Lactylation modification in lung cancer: A review of current research and future directions (Review)

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Abstract. Lung cancer is a common malignancy that poses risks to human health and quality of life. The primary treatment options currently available include surgery, chemotherapy and radiotherapy. However, the aggressive metastatic nature of the disease combined with the development of drug and radiation resistance results in suboptimal survival outcomes. Consequently, there is a need to explore novel therapeutic approaches and develop more effective drugs. Lactylation, an epigenetic modification induced by lactate, alters histone proteins to modify the chromatin structure, as well as non-histone proteins. This post-translational modification is associated with the initiation and progression of lung cancer. Lactylation carries out a considerable role in the onset, progression and resistance of the disease by influencing tumor metabolism and the surrounding microenvironment. Targeting lactylation could provide innovative strategies for the targeted therapy of lung cancer.

Contents

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1. Introduction

Cancer remains the leading cause of mortality worldwide, in 2024, there were ~19.3 million new cases of cancer and 10 million cancer-related mortalities globally, according to the World Health Organization (1). Lung cancer is primarily classified into two types: Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC being the most common form (1-3). The progression of lung cancer is largely influenced by genetic alterations and the tumor microenvironment (TME) (4). For early stage (I or II) NSCLC, the standard treatment involves surgical removal of the tumor, followed by adjuvant therapies, such as chemotherapy or radiation, aimed at complete tumor elimination and prevention of recurrence (5-23). Once the disease advances to stage III or IV and metastasis occurs, the treatment typically shifts to chemotherapy, radiation or targeted therapy (24-43). Despite their use, traditional chemotherapy regimens have limited efficacy, while targeted therapy and immunotherapy show potential but are not without challenges, such as inconsistent treatment responses, drug resistance and adverse effects (44-49). Consequently, future approaches may prioritize personalized therapies and further advancements in targeted drugs to treat lung cancer and improve patient survival (45-54).

Previous studies have revealed that metabolic reprogramming in cancer cells, particularly glycolysis, is a key process in tumor progression and has garnered widespread attention (55-61). Lactate, a byproduct of glycolysis, is considered a waste product and is recognized as a key metabolite that not only provides an energy source for various tissues, such as the skeletal muscle, heart, brain and cancer cells, but also acts as a signaling molecule involved in immune modulation, fat mobilization, wound healing and the maintenance of cellular homeostasis (62-71). The TME refers to the local environment surrounding tumor cells, including surrounding cells, blood vessels, immune cells and the extracellular matrix, which interact to influence tumor growth, spread and response to treatment (72-74). Lactate accumulation in the TME leads to acidification, which promotes immune evasion, angiogenesis and metastasis, thereby accelerating tumor progression and resistance to therapy (75-77).

Lactylation, the post-translational modification of proteins, is an important mechanism in the regulation of cellular metabolism (78-83). Owing to the Warburg effect, in which tumor cells predominantly rely on glycolysis for energy production, even in the presence of oxygen, rather than oxidative phosphorylation, lactate, as a byproduct of the Warburg effect, serves as the main driving force for lactylation (84-89). Lactylation regulates gene expression, protein function and the cellular processes involved in tumorigenesis, chemotherapy resistance and genomic stability (90-99). Cellular lactylation modifications in cells can occur on both histone and non-histone proteins, and the enzymes involved, including histone acetyltransferases [such as p300 and CREB binding protein (CBP)] and deacetylases [such as histone deacetylases (HDACs)], carry out notable roles in regulating this modification (100-107). Targeting of these enzymes may offer new strategies for the treatment of various types of cancer (100-107).

The relationship between lactylation, glycolysis and tumor progression in lung cancer is an emerging research field (108-113). Protein lactylation affects various processes such as immune evasion, cell migration and tumor metabolism (114-117). Despite progress, the precise regulation of lung cancer progression by lactylation and its therapeutic targets require further exploration (118-127).

Given the importance of lactylation in cancer biology, particularly in lung cancer, the present review aims to explore the molecular mechanisms of lactylation, its role in lung cancer progression and potential therapeutic strategies targeting lactylation (128-130). Since research on lactylation in lung cancer is still in its early stages, the present review also discusses the future directions of targeting lactylation and its regulatory pathways as a novel approach to the treatment of lung cancer.

2. Overview of lung cancer

Lung cancer is the leading cause of cancer-related mortalities worldwide, with ~2 million new cases and 1.76 million mortalities annually (1-3). The key risk factors include smoking, air pollution, occupational chemical exposure, family history and genetic predispositions (4-7). It is divided into two main types: SCLC and NSCLC, the latter accounting for 85-90% of cases (8-13).

The development of lung cancer is driven by genetic mutations in genes such as tumor protein 53 (14-16) and retinoblastoma 1, which impair DNA repair and cell cycle regulation, leading to uncontrolled cell proliferation (17-21). Additionally, MYC and dysregulated Pi3K/Akt and JAK/Stat signaling pathways contribute to tumor progression (Fig. 1) (22-26). The TME carries out a key role in promoting cancer growth, metastasis and resistance to therapy. This includes interactions between immune cells, blood vessels and fibroblasts, which aid in tumor survival (27-31). Tumor cells evade immune surveillance by secreting immunosuppressive factors such as programmed death ligand 1 (PD-L1), which suppresses T-cell function (32-35).

Surgical resection followed by chemotherapy or radiation is the primary treatment for early-stage NSCLC. In later stages (III and IV), chemotherapy, radiation or targeted therapies are used (36-43). Traditional chemotherapy, while effective, has limitations such as non-selectivity, damage to normal cells and the emergence of resistance (44-48).

Targeted therapies have advanced with a focus on specific molecular markers that inhibit tumor growth (49-53). Treatments for mutations in the EGFR, anaplastic lymphoma kinase and BRAF genes have shown promising results; however, challenges such as drug resistance (for example, the T790M mutation) and tumor heterogeneity persist. Newer-generation drugs such as osimertinib and alectinib are being developed to address these resistance mutations. Immunotherapy, particularly with PD-1/PD-L1 inhibitors, is a novel approach for activating the immune system to target cancer cells. However, these therapies face challenges, including inconsistent responses and side effects, which require further investigation (49-54).

Overall, while targeted therapies and immunotherapy reveal notable potential, ongoing challenges, such as resistance, side effects and tumor heterogeneity, highlight the need for personalized treatment strategies to improve the outcomes and survival of patients.

3. Lactic acid and lactylation modification

Lactic acid, once viewed as merely a byproduct of glycolysis, is now acknowledged as a vital metabolic fuel for various tissues, including the skeletal muscle, heart, brain and cancer cells (55-58). It carries out a key role in determining cell fate, particularly in processes such as macrophage polarization, and functions as a metabolic intermediary between glycolysis and oxidative phosphorylation (55-58). Additionally, lactic acid acts as a signaling molecule, influencing various regulatory pathways, such as immune cell modulation, lipolysis, wound healing and maintenance of cellular homeostasis (59-61). The TME refers to the local environment surrounding tumor cells, including surrounding cells, blood vessels, immune cells and the extracellular matrix, which interact to influence tumor growth, spread and response to treatment. During glycolysis, lactic acid is produced and subsequently enters the TME, where it induces acidification, a factor that contributes to treatment resistance. Moreover, lactic acid produced by peripheral tissues such as tumor-associated fibroblasts (TAFs) enters cells through monocarboxylate transporters (MCTs)1/4, thereby enhancing glycolysis and driving metabolic reprogramming (62-64). Accumulation of lactic acid and subsequent acidification are associated with inflammation within the tumor, promoting the polarization of tumor-associated macrophages (TAMs) towards the M2 phenotype, activation of oncogenes, suppression of tumor suppressor factors and facilitation of carcinogenesis (65-68). Furthermore, lactic acid assists tumor cells in evading the immune response by impairing dendritic cell antigen presentation and inducing apoptosis in NK cells (69-71). It can also lead to mutations in genes that drive tumor progression, resulting in genomic instability (72-74). Additionally, lactic acid mediates its effects through receptors such as MCT1/4 and G-protein coupled receptor 81, enhancing tumor angiogenesis, metastasis and adhesion of tumor cells to the extracellular matrix, ultimately promoting cancer cell migration (75-77).

Lactylation is a post-translational modification in proteins that was identified through a combination of peptide

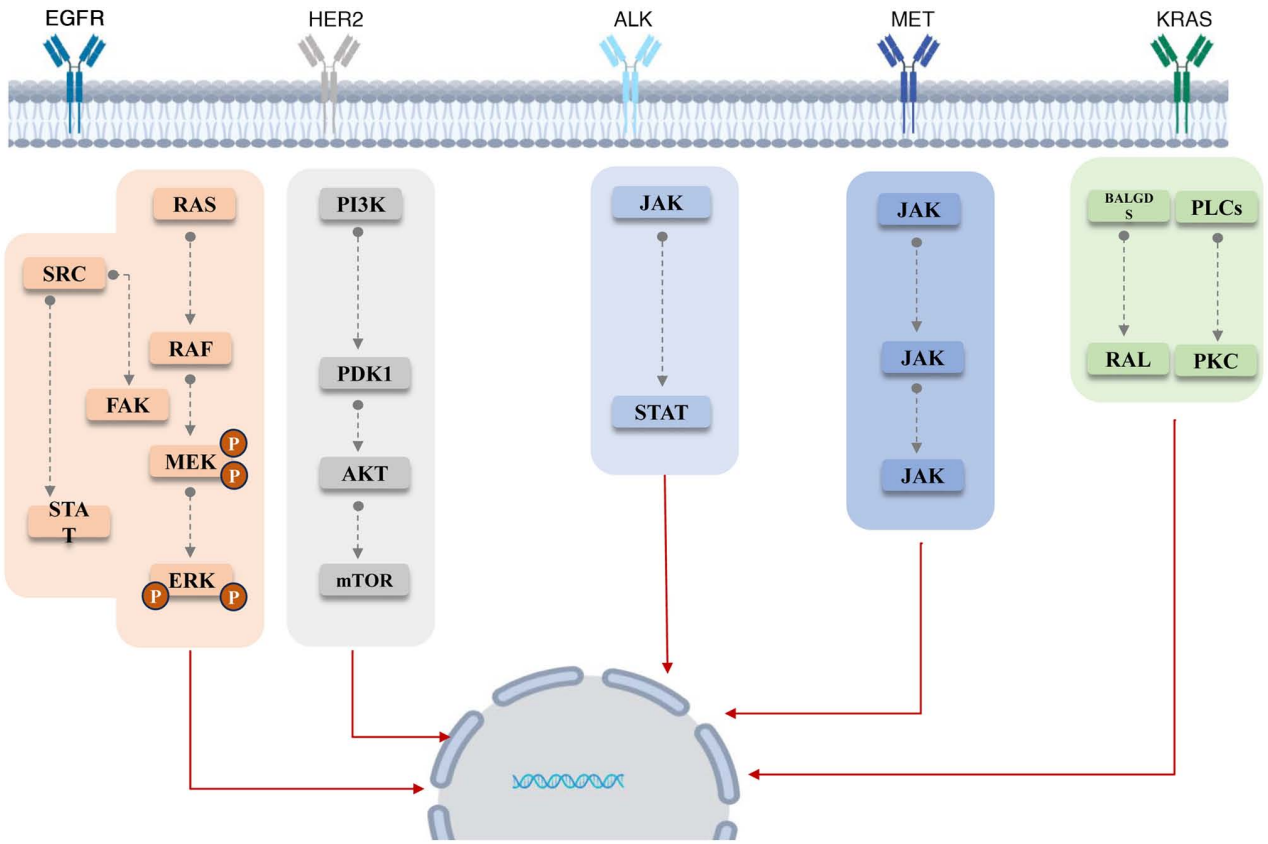

Figure 1. Molecular pathways associated with lung cancer initiation and progression. This diagram illustrates various molecular pathways involved in the initiation and progression of lung cancer. The pathways depicted include receptors and signaling molecules, such as EGFR, HER2, ALK, MET and KRAS. These signaling cascades, involving molecules such as RAS, PI3K, JAK, RAF and STAT, regulate cellular processes such as growth, proliferation and survival, ultimately contributing to the development and progression of lung cancer. ALK, anaplastic lymphoma kinase; MET, mesenchymal-epithelial transition factor; HER2, human epidermal growth factor receptor 2; SRC, proto-oncogene src; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase; STA, signal transducer and activator of transcription; PDK, pyruvate dehydrogenase kinase; RAL, ras-like GTPase; BALGDS, basal-like gene-differentiated subtypes; PLC, phospholipase C.

immunoprecipitation and high-sensitivity HPLC-MS/MS analysis (78-80). This modification occurs at lysine residues in both histone and non-histone proteins (78-80). To date, >1,000 lactylated proteins have been identified in various cancer cell types. Lactate, a metabolic byproduct of the Warburg effect, is the primary inducer of lactylation (81-83). Elevated levels of lactate (ranging from 10 to 30 mM in cancer cells) are essential for lactylation, suggesting that factors influencing glycolysis, such as lactate dehydrogenase (LDH) A, may regulate lactylation levels (84-86). This modification is catalyzed by histone acetyltransferases such as E1A-associated protein p300, CBP and tat interactive protein 60, which transfer the lactyl group from lactyl-CoA to specific target proteins (87-91). However, the low intracellular concentration of lactyl-CoA limits the activity of relevant enzymes, thus reducing the efficiency of lactylation. Additionally, delactylation is facilitated by delactylases, including HDACs, which regulate the stability and function of proteins by removing lactyl groups (92-95). The interaction between lactylation and delactylation carries out a key role in cellular metabolic regulation and functional modulation. While the mechanism underlying lactylation is well established, further investigation of key enzymatic parameters, such as the dissociation constant (Kd) and Michaelis constant (Km), is required. Moreover, the lactyl-CoA concentrations used in experimental settings may not accurately reflect *in vivo* physiological conditions (96-99). Lactylation carries out a key role in the regulation of gene transcription and protein function. Histone lactylation influences gene expression through epigenetic mechanisms, although its precise effect on transcription remains context-dependent. Non-histone lactylation can modulate the native functions of proteins and may impart new functional properties. For example, lactylation affects the activities of YAP, p53 and DNA repair-related proteins such as MRE11 and NBS1, which carry out important roles in tumorigenesis, cancer progression, chemotherapy resistance and maintenance of genomic stability (100-104). Furthermore, lactylation promotes cancer cell proliferation and metastasis by influencing processes such as protein nuclear localization, phase separation and transcriptional activation (105-107). The identification of lactylation provides new perspectives for understanding the functional relevance of the Warburg effect, as lactate serves as a central mediator of this modification. Consequently, lactylation carries out a pivotal role in the onset and progression of cancer and is emerging as a promising target for novel therapeutic strategies (Fig. 2).

4. Advancements in lactylation research in lung cancer

Prior to the introduction of lactylation as a concept, oncology research had already demonstrated that the modulation of

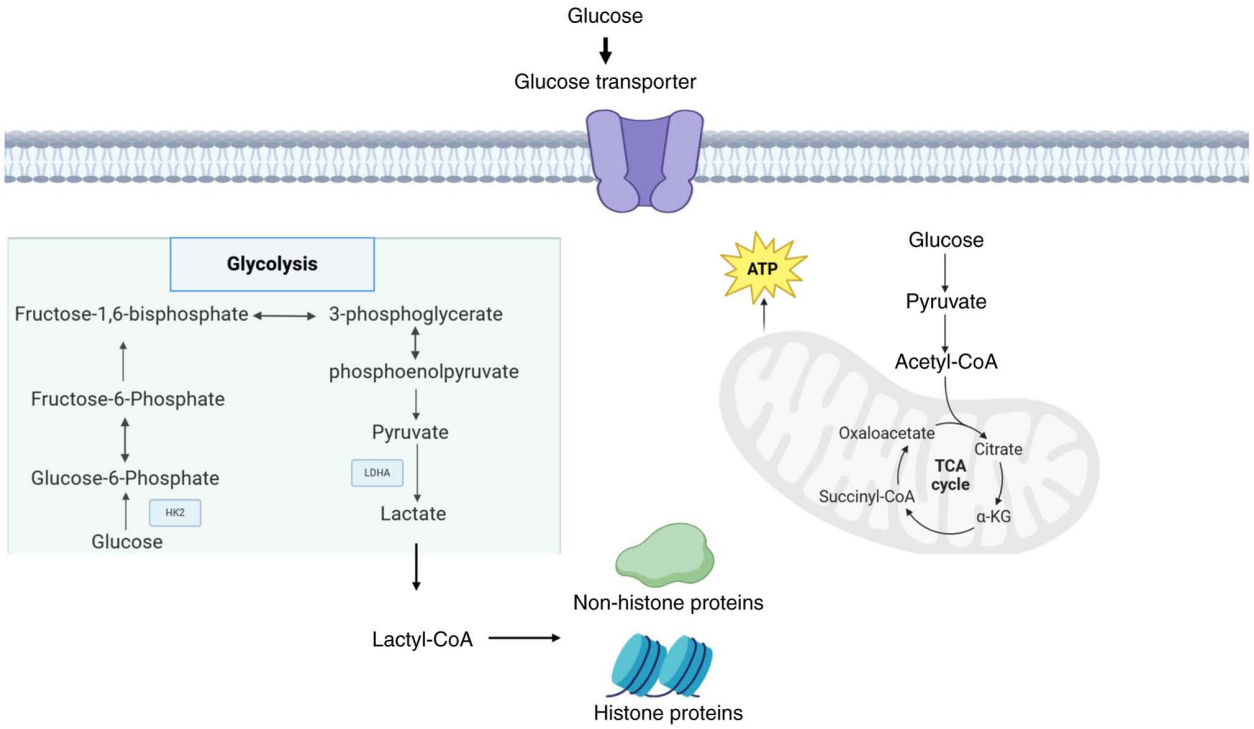

Figure 2. Schematic illustrating glycolysis, the TCA cycle and lactylation modifications. This diagram outlines the key metabolic pathways of glycolysis and the TCA cycle, along with the lactylation process. Glucose is transported into the cells and undergoes glycolysis to produce ATP and lactate. Lactate can subsequently be converted to lactyl-CoA, which is involved in the lactylation of histone and non-histone proteins. The diagram also shows the conversion of pyruvate into acetyl-CoA, which enters the TCA cycle and contributes to cellular metabolism. This illustration highlights the interconnectedness between metabolic processes and the role of lactylation in cellular function and regulation. TCA, tricarboxylic acid cycle; α-KG, α-ketoglutarate; CoA, co-enzyme A.

glycolysis could facilitate tumor progression, including lung cancer. For instance, Faubert *et al* (108) revealed that lung cancer cells sustain rapid proliferation and adapt to hypoxia in the TME through the accumulation and release of lactate. This metabolic shift not only aids in immune evasion but also promotes angiogenesis and metastasis through acidification of the surrounding tumor environment. Additionally, lactate buildup supports tumor growth by influencing various tumor-associated cells such as TAMs and TAFs. This study highlights the potential of targeting lactate metabolism as a therapeutic approach and suggests that blocking lactate production and transport could hinder lung cancer progression. Subsequent research focused on the regulation of glycolysis by specific proteins in lung cancer. Wang *et al* (109) demonstrated that protein tyrosine phosphatase receptor type H promotes the progression of NSCLC by enhancing glycolysis via the PI3K/AKT/mTOR signaling pathway. Similarly, Liu *et al* (110) revealed that hyperoxia induces glucose metabolic reprogramming and glycolysis by inhibiting the MYC/MCT1 axis in lung cancer. These studies consistently support the conclusion that enhanced glycolysis and lactate production are key drivers of lung cancer initiation and progression (111-119). Although glycolysis is widely known to promote tumor proliferation and metastasis, the precise mechanisms by which it exerts these effects are still debated. While glycolysis is generally considered a rapid source of energy, other studies have indicated that it also carries out a role in the regulation of several signaling pathways (109,110,120). Therefore, it is necessary to identify new regulatory mechanisms to clarify how glycolysis controls these pathways.

The concept of lactylation offers a new perspective on how glycolysis influences lung cancer progression. In 2021, Jiang *et al* (121) observed an increase in histone lactylation at the promoters of both the glycolytic enzyme hexokinase 1 (HK-1) and the tricarboxylic acid cycle enzyme isocitrate dehydrogenase [NAD(+)] 3 non-catalytic subunit γ (IDH3G) while exploring the role of lactate in lung cancer metabolism. Their findings suggested that lactate partially governs the metabolic pathways of lung cancer cells through histone lactylation. However, the study did not explain how lactylation directly influences cancer progression, and its methodology was restricted to ChIP-seq experiments, which revealed lactylation accumulation in the promoters of HK-1 and IDH3G, but lacked validation of the specific modification sites. Subsequently, Yang *et al* (122) analyzed lactylation in human lung tissues under normal physiological conditions and identified 724 Kla sites across 451 proteins. By cross-referencing these proteins with proteins listed in the human lactylation dataset, 141 proteins that underwent lactylation were identified (122), laying the groundwork for further investigation. The subsequent studies that varied in focus are detailed in Table I.

Lactylation modification as a prognostic indicator in lung cancer. Gao *et al* (123) developed 10 prognostic models for lung adenocarcinoma based on lactylation-related factors, utilizing machine learning techniques to predict both patient outcomes and immune infiltration levels. Their study identified key lactylation-related genes (LRGs) from publicly available datasets and constructed models that accurately forecasted survival outcomes associated with immune cell

Table I. Advances in lactylation modification research in lung cancer.

A, Lactylation modification as a predictor of lung cancer prognosis.

First Author/s, year	Protein modifications	Mechanisms of action	(Refs.)
Gao *et al*, 2024	NA	NA	(123)
Hua *et al*, 2025	NA	NA	(124)

B, Regulation of lung cancer progression by lactylation modification.

First Author/s, year	Protein modifications	Mechanisms of action	(Refs.)
Chen *et al*, 2024	Non-histone proteins	Lactylation of APOC2.	(125)
Wang *et al*, 2023		Lactylation of IDH3G.	(126)
Zhang *et al*, 2024		Lactylation of IGF1R.	(127)
Zhang *et al*, 2025	Histone proteins	CTHRC1 + CAFs enhance glycolysis via the TGF-b/Smad3 signaling pathway.	(150)
Wu *et al*, 2025		AIM2 histone lactylation modification regulates ACSL4 to inhibit ferroptosis.	(151)
He *et al*, 2023		The Numb/Parkin pathway stimulates lactate production, resulting in histone lactylation modification.	(152)
Liu *et al*, 2024		LKB1 promotes lactate production and suppresses histone H4 (Lys8) and H4 (Lys16) lactylation.	(153)

C, Targeting lactylation modifications to inhibit lung cancer progression.

First Author/s, year	Protein modifications	Mechanisms of action	(Refs.)
Guo *et al*, 2024	Histone proteins	FGS associates with PKM2 to regulate glycolysis and suppress H3 histone lactylation.	(131)

APOC2, Apolipoprotein C-II; IDH3G, isocitrate dehydrogenase (NAD(+)) 3 non-catalytic subunit γ; IGF1R, insulin-like growth factor 1 receptor; CTHRC1, collagen triple helix repeat containing 1; ACSL4, acyl-CoA synthetase long-chain family member 4; H, histone; PKM2, pyruvate kinase M2; CAFs, cancer-associated fibroblasts; AIM2, absent in melanoma 2; LKB1, liver kinase B1; FGS, fargesin; NA, not applicable.

infiltration within the TME. Upon validation, the model revealed high expression levels of keratin (KRT) 81 in both lung adenocarcinoma (LUAD) tissues and cell lines. Silencing KRT81 was revealed to inhibit cellular processes, such as proliferation, migration and invasion, while also inducing G0/G1 phase arrest and promoting apoptosis. Although their study demonstrated that KRT81 is a lactylation-related gene potentially undergoing lactylation modification during lung cancer development and progression and established its role in regulating malignant tumor progression, they were unable to provide direct evidence that KRT81 can indeed be lactylated. The specific lactylation sites on KRT81 remain unknown. Similarly, Hua *et al* (124) explored lactylation modifications as a predictive tool for lung cancer prognosis by integrating LRGs with multi-omics data. Through analysis of transcriptomic, epigenetic and somatic mutation data from The Cancer Genome Atlas LUAD cohort, they identified distinct lactylation-associated cancer subtypes. The authors validated two subtypes and a prognostic model utilizing nine central LRGs (HNRNPC, PPIA, BZW1, GAPDH, H2AFZ, RAN, KIF2C, RACGAP1 and WBP11) was established. This model successfully divided patients into high- and low-risk categories, with high-risk patients demonstrated worse prognosis, reduced survival and increased rates of recurrence and metastasis. TME analysis revealed that patients in the low-risk group exhibit heightened immune activity and respond favorably to both immunotherapy and chemotherapy. Although their study demonstrated the potential utility of lactylation modifications as a prognostic biomarker for patients with lung cancer, the conclusion that lactylation may function through immunomodulatory mechanisms remains unsupported by subsequent experimental validation.

Both studies (123,124) examined the involvement of LRG in LUAD but differed in their research approaches and focus areas. They both utilized multi-omics data, including gene expression, epigenetic information and mutation data, combined with machine learning techniques to investigate the molecular mechanisms of lactylation in LUAD and

develop predictive models for patient outcomes and immune responses. Both studies highlighted the considerable role of lactylation in the TME, cancer subtypes and prognosis. However, the research of Gao *et al* (123) emphasizes the molecular mechanisms underlying lactylation, particularly in immune evasion and tumor progression, where it influences key pathways (such as HIF-1α and mTOR) to promote tumor growth and resistance. By contrast, the study by Hua *et al* (124) concentrated on the molecular subtyping of lactylation-related genes using multi-omics data, successfully creating a highly accurate prognostic model for predicting patient outcomes and immunotherapy responses.

In conclusion, while the study by Gao *et al* (123) offers an in-depth analysis of the role of lactylation in immune evasion and the TME, it lacks detailed construction and validation of prognostic models. On the other hand, the study by Hua *et al* (124) creates a precise and validated prognostic model through the integration of multi-omics data and machine learning. However, the effectiveness of the model is dependent on dataset quality, requiring further validation for its clinical application.

Regulation of tumor progression by lactylation modification. Lactylation modifications are found in both histones and non-histones; previous research has focused on their role in lung cancer progression. Chen *et al* conducted a comprehensive lactome and metabolomic analysis of NSCLC samples. Their multi-omics methodology, supported by both *in vitro* and *in vivo* validation, revealed that lactate facilitates the breakdown of extracellular fats through lactylation of apolipoprotein C-II at the K70 position. This modification stabilizes apolipoprotein C-II, resulting in the release of free fatty acids, accumulation of regulatory T cells, enhanced resistance to immunotherapy and increased metastasis (125). Additionally, Wang *et al* (126) revealed that basic leucine zipper and W2 domains 2 (BZW2) increases glycolytic lactate production, subsequently leading to IDH3G lactylation and promoting LUAD progression. However, their study did not address whether the effect of BZW2 on lactate production affects histone lactylation, nor did it explore the potential interaction between IDH3G lactylation and pathways related to tumor metabolism, cell proliferation and metastasis. Similarly, Zhang *et al* (127) demonstrated that insulin-like growth factor 1 receptor lactylation accelerates aggressive lung cancer behavior and glycolysis, forming a self-perpetuating feedback loop. However, their study overlooked the influence of glycolytic regulation on histone lactylation. In the context of histone modification research, Zhang *et al* (127) proposed that lactylation and glycolysis may involve interconnected feedback loops, where glycolysis-promoting molecules enhance lactylation and, in turn, regulate their expression or activity.

Although studies on other tumor cells have revealed that lactylation modifications can regulate immune cells in the TME, thereby affecting tumor progression (128,129), other research has demonstrated that increased lactate production in tumor cells can promote gastric cancer progression by enhancing PD-L1 lactylation, which inhibits CD8 T cell anti-tumor immunity (130). These studies illustrate how lactylation modifications in tumor cells regulate immune cells. However, to the best of our knowledge, to date, no mechanisms by which lactylation modifications regulate immune cells have been identified in lung cancer.

Targeting lactylation modifications suppresses tumors. Guo *et al* (131) explored a novel approach targeting lactylation modifications to inhibit lung cancer progression. They examined the effects of Fargesin (FGS) on NSCLC using CCK8 and EdU assays, in addition to cell cycle analysis of A549 cells, in both *in vitro* and *in vivo* models involving nude mouse tumor transplants. Treatment with FGS (10-50 μM) led to a marked reduction in cell proliferation and a decrease in the expression of CDK1 and CCND1. Transcriptomic analysis revealed that FGS modulates cellular metabolic pathways, with differential metabolites showing enrichment in both the glycolysis and pyruvate metabolic pathways. Cell metabolism assays were used to measure the oxygen consumption rate and extracellular acidification rate of A549 cells. FGS treatment also suppressed lactate production and reduced the expression of key oncogenes including LDHA, LDHB, pyruvate kinase M2 (PKM2) and solute carrier family 2 member 1 (SLC2A1), which are key in lung cancer. Molecular docking simulations confirmed the interactions between these genes and FGS. Furthermore, overexpression and gene silencing experiments established PKM2 as a molecular target of FGS to prevent tumorigenesis. Finally, FGS inhibited H3 histone lactylation, a modification associated with tumorigenesis (131).

5. Potential of lactylation modifications in lung cancer therapy

Research on lactylation modifications in lung cancer is still in its early phases with limited foundational studies available. To the best of our knowledge, no drugs targeting lactylation modifications are undergoing clinical trials or have been specifically developed for lung cancer. Nevertheless, given the potential of lactylation, targeting this modification is a feasible therapeutic strategy. Building on existing findings, the present review explored potential targets for lactylation modifications in lung cancer therapy, establishing a foundation for future research.

Inhibitors of glycolytic enzymes. Glycolytic enzymes are key enzyme systems (for example, HK2, PKM2 and LDHA) that catalyze the glycolytic pathway (the breakdown of glucose to pyruvate). By regulating intracellular lactate production, they indirectly influence protein lactylation modifications (for example, histone lactylation), thereby associating cellular metabolism to epigenetic regulation. Studies have demonstrated that the increased expression of glycolytic enzymes in lung cancer promotes tumor progression (123,132). Targeting key enzymes in the glycolytic pathway can reduce lactate production. Drugs targeting enzymes such as HK, phosphofructokinase and LDH have revealed potential in preclinical studies (133-136). LDH inhibitors reduce lactate levels, suppress tumor growth and improve chemotherapy responses. LDHA inhibitors, such as oxamate, not only decrease lactate production but also enhance immune activation within the TME, demonstrating efficacy in preclinical models. For example, studies have revealed that oxamate notably inhibited

the growth of glioma cells. Mechanistically, oxamate inhibits LDHA, thereby suppressing C-C chemokine receptor 8 lactylation, which, in turn, enhances the inhibitory effect of immune cells on tumors (137). Furthermore, inhibition of pyruvate dehydrogenase kinase, which regulates the conversion of pyruvate to lactate, has been demonstrated to decrease lactate production and hinder tumor cell proliferation (138-141). A preclinical study targeting glycolysis to regulate lactylation and inhibit lung cancer have revealed that FGS binds to the key glycolytic enzyme PKM2, thereby inhibiting its function. This in turn suppresses histone lactylation in lung cancer cells and impairs their malignant phenotype of lung cancer cells (131).

MCT inhibitors. MCTs transport lactate to modulate lactylation, which generally acts as an oncogenic driver of lung cancer. One approach to inhibit lactate efflux from cancer cells is to target MCTs, particularly MCT1 and MCT4. MCT inhibitors prevent acidification of TME, enhance immune function and reduce tumor invasion (142). The MCT1 inhibitor AZD3965 has demonstrated promise in clinical trials for improving cancer treatment outcomes by disrupting lactate transport (143). Furthermore, as early as 2014, it was confirmed that AZD3965 can inhibit the proliferation of lung cancer cells (144). However, the specific mechanism remains unclear and we hypothesize that AZD3965 may inhibit lung cancer progression by suppressing lactylation modifications. MCT4 facilitates lactate efflux in glycolytic cancer cells, and the silencing of MCT4 results in cytoplasmic acidification, leading to tumor cell death. Predominantly expressed in hypoxic regions of rapidly proliferating tumors, MCT4 is a potential therapeutic target (145). Although existing MCT4-targeting drugs lack specificity, further investigation is essential to assess their efficacy in various types of cancer (such as, glioblastoma, NSCLC, oral squamous cell carcinoma, renal cell carcinoma) treatment (145). Moreover, CD147 carries out a key role in regulating the localization and stability of MCT1 and MCT4 on the plasma membrane, and targeting CD147 may provide a novel strategy for inhibiting both transporters. AC-73, a synthetic dimeric anti-CD147 antibody, has demonstrated antitumor activity in preclinical studies (146-148). While inhibiting MCT1 and MCT4 along with their partners (the auxiliary proteins CD147 and ancillary membrane protein of MCT) may have antitumor potential, to the best of our knowledge, clinical evidence supporting these findings is scarce. Targeting MCT1 and MCT4 may help normalize the pH of the TME, thereby enhancing immune responses and reducing metastatic potential (149).

Targeting lactylation or de-lactylation modifications. Targeting lactylation modifications provides a direct approach to cancer treatment, whereas intervening in both lactylation and delactylation modifications offers a more straightforward strategy. Research has revealed that increased lactylation in tumor cells can enhance the expression of pro-cancer molecules by regulating both non-histone and histone lactylation, while also affecting tumor-suppressive molecules. Lactylation modifications exhibit a wide range of effects, serving both pro- and anti-cancer functions. Consequently, more research is needed to explore effective targeting of lactylation modifications for tumor suppression.

6. Conclusion

Lactylation modifications are pivotal in the progression of lung cancer and influence tumor growth, invasion and immune evasion by modulating the TME, gene expression, and immune responses. The presence of lactylation in tumor cells can serve as a predictor of survival rates; targeting lactate metabolism and lactylation is a potential therapeutic approach. Future research should prioritize the identification of specific lactylation enzymes, development of reliable biomarkers, expansion of clinical trials and elucidation of the underlying mechanisms, all aimed at enhancing personalized therapies and improving clinical outcomes in patients with lung cancer. Furthermore, investigating the interplay between metabolic reprogramming and epigenetic modifications may reveal novel therapeutic targets and strategies to improve the effectiveness of cancer treatment.

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Authors' contributions

XW and JX were responsible for collecting and organizing the literature. NH, YZ, QL, TW and LT was responsible for organizing and writing the article. All authors read and approved the final manuscript. Data authentication 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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