

## Review Article

## Cancer

# Lactylation: A Pivotal Metabolic-Epigenetic Nexus Driving Hepatocellular Carcinoma Pathogenesis and Therapeutic Resistance

Dengwang Chen<sup>1#</sup>, Xinyue Jiang<sup>1#</sup>, Linna Wei<sup>2\*</sup> , Zudi Meng<sup>3\*</sup> , Dongmei Li<sup>4\*</sup> 

<sup>1</sup>Department of Histology and Embryology, Zunyi Medical University, Zunyi 563000, China

<sup>2</sup>Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xian 710061, China

<sup>3</sup>Department of Blood Transfusion, The First People's Hospital of Guiyang, Guiyang 550002, China

<sup>4</sup>Department of Clinical Laboratory, Guangyuan Central Hospital, Guangyuan 628000, China

\*These authors contributed equally to this work.

## ABSTRACT

Hepatocellular Carcinoma (HCC) remains a formidable global health challenge, characterized by its complex etiology, aggressive progression, and high mortality rates. Metabolic reprogramming is a hallmark of cancer, and lactate, a key end-product of glycolysis, has emerged as more than just a metabolic waste product. Recent groundbreaking research has unveiled lactate's role as a signaling molecule through a novel Post-Translational Modification (PTM) known as lactylation. Protein lactylation, particularly histone lactylation, directly links cellular metabolism to epigenetic regulation, profoundly influencing gene expression, protein function, and cellular phenotypes. In the context of HCC, an increasing body of evidence highlights the widespread and critical involvement of lactylation in various pathological processes, including tumor initiation, progression, metastasis, immune evasion, and therapeutic resistance. This comprehensive review synthesizes the current understanding of protein lactylation in HCC, detailing its intricate mechanisms, diverse functional roles in metabolic repro-

## Correspondence:

Linna Wei, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xian 710061, China, ORCID ID: 0009-0001-5446-8851; Email: weilinna2021@163.com

Zudi Meng, Department of Blood Transfusion, The First People's Hospital of Guiyang, Guiyang 550002, China, ORCID ID: 0000-0001-6512-9794; Email: 3519753404@qq.com

Dongmei Li, Department of Clinical Laboratory, Guangyuan Central Hospital, Guangyuan 628000, China, ORCID ID: 0000-0002-8188-1211; Email: 1113634559@qq.com

Received Dates: December 02, 2025;

Accepted Date: December 18, 2025;

Published Date: December 20, 2025:

Cite this article as: Chen D, Jiang X, Wei L, Meng Z, Li D, Lactylation: A Pivotal Metabolic-Epigenetic Nexus Driving Hepatocellular Carcinoma Pathogenesis and Therapeutic Resistance, *Glob. Open Access J. Sci.*, 2025; 1(3):179-191.



gramming, epigenetic regulation, immune modulation, and its significant implications as a diagnostic, prognostic, and therapeutic target. By elucidating the multifaceted contributions of lactylation, we aim to provide a deeper insight into HCC biology and pave the way for novel therapeutic strategies.

**Keywords:** Hepatocellular Carcinoma; Lactylation; Post-Translational Modification; Lactate; Metabolic Reprogramming; Immune Evasion; Drug Resistance

## INTRODUCTION

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy and a leading cause of cancer-related deaths worldwide (Befeler & Di Bisceglie, 2002; Shan & Jia, 2023; T. Yang et al., 2023). Its development is often linked to chronic liver diseases such as viral hepatitis (HBV, HCV), alcohol-related liver disease, Non-Alcoholic Fatty Liver Disease (NAFLD), and cirrhosis (Caldwell et al., 2004; Di Bisceglie et al., 1988; Ganne-Carrié & Nahon, 2024). The complex etiology and heterogeneous nature of HCC pose significant challenges for diagnosis and treatment (Befeler & Di Bisceglie, 2002). Despite advancements in surgical resection, liver transplantation, and systemic therapies, recurrence rates remain high, and treatment efficacy is often limited by acquired drug resistance (Shimada et al., 1996). A deeper understanding of the molecular mechanisms driving HCC pathogenesis is crucial for developing more effective therapeutic interventions.

Cancer cells exhibit profound metabolic alterations, collectively known as metabolic reprogramming, to support their rapid proliferation and survival (Yin et al., 2025). A prominent feature of this reprogramming is the Warburg effect, where cancer cells preferentially utilize glycolysis for energy production even in the presence of oxygen, leading to increased lactate production (Lin et al., 2022). Historically considered a metabolic waste product, lactate has recently been recognized as a crucial signaling molecule that can regulate various cellular processes, including gene expression, cell proliferation, and immune responses (Li et al., 2022; Lin et al., 2022).

In 2019, a novel post-translational modification (PTM), lysine lactylation (Kla), was discovered, directly linking lactate metabolism to epigenetic regulation (Izzo & Wellen, 2019; Liberti & Locasale, 2019). Lactylation involves the covalent attachment of a lactyl group to

lysine residues on proteins, utilizing lactyl-CoA as a substrate (Liberti & Locasale, 2019). This discovery revolutionized our understanding of lactate's biological roles, demonstrating its capacity to directly modulate protein function and gene expression through epigenetic mechanisms (Izzo & Wellen, 2019; Zhang et al., 2019). Since its identification, lactylation has been found to be widely present across the human proteome and plays critical roles in various physiological and pathological contexts, including cancer (Li et al., 2022; Wan et al., 2022).

In HCC, lactylation has emerged as a significant player, influencing a myriad of cellular processes that contribute to tumor initiation, progression, metastasis, and therapeutic resistance (Zhonghua Wang et al., 2025; Y. Yang et al., 2025; Yin et al., 2025). This review aims to provide a comprehensive overview of the current knowledge regarding protein lactylation in HCC, focusing on its mechanisms, functional implications, and potential as a diagnostic, prognostic, and therapeutic target.

## MECHANISMS AND REGULATION OF PROTEIN LACTYLATION IN HCC

Protein lactylation is a dynamic and reversible PTM that directly links cellular metabolic state, particularly lactate levels, to protein function and gene expression. Its regulation involves "writers" that add the lactyl group, "erasers" that remove it, and "readers" that interpret the lactylation signal.

### Histone Lactylation: An Epigenetic Switch in HCC

Histone lactylation, especially on lysine residues of histones, is a critical epigenetic modification that directly couples metabolic changes to transcriptional regulation (Izzo & Wellen, 2019; Liberti & Locasale, 2019; Yang et al., 2024). It often marks active enhancers and promoters, leading to gene activation, and has been shown to compete with histone acetylation for the

same lysine residues, acting as a “glycolytic switch” (Dai et al., 2021). In HCC, histone lactylation is extensively involved in shaping the tumor’s epigenetic landscape and driving its malignant phenotype (Zhonghua Wang et al., 2025).

#### Specific Histone Lactylation Sites and Their Impact:

**H3K18la:** This specific histone lactylation site has been frequently implicated in HCC progression. It promotes the expression of ESM1, a gene associated with tumor progression (Zhao et al., 2024). Moreover, H3K18la is upregulated after microwave ablation, leading to increased NFS1 transcription, which enhances ferroptosis resistance and promotes HCC metastasis (Huang et al., 2025). PYCR1, an enzyme involved in proline metabolism, has been shown to promote HCC progression by upregulating IRS1 expression through H3K18la (H. Wang et al., 2024). A positive feedback loop involving SRSF10, glycolysis, lactate, and H3K18la drives M2 macrophage polarization, contributing to immune evasion and PD-1 resistance in HCC (Cai et al., 2024). **H2B K58la:** Lactate, mediated by LDHA, drives the lactylation of H2B K58 on NDRG1, contributing to HCC senescence resistance (L. Li et al., 2025). **H3K9la and H3K14la:** These sites are targeted by RJA, a compound that exhibits anti-HCC activity by inhibiting their lactylation (H. Xu et al., 2023). **Histone Lactylation and Stemness:** Histone lactylation promotes MCM7 expression, which is crucial for maintaining HCC stem cell properties and resistance to radiotherapy (Z. Liu et al., 2025).

#### Regulators of Histone Lactylation: Writers

**(Lactyltransferases):** The acetyltransferase CBP (CREB-binding protein) has been identified as a lactyltransferase. It regulates TPX2 lactylation, which in turn enhances AURKA phosphorylation and promotes cell cycle progression in HCC (Shengzhi Liu et al., 2025). While CBP’s direct role as a histone lactyltransferase in HCC is strongly implied by its general function as an acetyltransferase and its involvement in TPX2 lactylation, further direct evidence for its specific histone lactyltransferase activity in HCC is still emerging. **Erasers (Delactylases):** Class I histone deacetylases (HDAC1, HDAC2, and HDAC3) have been identified as histone lysine delactylases (Moreno-

Yruela et al., 2022). High expression of HDAC1/2 is associated with poor prognosis in HCC (Cai et al., 2023), suggesting that their delactylase activity might play a role in HCC progression, although the precise substrates and mechanisms require further investigation. SIRT3, a sirtuin family deacetylase, has also been shown to act as a delactylase, inhibiting HCC growth by delactylating cyclin E2 (Jin et al., 2023). **Modulators:** DML (a small molecule) inhibits H3 lactylation, thereby suppressing HCC stem cells (Pan et al., 2022). Dihydroartemisinin (DHA) reverses the immune-cold microenvironment in HCC by inhibiting YAP1, which in turn reduces histone lactylation (Gao et al., 2025). YBX1 O-GlcNAcylation drives a positive feedback loop involving glycolysis and histone lactylation, promoting HCC (Ji et al., 2025). Liver stellate cells also contribute to HCC development by promoting histone lactylation (Yu et al., 2024).

#### Non-Histone Protein Lactylation: Expanding the Regulatory Landscape

Beyond histones, a growing number of non-histone proteins have been identified as targets for lactylation, significantly broadening the functional scope of this PTM in HCC (Hong et al., 2023; Song et al., 2024). These lactylated proteins are involved in diverse cellular processes, including metabolism, signal transduction, and immune responses.

#### Key Non-Histone Proteins and Their Lactylation in HCC:

**USP14 and ABCF1:** These proteins were among the first non-histone targets identified in the initial lactylation map of HCC (Hong et al., 2023). Their lactylation sites, along with MRPL3, serve as diagnostic indicators for HCC and its metastasis (Wu, 2023). Specifically, ABCF1-K430 lactylation activates the HIF1 pathway, promoting HCC progression (Hong et al., 2025). **MRPL3:** As mentioned, MRPL3 lactylation is associated with mitochondrial function and serves as a novel prognostic biomarker for HCC (Xing et al., 2025). **CA3:** Delactylation of CA3 has been shown to weaken its tumor-suppressive effect by restoring DUOX2 expression (Yan et al., 2024). This highlights that lactylation can also inhibit protein function, and its removal can have oncogenic consequences. **ZNF207 and PRDX1:** ZNF207 drives the lactylation of PRDX1, which in turn activates NRF2, leading to resistance to regorafenib (RGF) and

HES1 pathway, promoting immune suppression in HCC (Zengbin Wang et al., 2025).

**Enzymatic Regulation of Non-Histone Lactylation:**

Writers: CBP is a known lactyltransferase (Shengzhi Liu et al., 2025). PARK7 mediates IGF2BP3-K76 lactylation. ZNF207 drives PRDX1 lactylation (T. Yang et al., 2025). LDHA mediates NDRG1 H2B K58 lactylation (L. Li et al., 2025). Erasers: SIRT3 delactylates cyclin E2 (Jin et al., 2023). Class I HDACs (HDAC1-3) are also delactylases (Moreno-Yruela et al., 2022). Tools for Detection/Prediction: DeepKla is a computational tool for predicting protein lysine lactylation sites (Lv et al., 2022). YnLac chemical reporter genes can be used to detect protein lactylation (Sun et al., 2022). The intricate crosstalk between lactylation drivers, substrates, and downstream oncogenic processes is schematically summarized in Figure 1.

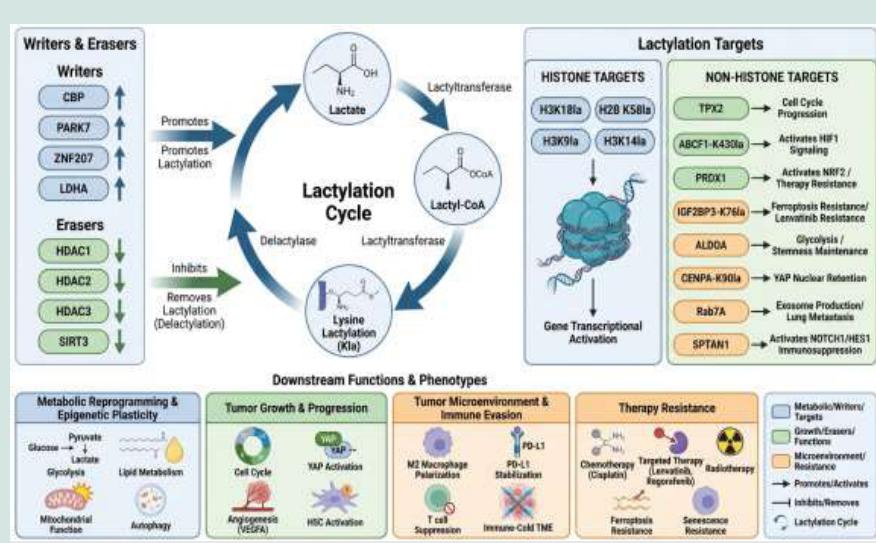
## FUNCTIONAL ROLES OF LACTYLATION IN HCC PATHOGENESIS

Lactylation, by modifying both histones and non-histone proteins, exerts profound effects on various aspects of HCC biology, from metabolic reprogramming to immune evasion and therapeutic resistance.

### Metabolic Reprogramming and Epigenetic Plasticity

Lactylation serves as a core metabolic-epigenetic node connecting metabolic reprogramming and epigenetic plasticity in HCC (Y. Yang et al., 2025; Yin et al., 2025). The abundance of lactate, a direct precursor for lactyl-CoA, directly influences the extent of protein lactylation (Li et al., 2022; Liberti & Locasale, 2019). Glycolysis and Lactate Production: The Warburg effect in HCC leads to increased lactate production, which fuels lactylation (Lin et al., 2022). This creates a positive feedback loop where glycolysis-driven lactate promotes histone lactylation, which in turn can upregulate glycolytic enzymes or related pathways (Cai et al., 2024; Dai et al., 2021; Ji et al., 2025). For instance, GPC3 knockdown inhibits HCC cell growth and glycolysis by reducing lactylation (Yao & Yang, 2023). Lipid Metabolism: Histone lactylation drives YTHDC1, which remodels lipid metabolism to promote HCC (Du et al., 2024). This highlights the intricate interplay between different metabolic

evasion of ferroptosis in HCC (T. Yang et al., 2025). TPX2: As discussed earlier, TPX2 lactylation, regulated by CBP and HDAC1, enhances AURKA phosphorylation, promoting cell cycle progression (Shengzhi Liu et al., 2025). IGF2BP3: Lactylation of IGF2BP3, mediated by PARK7 at K76, promotes lenvatinib resistance in HCC by upregulating FSP1, thereby leading to ferroptosis resistance (Zhu et al., 2025). Another study showed IGF2BP3 lactylation promotes lenvatinib resistance through the PCK2/NRF2-m6A loop (Zhu et al., 2025). AK2: Lactylation at the K28 site of AK2 inhibits its activity, promoting HCC progression (Z. Yang et al., 2023). YTHDC1: Driven by histone lactylation, YTHDC1 promotes HCC by remodeling lipid metabolism (Du et al., 2024). GP73: Activated by histone lactylation and c-Myc, GP73 promotes angiogenesis in HCC through STAT3 signaling (Ye et al., 2024). LDHA: Beyond its role in lactate production, LDHA activates YAP through lactylation, promoting HCC progression (Wei et al., 2025). It also mediates H2B K58 lactylation of NDRG1, driving senescence resistance (L. Li et al., 2025). USP34: Histone lactylation drives USP34 to promote cisplatin resistance in HCC (Fan et al., 2025). GPC3: Knockdown of GPC3 inhibits HCC cell growth and glycolysis by reducing lactylation (Yao & Yang, 2023). SRSF10: As part of a positive feedback loop with glycolysis/lactate/H3K18la, SRSF10 promotes M2 polarization, leading to immune evasion and PD-1 resistance (Cai et al., 2024). CENPA: K90 lactylation of CENPA hinders its binding with CRM1, leading to its nuclear retention and enhanced HCC malignancy (L. Wang et al., 2024). ALDOA: Lactylation of ALDOA inhibits its enzymatic activity (Wan et al., 2022). Furthermore, ALDOA lactylation weakens its interaction with DDX17, enhancing DDX17 function and maintaining liver cancer stem cell stemness (Feng et al., 2024). ASH2L-K312: Lactylation of ASH2L at K312 promotes angiogenesis in HCC by upregulating VEGFA (Han et al., 2025). HECTD2: Lactylation drives HECTD2, limiting the response of HCC to lenvatinib (Dong et al., 2025). Rab7A: Lactate promotes Rab7A lactylation, which in turn enhances HCC exosome production and lung metastasis (Jiang et al., 2025). NUPR1: Lactate drives the upregulation of NUPR1, promoting macrophage-mediated immunosuppression in HCC (Cai et al., 2025). SPTAN1: SPTAN1 lactylation activates the NOTCH1/



**Figure 1:** The molecular mechanism and functional network of lactylation in hepatocellular carcinoma. This schematic summarizes the regulatory axis and functional consequences of protein lactylation in HCC. The lactylation cycle (center) depicts how lactate is converted to lactyl-CoA to drive lysine lactylation (Kla). The process is regulated by writers (e.g., CBP, PARK7, ZNF207) and erasers (e.g., HDAC1–3, SIRT3). Lactylation targets include histone sites (e.g., H3K18la, H2B K58la) and non-histone proteins (e.g., TPX2, ABCF1, IGF2BP3, ALDOA, Rab7A, SPTAN1). These modifications collectively drive four key aspects of HCC biology: ① Metabolic Reprogramming & Epigenetic Plasticity, ② Tumor Growth & Progression, ③ Tumor Microenvironment & Immune Evasion, and ④ Therapy Resistance. Arrows indicate promoting effects; blunted lines indicate inhibitory effects. Abbreviations: HSC, hepatic stellate cell; TME, tumor microenvironment.

pathways regulated by lactylation. Mitochondrial Function: MRPL3, a mitochondrial ribosomal protein, is a lactylated protein whose lactylation is related to mitochondrial function and HCC prognosis (Xing et al., 2025). This suggests a role for lactylation in regulating mitochondrial activity, which is crucial for cancer cell bioenergetics. Autophagy: Lactate connects glycolysis with autophagy through lactylation, indicating a broader role in cellular homeostasis and stress responses (Sun et al., 2023).

## Tumor Growth, Proliferation, and Progression

Lactylation directly impacts HCC cell proliferation, growth, and overall tumor progression through various mechanisms. Cell Cycle Regulation: TPX2 lactylation, regulated by CBP/HDAC1, enhances AURKA phosphorylation, a key event in cell cycle progression (Shengzhi Liu et al., 2025). Lactate itself can influence cell cycle progression through various mechanisms (Lin et al., 2022). YAP Activation: LDHA-mediated lactylation activates YAP, a crucial oncogenic transcription factor, thereby promoting HCC progression (Wei et al., 2025). Similarly, K90 lactylation of CENPA promotes its nuclear retention by hindering its interaction

with CRM1, enhancing HCC malignancy by affecting YAP signaling (L. Wang et al., 2024). Gene Expression Regulation: Histone lactylation promotes the expression of oncogenes like ESM1, contributing to HCC progression (Zhao et al., 2024). ABCF1-K430 lactylation activates the HIF1 pathway, a central regulator of hypoxia-induced tumor progression (Hong et al., 2025). ASH2L-K312 lactylation upregulates VEGFA, a key pro-angiogenic factor (Han et al., 2025). PYCR1 promotes HCC progression by upregulating IRS1 through H3K18la (H. Wang et al., 2024). Tumor Suppressor Inactivation: CA3 de-lactylation, by restoring DUOX2 expression, weakens its tumor-suppressive role, indicating that maintaining lactylation on certain proteins can be tumor-suppressive (Yan et al., 2024). Conversely, SIRT3-mediated de-lactylation of cyclin E2 inhibits HCC growth (Jin et al., 2023). Liver Stellate Cells: Liver stellate cells, key players in liver fibrosis, promote HCC development through histone lactylation (Yu et al., 2024).

## Tumor Microenvironment and Immune Evasion

The tumor microenvironment (TME) is a complex ecosystem that profoundly influences tumor

progression and response to therapy. Lactylation plays a significant role in shaping the TME, particularly in promoting immune evasion (Y. Li et al., 2025; Piao et al., 2025; Zhonghua Wang et al., 2025; Yang et al., 2024). PD-L1 Stabilization: Histone lactylation contributes to immune therapy resistance by stabilizing PD-L1 through MVP, leading to immune evasion in HCC (Shuang Liu et al., 2025). Macrophage Polarization: A positive feedback loop involving SRSF10, glycolysis, lactate, and H3K18la drives M2 macrophage polarization, which is associated with immunosuppression and immune evasion (Cai et al., 2024). Lactate also drives NUPR1 upregulation, promoting macrophage-mediated immunosuppression in HCC (Cai et al., 2025). T Cell Modulation: Lactate can promote the differentiation of CD4+ T cells into Th1 cells and enhance the anti-tumor activity of JAML+ CD8+ T cells (Chen et al., 2025). However, the overall effect of lactylation on T cells in the HCC TME is complex and can be context-dependent, often leading to an immunosuppressive environment. Immune Suppression: SPTAN1 lactylation activates the NOTCH1/HES1 pathway, contributing to immune suppression (Zengbin Wang et al., 2025). Immune Cold Microenvironment: Dihydroartemisinin (DHA) has been shown to reverse the immune-cold microenvironment in HCC by inhibiting YAP1 and subsequently reducing histone lactylation (Gao et al., 2025). This suggests that targeting lactylation could be a strategy to “reheat” the immune-cold TME. Immune Therapy Resistance: Abnormal lactate metabolism and lactylation modifications significantly affect the efficacy of immunotherapy in HCC (Shuang Liu et al., 2025; Piao et al., 2025; Y. Xu et al., 2023; Zhang et al., 2025).

## Metastasis and Angiogenesis

Lactylation also contributes to the metastatic potential of HCC and promotes angiogenesis, a critical step for tumor growth and dissemination. Metastasis: H3K18la upregulation after microwave ablation enhances ferroptosis resistance and promotes HCC metastasis (Huang et al., 2025). Lactate promotes Rab7A lactylation, which in turn enhances HCC exosome production and lung metastasis (Jiang et al., 2025). Angiogenesis: GP73, activated by histone lactylation and c-Myc, promotes

angiogenesis through STAT3 signaling (Ye et al., 2024). ASH2L-K312 lactylation upregulates VEGFA, a potent pro-angiogenic factor, thereby promoting HCC angiogenesis (Han et al., 2025).

## DRUG RESISTANCE AND THERAPY RESPONSE

A major challenge in HCC treatment is the development of resistance to various therapies. Lactylation has been identified as a significant contributor to this resistance. Chemotherapy Resistance: Histone lactylation drives USP34 to promote cisplatin resistance in HCC (Fan et al., 2025). Lenvatinib Resistance: IGF2BP3 lactylation, mediated by PARK7, promotes lenvatinib resistance by upregulating FSP1, leading to ferroptosis resistance (Zhu et al., 2025). Another study also linked IGF2BP3 lactylation to lenvatinib resistance via the PCK2/NRF2-m6A loop (Lu et al., 2024). Lactylation driving HECTD2 also limits the response of HCC to lenvatinib (Dong et al., 2025). Regorafenib (RGF) Resistance: ZNF207 drives PRDX1 lactylation, activating NRF2 and leading to RGF resistance and ferroptosis evasion (T. Yang et al., 2025). Radiotherapy Resistance: Histone lactylation promotes MCM7 expression, maintaining liver cancer stem cell characteristics and resistance to radiotherapy (Z. Liu et al., 2025). Ferroptosis Resistance: Several lactylation events contribute to ferroptosis resistance, a form of regulated cell death that can be exploited in cancer therapy. These include H3K18la upregulation (Huang et al., 2025), ZNF207-driven PRDX1 lactylation (T. Yang et al., 2025), and PARK7-mediated IGF2BP3-K76 lactylation (Zhu et al., 2025). Senescence Resistance: Lactate, via LDHA-mediated H2B K58 lactylation of NDRG1, drives HCC senescence resistance (L. Li et al., 2025).

## Clinical Significance and Therapeutic Implications

The extensive involvement of lactylation in HCC pathogenesis highlights its potential as a valuable clinical tool for diagnosis, prognosis, and therapeutic intervention.

**Diagnostic and Prognostic Biomarkers:** Lactylation-related markers and gene signatures show promise for improving HCC diagnosis and predicting patient outcomes. **Specific Protein Lactylation:** USP14 and ABCF1 lactylation sites have been identified as diagnostic

indicators for HCC and its metastasis (Hong et al., 2023). MRPL3 lactylation is a novel prognostic biomarker for HCC, correlating with mitochondrial function (Xing et al., 2025). Lactylation-Related Gene Signatures: Several studies have developed lactylation-related gene signatures that can be used for HCC diagnosis, prognosis prediction, and even prediction of immune therapy response (Cheng et al., 2023; Luan, 2025; Yi et al., 2025; Yu et al., 2025; Zhang et al., 2025). These signatures can also identify distinct HCC subtypes (Chen et al., 2024) and characterize liver fibrosis phenotypes associated with HCC progression (Li et al., 2024). Cholangiocarcinoma-associated HCC: Lactylation remodeling influences the characteristics of cholangiocarcinoma-associated HCC, affecting patient survival (Lin et al., 2025). Hypoxia-Glycolysis-Lactylation Axis: A gene signature related to the hypoxia-glycolysis-lactylation axis can predict HCC prognosis and immune therapy efficacy (Yi et al., 2025).

**Therapeutic Targets:** The enzymes involved in lactylation and specific lactylated proteins represent promising therapeutic targets for HCC. Targeting Lactylation Writers/Erasers: Inhibiting lactyltransferases like CBP or PARK7 could reduce oncogenic lactylation events (Shengzhi Liu et al., 2025; Zhu et al., 2025). Activating delactylases like SIRT3 or enhancing the activity of Class I HDACs (in specific contexts where lactylation is oncogenic) could reverse pro-tumorigenic lactylation (Jin et al., 2023; Moreno-Yruela et al., 2022). However, given the dual role of HDACs in HCC (Cai, et al., 2023), careful consideration of their specific substrates and context is necessary. Targeting Specific Lactylated Proteins: Inhibiting the function of oncogenic lactylated proteins (e.g., USP34, GPC3, SRSF10, CENPA, ALDOA, ASH2L, HECTD2, Rab7A, NUPR1, IGF2BP3) or restoring the function of tumor-suppressive ones (e.g., CA3) could offer therapeutic benefits. Small Molecule Interventions: DML, an inhibitor of H3 lactylation, has shown promise in suppressing HCC stem cells (Gao et al., 2025). RJA inhibits H3K9la and H3K14la, demonstrating anti-HCC activity (H. Xu et al., 2023). Dihydroartemisinin (DHA) reverses immune-cold HCC by reducing histone lactylation via YAP1 inhibition (Gao et al., 2025). Targeting Downstream Pathways: Modulating pathways activated

by lactylation, such as YAP, NRF2, STAT3, NOTCH1/HES1, and HIF1, could also be effective (Hong et al., 2025; Zengbin Wang et al., 2025; Wei et al., 2025; T. Yang et al., 2025; Ye et al., 2024). Immunotherapy Enhancement: Given lactylation's role in immune evasion and immunotherapy resistance, targeting lactylation could sensitize HCC to existing immunotherapies (Shuang Liu et al., 2025; Piao et al., 2025; Y. Xu et al., 2023; Zhang et al., 2025). Novel Th Lactylated SPTAN1 Accelerates Hepatocellular Carcinoma Progression by Promoting NOTCH1/HES1 Acti erapeutic Targets: Specific histone lactylation genes like NR6A1, OSBP2, and UNC119B have been identified as potential therapeutic targets in HCC (Wu et al., 2023).

## CONCLUSION

Protein lactylation has emerged as a critical and pervasive post-translational modification in hepatocellular carcinoma, intricately linking metabolic reprogramming to epigenetic regulation and diverse cellular functions. From its initial discovery as a novel PTM, research has rapidly unveiled its profound impact on HCC pathogenesis, encompassing tumor initiation, progression, metastasis, immune evasion, and the development of therapeutic resistance. Both histone and non-histone protein lactylation events, regulated by specific "writers" and "erasers," orchestrate complex changes in gene expression, protein activity, and cellular phenotypes. The widespread involvement of lactylation in key oncogenic pathways and its direct correlation with clinical outcomes underscore its significant potential as a diagnostic and prognostic biomarker. Furthermore, the identification of specific lactylation sites, their regulatory enzymes, and the downstream signaling cascades they influence, opens new avenues for developing targeted therapeutic strategies. By precisely modulating lactylation, either through inhibiting lactyltransferases, activating delactylases, or targeting specific lactylated proteins, we may be able to disrupt critical oncogenic processes, overcome drug resistance, and enhance the efficacy of current HCC treatments. The continued exploration of lactylation's multifaceted roles promises to yield innovative approaches for combating this challenging malignancy. A comprehensive roadmap translating

these mechanistic insights into clinical applications-encompassing biomarker discovery and therapeutic intervention-is presented in Figure 2.

## ACKNOWLEDGMENTS

Not applicable.

## FUNDING

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

Not applicable.

## AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. All authors declared no competing interests. Dengwang Chen and Xinyue Jiang: Conceptualization,

Methodology, Investigation, Writing - Original Draft, Writing - Review & Editing. (These authors contributed equally to this work.). Linna Wei, Dongmei Li and Zudi Meng: Supervision, Project administration, Resources, Writing - Review & Editing.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

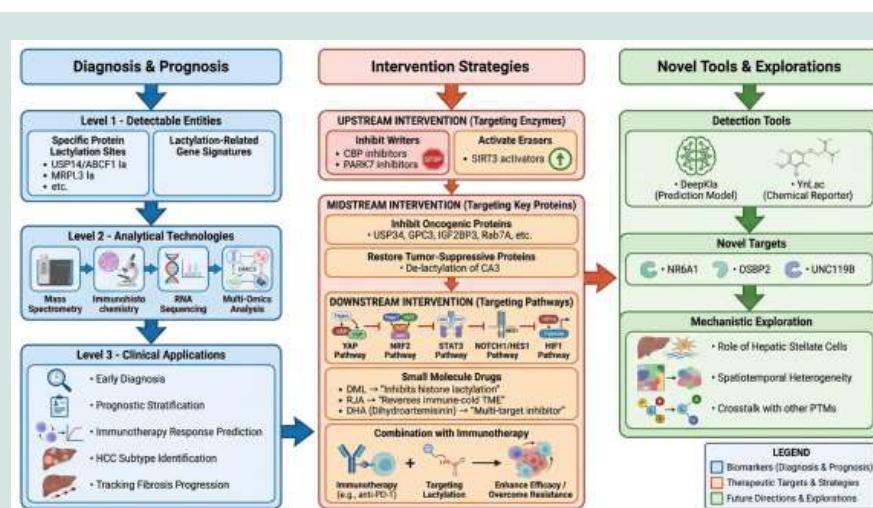
Not applicable.

## PATIENT CONSENT FOR PUBLICATION

Not applicable.

## COMPETING INTERESTS

The authors declare that they have no competing interests.



**Figure 2:** Lactylation as a clinical translation roadmap in hepatocellular carcinoma. This roadmap illustrates the diagnostic, prognostic, and therapeutic potential of lactylation in HCC. Left panel (Biomarkers): Lactylation-based biomarkers include specific protein lactylation sites (e.g., USP14/ABCF1, MRPL3) and lactylation-related gene signatures, which can be detected via multi-omics approaches and applied for early diagnosis, prognosis stratification, immunotherapy response prediction, and fibrosis tracking. Center panel (Therapeutic Strategies): Interventions targeting lactylation include inhibiting writers (e.g., CBP, PARK7), activating erasers (e.g., SIRT3), targeting key lactylated proteins (e.g., IGF2BP3, GPC3, Rab7A), using small-molecule modulators (e.g., DML, RJA, DHA), and combining with immunotherapy to overcome resistance. Right panel (Future Directions): Emerging tools (e.g., DeepKla, YnLac) and novel targets (e.g., NR6A1, OSBP2) are highlighted for further exploration of lactylation in HCC. Solid arrows indicate established or ongoing translational paths; dashed arrows indicate emerging research directions.

## • REFERENCE

- Befeler, A. S., & Di Bisceglie, A. M. (2002). Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology*, 122(6), 1609-1619. <https://pubmed.ncbi.nlm.nih.gov/12016426>
- Cai, D., Yuan, X., Cai, D. Q., Li, A., Yang, S., Yang, W., Duan, J., Zhuo, W., Min, J., Peng, L., & Wei, J. (2023). Integrative analysis of lactylation-related genes and establishment of a novel prognostic signature for hepatocellular carcinoma. *Journal of Cancer Research and Clinical Oncology*, 149(13), 11517-11530. <https://doi.org/10.1007/s00432-023-12540-1>

023-04947-0

- Cai, J., Song, L., Zhang, F., Wu, S., Zhu, G., Zhang, P., Chen, S., Du, J., Wang, B., Cai, Y., Yang, Y., Wan, J., Zhou, J., Fan, J., & Dai, Z. (2024). Targeting SRSF10 might inhibit M2 macrophage polarization and potentiate anti-PD-1 therapy in hepatocellular carcinoma. *Cancer Communications (London, England)*, 44(11), 1231-1260. <https://doi.org/10.1002/cac2.12607>
- Cai, J., Zhang, P., Cai, Y., Zhu, G., Chen, S., Song, L., Du, J., Wang, B., Dai, W., Zhou, J., Fan, J., Yu, Y., & Dai, Z. (2025). Lactylation-Driven NUPR1 Promotes Immunosuppression of Tumor-Infiltrating Macrophages in Hepatocellular Carcinoma. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, 12(20), e2413095. <https://doi.org/10.1002/advs.202413095>
- Caldwell, S. H., Crespo, D. M., Kang, H. S., & Al-Osaimi, A. M. S. (2004). Obesity and hepatocellular carcinoma. *Gastroenterology*, 127(5 Suppl 1), S97-103. <https://pubmed.ncbi.nlm.nih.gov/15508109>
- Chen, H., Xiao, Z., Lu, Z., Xu, N., Wei, Q., & Xu, X. (2025). Targeted activation of junctional adhesion molecule-like protein+ CD8+ T cells enhances immunotherapy in hepatocellular carcinoma. *Chinese Journal of Cancer Research = Chung-kuo Yen Cheng Yen Chiu*, 37(2), 212-226. <https://doi.org/10.21147/j.issn.1000-9604.2025.02.08>
- Chen, Y., Chang, L., Hu, L., Yan, C., Dai, L., Shelat, V. G., Yarmohammadi, H., & Sun, J. (2024). Identification of a lactylation-related gene signature to characterize subtypes of hepatocellular carcinoma using bulk sequencing data. *Journal of Gastrointestinal Oncology*, 15(4), 1636-1646. <https://doi.org/10.21037/jgo-24-405>
- Cheng, Z., Huang, H., Li, M., Liang, X., Tan, Y., & Chen, Y. (2023). Lactylation-Related Gene Signature Effectively Predicts Prognosis and Treatment Responsiveness in Hepatocellular Carcinoma. *Pharmaceuticals (Basel, Switzerland)*, 16(5). <https://doi.org/10.3390/ph16050644>
- Dai, X., Lv, X., Thompson, E. W., & Ostrikov, K. K. (2021). Histone lactylation: epigenetic mark of glycolytic switch. *Trends In Genetics : TIG*, 38(2), 124-127. <https://doi.org/10.1016/j.tig.2021.09.009>
- Di Bisceglie, A. M., Rustgi, V. K., Hoofnagle, J. H., Dusheiko, G. M., & Lotze, M. T. (1988). NIH conference. Hepatocellular carcinoma. *Annals of Internal Medicine*, 108(3), 390-401. <https://pubmed.ncbi.nlm.nih.gov/2449110>
- Dong, R., Fei, Y., He, Y., Gao, P., Zhang, B., Zhu, M., Wang, Z., Wu, L., Wu, S., Wang, X., Cai, J., Chen, Z., & Zuo, X. (2025). Lactylation-Driven HECTD2 Limits the Response of Hepatocellular Carcinoma to Lenvatinib. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, 12(15), e2412559. <https://doi.org/10.1002/advs.202412559>
- Du, W., Tan, S., Peng, Y., Lin, S., Wu, Y., Ding, K., Chen, C., Liu, R., Cao, Y., Li, Z., Gu, S., Feng, H., Wan, B., Tao, S.-C., Wang, N., Fan, Y., & Zhao, X. (2024). Histone lactylation-driven YTHDC1 promotes hepatocellular carcinoma progression via lipid metabolism remodeling. *Cancer Letters*, 611, 217426. <https://doi.org/10.1016/j.canlet.2024.217426>
- Fan, M., Liu, J. S., Wei, X. L., Nie, Y., & Liu, H. L. (2025). Histone Lactylation-Driven Ubiquitin-Specific Protease 34 Promotes Cisplatin Resistance in Hepatocellular Carcinoma. *Gastroenterology Research*, 18(1), 23-30. <https://doi.org/10.14740/gr1796>
- Feng, F., Wu, J., Chi, Q., Wang, S., Liu, W., Yang, L., Song, G., Pan, L., Xu, K., & Wang, C. (2024). Lactylome Analysis Unveils Lactylation-Dependent Mechanisms of Stemness Remodeling in the Liver Cancer Stem Cells. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, 11(38), e2405975. <https://doi.org/10.1002/advs.202405975>
- Ganne-Carrié, N., & Nahon, P. (2024). Differences between hepatocellular carcinoma caused by alcohol and other aetiologies. *Journal of Hepatology*, 82(5), 909-917. <https://doi.org/10.1016/j.jhep.2024.12.030>
- Gao, Y., Gong, Y., Song, X., Xiong, Y., Lu, J., Yang, Y., Gong, Y., Du, Z., Wang, S., Jia, R., Gong, P., & Shi, X. (2025). Dihydroartemisinin inhibits histone lactylation through YAP1 to act as a 'hot' switch for 'cold' tumor in hepatocellular carcinoma. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*, 148, 157307. <https://doi.org/10.1016/j.phymed.2025.157307>
- Han, H., Wang, S., Ma, L., Yin, H., Cheng, X., Wang, Y., Xia, S., Zhang, Y., Zhang, Y., Zhu, R., Liu, C., Zhao, D., Gu, X., Zhu, H., & Yuan, Y. (2025). ASH2L-K312-Lac Stimulates Angiogenesis in Tumors to Expedite the Malignant Progression of Hepatocellular Carcinoma. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, 12(40), e09477. <https://doi.org/10.1002/advs.202509477>
- Hong, H., Chen, X., Wang, H., Gu, X., Yuan, Y., & Zhang, Z. (2023). Global profiling of protein lysine lactylation and potential target modified protein analysis in hepatocellular carcinoma. *Proteomics*, 23(9), e2200432. <https://doi.org/10.1002/pmic.202200432>

- Hong, H., Han, H., Wang, L., Cao, W., Hu, M., Li, J., Wang, J., Yang, Y., Xu, X., Li, G., Zhang, Z., Zhang, C., Xu, M., Wang, H., Wang, Q., & Yuan, Y. (2025). ABCF1-K430-Lactylation promotes HCC malignant progression via transcriptional activation of HIF1 signaling pathway. *Cell Death and Differentiation*, 32(4), 613-631. <https://doi.org/10.1038/s41418-024-01436-w>
- Huang, J., Xie, H., Li, J., Huang, X., Cai, Y., Yang, R., Yang, D., Bao, W., Zhou, Y., Li, T., & Lu, Q. (2025). Histone lactylation drives liver cancer metastasis by facilitating NSF1-mediated ferroptosis resistance after microwave ablation. *Redox Biology*, 81, 103553. <https://doi.org/10.1016/j.redox.2025.103553>
- Izzo, L. T., & Wellen, K. E. (2019). Histone lactylation links metabolism and gene regulation. *Nature*, 574(7779), 492-493. <https://doi.org/10.1038/d41586-019-03122-1>
- Ji, Y., Xu, Z., Tang, L., Huang, T., Mu, X., Ni, C., Tang, B., Lu, H., Zhang, C., Yang, S., & Wang, X. (2025). O-GlcNAcylation of YBX1 drives a glycolysis-histone lactylation feedback loop in hepatocellular carcinoma. *Cancer Letters*, 631, 217957. <https://doi.org/10.1016/j.canlet.2025.217957>
- Jiang, C., He, X., Chen, X., Huang, J., Liu, Y., Zhang, J., Chen, H., Sui, X., Lv, X., Zhao, X., Xiao, C., Xiao, J., Zhang, J., Lu, T., Chen, H., Li, H., Wang, H., Lv, G., Ye, L., ... Yang, Y. (2025). Lactate accumulation drives hepatocellular carcinoma metastasis through facilitating tumor-derived exosome biogenesis by Rab7A lactylation. *Cancer Letters*, 627, 217636. <https://doi.org/10.1016/j.canlet.2025.217636>
- Jin, J., Bai, L., Wang, D., Ding, W., Cao, Z., Yan, P., Li, Y., Xi, L., Wang, Y., Zheng, X., Wei, H., Ding, C., & Wang, Y. (2023). SIRT3-dependent delactylation of cyclin E2 prevents hepatocellular carcinoma growth. *EMBO Reports*, 24(5), e56052. <https://doi.org/10.15252/embr.202256052>
- Li, L., Dong, J., Xu, C., & Wang, S. (2025). Lactate drives senescence-resistant lineages in hepatocellular carcinoma via histone H2B lactylation of NDRG1. *Cancer Letters*, 616, 217567. <https://doi.org/10.1016/j.canlet.2025.217567>
- Li, L.-N., Li, W.-W., Xiao, L.-S., & Lai, W.-N. (2024). Lactylation signature identifies liver fibrosis phenotypes and traces fibrotic progression to hepatocellular carcinoma. *Frontiers In Immunology*, 15, 1433393. <https://doi.org/10.3389/fimmu.2024.1433393>
- Li, X., Yang, Y., Zhang, B., Lin, X., Fu, X., An, Y., Zou, Y., Wang, J.-X., Wang, Z., & Yu, T. (2022). Lactate metabolism in human health and disease. *Signal Transduction and Targeted Therapy*, 7(1), 305. <https://doi.org/10.1038/s41392-022-01151-3>
- Li, Y., Bai, S., Hu, J., Li, H., Hu, C., Zhao, J., Qian, H., Tang, Z., & Feng, Y. (2025). Post-translational acylation modulates immunosuppression and immunotherapy efficacy in hepatocellular carcinoma. *Genes and Immunity*, 26(6), 599-612. <https://doi.org/10.1038/s41435-025-00362-2>
- Liberti, M. V., & Locasale, J. W. (2019). Histone Lactylation: A New Role for Glucose Metabolism. *Trends In Biochemical Sciences*, 45(3), 179-182. <https://doi.org/10.1016/j.tibs.2019.12.004>
- Lin, J., Liu, G., Chen, L., Kwok, H. F., & Lin, Y. (2022). Targeting lactate-related cell cycle activities for cancer therapy. *Seminars In Cancer Biology*, 86(Pt 3), 1231-1243. <https://doi.org/10.1016/j.semcaner.2022.10.009>
- Lin, Q., Chen, J., Zhou, L., Fang, M., Wei, C., Huang, T., Xu, Y., Gao, J., Liu, F., Tang, Z., Zhu, J.-K., & Yang, W. (2025). Multi-omics analysis of lactate metabolism gene regulation in Clonorchis sinensis-associated hepatocellular carcinoma. *Parasites & Vectors*, 18(1), 301. <https://doi.org/10.1186/s13071-025-06947-0>
- Liu, S., Cai, J., Qian, X., Zhang, J., Zhang, Y., Meng, X., Wang, M., Gao, P., & Zhong, X. (2025). TPX2 lactylation is required for the cell cycle regulation and hepatocellular carcinoma progression. *Life Science Alliance*, 8(6). <https://doi.org/10.26508/lsa.202402978>
- Liu, S., Pan, Y., Liu, W., Bu, X., Shao, R., Wang, Q., Wu, J., Wu, C., Hu, W., Xu, J., Wu, C., & Jiang, J. (2025). Lactylation-driven MVP upregulation boosts immunotherapy resistance by inhibiting PD-L1 degradation in hepatocellular carcinoma. *Journal For Immunotherapy of Cancer*, 13(9). <https://doi.org/10.1136/jitc-2025-012230>
- Liu, Z., Han, J., Su, S., Zeng, Q., Wu, Z., Yuan, J., & Yang, J. (2025). Histone lactylation facilitates MCM7 expression to maintain stemness and radio-resistance in hepatocellular carcinoma. *Biochemical Pharmacology*, 236, 116887. <https://doi.org/10.1016/j.bcp.2025.116887>
- Lu, Y., Zhu, J., Zhang, Y., Li, W., Xiong, Y., Fan, Y., Wu, Y., Zhao, J., Shang, C., Liang, H., & Zhang, W. (2024). Lactylation-Driven IGF2BP3-Mediated Serine Metabolism Reprogramming and RNA m6A-Modification Promotes Lenvatinib Resistance in HCC. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, 11(46), e2401399. <https://doi.org/10.1002/advs.202401399>

- Luan, S. (2025). The role of histone lactylation genes in hepatocellular carcinoma prognostic models and their immune cell infiltration features: a comprehensive analysis of single-cell, spatial transcriptome, Mendelian randomization and experiment. *Discover Oncology*, 16(1), 29. <https://doi.org/10.1007/s12672-025-01775-1>
- Lv, H., Dao, F.-Y., & Lin, H. (2022). DeepKla: An attention mechanism-based deep neural network for protein lysine lactylation site prediction. *IMeta*, 1(1), e11. <https://doi.org/10.1002/imt2.11>
- Moreno-Yruela, C., Zhang, D., Wei, W., Bæk, M., Liu, W., Gao, J., Danková, D., Nielsen, A. L., Bolding, J. E., Yang, L., Jameson, S. T., Wong, J., Olsen, C. A., & Zhao, Y. (2022). Class I histone deacetylases (HDAC1-3) are histone lysine delactylases. *Science Advances*, 8(3), eabi6696. <https://doi.org/10.1126/sciadv.abi6696>
- Pan, L., Feng, F., Wu, J., Fan, S., Han, J., Wang, S., Yang, L., Liu, W., Wang, C., & Xu, K. (2022). Demethylzeylasteral targets lactate by inhibiting histone lactylation to suppress the tumorigenicity of liver cancer stem cells. *Pharmacological Research*, 181, 106270. <https://doi.org/10.1016/j.phrs.2022.106270>
- Piao, Y., Zhai, N., Zhang, X., Zhao, W., & Li, M. (2025). Post-translational modifications in hepatocellular carcinoma: unlocking new frontiers in immunotherapy. *Frontiers In Immunology*, 16, 1554372. <https://doi.org/10.3389/fimmu.2025.1554372>
- Shan, S., & Jia, J. (2023). The clinical management of hepatocellular carcinoma in China: Progress and challenges. *Clinical and Molecular Hepatology*, 29(2), 339-341. <https://doi.org/10.3350/cmh.2023.0077>
- Shimada, M., Takenaka, K., Gion, T., Fujiwara, Y., Kajiyama, K., Maeda, T., Shirabe, K., Nishizaki, T., Yanaga, K., & Sugimachi, K. (1996). Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. *Gastroenterology*, 111(3), 720-726. <https://pubmed.ncbi.nlm.nih.gov/8780578>
- Song, F., Hou, C., Huang, Y., Liang, J., Cai, H., Tian, G., Jiang, Y., Wang, Z., & Hou, J. (2024). Lactylome analyses suggest systematic lysine-lactylated substrates in oral squamous cell carcinoma under normoxia and hypoxia. *Cellular Signalling*, 120, 111228. <https://doi.org/10.1016/j.cellsig.2024.111228>
- Sun, W., Jia, M., Feng, Y., & Cheng, X. (2023). Lactate is a bridge linking glycolysis and autophagy through lactylation. *Autophagy*, 19(12), 3240-3241. <https://doi.org/10.1080/15548627.2023.2246356>
- Sun, Y., Chen, Y., & Peng, T. (2022). A bioorthogonal chemical reporter for the detection and identification of protein lactylation. *Chemical Science*, 13(20), 6019-6027. <https://doi.org/10.1039/d2sc00918h>
- Wan, N., Wang, N., Yu, S., Zhang, H., Tang, S., Wang, D., Lu, W., Li, H., Delafield, D. G., Kong, Y., Wang, X., Shao, C., Lv, L., Wang, G., Tan, R., Wang, N., Hao, H., & Ye, H. (2022). Cyclic immonium ion of lactyllysine reveals widespread lactylation in the human proteome. *Nature Methods*, 19(7), 854-864. <https://doi.org/10.1038/s41592-022-01523-1>
- Wang, H., Xu, M., Zhang, T., Pan, J., Li, C., Pan, B., Zhou, L., Huang, Y., Gao, C., He, M., Xue, Y., Ji, X., Zhang, X., Wang, N., Zhou, H., Wang, Q., & Li, J. Z. (2024). PYCR1 promotes liver cancer cell growth and metastasis by regulating IRS1 expression through lactylation modification. *Clinical and Translational Medicine*, 14(10), e70045. <https://doi.org/10.1002/ctm2.70045>
- Wang, L., Zeng, T., Wang, Y., Wang, G., Yu, W., Zhang, J., Shi, Y., Li, J., & Ding, J. (2024). K90 lactylation orchestrates YAP nuclear sequestration by impairing binding with exportin CRM1 and enhances HCC malignancy. *Cancer Letters*, 611, 217386. <https://doi.org/10.1016/j.canlet.2024.217386>
- Wang, Z., Liu, Z., Lv, M., Luan, Z., Li, T., & Hu, J. (2025). Novel histone modifications and liver cancer: emerging frontiers in epigenetic regulation. *Clinical Epigenetics*, 17(1), 30. <https://doi.org/10.1186/s13148-025-01838-8>
- Wang, Z., Ye, D., Wu, L., Liu, J., Pan, B., Zhang, Z., Zhang, X., Yao, Y., & Tang, N. (2025). Lactylated SPTAN1 Accelerates Hepatocellular Carcinoma Progression by Promoting NOTCH1/HES1 Activation and Immunosuppression. *Advanced Science (Weinheim, Baden-Wurttemberg, Germany)*, e07068. <https://doi.org/10.1002/advs.202507068>
- Wei, X., Zou, L., Huang, Y., Qiu, C., Cheng, G., Chen, Y., & Rao, J. (2025). LDHA-mediated YAP lactylation promotes the tumor progression of hepatocellular carcinoma by inducing YAP dephosphorylation and activation. *Biology Direct*, 20(1), 64. <https://doi.org/10.1186/s13062-025-00655-6>
- Wu, Q., Li, X., Long, M., Xie, X., & Liu, Q. (2023). Integrated analysis of histone lysine lactylation (Kla)-specific genes suggests that NR6A1, OSBP2 and UNC119B are novel therapeutic targets for hepatocellular carcinoma. *Scientific Reports*, 13(1), 18642. <https://doi.org/10.1038/s41598-023-46057-4>
- Wu, X. (2023). In-depth discovery of protein lactylation in hepatocellular carcinoma. *Proteomics*, 23(9), e2300003. <https://doi.org/10.1002/pmic.202300003>

- Xing, W., Zhou, Y., Long, Q., Yi, N., Wang, G., Shi, R., Huang, J., Yin, X., Zhu, T., & Cao, S. (2025). Multiomic analysis of lactylation and mitochondria-related genes in hepatocellular carcinoma identified MRPL3 as a new prognostic biomarker. *Frontiers In Oncology*, 14, 1511958. <https://doi.org/10.3389/fonc.2024.1511958>
- Xu, H., Li, L., Wang, S., Wang, Z., Qu, L., Wang, C., & Xu, K. (2023). Royal jelly acid suppresses hepatocellular carcinoma tumorigenicity by inhibiting H3 histone lactylation at H3K9la and H3K14la sites. *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology*, 118, 154940. <https://doi.org/10.1016/j.phymed.2023.154940>
- Xu, Y., Hao, X., Ren, Y., Xu, Q., Liu, X., Song, S., & Wang, Y. (2023). Research progress of abnormal lactate metabolism and lactate modification in immunotherapy of hepatocellular carcinoma. *Frontiers In Oncology*, 12, 1063423. <https://doi.org/10.3389/fonc.2022.1063423>
- Yan, J., Zhou, Y., Xu, J., Dong, Y., Yang, X., Yang, X., Wu, A., Chang, S., Wang, Y., Zhang, Q., Ayaka, T., Yu, L., Zhao, L., Meng, H., & Liu, D. (2024). Delactylation diminished the growth inhibitory role of CA3 by restoring DUOX2 expression in hepatocellular carcinoma. *Experimental Cell Research*, 444(2), 114392. <https://doi.org/10.1016/j.yexcr.2024.114392>
- Yang, T., Wang, M.-D., Xu, X.-F., Li, C., Wu, H., & Shen, F. (2023). Management of hepatocellular carcinoma in China: Seeking common grounds while reserving differences. *Clinical and Molecular Hepatology*, 29(2), 342-344. <https://doi.org/10.3350/cmh.2023.0106>
- Yang, T., Zhang, S., Nie, K., Cheng, C., Peng, X., Huo, J., & Zhang, Y. (2025). ZNF207-driven PRDX1 lactylation and NRF2 activation in regorafenib resistance and ferroptosis evasion. *Drug Resistance Updates : Reviews and Commentaries In Antimicrobial and Anticancer Chemotherapy*, 82, 101274. <https://doi.org/10.1016/j.drup.2025.101274>
- Yang, Y., Hou, Y., Yi, L., Chen, C., Li, X., Wang, Y., Fu, Y., Hu, M., & Xing, R. (2025). Machine learning-based identification of core regulatory genes in hepatocellular carcinoma: insights from lactylation modification and liver regeneration-related genes. *Frontiers In Oncology*, 15, 1683704. <https://doi.org/10.3389/fonc.2025.1683704>
- Yang, Z., Yan, C., Ma, J., Peng, P., Ren, X., Cai, S., Shen, X., Wu, Y., Zhang, S., Wang, X., Qiu, S., Zhou, J., Fan, J., Huang, H., & Gao, Q. (2023). Lactylome analysis suggests lactylation-dependent mechanisms of metabolic adaptation in hepatocellular carcinoma. *Nature Metabolism*, 5(1), 61-79. <https://doi.org/10.1038/s42255-022-00710-w>
- Yang, Z., Zheng, Y., & Gao, Q. (2024). Lysine lactylation in the regulation of tumor biology. *Trends In Endocrinology and Metabolism: TEM*, 35(8), 720-731. <https://doi.org/10.1016/j.tem.2024.01.011>
- Yao, G., & Yang, Z. (2023). Glypican-3 knockdown inhibits the cell growth, stemness, and glycolysis development of hepatocellular carcinoma cells under hypoxic microenvironment through lactylation. *Archives of Physiology and Biochemistry*, 130(5), 546-554. <https://doi.org/10.1080/13813455.2023.2206982>
- Ye, J., Gao, X., Huang, X., Huang, S., Zeng, D., Luo, W., Zeng, C., Lu, C., Lu, L., Huang, H., Mo, K., Huang, J., Li, S., Tang, M., Wu, T., Mai, R., Luo, M., Xie, M., Wang, S.,...,Liang, R. (2024). Integrating Single-Cell and Spatial Transcriptomics to Uncover and Elucidate GP73-Mediated Pro-Angiogenic Regulatory Networks in Hepatocellular Carcinoma. *Research (Washington, D.C.)*, 7, 0387. <https://doi.org/10.34133/research.0387>
- Yi, F., Long, S., Yao, Y., & Fu, K. (2025). A Novel Signature Composed of Hypoxia, Glycolysis, Lactylation Related Genes to Predict Prognosis and Immunotherapy in Hepatocellular Carcinoma. *Frontiers In Bioscience (Landmark Edition)*, 30(4), 33422. <https://doi.org/10.31083/FBL33422>
- Yin, Y.-C., He, J., Feng, Y., Xu, Y.-Y., Shi, X.-H., Tan, X., & He, Q.-J. (2025). FiLactate-Induced Lysine Lactylation: A Central Node Linking Metabolic Rewiring, Epigenetic Plasticity and Therapeutic Vulnerabilities in Hepatocellular Carcinoma. *Journal of Biochemical and Molecular Toxicology*, 39(12), e70622. <https://doi.org/10.1002/jbt.70622>
- Yu, L., Shi, Y., Zhi, Z., Li, S., Yu, W., & Zhang, Y. (2025). Establishment of a Lactylation-Related Gene Signature for Hepatocellular Carcinoma Applying Bulk and Single-Cell RNA Sequencing Analysis. *International Journal of Genomics*, 2025, 3547543. <https://doi.org/10.1155/ijog/3547543>
- Yu, Y., Li, Y., Zhou, L., Cheng, X., & Gong, Z. (2024). Hepatic stellate cells promote hepatocellular carcinoma development by regulating histone lactylation: Novel insights from single-cell RNA sequencing and spatial transcriptomics analyses. *Cancer Letters*, 604, 217243. <https://doi.org/10.1016/j.canlet.2024.217243>
- Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., Liu, W., Kim, S., Lee, S., Perez-Neut, M., Ding, J., Czyz, D., Hu, R., Ye, Z., He, M., Zheng, Y. G., Shuman, H. A., Dai, L., Ren, B.,...,Zhao, Y. (2019). Metabolic regulation of gene expression by histone lactylation. *Nature*, 574(7779), 575-580. <https://doi.org/10.1038/s41586-019-1678-1>

- Zhang, J., Dong, C., Wu, L., Chen, L., Zhang, L., & Shi, L. (2025). Diagnostic value of a lactylation-related gene signature in hepatocellular carcinoma. *Translational Cancer Research*, 14(1), 296-312. <https://doi.org/10.21037/tcr-24-1023>
- Zhao, P., Qiao, C., Wang, J., Zhou, Y., & Zhang, C. (2024). Histone lactylation facilitates hepatocellular carcinoma progression by upregulating endothelial cell-specific molecule 1 expression. *Molecular Carcinogenesis*, 63(11), 2078-2089. <https://doi.org/10.1002/mc.23794>
- Zhu, Z., Xia, X., Lu, Y., Li, D., He, X., Zhang, B., Xiong, G., Zhang, W., Liang, H., & Zhu, H. (2025). PARK7-driven IGF2BP3-K76 lactylation mediates ferroptosis and HAIC resistance in hepatocellular carcinoma. *Redox Biology*, 87, 103869. <https://doi.org/10.1016/j.redox.2025.103869>

©2025 Wei L, Meng Z, Li D, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License 4.0 International License.

Cite this article as: Chen D, Jiang X, Wei L, Meng Z, Li D, Lactylation: A Pivotal Metabolic-Epigenetic Nexus Driving Hepatocellular Carcinoma Pathogenesis and Therapeutic Resistance, *Glob. Open Access J. Sci.*, 2025; 1(3):179-191.

