cysteine or serine in the protein; the 'readers' recognize and bind to the modified amino acid residues through specific structural domains, and initiates the downstream functional effect; the 'erasers' can remove the acyl group on the amino acid residues, so as to realize the dynamic reversible regulation of the modification process (14).

Since both lactic acid and alanine are three-carbon compounds with carboxylic acid groups, their molecular structures are highly similar. The core difference lies only in that alanine contains an amino group (-NH_2), while lactic acid contains a hydroxyl group (-OH). Consequently, it may be deduced that lactylation adheres to the previously indicated 'write-recognize-erase' regulatory framework (Fig. 1). The alteration process is predominantly governed by four principal variables, as indicated by current study advancements (Table I).

Lactate transferases. Lactate transferases function as the principal enzymes that initiate enzymatic lactylation. The presently recognized members predominantly belong to the histone acetyltransferase (HAT) family and the aminoacyl-tRNA synthetase (AALS) family. P300, as a member of the traditional HAT family, was the first identified lactoyl-transferase capable of dynamically modulating histone lactylation levels. Experimental results indicated that the inhibition of p300 function through gene knockdown or pharmacological inhibitors markedly decreases intracellular histone lactylation levels (7,15,16). Subsequent investigations showed that the inhibition of p300/CREB-binding protein (p300/CBP) acetyltransferase activity or the suppression of p300/CBP gene expression in macrophages significantly reduced the lactate-induced lactylation of the high mobility group box 1, indicating that p300/CBP also plays a role in non-histone lactylation (17). Of note, the evidence supporting p300 as a lactylation writer is still largely based on correlative and mechanistic studies, and its substrate selectivity in HCC requires a deeper validation. AALS1/2, functioning as ATP-dependent lactate transferases, specifically recognize and bind lactate through designated domains. Utilizing ATP as an energy donor, they transform lactate into the high-energy intermediate 'lactyl-CoA', subsequently facilitating the lactylation modification of lysine residues in substrate proteins (18-21). HAT binding to ORC1, a member of the MOZ, Ybf2/Sas3, Sas2, Tip60 HAT family, operates as a lactylating transferase. It aggregates at transcription start sites and facilitates carcinogenesis by modulating histone H3 lysine 9 lactylation and oncogene expression (22).

Delactylases. Deacetylases are essential components that sustain the dynamic balance of histone acetylation modifications. Previous studies have preliminarily identified a variety of enzymes with delactylase activity, mainly including members of the histone deacetylase (HDAC) family and members of the silencing information regulator (SIRT) family (23,24). Among them, studies have proved that HDAC1-3 are able to remove the lactylation of histone H3 lysine 18 (H3K18) (24,25), among which HDAC3 has the strongest delactylase activity (26). SIRT2 and SIRT3 are also delactylases, but their activity is markedly lower than that of HDAC3. Zessin *et al* (27) found that the delactylase activity of SIRT2 is several order of magnitude lower than that of HDAC3. However, in general, the identification of delactylases is still incomplete, and their specific role and regulatory network in liver cancer have not been fully clarified. This remains a key area for future research.

Upstream metabolic regulation. The upstream metabolic regulation maintains the balance between lactate production and clearance, hence ensuring a consistent substrate supply for lactylation and acting as a vital upstream regulator. This process is predominantly regulated by two fundamental metabolic pathways: As tumor cells expand fast, the requirement for cellular energy escalates. At this time, lactate dehydrogenase (LDH) becomes a key regulatory enzyme of metabolic flux.

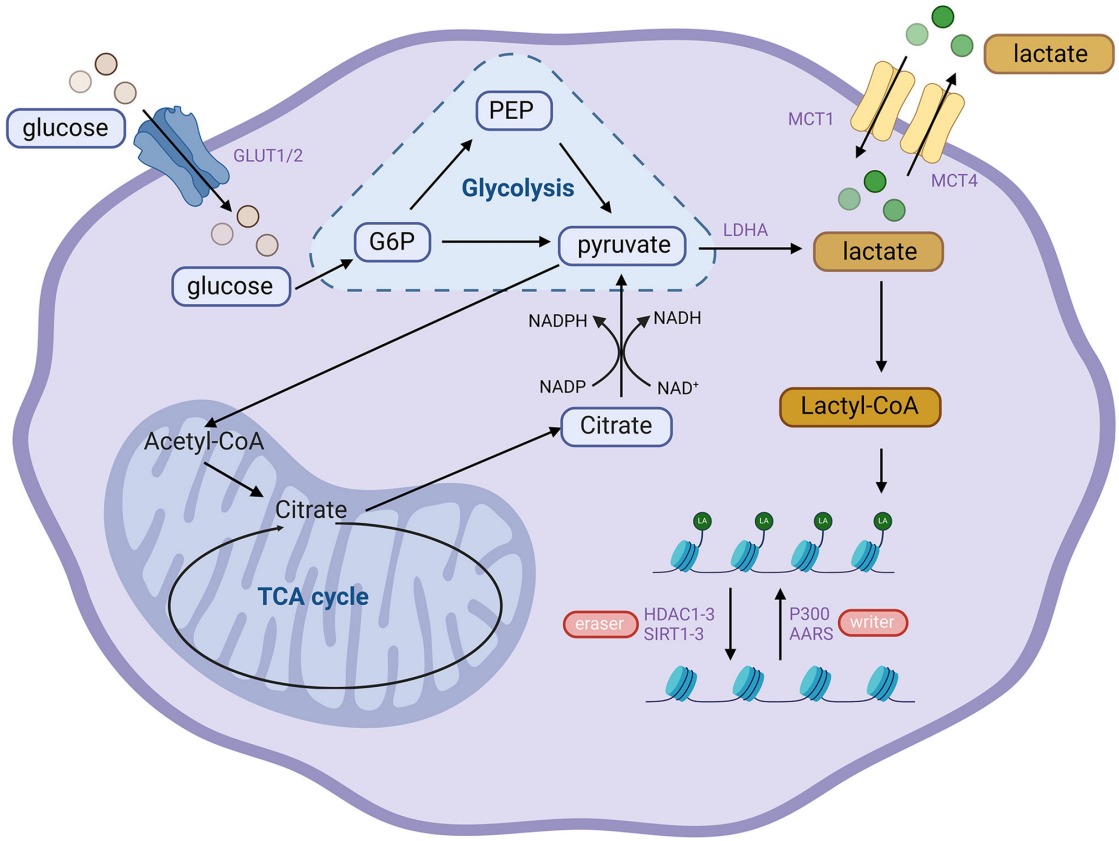

Figure 1. Molecular regulatory network of lactylation. HDAC, histone deacetylase; TCA, tricarboxylic acid; LDH, lactate dehydrogenase.

Under the catalysis of LDH, pyruvate is reduced to lactate, providing a core substrate for lactylation (28-30). In contrast to the role of LDH, pyruvate dehydrogenase (PDH) can catalyze the oxidation and decarboxylation of pyruvate to generate acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle for complete oxidation and energy supply. This procedure diverts pyruvate from the lactate generation pathway, facilitating indirect lactate clearance. The PDH-catalyzed process is irreversibly functioning as a critical 'shunt valve' that preserves intracellular lactate homeostasis (31).

In addition to LDH and PDH, the polyol pathway constitutes a metabolic branch that indirectly modulates the intracellular lactate pool available for lactylation. Under the hyper-glycolytic conditions in HCC, aldose reductase (AR) competes directly with the glycolytic pathway for the glucose (32). This competitive metabolic shunting effectively diverts glucose flux, thereby limiting pyruvate availability and the subsequent generation of lactate (32,33). Through this mechanism, elevated AR activity functions as a metabolic gate that attenuates intracellular lactate accumulation and constrains the substrate supply for downstream Kla. Concurrently, the consumption of NADPH by AR may further perturb the redox environment required for the optimal function of lactylation regulatory enzymes (34). Therefore, the polyol pathway represents an indirect upstream modulator that governs lactylation substrate availability in HCC.

Readers. Readers bind lactylated lysine residues and mediate downstream transcriptional regulation. Recent studies have identified several candidate readers. Brahma-related gene 1 (BRG1), a core subunit of the SWItch/sucrose non-fermentable chromatin-remodeling complex, recognizes histone H3 lysine 18 lactylation (H3K18la) and promotes transcriptional activation through chromatin remodeling (35). Double PHD fingers 2 preferentially binds H3K14la and facilitates tumor-associated gene expression, linking lactylation to oncogenic transcriptional programs (36). In addition, the bromodomain-containing protein tripartite motif-containing 33 can directly recognize lactylated lysine residues, suggesting that canonical acetyl-lysine reader domains may also accommodate lactylation (37). However, the number of identified lactylation readers remains limited, and their functional roles in HCC require further investigation.

3. Lactylation and HCC development

Lactylation plays a crucial role in the development, progression and treatment resistance of HCC. This chapter focuses on how lactylation drives the malignant phenotype of HCC through multidimensional pathways and explains its underlying molecular mechanisms in detail (Fig. 2).

Regulation of malignant phenotypes in HCC cells. Lactylation is essential for maintaining the equilibrium between proliferation and death in HCC cells. Research has shown that Kla of cyclin E2 (CCNE2) accelerates cell cycle progression and promotes HCC cell proliferation. This process is governed by SIRT3. Honokiol (HKL), acting as an activator of SIRT3, enhances the delactylase activity of SIRT3 toward CCNE2, which induces apoptosis in HCC cells and suppresses tumor growth *in vivo* (50). Lactylation at the K124 location of centromeric protein A similarly enhances its transcriptional

Table I. Key regulators and mechanisms of lactylation in tumors involving three enzyme categories.

Authors, year	Category	Key factor	Mechanism	Tumor-associated function/ phenotype	(Refs.)
Zhang *et al*, 2019; Cui *et al*, 2021; Ogryzko *et al*, 1996; Narita *et al*, 2021; Chen *et al*, 2022; Li *et al*, 2024; Wang *et al*, 2023	Lactyl-transferases	p300	1. Utilizes Lactyl-CoA as a donor to catalyze lactylation modification of histone lysine residues. 2. Induces non-histone lactylation	1. Overexpressed in pancreatic ductal adenocarcinoma, lung cancer, and other cancer cells, activating oncogene transcription and inducing cancer cell proliferation, metastasis, immune evasion, and drug resistance. 2. Induces lactylation of transcription factor YY1, promoting angiogenesis	(7,15, 38-42)
Ju *et al*, 2024; Zong *et al*, 2024; Li *et al*, 2023; Chen *et al*, 2022; Liu *et al*, 2023; Zhu *et al*, 2022		AARS1/2	1. Catalyzes the formation of 'lactic acid-AMP' and transfers the lactyl group to lysine residues. 2. Directly binds to lactate and catalyzes global lysine lactylation	1. AARS1 is significantly overexpressed in cancers such as gastric cancer and duodenal cancer and negatively correlates with patient survival rates. 2. AARS1 mediates p53-specific lactylation, promoting tumor progression. 3. AARS2 is highly expressed in colorectal cancer, HCC, and colorectal adenocarcinoma, and is closely associated with poor patient prognosis and reduced survival. 4. AARS2 participates in mTOR signaling pathway and the cell cycle, promoting the proliferation and migration of HCC cells	(19,20, 43-46)
Niu *et al*, 2024		HBO1	Essential for catalysing histone H3K9 lactylation at transcription start sites	Regulated H3K9la promotes key signaling pathways and tumorigenesis processes	(22)
Moreno-Yruela *et al*, 2022; Ishihama *et al*, 2007; Eichner *et al*, 2023; Wang *et al*, 2020	Delactylases	HDAC1-3	1. Possess deacetylase activity, removing acetylation modifications from histone H3/H4. 2. HDAC3 exhibits the strongest activity	1. In colorectal cancer, HDAC1 downregulation indirectly promotes Treg-mediated immunosuppression. 2. In NSCLC, HDAC3 deficiency will maintain H3K18 lactylation at the PD-L1 promoter, leading to an upward regulation of the immune checkpoint	(24, 47-49)
Jin *et al*, 2023; Zu *et al*, 2022		SIRT1-3	Deacetylates histone and non-histone substrates	1. SIRT2 removes H3K18la/H4K8la. 2. SIRT3 removes histone acetylation at K348 of cyclin E2, promoting apoptosis and inhibiting tumor cell proliferation	(50,51)
Yao *et al*, 2023; Comandatore *et al*, 2022; Jena *et al*, 2022; Hu *et al*, 2025; Huang *et al*, 2026	Upstream Regulatory Network	LDH	LDHA preferentially reduces pyruvate to lactate and regenerates NAD+. 2. LDHB oxidizes lactate to pyruvate	1. Dysregulated LDH levels, characterized by LDHA overexpression and LDHB downregulation, typically promote tumor proliferation. 2. The level of LDH in serum is related to the prognosis of the tumor and can be used as a biomarker for the efficacy of anticancer treatment	(29,30, 52-54)

Table I. Continued.

Authors, year	Category	Key factor	Mechanism	Tumor-associated function/ phenotype	(Refs.)
Jha *et al*, 2016; Bennis *et al*, 2020; Arce-Molina *et al*, 2020		PDH	Catalyzes the oxidative decarboxylation of pyruvate to produce acetyl groups, which enter the tricarboxylic acid cycle for complete oxidation and energy production	By indirectly reducing lactate levels, it may decrease the likelihood of lactylation	(55-57)
Schwab *et al*, 2025; Liu *et al*, 2026; Liu *et al*, 2026		AKR	1. Enhances glycolytic flux and promotes lactate production via the AKT/mTOR signaling axis. 2. Induces CD8+ T-cell dysfunction	1. Promotes the proliferation, antioxidant defense, and malignant transformation of HCC cells. 2. Establishes an AKR1B10-Lactate-LDHA amplification loop that mediates resistance to Lenvatinib. 3. Reshapes TME, reduces the efficacy of immune checkpoint inhibitors	(58-60)
Miranda-Gonçalves *et al*, 2021; Payen *et al*, 2020; Singh *et al*, 2023		MCT1/MCT4	1. MCT1 primarily facilitates the influx of extracellular lactate into cells. 2. MCT4 primarily transports intracellular lactate out of cells	1. In LAC, colorectal adenocarcinoma and cervical squamous cell carcinoma, inhibiting or silencing MCT1 can inhibit tumor growth. 2. In tumors such as melanoma, glioblastoma and non-small cell lung cancer, high expression of MCT1/4 is associated with poor prognosis	(61-63)
Clem *et al*, 2008; Feng *et al*, 2018; Basheeruddin and Qausain, 2024; Gordan *et al*, 2007; Dang *et al*, 2011		HIF-1α	1. Induces LDHA gene expression and suppresses LDHB gene expression. 2. Accelerate glycolysis to enhance pyruvate production. 3. Induce PDK-1 to inhibit PDH-mediated mitochondrial pyruvate metabolism	HIF-1α is a key transcription factor maintaining high glycolytic activity in cancer cells	(64-68)
Mossmann *et al*, 2018; Allen *et al*, 2016		mTOR	1. Increases HIF-1α and c-Myc expression to promote lactate production in cancer cells. 2. Mediates lactate shuttling induced by certain substances in PanNET	Induces Lactylation by indirectly increasing cellular lactate content	(69,70)
Hu *et al*, 2024	Readers	Brg1	Recognizes H3K18la at promoter regions	1. Promotes transcriptional reprogramming during cell fate transition; 2. Enhances tumor progression by activating oncogenic gene expression programs	(35)
Zhai *et al*, 2024		DPF2	1. Specifically binds H3K14la through PHD finger domains; 2. Recruits transcriptional regulatory complexes to target gene promoters	1. Activates tumor-associated transcriptional programs; 2. Contributes to cancer cell proliferation and tumor progression	(36)

Table I. Continued.

Authors, year	Category	Key factor	Mechanism	Tumor-associated function/ phenotype	(Refs.)
Nunez *et al*, 2024		TRIM33	1. Recognizes lactylated lysine residues via bromodomain; 2. Binds modified histones to regulate chromatin accessibility	1. Participates in transcriptional regulation associated with tumor development; 2. Suggests functional extension of acetylation reader domains in cancer	(37)

P300, E1A-binding protein p300; AARS1/2, alanyl-tRNA synthetases 1/2; HBO1, histone acetyltransferase dinding to ORC1; HDAC1-3, class I histone deacetylases 1-3; SIRT1-3, silent mating type information regulation 2 homolog 1-3; LDH, lactate dehydrogenase; NAD+, nicotinamide adenine dinucleotide; AKR, aldo-keto reductase; PDH, pyruvate dehydrogenase; MCT, monocarboxylate transporter; HIF-1α, hypoxia-inducible factor 1α; PDK-1, pyruvate dehydrogenase kinase-1; mTOR, mechanistic target of rapamycin; Brg1, Brahma-related gene 1; DPF2, double PHD fingers 2; TRIM33, tripartite motif containing 33; HCC, hepatocellular carcinoma.

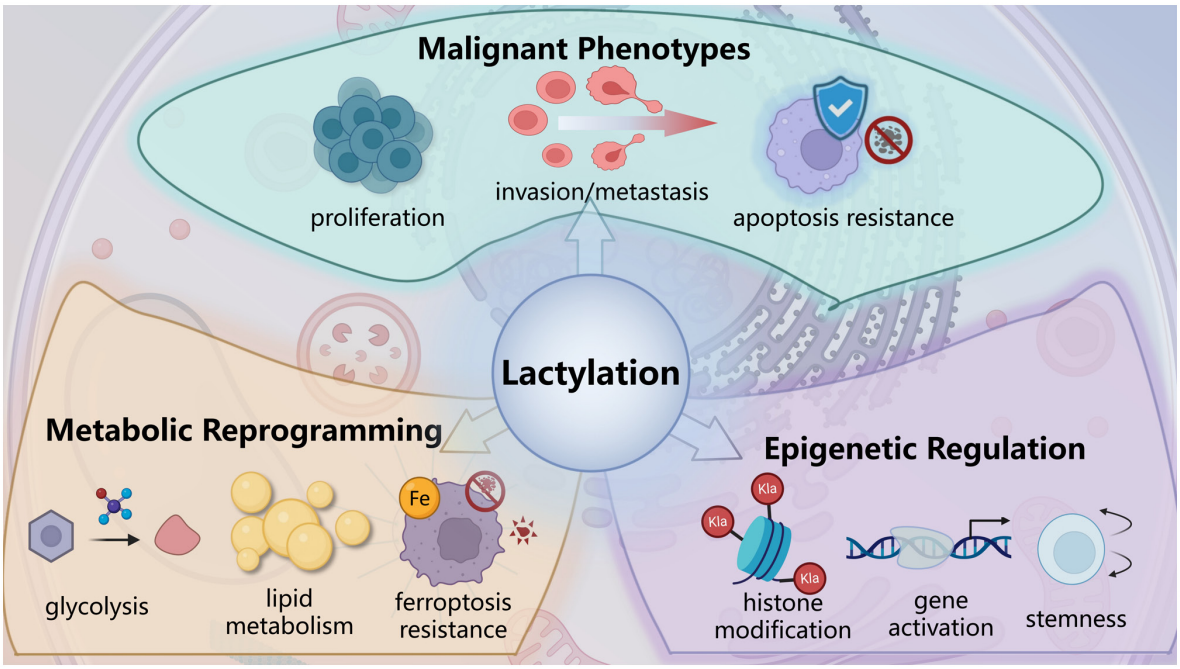

Figure 2. Impact of lactylation on the pathogenesis and progression of hepatocellular carcinoma.

regulatory function. This modification synergizes with transcription factor Yin Yang 1 to promote mitosis and proliferation in liver cancer cells (71). In addition, certain natural substances can demonstrate anticancer properties by inhibiting lactylation. Demethyl zelasterol and royal jelly acid can reduce the level of histone lactylation, thus inhibit the proliferation and migration of liver cancer cells (13,72).

Lactylation can also affect the invasion and metastasis of HCC. Yang *et al* (73) found that the lactylation of AK2 at the K28 site will influence the p53 signaling pathway, thus promoting the proliferation and metastasis of tumor cells through lactomics analysis of hepatitis B virus-related HCC samples. Furthermore, particular lactylation sites of ubiquitin-specific protease 14 and ATP-binding cassette subfamily F member 1 in HCC samples may function as prospective molecular markers for HCC metastasis (74). Of note, insufficient microwave ablation is a contributing factor to HCC progression. Studies reveal that sublethal thermal stress induces elevated lactate levels in HCC cells, accompanied by enhanced histone lactylation, which promotes cell migration and drug resistance, thereby accelerating tumor progression (75). While these findings are compelling, most evidence is derived from *in vitro* or preclinical models, and their physiological relevance in human HCC remains to be fully validated.

Involvement in metabolic reprogramming. HCC cells depend on effective glycolysis to satisfy their accelerated energy requirements for proliferation (76). Lactylation forms a positive feedback loop in this process, promoting HCC initiation and progression. On the one hand, lactate produced by glycolysis provides ample substrate for lactylation. On the other

hand, lactylation, particularly histone lactylation, activates gene expression of multiple key glycolytic enzymes, including hexokinase 2 (77,78), further enhancing lactate production and sustaining high glycolysis.

Meanwhile, lipid metabolism in HCC cells is also significantly reprogrammed to support cell membrane synthesis and energy storage (79). It has been found that in non-alcoholic fatty liver disease, the lactylation of fatty acid synthase at the K673 site inhibits its enzymatic activity, thereby mediating the downregulation of hepatic lipid accumulation by mitochondrial pyruvate carrier (MPC) 1 and reducing lipid accumulation (80). However, in certain cases, lactylation can also promote lipid synthesis. Meng *et al* (81) demonstrated that lactate dehydrogenase A (LDHA)-induced mutations in the H3K18lac gene can increase total cholesterol and triglyceride levels, as well as the expression of fatty acid synthesis-related proteins stearoyl-CoA desaturase 1, fatty acid synthase and sterol regulatory element-binding protein 1, providing material and energy reserves for the rapid growth of liver cancer cells. However, the conclusions are mainly based on specific cell models, and their universality in the complex metabolic environment of the human body still needs to be verified.

Furthermore, lactylation is intricately linked to resistance against ferroptosis. Ferroptosis depends on iron molecules, which is a type of programmed cell death characterized by lipid peroxidation (82). An increasing number of studies have shown that ferroptosis can closely influence the proliferation, metastasis and drug resistance of HCC. It has been demonstrated that following sublethal thermal stress, such as microwave ablation, lactate levels and histone lactylation (particularly H3K18la) are significantly upregulated in HCC cells. Histone lactylation promotes the expression of cysteine desulfurase NFS1, thus enhancing the synthesis of iron-sulphur clusters. Through this step, the resistance of HCC cells to iron death is improved, which ultimately promotes their survival and metastasis (75). This elucidates a novel mechanism through which lactylation modifications impart therapeutic resistance to HCC cells by modulating the ferroptosis pathway.

Epigenetic regulation. In liver cancer cells, enhanced glycolysis leads to a large accumulation of lactates, which acts as a substrate to drive lactylation modification of histones, thereby triggering changes in gene transcription programs related to tumor malignancy. Numerous histone lactylation sites have been shown to be intricately associated with malignant progression in HCC. H3K18la is among the most thoroughly investigated lactylated modifications. It primarily accumulates in the promoter regions of active genes and is considered an activating epigenetic marker (7). Research demonstrates that O-linked β-N-acetyl-glucosamin glycosylation of Y-box binding protein 1 (YBX1), a crucial regulator of glycolysis, stabilizes pyruvate kinase M2 mRNA and increases glycolytic activity, consequently leading to increased H3K18la levels. H3K18la enhances YBX1 expression, creating a positive feedback loop that stimulates metabolic activation and malignant advancement in HCC (83). Furthermore, an elevated histone H3 lysine 56 lactylation (H3K56la) has been demonstrated to be closely associated with the tumorigenicity and stemness maintenance of liver cancer stem cells (LCSCs) (84). In LCSCs, H3K56la levels are significantly upregulated, and its enrichment directly activates the transcription of multiple stemness-related genes, including the oncogene MYC and the pro-angiogenic factor vascular endothelial growth factor A (VEGFA), promoting the self-renewal and tumorigenicity of LCSCs (85). Targeting lactate production or interfering with lactylation can effectively reduce H3K56la levels, thereby inhibiting the malignant phenotype of LCSCs and providing a new target for the treatment of HCC.

The epigenetic regulation of lactylation also transpires through non-histone mechanisms. The chromatin remodeling protein BRG1 has been recognized as a 'reader' for histone lactylation (86). It recognizes and binds to H3K18la-enriched promoter regions, utilizing its ATPase activity to remodel chromatin structure and alter its accessibility. This mechanism enables BRG1 to mediate lactylation-driven transcriptional reprogramming, profoundly influencing cellular pluripotency and tumor progression (Fig. 2) (35). Beyond the aforementioned examples, an expanding repertoire of lactylation targets has been implicated in HCC pathogenesis and therapeutic resistance, which are systematically summarized in Table II.

4. Lactylation and TME in HCC

The TME of HCC is a complex ecosystem comprising multiple components, including cancer cells, blood vessels, immune cells and extracellular matrix (103). Dynamic interaction networks form between cell populations through cell-cell contact, cytokine exchange and metabolic product sharing, significantly influencing tumor immune evasion and progression. Within this environment, lactate functions as both the last result of glycolysis and an essential signaling molecule and immunosuppressive agent (Fig. 3). It remodels the function of a variety of immune cells and promotes angiogenesis through lactate modification. This non-mutant epigenetic reprogramming and phenotypic plasticity is a fundamental driver of malignancy and provides a broader conceptual basis for how lactylation promotes HCC progression (104).

Regulation of the immunosuppressive microenvironment

Augmenting the immunological capabilities of regulatory T cells (Tregs). Tregs are a crucial cell type that sustains immunological tolerance and inhibits antitumor immune responses, with their differentiation and function significantly influenced by the tumor metabolic environment (105). In the high-lactic acid, low-glucose microenvironment of HCC, Tregs actively absorb lactate through the pronounced expression of monocarboxylate transporter 1 (MCT1). They convert lactate to pyruvate, which then enters the TCA cycle to support mitochondrial oxidative phosphorylation (OXPHOS) energy production. This allows Tregs to sustain functional stability amid metabolic stress and assume a predominant role within the tumor immunosuppressive network (106,107). Watson *et al* (106) conducted research indicating that the Treg-specific deletion of MCT1 markedly diminished lactate absorption and immunosuppressive function, hence reinforcing the essential role of lactate metabolism in Treg homeostasis. However, the complete mechanism by which it regulates immunosuppressive molecules in the complex TME still needs further investigation.

Gu *et al* (108) found that in the HCC model, the lactate produced by tumor cells, when absorbed by Tregs, causes the

Table II. Summary of lactylation targets and molecular mechanisms in HCC.

Authors, year	Target protein	Site/Mark	Molecular mechanism	(Refs.)
Wei *et al*, 2025	YAP	K102	Antagonizes Ser127 phosphorylation, inducing YAP dephosphorylation and nuclear translocation/activation.	(87)
Wang *et al*, 2024	YAP	K90	Impairs binding with exportin CRM1, leading to YAP nuclear sequestration and persistent activation.	(88)
Hong *et al*, 2025	ABCF1	K430	Binds KDM3A promoter to activate HIF1A signaling.	(89)
Lu *et al*, 2024	IGF2BP3	K76	Strengthens affinity for m6A-modified PCK2/NRF2/FSP1 mRNAs; drives Lenvatinib resistance.	(90)
Han *et al*, 2025	ASH2L	K312	Recruits MLL1 complex to VEGFA promoter, stimulating angiogenesis.	(91)
Jiang *et al*, 2025	Rab7A	K-site	Inhibits GTPase activity, facilitating MVB trafficking toward the plasma membrane to boost exosome release and lung metastasis.	(92)
Sun *et al*, 2026	ABHD6	K245	Triggers mitochondrial translocation and competitive binding to FIS1, inhibiting mitochondrial fission and apoptosis	(93)
Li *et al*, 2026	PGAM1	K251	Regulates a ubiquitination-lactylation switch mediated by JOSD1-AARS1, stabilizing PGAM1 to fuel glycolysis and suppress T-cell infiltration.	(94)
Liao *et al*, 2023	CENPA	K124	Enhances interaction with YY1 to co-activate CCND1/NRP2, accelerating cell cycle progression.	(71)
Liu *et al*, 2025	MVP	H3K18la	H3K18la activates MVP transcription; MVP inhibits PD-L1 degradation to drive immunotherapy resistance.	(95)
Chen *et al*, 2026	KIF20A	H3K18la	Directly activates KIF20A transcription, stabilizing c-Myc and enhancing PD-L1 expression.	(96)
Ye *et al*, 2024	GP73	H3K18la	H3K18la collaborates with c-Myc to activate GP73; promotes STAT3 phosphorylation to drive angiogenesis.	(97)
Wei *et al*, 2026	Oncogene network	H3K18la	BRD9 recognizes H3K18la and recruits ncBAF complex to drive oncogenic chromatin remodeling.	(98)
CAI *et al*, 2025	NUPR1	H3K18la	Induces NUPR1 expression in TAMs and suppress ERK/JNK signaling and mediate immunosuppression.	(99)
Cai *et al*, 2024	M2 markers	H3K18la	SRSF10/MYB axis induces H3K18la in TAMs to activate ARG1/CD206 and promote M2 polarization.	(100)
Zou *et al*, 2026	PRC1	H4K12la	H4K12la enriches the PRC1 promoter to maintain expression, accelerating MAFLD-to-HCC progression.	(101)
Xie *et al*, 2026	ADCY5	H4K12la	PDP1 deficiency enhances H3K18la to silence ADCY5 via DNMT1, driving SASP-mediated epithelial-mesenchymal transition.	(102)

HCC, hepatocellular carcinoma; YAP, Yes-associated protein; ABCF1, ATP binding cassette subfamily F member 1; IGF2BP3, insulin like growth factor 2 MRNA binding protein 3; ABHD6, alpha/beta-hydrolase domain containing 6; PGAM1, phosphoglycerate mutase 1; CENPA, centromere protein A; MVP, major vault protein; KIF20A, Kinesin Family Member 20A; GP73, Golgi protein 73; NUPR1, nuclear protein 1; PRC1, protein regulator of cytokinesis 1; ADCY5, adenylate cyclase 5.

lactylation of lysine 72 in the intracellular membrane-organizing extension spike protein (MOESIN) protein (MOESIN lysine 72 lactylation). This alteration increases the binding affinity of MOESIN to the transforming growth factor beta receptor type I, consequently augmenting the transforming growth factor-β/SMAD family member 3 signaling cascade. This facilitates the consistent production of the transcription factor forkhead box P3 (FOXP3) and amplifies the immunosuppressive capabilities of Tregs. The lactic acid accumulated in the TME can be absorbed by Tregs and converted into lactyl-CoA in the cell. As a substrate, it can promote p300/CBP-mediated histone H3 lactate modification (109). These modifications accumulate in promoter regions of genes closely associated with Treg function, particularly the FOXP3 gene, activating the transcription of key immune regulatory genes such as FOXP3, and thereby reinforcing the immunosuppressive phenotype of Tregs (110).

Promoting M2 macrophage polarization. Tumor-associated macrophages (TAMs) constitute a significant population of immune cells within the HCC TME, serving a pivotal function

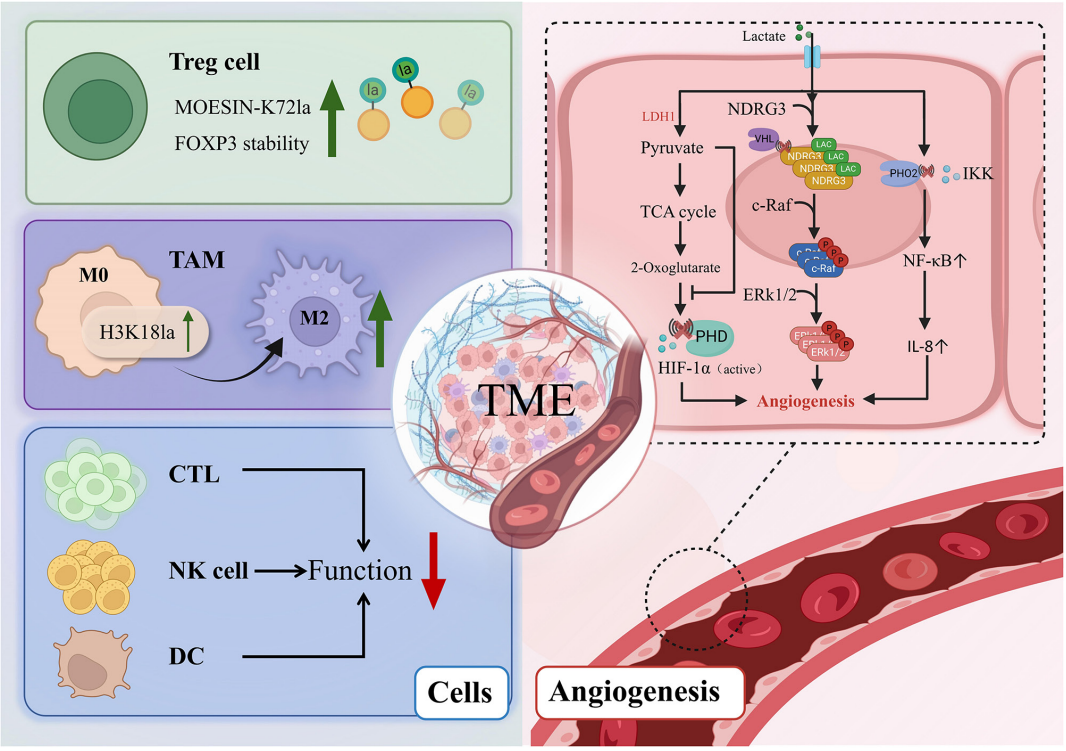

Figure 3. Lactylation promotes tumor progression by regulating the TME. TME, tumor microenvironment; TAM, tumor-associated macrophage; CTL, cytotoxic T lymphocyte; DC, dendritic cell; NK cell, natural killer cell; NDRG3, N-Myc downstream regulatory gene 3; HIF, hypoxia-inducible factor; TCA, tricarboxylic acid; LDH, lactate dehydrogenase.

in tumor initiation, development and immune evasion. TAMs can be traditionally classified into pro-inflammatory, anti-tumor M1-type and anti-inflammatory, pro-tumor M2-type based on their functional and phenotypic properties (111). In the TME of HCC, macrophages exhibit significant plasticity. After being regulated by signals such as tumor cell metabolites, hypoxia and cytokines, most are induced to polarize into the pro-tumor M2 TAMs (112). Clinicopathological analysis has shown that, in HCC tissues, the high infiltration of M2 TAMs (cluster of differentiation $CD206^+$ or $CD163^+$) is closely associated with tumor invasiveness, angiogenesis and poor prognosis (113,114). Numerous evidence has confirmed that high lactic acid accumulation in the TME can induce the polarization of TAMs into the immunosuppressive M2 phenotypes (115). The study by Zhang *et al* (7) first revealed that lactate from tumor cells can be taken up by macrophages through MCTs and mediated by histone Kla under the catalysis of acetyltransferase p300/CBP. This process exhibits a 'lactate clock'-like dynamic amplification, progressively enhancing M2-associated gene expression as lactate accumulates (7). Chromatin immunoprecipitation sequencing analysis showed that H3K18la enriched in the promoter regions of M2-associated genes such as arginase 1 and VEGFA, directly promoting their transcriptional activation and TAM from M1 phenotype to M2 phenotype, enhancing the immune escape of tumors. In addition, lactylation changes enhanced the stability of the M2 phenotype through the regulation of metabolic reprogramming. Lactate increases tumor-associated macrophage reliance on OXPHOS and the TCA cycle (116), further stabilizing the M2-like metabolic phenotype and reinforcing immunosuppressive functions. A recent study highlighted the significant functional heterogeneity of TAMs in HCC. Emerging evidence has suggested that specific subsets, such as $CD48^+$ macrophages, play an irreplaceable role in shaping the immunosuppressive landscape and are priority targets for next-generation immunotherapies (111).

Impact on the functioning of other immune cells. The accumulation of lactate markedly diminishes the anticancer efficacy of cytotoxic T lymphocytes (CTLs). It has been shown that lactate can inhibit the activity of the CTL effect by activating the c-Jun N-terminal kinase/c-Jun signaling pathway. Simultaneously, lactate reduces the release of inflammatory cytokines such as interferon (IFN)-γ and TNF-α, and downgrades the expression of perforin and granzyme B, thus significantly weakening the cytotoxic response mediated by CTL and weakening the antitumor immune response (117).

Natural killer (NK) cells are also strongly inhibited by lactate. Increased lactate concentration in tumor tissues can weaken NK cell function through multiple pathways, including by downregulating the expression of surface-activated receptor NKp46, inhibiting mechanistic target of rapamycin signaling and preventing the nuclear translocation of promyelocytic leukemia zinc finger, thereby reducing metabolic activity and cytotoxicity (76,118-120). In addition, the lactate-mediated acidic environment can also directly induce the apoptosis of liver-resident NK cells, further weakening innate immune defense (76). However, the aforementioned study mainly focuses on the CRLM model, and its universality in HCC still needs further exploration.

Dendritic cells (DCs) are key antigen-presenting cells that bridge innate and adaptive immunity. A recent study has shown that lactate can activate the sterol regulatory

element-binding protein 2 pathway (121). Through the action of Toll-like receptor (TLR), lactate can upregulate IL-10 and inhibit the expression of IL-12, thus hindering the maturation and antigen presentation function of DC. In melanoma and prostate cancer, there are tumor-associated DCs, which are characterized by reduced IL-12 secretion and reduced CD1a expression. Gottfried *et al* (122) found that lactate accumulation can induce this DC phenotype (122). Plasmacytoid DCs (pDCs) can produce type I interferon, which promotes tumors to avoid immune attacks. On the contrary, lactate can activate the G-protein-coupled receptor 81 (also known as HCAR1) receptor, induce cytoplasmic Ca^{2+} mobilization and then downgrade the IFN-I, thus weakening its antitumor immune activity (123). In addition, glycolysis functions as the principal energy source for pDC IFN-γ generation upon TLR stimulation; thus, lactate accumulation hinders pDC energy metabolism by obstructing glycolysis, therefore further reducing their antitumor efficacy (124).

Angiogenesis. Lactate is a principal metabolic byproduct in the TME, which functions both as an indicator of active glycolysis and an essential signaling molecule. It promotes angiogenesis through multiple mechanisms, hence endorsing persistent tumor cell proliferation and invasion in hypoxic environments. Depending on whether hypoxia-inducible factor (HIF) is involved, the pro-angiogenic effect mainly involves the following two mechanisms.

HIF-dependent mechanism. In a hypoxic environment, the accumulated lactate can stabilize HIF-1α, thereby enhancing multiple angiogenesis-related pathways and promoting neovascularization. Lactate specifically competes with 2-ketoglutarate for binding and decreases the action of pyruvate dehydrogenase E1 component subunit beta (PDH2) (125). Decreased PDH2 activity inhibits its degradation and then impairs HIF-1α hydroxylation through the PHD2/von Hippel-Lindau pathway, thereby increasing HIF-1α stability (126). Stable HIF-1α can increase the expression of downstream related factors (including VEGFA and basic fibroblast growth factor), which can promote the proliferation of tumor-associated endothelial cells and angiogenesis (127).

HIF-independent mechanism. In addition to stabilizing HIF-1α, lactate can also promote angiogenesis independently of HIF signaling. After entering tumor-associated endothelial cells through MCT1, lactate can activate the NF-κB pathway by inhibiting the hydroxylation of IκB kinase by PDH2, thereby enhancing IL-8 transcriptional expression and promoting angiogenesis maturation and stabilization (128). Furthermore, lactate can also inhibit the PHD2/VHL-dependent degradation of N-Myc downstream regulatory gene 3 (NDRG3) by binding to it, further prolonging the half-life of NDRG3. Under hypoxic conditions, stable NDRG3 and cellular rapidly accelerated fibrosarcoma (C-Raf) jointly activate the Raf-extracellular signal-regulated kinase pathway and promote angiogenesis (129). This constitutes the HIF-independent lactate-NDRG3-C-Raf axis, which is an important compensatory pathway for tumors to maintain blood supply in a hypoxic environment.

In conclusion, lactylation and lactate signaling jointly participate in the multifaceted regulation of HCC angiogenesis, providing a new metabolic target for anti-angiogenic therapy.

5. Clinical translation potential

As research into lactylation deepens, its crucial role in the development and progression of HCC is becoming increasingly clear, providing new directions for clinical diagnosis, prognostic assessment and treatment. By linking metabolic reprogramming with epigenetic regulation, lactylation not only reveals the molecular mechanisms of metabolic adaptation in HCC but also provides a theoretical basis for combined 'metabolic-epigenetic-immune' intervention.

Lactylation as a potential prognostic and diagnostic indicator. Early diagnosis and recurrence prediction of HCC still face significant challenges. Currently, commonly used clinical biomarkers, such as α-fetoprotein, lack sufficient specificity, and therefore new molecular indicators are urgently needed. Zhang *et al* (130) established a dual-purpose model based on lactate-associated genes based on multi-cohort data from The Cancer Genome Atlas (TCGA; https://www.cancer.gov/ccg/research/genome-sequencing/tcga) and Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/). Their analysis showed that specific markers, including basigin, lysine acetyltransferase 2A and zinc finger E-box binding homeobox 1, not only had a strong diagnostic performance (area under the curve of >0.8) in distinguishing between HCC and normal tissue, but also effectively predict patients' response to immunotherapy. Similarly, Luan (131) also conducted related studies. Using single-cell and spatial transcriptomics techniques, they found that multiple histone lactylation-related genes, such as EP300, SIRT2 and LDHA were significantly upregulated in HCC tissues and were associated with $CD8^+$ T cell infiltration, providing a new direction for lactylation-modified radiomics and liquid biopsy. Of note, lactylation modification can also activate gene transcription by remodeling the epigenetic state, promoting cell proliferation, invasion and immune escape (132). In HCC, elevated lactylation-related risk scores are associated with significantly poorer OS and disease-free survival (131). Therefore, detecting serum or tissue lactate levels, LDHA/MCT4 (SLC16A3) expression, and lactylation modification markers may become a new method for predicting the probability of HCC recurrence and progression. Despite the promising diagnostic performance of these gene signatures, the current evidence is predominantly limited by its retrospective nature and heavy reliance on public databases, such as TCGA and GEO. To transition into clinical practice, these markers must undergo rigorous testing in large-scale, multi-center prospective cohorts to account for the high inter-patient heterogeneity of HCC.

However, it is noteworthy that the interpretation of lactylation-related biomarkers in clinical studies can be significantly interfered with by acetylation, as these two PTMs share significant biochemical and regulatory similarities. Structurally, the highly similar physicochemical properties and small mass difference between lactyl and acetyl groups make accurate differentiation using conventional mass spectrometry and antibody-based detection methods difficult (14,26). Both lactylation and acetylation can occur on lysine residues and are catalyzed by overlapping enzyme systems, particularly HATs, such as p300/CBP (7,17,40). Furthermore, members of the HDAC and SIRT families can also function as deacetylases

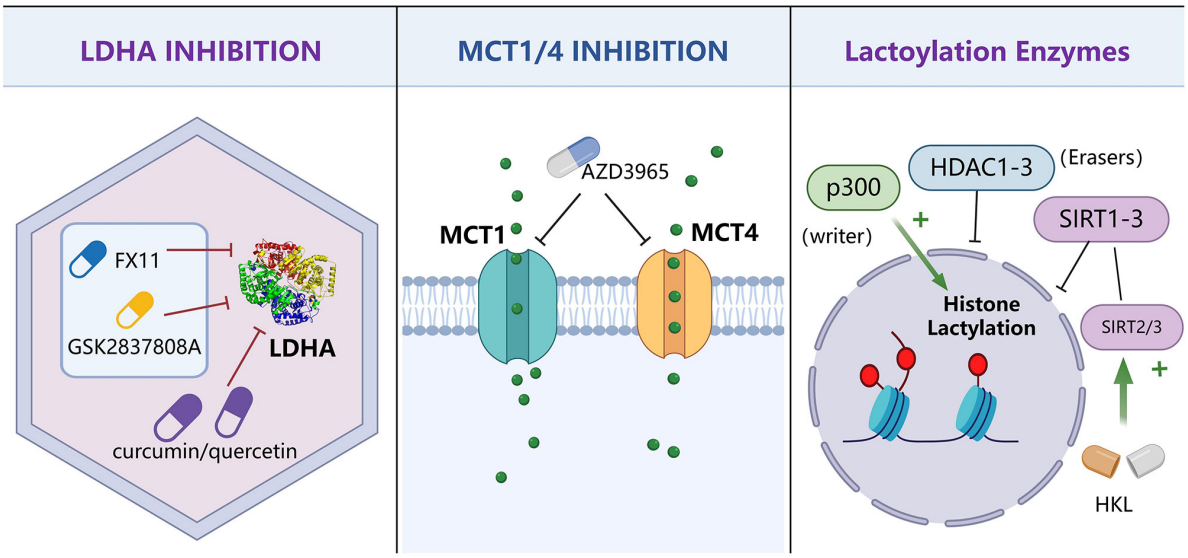

Figure 4. Therapeutic targeting of the lactate-lactylation axis in hepatocellular carcinoma. LDH, lactate dehydrogenase; HDAC, histone deacetylase; MCT, monocarboxylate transporter.

and delactylases, further increasing the overlap in their regulatory networks (24,50,133,134). This leads to signals attributed to lactylation in clinical settings potentially reflecting acetylation or mixed acylation states, reducing the specificity of biomarkers. Therefore, improving detection specificity and developing reliable strategies to differentiate these modifications are crucial steps in advancing the clinical translation of lactylation in HCC.

Therapeutic strategies. In HCC, lactylation can regulate metabolic reprogramming and epigenetic regulation, providing a new theoretical basis and breakthrough point for treatment. There are two types of mainstream treatment methods. The first targets lactate production, efflux and signaling pathways, reducing immunosuppression and invasiveness by inhibiting tumor metabolism. The second regulates the activity of lactylation-related enzymes to intervene in lactate-mediated transcriptional reprogramming and immune escape processes (Fig. 4).

Inhibiting lactate production and transport

Targeting LDH. LDHA is a key enzyme in the Warburg effect, which can catalyze the reduction of pyruvate to lactate. It can be inferred that inhibiting LDHA can effectively reduce the accumulation of lactate, thus inhibiting lactylation in tumors. Studies have shown that the high expression of LDHA is significantly associated with the aggressive enhancement, immunosuppression and poor prognosis of HCC. Some experimental small molecules act as competitive LDHA inhibitors, such as FX11, quinolin-3-sulfonamide derivatives, such as GSK2837808A, and natural product derivatives, such as curcumin and quercetin, have exhibited significant antitumor activity in various cancer models (135). In the HCC model, LDHA inhibitors can inhibit tumor proliferation and reduce the level of histone lactylation, thus reducing the expression of oncogenes such as VEGFA (136). It is worth noting that the excessive inhibition of LDH may disrupt the normal hepatocyte metabolism.

Blocking lactate export and uptake. Lactate is transported between the tumor and its microenvironment through MCTs. MCT1 is responsible for lactate uptake, while MCT4 is involved in lactate efflux. MCT overexpression promotes tumor metabolic symbiosis and the formation of an immunosuppressive microenvironment. AZD3965, the first MCT1 inhibitor to enter clinical trials (NCT01791595), has demonstrated favorable safety and tolerability in a variety of solid tumors (137,138). In HCC cells, MCT1/MCT4 downregulation can prevent lactate efflux and increase the pH value in the tumor, thus restoring the effect of T cells and DCs (139).

Zhao *et al* (136) have reported that MCT inhibitors can significantly reduce PD-L1 expression in HCC models. However, tumor cells usually circumvent MCT1 inhibition by upregulating MCT4 or other compensatory mechanisms. Therefore, simultaneously inhibiting MCT1 and MCT4, or in combination with LDH or MPC inhibitors, is an important strategy to overcome drug resistance.

Targeting lactylation enzymes. Research indicates that the acetyltransferase p300 may act as a potential 'acylation-writing' enzyme, facilitating the acetylation of histone lysine residues (109). A recent study indicated that HDAC1-3 and SIRT1-3 are capable of removing lactyl modifications from both histones and non-histones (131). In HCC models, SIRT3 has been demonstrated to remove lactylation from CCNE2, consequently inhibiting cell cycle progression (50). HKL activates SIRT2 and SIRT3, demonstrating the inhibition of HCC cell proliferation in preclinical studies. Of note, HKL treatment significantly reduced the liver tumor burden in mice without causing pathological damage to the kidneys and spleen (140). However, its actual impact on clinical treatment requires further research.

Combination therapy strategy. Lactate accumulation can promote tumor immune escape, which provides a new opportunity for 'metabolism-immune combination therapy'. A high-lactate environment promotes the polarization of TAMs towards an immunosuppressive phenotype, and influences PD-L1 expression through lactate, consequently reducing the effectiveness of immune checkpoint inhibitors (141).

Furthermore, lactate is closely associated with stem cell-like phenotypes and tyrosine kinase inhibitor (TKI) resistance (142). Numerous studies have demonstrated that lactylation facilitates epithelial-mesenchymal transition and activates pathways associated with drug tolerance (143-145). The combined use of lactylation inhibitors with multi-target TKIs, such as sorafenib or lenvatinib can simultaneously inhibit drug resistance mechanisms at the metabolic and epigenetic levels (146). In addition, combining HDAC inhibitors or DNA methylation inhibitors can synergistically affect the open state of chromatin and further enhance the epigenetic effect of lactylation inhibition (131). These strategies are expected to be key breakthroughs in overcoming the challenges of precision treatment for HCC.

While intervention strategies targeting lactylation in HCC have shown antitumor activity in preclinical studies, their clinical translation still faces two major challenges: Insufficient target selectivity and potential toxicity (147). These drugs often do not only act on tumor cells but may also affect normal tissues. Therefore, lactylation-targeted therapy cannot simply adopt a 'one-size-fits-all' strategy. Taking LDHA inhibitors as an example, although existing studies have confirmed that they can enhance the antitumor effect of drugs such as sorafenib on HCC by inhibiting lactate production and inhibiting tumor cell proliferation (148,149), the direct toxicological evidence on normal hepatocytes is still limited. Considering that the healthy liver undertakes most of the body's lactate clearance function, systemic LDHA inhibition may theoretically interfere with the function of normal hepatocytes, thereby bringing metabolic toxicity risks. Based on this, a more feasible direction in the future could be to combine tumor-targeted delivery, combination therapy, and lactylation feature stratification to improve the therapeutic index and minimize the impact on normal liver tissue.

6. Summary and future perspectives

Lactylation is an emerging research epigenetic modification, which affects gene transcription, factor secretion and cellular phenotypic remodeling through histone and non-histone mechanisms, thus playing a role in the progression of HCC. As our understanding of the regulatory mechanisms of lactylation deepens, an increasing number of regulatory factors are being discovered.

However, several key scientific questions still remain to be addressed. First, the regulatory system of lactylation is not fully defined, including whether tissue- or context-specific enzymes exist. Secondly, the association between lactylation and other acylation modifications, particularly acetylation, requires clarification due to shared substrates and enzymes. Thirdly, the role of lactylation in the TME, especially in immune regulation, remains incompletely understood. Finally, the way to precisely and safely target lactylation in HCC remains challenging, given the essential role of lactate metabolism and the limited clinical validation of related biomarkers. Addressing these questions will be essential for bridging the gap between mechanistic insights and the clinical application of lactylation in HCC.

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Availability of data and materials

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Authors' contributions

XF and QC conceptualized the review. LC and FG wrote the draft of the manuscript. QM reviewed the literature. YL revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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