# Role of lysine lactylation in neoplastic and inflammatory pulmonary diseases (Review)

SHANSHAN WANG*, HONGYAN ZHENG*, JIANPING ZHAO and JUNGANG XIE

Department of Respiratory and Critical Care Medicine, National Clinical Research Center of Respiratory Disease, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

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**Abstract.** Protein lysine lactylation is a ubiquitous and post-translational modification of lysine residues that involves the addition of a lactyl group on both histone and non-histone proteins. This process plays a pivotal role in human health and disease and was first discovered in 2019. This epigenetic modification regulates gene transcription from chromatin or directly influences non-histone proteins by modulating protein-DNA/protein interactions, activity and stability. The dual functions of lactylation in both histone and non-histone proteins establish it as a crucial mechanism involved in various cellular processes, such as cell proliferation, differentiation, immune and inflammatory responses and metabolism. Specific enzymes, referred to as 'writers' and 'erasers', catalyze the addition or removal of lactyl groups at designated lysine sites, thereby dynamically modulating lactylation through alterations in their enzymatic activities. The respiratory system has a remarkably intricate metabolic profile. Numerous pulmonary diseases feature an atypical transition towards glycolytic metabolism, which is linked to an overproduction of lactate, a possible substrate for lactylation. However, there has yet to be a comprehensive review elucidating the full impact of lactylation on the onset, progression and potential treatment of neoplastic and inflammatory pulmonary diseases. In the present review, an extensive overview of the discovery of lactylation and advancements in research on the existing lactylation sites were discussed. Furthermore, the review particularly investigated the potential roles and mechanisms of histone and non-histone lactylation in various neoplastic and inflammatory pulmonary diseases, including non-small cell lung cancers, malignant pleural effusion, pulmonary fibrosis, acute lung injury and asthma, to excavate the new therapeutic effects of post-translational modification on various pulmonary diseases.

*Correspondence to:* Professor Jungang Xie or Professor Jianping Zhao, Department of Respiratory and Critical Care Medicine, National Clinical Research Center of Respiratory Disease, Key Laboratory of Pulmonary Diseases of Health Ministry, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan, Hubei 430030, P.R. China
E-mail: xiejjgg@hotmail.com
E-mail: zhaojp88@126.com

*Contributed equally

*Abbreviations:* ALI, acute lung injury; HK-1, hexokinase 1; H3K18la, lactylation of histone 3 on lysine residue 18; Hif-1α, hypoxia-inducible factor-1α; IL, interleukin; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MPE, malignant pleural effusion; NSCLC, non-small cell lung cancer; p300/CBP, p300/CREB binding protein; PKM2, pyruvate kinase isozyme M2; PTM, post-translational modification; RUNX2, runt-related transcription factor 2; SLC25A29, solute carrier family 25 member 29; TGF-β, transforming growth factor β; VEGFA, vascular endothelial growth factor A; VPS34, vacuolar protein sorting 34; YTHDF1, YTH N6-methyladenosine RNA-binding protein F1; YY1, Yin Yang-1

*Key words:* lung cancer, pulmonary inflammatory diseases, lysine lactylation, histone, writers and erasers

## Contents



## 1. Introduction

Lactate, traditionally regarded solely as a by-product of anaerobic glycolysis and long deemed insignificant in cellular functions, has undergone a reassessment in light of the discovery of metabolic reprogramming in the 1920s (1). Metabolic reprogramming is defined as the adjustment of

metabolic pathways to support cellular functions such as proliferation, differentiation, survival and stress responses, particularly the transition to aerobic glycolysis (2). Aerobic glycolysis and the Warburg effect are essentially the same concept, referring to the phenomenon where cells primarily use glycolysis to generate energy even when oxygen is readily available, instead of the more efficient oxidative phosphorylation pathway. This often occurs under stress or pathological conditions (3). This shift from mitochondrial respiration to glycolysis, along with the subsequent production of lactate in oxygen-sufficient environments, is not only important in understanding cancer development but also plays a crucial role in the mechanisms behind inflammatory diseases, indicating a shared metabolic pathway between the two conditions (3,4). In the past three decades, numerous studies have revealed a diverse array of novel and previously undocumented biological functions of lactate. It is now acknowledged not only as an essential carbon source for metabolic reprogramming and cellular metabolism but also as a significant signaling involved in gene expression, immune activation, energy supply and metabolic regulation (5,6). In a significant advancement in 2019, Zhang *et al* (7) uncovered that lactate serves as an essential substrate in a new form of epigenetic modification known as histone lysine lactylation. This finding was established through mass spectrometry analyses of core histones in human and mouse cells (7). Lactylation is a ubiquitous and reversible post-translational modification (PTM) characterized by the addition of a lactyl group to a lysine residue in the histone or non-histone tail. Lactylation was first discovered on histones within the nucleosome and this modification is now understood to significantly impact gene expression by influencing the initiation of transcription and consequently affecting important cellular functions. Furthermore, lactylation has also been observed to occur in non-histone proteins, directly impacting their functions and corresponding protein functions. In the last five years, research from various studies has provided greater insight into the molecular mechanisms underlying histone and non-histone lactylation, highlighting their significant roles in a diverse array of diseases, such as cancers, inflammatory conditions, cardiovascular disorders and certain pulmonary ailments (8-11). The primary function of the lungs is to facilitate gas exchange (respiration), however, they also serve as a significant immune organ. Furthermore, these intricate metabolic processes occurring in the lungs can be susceptible to various diseases (12). Metabolic reprogramming has been identified as a significant factor in pulmonary diseases, as it influences cellular energy mechanisms and biosynthetic requirements. This modulation subsequently affects tumor proliferation in lung cancers and alters immune responses in inflammatory disorders, including asthma and lung fibrosis (13,14). The discovery of lysine lactylation opens new avenues for understanding the interaction of metabolic reprogramming and epigenetic modification in the context of pulmonary diseases. In lung cancer, for example, cancer cells prioritize glycolysis as their primary energy source even when oxygen is available, leading to the production and accumulation of lactate within the tumor microenvironment (TME) (15). Elevated lactate subsequently promotes lysine lactylation, which in turn activates or represses oncogenes or tumor suppressor genes, contributing to tumorigenesis and cancer progression (16). However, a comprehensive review that consolidates and summarizes its effects on neoplastic and inflammatory pulmonary diseases remains notably lacking.

In this review, the latest significant advances concerning the roles of both histone and non-histone lactylation in neoplastic and inflammatory pulmonary diseases were examined, with a primary focus on non-small cell lung cancers (NSCLC), malignant pleural effusion, pulmonary fibrosis, acute lung injury and asthma. These explorations aim to deepen the understanding of lung physiology by introducing a novel perspective that could potentially revolutionize therapeutic approaches through the targeted modulation of specific lactylation sites. Furthermore, the study advocates more extensive and detailed future research to fully elucidate the involvement of PTMs, particularly lactylation, in the pathogenesis of various pulmonary diseases.

## 2. Discovery of lactylation modification

In 2019, a landmark study published in the Nature Journal was the first to identify 28 lactylation sites on core histones in mouse bone marrow-derived macrophages and human HeLa cells. This groundbreaking study revealed that lactate-derived lactylation of histone lysine residues serves as an epigenetic modification that directly enhances gene transcription from chromatin (7). In 2020, scientific research began to concentrate on lactylation in non-histone proteins, highlighted by the pioneering study conducted by Gao *et al* (17), which identified the presence of lactylation in the necrotic fungal pathogen Botrytis cinerea. Their extensive global lysine lactylome analysis of 166 proteins revealed 273 lactylation sites (17). This period also saw the identification of lactylation sites in plants and protists, further expanding the known range of lactylation's biological significance (18,19). Subsequently, research into lactylation expanded to encompass various major systemic diseases. In 2021, significant research findings revealed that patients with pulmonary fibrosis demonstrated markedly elevated lactate levels in the lungs. This elevation facilitated lactylation through the action of acetyltransferase p300 on the promoters of profibrotic genes, consequently inducing a pro-fibrotic macrophage phenotype. This discovery marked the first identification of the involvement of lactylation in pulmonary diseases (11). Furthermore, Yu *et al* (8) identified an association between elevated histone lactylation and poor prognosis in patients with ocular melanoma. Additionally, scientists elucidated the role of histone lactylation in uterine remodeling through a proteomic map of ligand-receptor interactions at the ovine maternal-fetal interface (20). Furthermore, Pan *et al* (21) first detected that histone lactylation is increased in the brain tissues of patients with Alzheimer's disease, proposing that the positive feedback loop glycolysis/lactylation further exacerbated microglial functional impairment. In 2022, a subsequent exploration indicated that, in the early stages of post-myocardial infarction, elevated levels of H3 lysine 18 lactylation (H3K18la) in monocytes-macrophages promoted the transcription of reparative genes, suggesting a beneficial role for histone lactylation in cardiac function improvement following myocardial infarction (10). A more recent comprehensive global analysis conducted in 2023 of lactylation in the human lung under normal physiological

conditions identified 724 lactylation sites in 451 proteins, with 141 proteins newly identified as undergoing lactylation (22). In summary, the discovery of lactylation modification as an epigenetic modification in 2019 has significantly expanded the understanding of metabolic and epigenetic crosstalk in cellular regulation. Lactylation, originally discovered in histones, was first recognized for its role in modulating gene transcription. Subsequent studies have demonstrated its occurrence in non-histone proteins and across a range of species, thereby expanding its biological significance. The connection of lactylation to systemic conditions like pulmonary fibrosis, neoplastic disease, myocardial infarction and Alzheimer's disease highlights its potential impact on health and disease. Furthermore, the identification of multiple lactylation sites across various proteins in the lung represents a vital area of study with profound implications for future research and medicine.

## 3. Histone lactylation and gene regulation

Histone modifications are pivotal in the field of epigenetics, serving as crucial regulators of chromatin structure and gene expression and thereby influencing a vast array of cellular processes (23). Among various histone modifications, lactylation is a relatively novel PTM that has garnered significant attention from researchers. Lactylation involves the addition of lactyl groups to lysine residues on histone proteins, forming ε-N-lactyl lysine (24). Lactylation influences the interaction between histones and DNA, thereby impacting the compaction of chromatin. This alteration regulates the accessibility of transcription factors and various epigenetic regulators to genetic material. Consequently, this indicates that histone lactylation plays a crucial role in the regulation of gene activation and repression, as well as in shaping cell fate and responding to environmental changes (Fig. 1).

*Cellular proliferation and differentiation*. Recent research has demonstrated that the lactylation of histones in key genes participates in the proliferation of tumor cells as well as tumor-associated macrophages, thereby impacting the progression of various neoplastic diseases (25,26). For instance, Li *et al* (27) discovered that H3K18la was fueled by tumor-derived lactate in the retinoic acid receptor-γ promoter, which endowed macrophages with a protumor phenotype and further activated TRAF6-IL-6-STAT3 signaling in colorectal cancer cells. Similarly, H3K18la enrichment regulated by lactyltransferases p300 in the promoter of YTH N6-methyladenosine RNA-binding protein 2 in ocular melanoma cells, as well as c-Myc in breast cancer cells, facilitated the increase in their transcription and translation levels. This promoted the proliferation of cancer cells and contributed to the tumorigenesis of both ocular melanoma and breast cancer (8,28). In addition to H3K18la, genes with promoters marked by H4K12la have been found to be enriched in pathways related to cancer cell proliferation, including connective tissue growth factor and cyclin E1 (CCNE1) in anaplastic thyroid cancer cells (29). Histone lactylation also plays an important role in cell differentiation and self-renewal. H3K18la has been shown to be enriched on the proximal promoter of JunB, where it can activate its expression and subsequently facilitate osteoblast differentiation (30). Previous research indicated that neuraminidase 2 (Neu2) can induce myoblast differentiation (31). Dai *et al* (32) further established the prevalence of H3K9la in the promoter region of Neu2 during the process of cell differentiation which were modulated by p300. During the Warburg effect in glioblastoma cells, histone lactylation is increased at the H3K18la site, which in turn leads to the enhanced transcription of LINC01127; this long non-coding RNA is linked to the NF-κB signaling pathway and ultimately promotes the self-renewal capacity of the glioblastoma cells (33,34). In conclusion, the emerging evidence highlights the critical role of histone lactylation, particularly on H3K18la and H4K12la, in regulating both cellular proliferation and differentiation, underscoring its significant impact on tumorigenesis and cell fate determination.

*Cellular senescence*. Cellular senescence is a complex and multifactorial process marked by an irreversible cessation of cell division, accompanied by changes in gene expression, chromatin organization and the secretion of pro-inflammatory factors, collectively known as the senescence-associated secretory phenotype (SASP) (35,36). Enhanced expression of H3K18la was reported to result from elevated lactate levels in senescent microglia, which in turn upregulated SASP components IL-6 and IL-8. This upregulation occurred through the stimulation of the NF-κB pathway through increasing binding to the promoter of *Rela*(*P65*) and *NF-κB1*(*P60*). These changes not only accelerated the aging of the brain and the progression of Alzheimer's disease pathology but also highlighted the remarkable adaptability of senescent cells to fluctuating metabolic states. Acetyltransferase p300/CBP and PCAF also worked as histone lacyltransferases in cells, upregulating H3K18la in senescent microglia and hippocampus tissues (37). Additionally, senescent cells, characterized by increased glycolysis and reduced mitochondrial function, could enhance histone lactylation through metabolic reprogramming. This process can further strengthen the senescence program and SASP (38). This metabolic-epigenetic coupling underscores the adaptability of senescent cells to their metabolic state. For instance, accumulated lactate inhibited histone lysine delactylase HDAC3 and promoted H4K12la. Consequently, enriched H4K12la was assembled in the SASP promoter, activating SASP transcription, which exacerbated vascular smooth muscle cell senescence and atherosclerosis, further demonstrating the far-reaching implications of histone lactylation beyond individual cellular states (39). As elucidated, the intricate interplay between histone lactylation and cellular senescence offers profound insights into the mechanisms driving age-related pathologies. Furthermore, the irreversible arrest in cell division that defines senescence is intricately linked to notable changes in gene expression and chromatin dynamics, notably exemplified through metabolic reprogramming-mediated histone lactylation modifications.

*Myeloid immune cell activation*. Myeloid cells, including macrophages and neutrophils, serve as the first line of defense against pathogens and are essential in maintaining homeostasis. Studies have demonstrated that histone lactylation represents a critical epigenetic mechanism in myeloid immune cell activation and function (40,41). For instance, p300-mediated

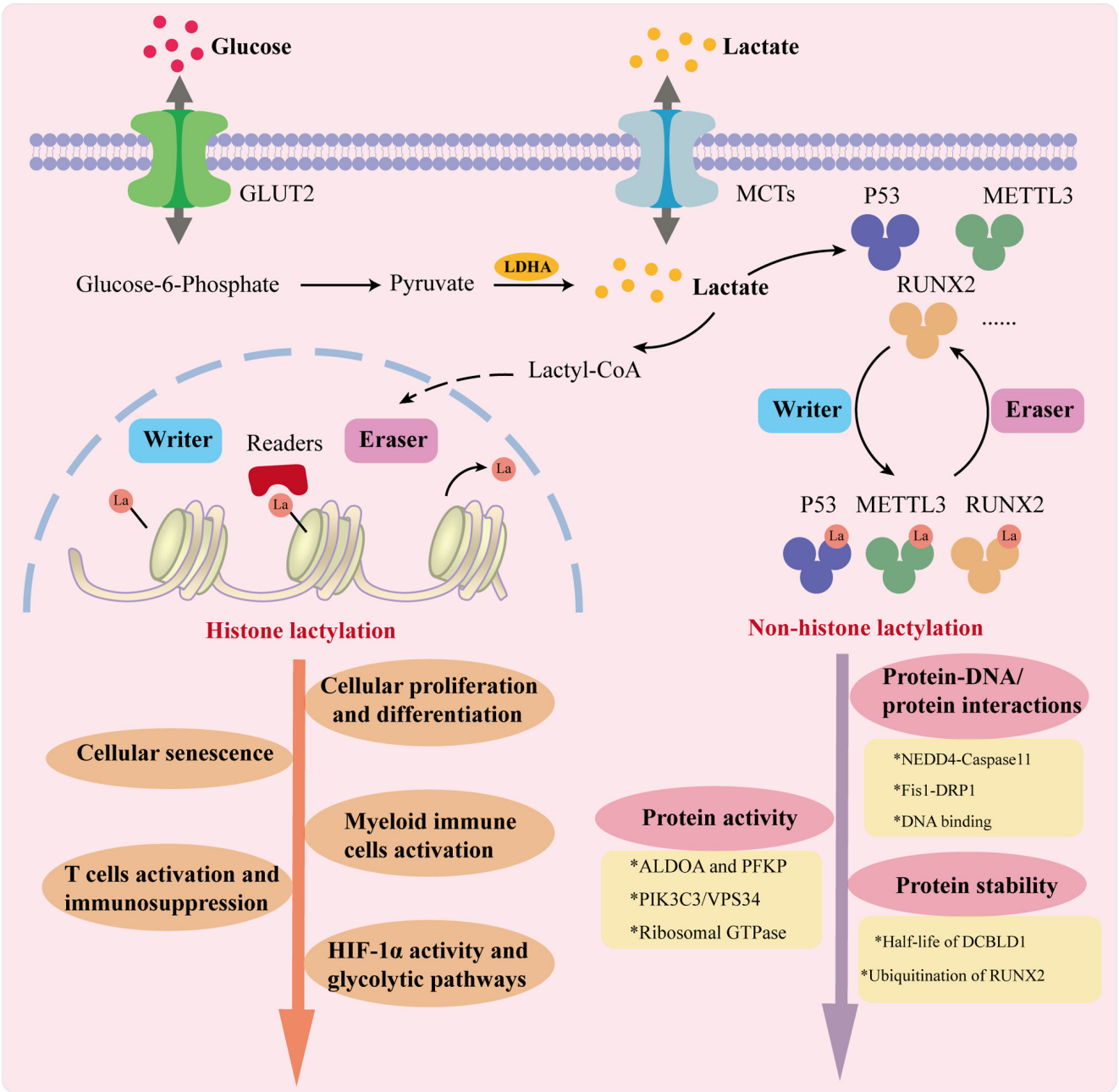


Figure 1. Simplified diagram of histone and non-histone lactylation. Cells produce lactate through glycolysis or obtain it from the extracellular environment, with lactate serving as a substrate for lactylation. Elevated levels of histone lactylation, particularly at gene promoters, are linked to the activation of transcription, which plays a crucial role in regulating cell fate. This includes processes such as cellular proliferation, differentiation and senescence, as well as the functions of HIF-1α, glycolysis, tumor immunity and inflammation. Meanwhile, lactate-induced lysine lactylation of non-histone proteins such as P53, METTL3 and RUNX2, under the influence of writers and erasers, can affect protein-DNA/protein interactions, protein activity and protein stability, ultimately influencing the pathogenesis and progression of various diseases. ALDOA, aldolase A; DRP1, dynamin-related protein 1; DCBLD1, discoidin, CUB and LCCL domain-containing type I; Fis1, fission 1; GTPase, GTP hydrolase; GLUT1, glucose transporter type 1; HIF-1α, hypoxia-inducible factor-1α; LDHA, lactate dehydrogenase A; METTL3, methyltransferase 3; MCTs, monocarboxylate Transporters; NEDD4, neuronally expressed developmentally downregulated 4; NUSAP1, nucleolar and spindle associated protein 1; PFKP, phosphofructokinase, platelet; PIK3C3, phosphatidylinositol 3-kinase catalytic subunit type 3; RUNX2, runt-related transcription factor 2; VPS34, vacuolar protein sorting 34.

histone lactylation binding to interleukin (*IL)-10* promotor in monocyte-derived macrophages, promoted IL-10 expression and enhanced their immunosuppressive activity in glioblastoma (42). This complex interplay between metabolism and immune response suggests a nuanced role of histone lactylation in shaping the immune landscape, likely influencing inflammation and cancer pathogenesis. Lactate-induced H4K12 lactylation and subsequent hypoxia-inducible factor-1α (*Hif-1α*) transcription in macrophages further aggravate metabolic dysregulation and inflammatory infiltration within the microenvironment in type 2 diabetes (43). Methylsulfonyl-methane increases lactate levels in peritoneal lavage fluids and subsequently results in the elevation of histone H3K18la levels. This elevation directly facilitates the transcription of downstream target genes, including Arg1, thereby promoting the M2 polarization of peritoneal macrophages during infection

and sepsis (44). Furthermore, elevated H3K18la levels also upregulate C-X-C motif cytokine ligand 1 (CXCL1) and CXCL5, promoting neutrophil recruitment, which is crucial for clearing the infection (45,46). Overall, histone lactylation functions as a multifaceted regulatory mechanism, influencing innate immune responses and the activities of myeloid immune cells across various pathological scenarios, which may have significant implications for therapeutic interventions in inflammatory diseases.

*T-cell activation and immunosuppression*. Histone lactylation has also emerged as a significant epigenetic modification influencing T-cell activation and immunosuppression, critical processes in the TME that affect tumor progression and immune surveillance (47). Notably, H4K5la enrichment at the programmed cell death-ligand promoter in leukemic cells attenuates $CD8^+$ T-cell activation, mediating immunosuppression in acute myeloid leukemia (48). Similarly, H3K18la activated CD39, CD73 and CCR8 promoters in glioma stem cell-co-cultured $CD4^+$ T cells and macrophages, as well as vascular cellular adhesion molecule 1 in gastric cancer cells, thereby nurturing an immunosuppressive TME (49,50). Furthermore, histone lactylation may equivalently influence regulatory T cells (Tregs), which are critical mediators of immunosuppression. Improved lactylation may facilitate the expression of genes that stabilize and increase the populations of Tregs, thereby strengthening the immunosuppressive environment. This environment not only inhibits the activity of effector T cells but also aids in tumor survival by suppressing anti-tumor immunity (42,51). These findings underscore the importance of histone lactylation as a potential target for therapeutic interventions to counteract tumor-induced immunosuppression, enhance T cell activation and improve the efficacy of cancer immunotherapies. Further, understanding the precise mechanisms of histone lactylation in the TME may pave the way for novel strategies designed to restore immune surveillance against tumors.

*Hif-1α activity and glycolytic pathways*. HIF-1α acts as a central transcription factor that regulates the metabolic reprogramming process, primarily by significantly enhancing glycolysis when cells experience low oxygen conditions (hypoxia), effectively switching the cell's energy production towards a more efficient anaerobic pathway (52,53). In microglia and uterine stromal cells, for instance, lactate-dependent H4K12la enrichment at the *HIF-1α* promoter upregulates HIF-1α transcription, thereby forming a feedback loop that enhances glycolysis. This underscores the influence of histone lactylation in fine-tuning the expression levels of HIF-1α, which in turn sustains the glycolytic pathway vital for energy production under hypoxia (21,54). Similarly, the enrichment of H3K18la at the promoter of ubiquitin-specific peptidase 39 enhanced its expression, subsequently activating the PI3K/AKT/HIF-1α signaling pathway. This elucidates the molecular interconnections in which histone lactylation, metabolic enzymes such as phosphoglycerate kinase 1, and key signaling pathways converge to promote glycolytic flux (55). Furthermore, H3K18la promotes platelet-derived growth factor receptor β transcription, which leads to an increase of glycolysis, also forming a glycolytic positive feedback loop in clear cell renal cell carcinoma (56). Chen *et al* (57) also explored the vital role of histone lactylation in hypoxic pulmonary hypertension (PH). They revealed that hypoxia environments specifically promote pulmonary artery smooth muscle cell (PASMC) proliferation in a mitochondrial reactive oxygen species (mtROS)-dependent manner, the chemically reactive molecules containing oxygen and free radicals produced within the mitochondria. The mtROS-HIF-1α axis triggers the PASMC glycolytic switch through the HIF-1α/pyruvate dehydrogenase (PDH) kinase 1 (PDK1)&PDK2/p-PDH-E1α axis. This process promotes lactate secretion and subsequently induces H3K18la and H4K5la of HIF-1α targets, leading to PASMC proliferation, vascular remodeling and the occurrence of hypoxic PH (57). Collectively, the crosstalk between histone lactylation and glycolytic pathways denotes a feedback mechanism and a vital axis in metabolic adaptation. Histone lactylation influences gene expression with precision by modulating HIF-1α activity and enhancing glycolysis, thereby directly affecting cellular behavior and phenotype in pathological conditions marked by altered metabolic states, including cancer and hypoxic diseases. A comprehensive summary of research on histone lactylation and gene regulation studies is provided in Table I.

## 4. Non-histone lactylation and protein modification

Lactylation has also been shown to alter the functions of non-histone proteins by regulating their activity, interactions and stability, subsequently influencing cellular processes, particularly in inflammation and cancer (Fig. 1). Central to these regulatory mechanisms is the alteration of enzymatic activities through specific lysine lactylation sites. In cancer metabolism, for instance, lactylation of glycolytic enzymes such as aldolase A at K147 and phosphofructokinase at K688 decreases their enzyme activities. This highlights a pivotal shift in metabolic reprogramming in colon cancer cells. The decreased activity of these metabolic enzymes due to lysine lactylation is suggestive of an adaptive mechanism within the TME that promotes cellular proliferation and cancer progression. This is not merely an incidental modification but hints at a broader strategy where tumors exploit metabolic plasticity conferred by lactylation to sustain growth and evade regulatory checkpoints (58,59). Furthermore, the lactylation at K45 leads to the inhibition of glucose-6-phosphate dehydrogenase, which impairs its capacity to form functional dimers and consequently disrupts its function in antioxidant defense. This inhibition is crucial during oxidative stress as it hinders the cell's capacity to counteract the redox imbalance, potentially influencing the fate of cells under duress. Likewise, pyruvate kinase isozyme M2 (PKM2) modulation in macrophages through lactylation illustrates lactate's role in immune-cell metabolism and function. The inhibition of tetramer-to-dimer transitions of PKM2 through K62 lactylation enhances its pyruvate kinase activity and reorients macrophages towards a reparative phenotype. This shift not only impacts local inflammatory responses but also mirrors wider systemic changes that occur during infection and tumor evolution, highlighting a potential therapeutic angle to modulate macrophage function (60,61). In the realm of endolysosomal trafficking, lactate-induced vacuolar protein sorting 34 (VPS34) K356 and K781 lactylation promoted the interaction of PIK3C3

Table I. Histone lactylation and cellular functions.

| Functions of histone lactylation | Target | Promoters | Writers/erasers | Cell type | Specific functions | (Refs.) |
|---|---|---|---|---|---|---|
| Cellular proliferation and differentiation | H3K18 | YTHDF2 | p300/CBP | Melanoma cell | Accelerated tumorigenesis of ocular melanoma | (8) |
| | H3K18 | RARγ | / | Macrophage | Endowed macrophages with tumor-promoting functions | (27) |
| | H3K18 | c-Myc | p300/CBP | Breast cancer cell | Promoted the proliferation of breast cancer cells | (28) |
| | H3K9 | Neu2 | p300/CBP | Myoblast | Affected myoblast differentiation | (32) |
| | H3K18 | LINC01127 | / | Glioma stem cell | Promoted self-renewal in glioma stem cells | (33) |
| Cellular senescence | H3K18 | Rela (P65) and NF-κB1(P60) | p300/CBP and PCAF | Microglia | Upregulated SASP components IL-6 and IL-8, regulates brain aging and Alzheimer's disease. | (37) |
| | H4K12 | SASP | HDAC3 | VSMC | Activated SASP transcription, exacerbated VSMC senescence and atherosclerosis. | (39) |
| Myeloid immune cell activation | Histone | IL-10 | p300/CBP | MDM | Enhanced MDM immunosuppressive activity in glioblastoma | (42) |
| | H3K18 | Arg1 | / | Macrophage | Promoted anti-inflammatory differentiation of macrophages during infection and sepsis | (44) |
| | H3K18 | CXCL1, CXCL5 | / | Colorectal cancer cell | Promoted neutrophil recruitment and modulated the tumor metabolism | (46) |
| T cell activation and immunosuppression | H4K5 | PD-L1 | / | Leukemic cell | Attenuated CD8+ T-cell activation and mediated immunosuppression | (48) |
| | H3K18 | CD39, CD73, CCR8 | / | Glioma stem cell | Induced immunosuppressive TME formation | (49) |
| HIF-1α activity and glycolytic pathways | H4K12 | Hif-1α, Pkm, Ldha | / | Microglia | Increased glycolytic activity and exacerbated microglial dysfunction | (21) |
| | H4K12 | Hif-1α | / | Uterine stromal cell | Formed a H4K12la-HIF-1α-glycolysis feedback loop to promote decidualization | (54) |
| | H3K18 | USP39 | / | Endometrial carcinoma cell | Activated the PI3K/AKT/HIF-1α signaling pathway to stimulate glycolysis | (55) |
| | H3K18 | PDGFRβ | / | Clear cell renal cell | Formed a H3K18la-PDGFRβ-glycolysis feedback loop and promoted the growth and metastasis of tumor | (56) |

Arg1, arginase 1; Hif-1α, hypoxia-inducible factor-1α; IL-10, interleukin 10; MDM, monocyte-derived macrophage; Neu2, neuraminidase 2; PDGFRβ, platelet-derived growth factor receptor β; PD-L1, programmed cell death-ligand 1; RARγ, retinoic acid receptor γ; SASP, senescence-associated secretory phenotype; USP39, ubiquitin specific peptidase 39; VSMC, vascular smooth muscle cell; YTHDF2, YTH N6-methyladenosine RNA-binding protein 2.

complex I and II subunits to enhance VPS34 kinase activity and facilitate sophisticated autophagy. This axis fostered cancer cell endurance through increased autophagic flux that affected intracellular signaling and substrate degradation.

Lactylation-induced autophagic modulation appears to be an attractive target for interventions aiming to disrupt cancer cell homeostasis and promote cellular death pathways (62). Furthermore, the K408 lactylation of elongation factor 1α, which intensifies ribosomal GTPase activity and influences protein synthesis, provides substantial insight into how cellular machinery is co-opted for oncogenic purposes. The involvement of lactyltransferases like KAT8 in modulating this effect suggests a complex interplay between enzymatic regulation and protein translation that could be harnessed for therapeutic innovation in tumorigenesis (63). In acute promyelocytic leukemia, a variety of non-histone protein targets susceptible to lactylation is revealed during lactylation of methyltransferase 3. The complex regulation of methyltransferase activity by lactylation highlights a distinctive regulatory role that may offer insights into cellular dysregulation in leukemia and possible strategies for therapeutic intervention. Additionally, the lactylation of methyltransferase 3 significantly influences its enzymatic activity in acute promyelocytic leukemia cells, emphasizing a unique regulatory role that could shed light on cellular dysregulation in leukemia and potential therapeutic pathways (64).

Further, non-histone lactylation also emerges as a critical modifier of protein interactions and stability, influencing a variety of cellular processes and pathways with profound implications for health and disease. The addition of a lactyl group alters the surface charge of proteins, thereby modulating their interactions with other partner(s) and stability. This modification can significantly impact cellular functionality by either enhancing or inhibiting protein interactions, consequently affecting pathways ranging from inflammation to tumor metabolism regulation and transcriptional dynamics (65,66). For instance, lactate-induced neuronally expressed developmentally downregulated 4 lactylation at K33 in macrophages hinders its interaction with caspase-11, which in turn prevents the subsequent ubiquitination of caspase-11, ultimately promoting macrophage pyroptosis. This process underscores a crucial regulatory mechanism in inflammation and cell death pathways, potentially indicating new therapeutic interventions in inflammatory diseases (67). By contrast, lactylation can also facilitate interactions, as seen in renal tubular epithelial cells where mitochondrial fission 1 lactylation at K20 promotes mitochondrial fission and oxidative stress through enhanced interaction with dynamin-related protein 1. This finding highlights lactylation's significant role in mitochondrial dynamics and emphasizes its potential impact on cellular stress responses (68). Furthermore, lactylation has the potential to enhance signaling pathways. Specifically, lactylation at K72 of the membrane-organizing extension spike increases its interaction with transforming growth factor β (TGF-β) receptor I, thereby promoting downstream SMAD3 signaling. This process strengthens TGF-β signaling in Tregs within the TME, indicating that lactylation may contribute to tumor progression and immune evasion. Consequently, it represents a promising target for cancer immunotherapy (51). Lactylation's influence also extends to transcription factors, where it can alter their binding capacity with corresponding DNA and thus transcriptional activity. For instance, lactylation of p53 at K120 and K139 impairs its liquid-liquid phase separation, DNA binding and transcriptional activation, correlating with poor prognosis among cancer patients carrying wild-type p53 (69). This modification can critically affect tumor suppressor function, providing insights into cancer biology and potential targets for anti-tumor therapeutic intervention. Similarly, the lactylation of Yin Yang-1 (YY1) enhances EGF2 transcription, promoting angiogenesis under hypoxic conditions. This finding links lactylation with pathological conditions such as blindness, offering new perspectives on the regulation of angiogenesis (70). In hepatocellular carcinoma, lactylation of centromere protein A (CENPA) at K124 accelerates CENPA binding at *YY1* promoter regions to drive oncogene CCND1 and neuropilins-2 expression (71). Exercise-induced lactylation at methyl CpG binding protein 2 K271 also binds to the promoter of epiregulin, leading to the inhibition of its transcription and facilitating the remission of atherosclerosis (72). These diverse effects on transcription underscore the broad regulatory potential of non-histone lactylation in various disease contexts. In addition to influencing interactions and transcription, lactylation also affects protein stability by competing with ubiquitination. This competition can alter protein half-lives, impacting cellular dynamics and processes. In cervical cancer, for instance, the lactylation at K172 of discoidin, CUB and LCCL domain-containing type I enhances its expression while shortening its half-life. This modification concurrently diminishes its ubiquitination, indicating a complex role for non-histone lactylation in cancer, as it influences protein turnover and maintains cellular homeostasis (73). Similarly, lactylation of Runt-related transcription factor 2 stabilized the protein by reducing its ubiquitination, further promoting the osteogenic differentiation of periodontal ligament stem cells (74). This highlights the positive regulatory potential of lactylation in tissue regeneration and healing, illustrating its therapeutic promise beyond disease mitigation. Overall, non-histone lactylation represents a multifaceted regulatory mechanism with extensive implications for cellular function and disease development. By modulating protein interactions, stability and transcriptional activity, non-histone lactylation influences a spectrum of biological processes, enhances the current understanding of cellular regulation and broadens the horizon for potential therapeutic applications. As research continues to unveil the complexities of protein modifications, lactylation stands out as a pivotal modification that could be harnessed in novel treatment strategies targeting various pathological conditions, from cancer to inflammatory diseases. Future studies will benefit from elucidating the precise molecular mechanisms through which non-histone lactylation exerts its effects, paving the way for targeted modulation in clinical settings. Information on additional research on non-histone lactylation and studies related to protein modification is provided in Table II.

## 5. Writers and erasers

*Writers*. As with many PTMs, lysine lactylation is orchestrated by a specific set of enzymes that include lactyltransferases, or 'writers', which introduce lactate groups to lysine residues, delactylases (erasers), which remove these modifications from proteins, and recognition enzymes, often dubbed 'readers', which interpret the presence of lactyl marks to elicit biological effects (75). The enzymes responsible for writing the lactyl

Table II. Non-histone lactylation and protein modification.

| Functions of non-histone lactylation | Sites | Target | Writers/erasers | Cell types | Specific functions | (Refs.) |
|---|---|---|---|---|---|---|
| Protein activity | K28 | AK2 | p300/CBP and HDAC3 | Hepatoma carcinoma cell | Inhibited the function of AK2, facilitated the proliferation and metastasis of hepatoma carcinoma cells | (58) |
| | K147<br>K688 | ALDOA<br>PFKP | / | Colon cancer cell | Disrupted their enzyme activity and formed a negative feedback pathway in glycolysis and lactic acid production | (59) |
| | K62 | PKM2 | / | Macrophage | Activated PKM2 and promoted the transition of pro-inflammatory macrophages towards a reparative phenotype | (61) |
| | K356 and K781 | VPS34 | KAT5/TIP60 | Skeletal muscle cell | Increased PIK3C3/VPS34 lipid kinase activity and facilitated autophagy | (62) |
| | K408 | eEF1A | KAT8 | Colon cancer cell | Enhanced ribosomal GTPase activity | (64) |
| protein-DNA/protein interactions | K33 | NEDD4 | p300/CBP and SIRT1 | Macrophage | Inhibited its binding to caspase-11 and reduced caspase-11 ubiquitination | (67) |
| | K20 | Fis1 | SIRT3 | Renal tubular epithelial cell | Improved Fis1 interaction with DRP1, promoting mitochondrial dysfunction | (68) |
| | K72 | MOESIN | / | Regulatory T cell | Improved the interaction of MOESIN with TGF-βRI, reinforcing TGF-β signaling | (51) |
| | K120 and K139 | P53 | AARS1 | Tumor cell | Impaired p53 liquid-liquid phase separation, DNA binding and transcriptional activation | (69) |
| | K271 | MECP2 | p300/CBP | Endothelial cell protein stability | Promoted its binding to Ereg promoter regions and inhibited its transcription | (72) |
| | K172 | DCBLD1 | / | Cervical cancer cell | Enhanced the post transcriptional expression and shortened the half-life of DCBLD1 | (73) |
| | K176 | RUNX2 | / | Periodontal ligament stem cells | Decreased the ubiquitination level of RUNX2 and shortened its half-life | (74) |

AK2, adenylate kinase 2; ALDOA, aldolase A; DCBLD1, discoidin, CUB and LCCL domain-containing type I; eEF1A, elongation factor 1α; Fis1, fission 1; GTPase, GTP hydrolase; HDAC, histone deacetylase; KAT, lysine acetyltransferase; MECP2, methyl CpG binding protein 2; MOESIN, membrane-organizing extension spike protein; NEDD4, neuronally expressed developmentally downregulated 4; PFKP, phosphofructokinase, platelet; PIK3C3, phosphatidylinositol 3-kinase catalytic subunit type 3; RUNX2 runt-related transcription factor 2; TGF-βRI transforming growth factor β receptor I; VPS34, vacuolar protein sorting 34.

marks have not been fully characterized, yet preliminary evidence suggests a likely overlap with enzyme families known to mediate other forms of PTMs, such as acetylation and methylation (76). Among these, histone acetyltransferase families such as p300/CREB binding protein (p300/CBP), the Moz, Ybf2/Sas3, Sas2 and Tip60 (MYST) proteins and the GCN5 related N-acetyltransferases (GNAT superfamily) have drawn particular attention for their potential roles in histone lactylation (77). A study conducted by Zhao *et al* (7) in 2019, for example, identified the catalytic role of p300 in histone H3 and H4 lactylation and corresponding transcriptional activation of arginine in a p53-dependent manner. The

p300 enzyme has been demonstrated to influence the levels of histone lactylation; specifically, its overexpression resulted in an increase in lactyl marks, whereas its deletion caused a decrease in this modification. These findings position p300 not only as a likely writer of histone lactylation but also as a key player in the regulatory network that links cellular metabolism with gene expression, particularly in contexts significant to cancer biology and inflammation. Further insights come from studies on the GNAT superfamily, specifically the role of GCN5. This enzyme has emerged as an important writer in monocyte-macrophage function and reparative gene expression following myocardial infarction. The silencing of GCN5 in these cells resulted in significant decreases in H3K18la, underscoring its role as an upstream regulatory writer in facilitating the lactylation process. This highlights the broader biological relevance of lactylation as a modification that might modulate immune responses and repair mechanisms (10). Beyond these enzymes, the MYST family member lysine acetyltransferase 7 (KAT7, also known as HBO1) has been implicated in directing lactylation at specific histone sites, notably H3K9. Niu *et al* (78) demonstrated that HBO1, alongside scaffold proteins like jade family PHD finger 1 and bromodomain-containing 1, could specifically catalyze the addition of lysine residues to H3K9. This targeted activity further underscores the potential specificity and regulatory precision of histone lactylation, as each writer might differentially influence various histone sites and subsequent gene expression outcomes (78). The characterization of lactylation writers like p300, GCN5 and HBO1 in histone modification marks a promising frontier in the study of lysine lactylation, while understanding these 'writers' extends the possibility for targeted therapeutic interventions.

*Erasers and readers*. While 'writers' add lactyl groups to proteins, 'erasers' remove them, thereby maintaining the equilibrium of lactylation and influencing protein function. Just like writers, the exploration into the specific 'eraser' enzymes involved in lactylation is under continuous research. However, due to similarities with the acetylation process, it is plausible to assume that analogous enzymes to those that erase acetylation, such as deacetylases, may also serve as 'erasers' for lactylation (79). Screening studies in mammals underscore the role of histone deacetylases (HDACs) in this capacity. Specifically, HDAC1-3 has been identified to possess delactylase activity, which allows it to effectively remove lactyl groups from lysine residues on histones. These findings suggest a conserved mechanism whereby deacetylases not only regulate acetylation but also participate in modulating lactylation, thereby influencing gene expression and chromatin dynamics (80,81). Li *et al* (79) have identified p300 and HDAC2 as potential 'writer' and 'eraser' enzymes, respectively, involved in the regulation of H3K18la in pancreatic ductal adenocarcinoma cells. This discovery highlights the potential cross-talk and shared pathways between lactylation and other histone modifications, further explaining the intricate control of gene expression in cancer cells. The implications of these regulatory mechanisms extend beyond cancer, as similar processes may be involved in inflammatory responses and other pathological conditions of the lung (79). Furthermore, the involvement of 'readers' in the interpretation of lactylation signals introduces an extra dimension of enzymatic regulation. These readers, which identify and attach to lactylated sites, can influence the functional outcomes of the modifications made by 'writers' and 'erasers' (8). Proteomic analysis of the H3K18la immunoprecipitation experiment conducted by Hu *et al* (82) revealed the specific recruitment of BRM/SWI2-related gene 1 (Brg1), a gene that encodes a protein component of the SWI/SNF chromatin-remodeling complex which alters the structure of chromatin and modulates access to DNA, during cellular reprogramming. This study found that both H3K18la and Brg1 were enriched on the promoters of genes linked to pluripotency and epithelial junctions, providing insights into how lactylation can influence cellular identity and transformation processes (82).

*Regulation of non-histone lactylation*. P300/CBP, recognized as a writer of histone lactylation, has also been identified as a writer of non-histone lactylation. For instance, p300 catalyzed the lactylation of nucleolin at K477 in response to hyperglycolytic conditions, suggesting a direct link between metabolic shifts and PTMs. Similarly, p300 also acted as a key lactyltransferase responsible for lactylation at the 128th lysine residue of nicotinamide nucleotide adenylyltransferase 1 (83,84). The function of p300/CBP extends into the modulation of key transcription factors such as Snail1, a well-known TGF-β transcription factor in transformation processes like endothelial-to-mesenchymal transition (EMT). Lactylation mediated by p300/CBP was reported to enhance the transcriptional activity of Snail1, which may contribute to the exacerbation of conditions such as cardiac fibrosis. This serves as a clear illustration of how non-histone lactylation connects cellular metabolism with transcriptional regulation (85). The interaction between PKM2 and p300 appears to facilitate PKM2 lactylation, consequently influencing its cellular localization and the cell cycle, demonstrating the far-reaching effects of lactylation in cell fate decisions (85,86). In addition to p300/CBP, other lysine acetyltransferases, including KAT5/TIP60, play a role in shaping the non-histone lactylation landscape. For instance, the reduction in KAT5/TIP60 levels results in diminished vacuolar protein sorting 34 homolog (VPS34) lactylation at lysine-356 and lysine-781 during intense physical activity, pointing to its role in muscle adaptation and energy metabolism (62). KAT8, another acetyltransferase, has been identified as a pan-Kla writer, capable of installing lactylation across a wide range of substrates. This expands the spectrum of lactylation beyond individual proteins to encompass diverse biological processes including translation and signal transduction (63). In addition, mitochondrial alanyl-tRNA synthetase 1/2 has recently been recognized as a non-histone protein lysine lactyltransferase, which specifically targets metabolic enzymes such as pyruvate dehydrogenase E1 subunit α1 (PDHA1) and carnitine palmitoyltransferase 2 (CPT2). This finding introduces an additional functional role, demonstrating the potential role of lactylation in the regulation of mitochondrial metabolism and underscoring possible targets for addressing metabolic disorders (87,88). Research indicates that sirtuin (SIRT)3, a class III lysine deacetylase, functions as an eraser of non-histone lactylation by reversing the lactylation of specific proteins, including CCNE2, PDHA1 at K336, and CPT2 at K457/8. In addition, SIRT1 has been identified as the delactylase for α-myosin heavy chain and canopy FGF

signaling regulator 3 (87-91). Collectively, these studies indicate a sophisticated network of enzymes that facilitate lysine lactylation, although the landscape remains incompletely mapped. The enzymatic machinery responsible for lactylation involves multifaceted roles across different enzyme families, some of which are shared with other acyl modifications. This points to evolutionary conservation and potential functional redundancy or specialization within the realm of PTMs, where similar enzymes may diversify their substrate preferences and actions under distinct physiological and pathological conditions. By clarifying the functions of these regulatory enzymes, knowledge gaps in the understanding of intricate diseases may be effectively bridged, thereby enhancing the prognosis for patients afflicted with severe lung disorders.

## 6. NSCLC

Lung cancer remains the leading cause of cancer-related deaths globally, attributed to its significant prevalence and poor prognosis, with a 5-year survival rate of <17% (92). Based on histological type, therapy and prognosis, lung cancers can be classified into two major types, SCLC and NSCLC. NSCLC, which constitutes ~85% of all lung cancer diagnoses, is further subclassified into three primary types: Lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC) and large cell carcinoma (93). The investigation of lysine lactylation, which involves the modification of lysine residues by lactate in both histones and non-histone proteins, provides valuable insights into the significant impact of metabolic dysregulation on cancer biology (Fig. 2). For instance, Jiang *et al* (94) reported the relevance of lactate metabolism and its aberrations in poor NSCLC prognosis. In hypoxic tumor environments, lactate accumulates modulated gene transcription through histone lactylation at hexokinase 1 (*HK-1*) and isocitrate dehydrogenase (*IDH3G*) promoters, which govern critical metabolic enzymes involving glycolysis and the tricarboxylic acid cycle. This metabolic reprogramming supports tumor growth and survival, creating a robust link between metabolic pathways and cancer progression (94). Furthermore, hypoxia-induced lactylation of SRY-related high mobility group box 9 (SOX9), a transcription factor overexpressed in NSCLC, exemplifies how lactylation modification promotes the stemness, migration and invasion of NSCLC cells by enhancing glycolysis-a vital adaptation for tumor growth. This finding highlights the multifaceted nature of NSCLC pathogenesis where metabolic shifts dovetail with transcriptional reprogramming (95).

*LUAD*. As the most common subtype of NSCLC, LUAD accounts for a significant proportion of global lung cancer cases (96). Specific lactylation sites have been implicated in LUAD biology. SLC25A29 belongs to the solute carrier family and works as a key regulator linked to LUAD staging (97). Zheng *et al* conducted a comprehensive bioinformatics and revealed that lactate increased the levels of H3K14la and H3K18la at the promoter of SLC25A29, subsequently enhancing its transcription. This process, in turn, influenced the proliferation, migration and apoptosis of endothelial cells, which are critical factors in angiogenesis-a key characteristic of cancer progression (98). Furthermore, another study focused on the adenocarcinoma-to-neuroendocrine cell fate transition and the pivotal role of lactylation in cell energy metabolism. They discovered that a deficiency in the cell fate determinant Numb/Parkin pathway in LUAD led to metabolic reprogramming by upregulated H3K18la and the transcription of neuroendocrine-associated genes (16). Non-histone lactylation plays a crucial role in the pathogenesis of LUAD, extending its influence beyond that of histones. Jia *et al* (62) highlighted the integral role of lactylation in autophagy regulation, a pivotal process for cellular homeostasis in cancer cells. The enhanced activity of the autophagic mechanism via lactylation, particularly of VPS34 at K356 and K781, emphasizes how metabolic products like lactate orchestrate cellular survival and proliferation strategies, exacerbating cancer progression (62).

*LUSC*. LUSC accounts for ~30% of NSCLC cases; however, it has been less extensively researched regarding lactylation (99). However, Hao *et al* (100) reported that SLC2A1 may act as a predictive biomarker for the survival and response to immunotherapy in LUSC. Tumor tissues with high expression of SLC2A1 were associated with an elevated risk of lactylation, potentially influencing immune modulation and tumor progression (100). This gap in research presents an opportunity to investigate the wider implications of lactylation across different subtypes of NSCLC, particularly given LUSC's varying response to conventional therapies.

*Lung cancer brain metastasis (BM)*. BM is a malignant event leading to poor prognosis in NSCLC (101). Lactylation also contributes to the challenges of treating BM in LUAD. The enzyme aldo-keto reductase family 1 member B10 (AKR1B10) is significantly upregulated in both LUAD cells with high BM propensity and in patients suffering from brain metastases (102). AKR1B10 functions as a cyto-detoxification agent within the intestinal system. It facilitates anaerobic glycolysis and the secretion of lactate, while also promoting the transcription of the cell cycle-related gene cyclin B1 through H4K12la. This mechanism may limit the therapeutic effectiveness for patients with lung cancer BM (103). This metabolic feedback loop highlights lactylation as both an indicator of disease advancement and a promising target for therapeutic strategies.

Conclusively, lysine lactylation emerges as a central theme in the molecular landscape of NSCLC, particularly LUAD. Its involvement in modulating genes crucial for metabolism, angiogenesis and autophagy underlines the profound influence of metabolic dysregulation in cancer. Future research should explore the therapeutic possibilities associated with targeting lactylation, extending beyond its function as a biomarker to examine its viability as a targeted element within cancer treatment strategies. Advances in understanding lactylation-specific pathways could lead to more precise and personalized treatment strategies, potentially improving outcomes for patients afflicted with this challenging disease. Given the dynamic nature of cancer biology, integrating these insights could redefine how to approach NSCLC, offering new hope for improved prognostic and therapeutic avenues.

## 7. Malignant pleural effusion

The exploration of lysine lactylation's role in malignant pleural effusion (MPE) further advances the understanding

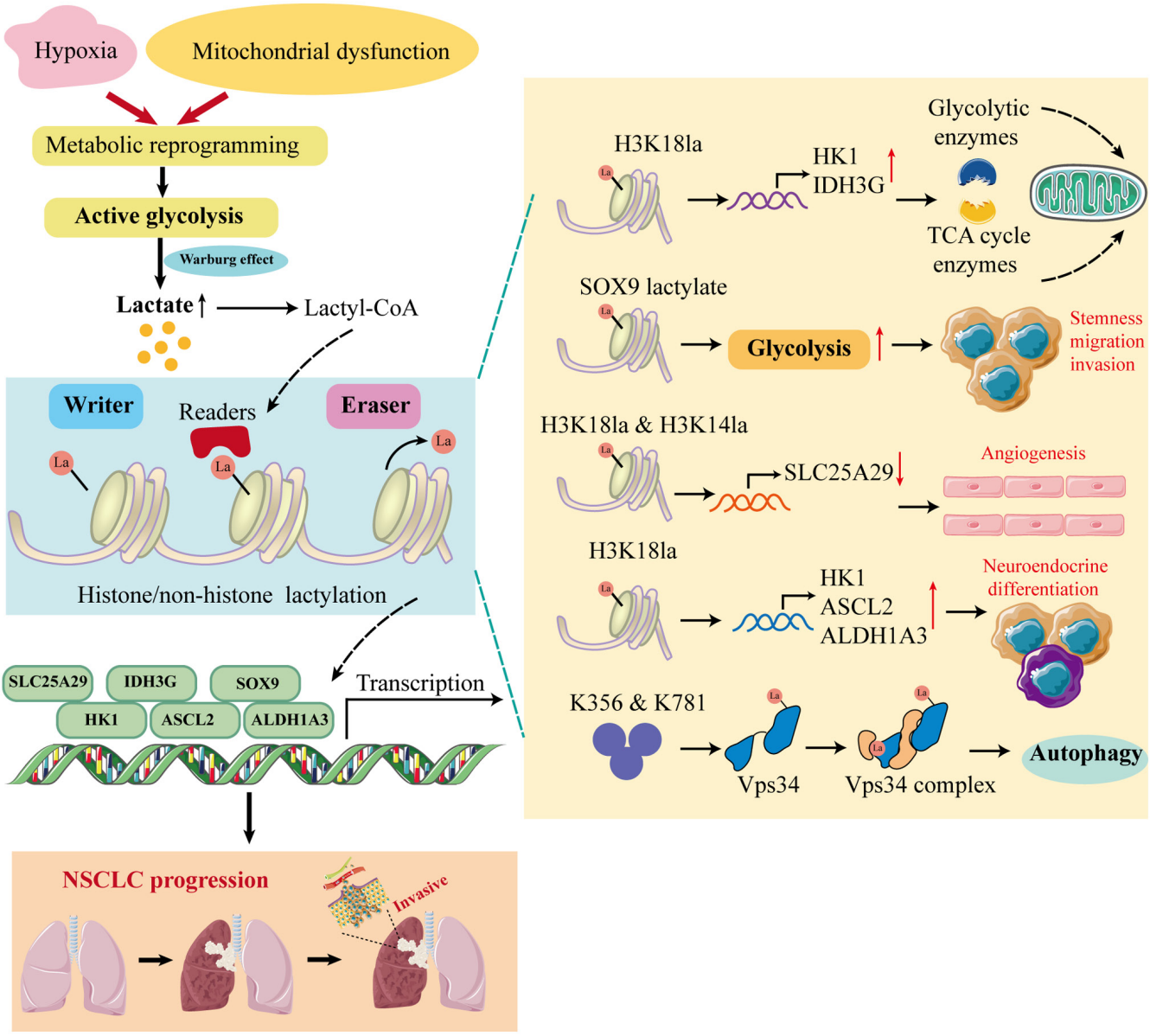


Figure 2. Mechanisms of lactylation that contribute to NSCLC. In NSCLC, metabolic reprogramming leads to increased lactate production, which subsequently provides the substrate lactyl-CoA for lactylation, ultimately contributing to tumorigenesis and progression. Elevated H3K18la enrichment at promoters of glycolysis-related genes such as *HK-1* and *IDH3G* leads to their increased transcription and regulates cellular metabolism in tumor cells, while its enrichment at promoters of *ASCL2* and *ALDH1A3* promotes neuroendocrine differentiation. H3K18la can also promote the proliferation, migration and apoptosis of endothelial cells through its enrichment at the SLC25A29 promoter in non-tumor endothelial cells. Specifically, lactylation of the non-histone protein SOX9 enhances stemness, migration and invasion in NSCLC cells by promoting glycolysis, while lactylation of VPS34 at K356 and K781 enhances its lipid kinase activity to facilitate cell autophagy and endolysosomal degradation. ASCL2, achaete-scute family BHLH transcription factor 2; ALDH1A3, aldehyde dehydrogenase 3 family member A1; HK1, hexokinase 1; H3K14la, lactylation of histone 3 on lysine residue 14; H3K18la, lactylation of histone 3 on lysine residue 18; IDH3G, isocitrate dehydrogenase 3 non-catalytic subunit gamma; Lactyl-CoA, lactyl-coenzyme A; NSCLC, non-small cell lung cancer; SLC25A29, solute carrier family 25 member 29; SOX9 SRY-box transcription factor 9; VPS34, vacuolar protein sorting 34; TCA, tricarboxylic acid cycle.

of the metabolic dynamics and immunological adaptations in neoplastic environments. MPE, usually caused by the invasion of the pleura, serves as an independent prognostic marker in NSCLC (104-106). This phenomenon underscores a complex interplay of elevated metabolites and versatile cellular components that harmonize to perpetuate immunosuppression. Within this milieu, lactate emerges as a particularly influential metabolite, reshaping the metabolic pathways in the effusion microenvironment (107,108). Research into lactylation modifications sheds light on a unique subset of natural killer T (NKT)-like cells present in MPE. These cells are characterized by their expression of forkhead box P3 (FOXP3), a transcription factor typically associated with regulatory T cells and immunosuppression. The presence of these FOXP3-expressing NKT-like cells signals an intriguing deviation from their expected antitumor responses, revealing instead augmented immunomodulatory properties. This shift is supported by a marked increase in glycolytic activity and enhanced lactate metabolism, offering insight into how the metabolic landscape orchestrates immunological roles within the pleural effusion. *In vitro* studies revealed that increased levels of H3K18la lactylation at the promoter region of the

*FOXP3* gene correlate with elevated *FOXP3* expression. This suggests that lactylation acts as an epigenetic regulator, modulating gene expression and function in a metabolically adapted immune cell population (109). Consequently, the findings highlight the potential of targeting lactylation pathways in therapeutic strategies, particularly for reprogramming immune responses to restore antitumor activity in MPE environments.

## 8. Pulmonary fibrosis

Pulmonary fibrosis, also known as interstitial lung disease (ILD), is a significant challenge in respiratory medicine, primarily because it is a chronic, progressive disease with significant scarring in the lungs that often leads to high mortality rates due to its irreversible nature and limited treatment options (110). The etiology of ILD remains largely elusive. However, since its first discovery, numerous studies have emerged regarding the lactylation of profibrotic genes, highlighting the crucial role that lactylation modification plays in the development of pulmonary fibrosis (Fig. 3).

*Idiopathic pulmonary fibrosis (IPF)*. As the most severe form of ILD with a median survival of only 3 to 5 years post-diagnosis, the specific causes of IPF are unknown, distinguishing it from pulmonary fibrosis linked to environmental factors, medications or other identifiable causes (111). Alveolar macrophages (AMs) are pivotal in pulmonary health, maintaining homeostasis and modulating immune responses within the alveolar spaces. In a healthy respiratory environment, these cells typically manifest with an anti-inflammatory and pro-resolving phenotype. Yet, in fibrotic lung conditions like IPF, AMs undergo a phenotypic shift toward a pro-fibrotic state. Pro-fibrotic AMs produce several soluble factors, such as transforming growth factor-β (*TGF-β*), platelet-derived growth factor (*PDGF*), vascular endothelial growth factor (*VEGF*) and thrombospondin 1 (*THBS1*), which differentiate resident fibroblasts into myofibroblasts and accelerate the fibrotic processes (112-115). The biochemical environment of the fibrotic lung is characterized by elevated lactate concentrations, which serve as a significant indicator of metabolic reprogramming. A research investigation conducted by Cui *et al* (11) revealed increased levels of lactate in the conditioned media derived from TGF-β1 stimulated lung myofibroblasts, as well as in bronchoalveolar lavage fluid obtained from fibrotic mouse lungs. This elevation in lactate was found to play a role in histone lactylation at the promoters of significant pro-fibrotic genes, such as arginase 1, *PDGFA*, *THBS1* and *VEGFA*. This finding not only underscores the influence of altered metabolic states in pulmonary fibrosis but also highlights lactylation as a regulatory mechanism that exacerbates the pro-fibrotic behaviors of AMs. Notably, these lactylation modifications are facilitated by acetyltransferase p300, emphasizing a potential target for therapeutic intervention (11).

*Secondary pulmonary fibrosis*. Beyond IPF, pulmonary fibrosis can also stem from secondary environmental influences, such as inhaled small particulate debris [such as particulate matter of 2.5 microns or less in diameter ($PM_{2.5}$)] and microbial agents (116). According to a study by Li *et al* (117), exposure to urban airborne $PM_{2.5}$ causes lung fibrotic changes and encourages a metabolic shift toward glycolysis. Mechanically, $PM_{2.5}$-induced glycolysis and lactate production promoted histone lactylation levels at the promoters of the pro-fibrotic genes *TGFB*, *VEGFA* and *PDGFA* in macrophages. Furthermore, the upregulated pro-fibrotic genes induced the excessive secretion of pro-fibrotic cytokines and consequently triggered EMT through activating TGF-β/Smad2/3 and VEGFA/MEK/ERK pathways, contributing to fibrosis (117). Arsenic exposure offers another model for secondary pulmonary fibrosis, with recent research highlighting elevated pan-lactylation and histone lactylation, specifically H3K18la, in alveolar epithelial cells among arsenic-induced fibrotic mice. These modifications foster fibroblast-to-myofibroblast transition via mechanisms mediating the m6A methylation site of neuronal regeneration-related protein by readers like YTH N6-methyladenosine RNA-binding protein F1, showcasing the intricate epigenetic interplay in environmentally induced fibrosis (64). Overall, the exploration of lactylation modifications within pulmonary fibrosis provides a promising avenue to deepen our understanding of this complex disease and identify potential therapeutic targets. As research in this area continues to evolve, it beckons a shift toward investigating metabolic and epigenetic interventions as viable strategies to mitigate the progression of pulmonary fibrosis, ultimately aiming to improve the prognosis of this devastating illness.

## 9. Acute and chronic pulmonary inflammatory diseases

Pulmonary inflammatory disorders represent a wide range of conditions that involve inflammation and damage to lung tissue, which manifest as both acute (short-term) and chronic (long-term) conditions, including acute lung injury (ALI), asthma and pulmonary fibrosis (118). The exploration of lysine lactylation in the context of pulmonary inflammatory disorders offers a fresh perspective on the underlying biochemical and molecular changes accompanying these conditions. Current research has predominantly focused on lactylation in relation to pulmonary fibrosis; however, its significance in other pulmonary inflammatory diseases is still relatively underexplored. This limited focus represents a significant gap considering the broad spectrum of pulmonary conditions characterized by inflammation and tissue damage. However, studies have begun to shed light on the potential significance of lactylation in these disorders. For instance, the biomimetic anti-inflammation nanoparticle delivery system developed by Jin *et al* (119) demonstrated a promising approach to treating ALI by targeting inflamed lungs with curcumin and resveratrol. This approach not only showcased the therapeutic potential of natural compounds but also highlighted the importance of inhibiting histone lactylation to modulate macrophage polarization and reduce lung injury and vascular permeability (119). Similarly, the investigation into the effects of corticosteroids on asthma presents another facet of lactylation's role in pulmonary inflammation. The study revealed that dexamethasone attenuates the Hif-1α-glycolysis axis, effectively reducing lactate production and associated histone lactylation in lung macrophages. These results underscore the potential of targeting metabolic pathways and histone modifications to mitigate chronic inflammatory responses in asthma. Furthermore, ovalbumin stimulation also

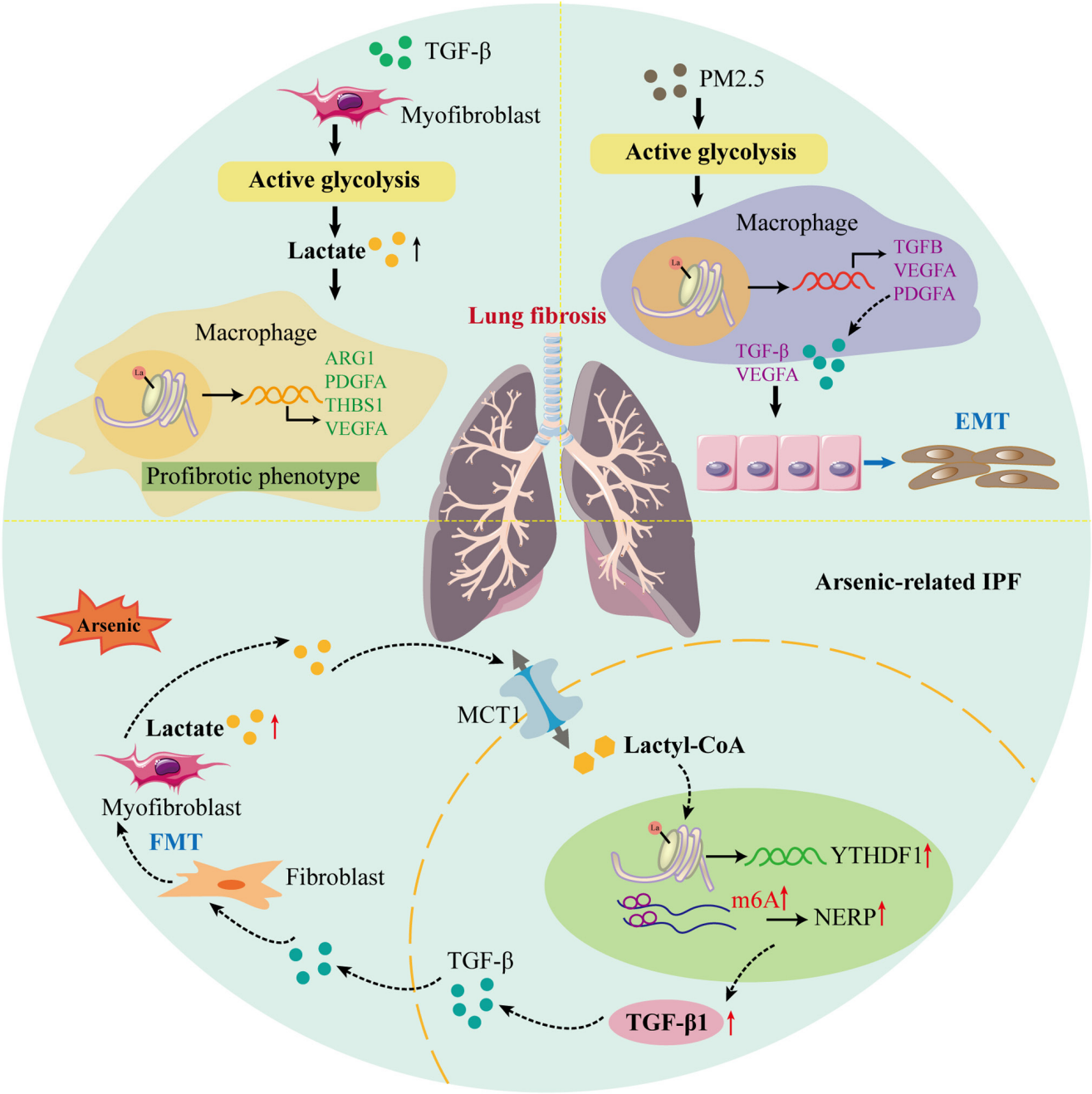


Figure 3. Lactylation plays a significant role in the progression of lung fibrosis. The abnormally elevated glycolysis in myofibroblasts, stimulated by TGF-β, causes an increase in lactate levels that subsequently enhances histone lactylation at the promoters of pro-fibrotic genes (*ARG1*, *PDGFA*, *THBS1* and *VEGFA*) in macrophages. Additionally, PM2.5 directly promotes the elevation of macrophage glycolysis, ultimately leading to histone lactylation at the promoters of pro-fibrotic genes (*TGFB*, *VEGFA* and *PDGFA*). This mechanism further promotes EMT by activating the TGF-β/Smad2/3 and VEGFA/MEK/ERK pathways. Furthermore, in arsenic-related lung fibrosis, the extracellular lactate secreted by myofibroblasts is absorbed and converted into lactyl-CoA, which elevates the H3K18la enriched in the promoter of *YTHDF1* in alveolar epithelial cells. The upregulated YTHDF1 promotes the translation of *Nrep* mRNA via recognizing the m6A sites on the mRNA and activates the secretion of TGF-β1, which further promotes the FMT. ARG1, arginase 1; EMT, epithelial-to-mesenchymal transition; FMT, fibroblast-to-myofibroblast transition; IPF, idiopathic pulmonary fibrosis; Lactyl-CoA, lactyl-coenzyme A; m6A, N6-methyladenosine; MCT1, monocarboxylate transporter 1; NERP, neuronal protein 3.1; PDGFA, platelet-derived growth factor receptor α; TGF-β, transforming growth factor β; THBS1, thrombospondin-1; VEGFA, vascular endothelial growth factor A; YTHDF1, YTH N6-methyladenosine RNA-binding protein.

leads to histone lactylation in macrophages and the lungs of asthmatic mice, a process that can be significantly diminished following dexamethasone treatment; however, the precise mechanism underlying this phenomenon has yet to be clarified (120). Despite these insights, significant gaps remain in understanding the precise mechanisms by which lactylation influences inflammatory processes, warranting further research. Filling these gaps could unveil novel therapeutic targets, ultimately improving management strategies for both acute and chronic pulmonary inflammatory diseases. As Table III indicates, expanding our knowledge in this area holds great promise for enhancing patient outcomes in a variety of neoplastic and inflammatory pulmonary conditions, emphasizing the need for continued exploration in this emerging field.

Table III. Lactylation and corresponding targets in neoplastic and inflammatory pulmonary diseases.

| Condition | Lactylation sites | Targets | Biological functions | (Refs.) |
|---|---|---|---|---|
| NSCLC | H4K8 | HK1 and IDH3G | Regulated cellular metabolism reprogramming | (94) |
| | / | SOX9 | Promoted glycolysis in NSCLC cells, accelerating their stemness, migration and invasion | (95) |
| LUAD | H3K18 and K3K14 | SLC25A29 | Affected endothelial cell proliferation, migration and apoptosis associated with angiogenesis | (98) |
| | H3K18 | ASCL2, HK1, ALDH1A3 | Induced neuroendocrine differentiation | (16) |
| | K356 and K781 | VPS34 | Promoted cancer cell autophagy to facilitate cancer progression | (62) |
| LUSC | / | / | High SLC2A1 contributed to high protein lactylation levels | (100) |
| BM | H4K12 | CCNB1 | Activated the transcription of CCNB1 and accelerated the DNA replication and cell cycle. | (103) |
| MPE | H3K18 | FOXP3 | Maintained immunosuppressive function in NKT-like cells | (109) |
| Lung fibrosis | Histone | ARG1, PDGFA, THBS1, VEGFA | Induced the pro-fibrotic phenotype of macrophages | (11) |
| | Histone | TGFB, VEGFA, | Induced the expression of pro-fibrotic genes | (117) |
| | H3K18 | PDGFA YTHDF1 | Mediated m6A methylation and participated in the fibroblast-to-myofibroblast transition | (64) |
| Acute lung injury | Histone | / | Contributed to the anti-inflammation effects of macrophages | (119) |
| Asthma | / | / | Induced elevated lactylation levels in lung macrophages | (120) |

ALDH1A3, aldehyde dehydrogenase 3 family member A1; ASCL2, achaete-scute family BHLH transcription factor 2; ARG1, arginase 1; BM, brain metastasis; CCNB1, cyclin B1; FOXP3, forkhead box P3; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MPE, malignant pleural effusion; NSCLC, non-small cell lung cancer; PDGFA, platelet-derived growth factor receptor α; SLC25A29, solute carrier family 25 member 29; TGFB, transforming growth factor β; THBS1, rhrombospondin-1; VEGFA, vascular endothelial growth factor.

## 10. Conclusion and future perspectives

The human genome contains ~20,000 genes; however, the variety of transcripts and post-translational modifications that create what are known as 'proteoforms' significantly expands the scale of the proteome. This expansion results in a diverse protein library capable of engaging in numerous cellular biological processes (121). As a newly identified post-translational modification, the lactylation process has been under investigation and the understanding of it has significantly advanced in the last five years, revealing its involvement in numerous diseases including cancers and systemic diseases. Of note, the various roles and molecular mechanisms of lactylation in pulmonary diseases ranging from pulmonary fibrosis to lung cancers are an emerging research frontier. Currently, there are no comprehensive literature reviews addressing the effects of lactylation in various pulmonary disorders. This article presents the findings related to lactylation and provides a thorough examination of the essential roles that histone and non-histone lactylation fulfill within cellular and protein contexts, respectively. Research on histone lactylation has yielded a significant understanding of how lactate generated during cellular metabolism can directly alter the chromatin structure, thereby influencing gene transcription. This novel finding has opened a new avenue in the field of epigenetics and various cellular functions including cell fate determination, regulation of immunity and inflammation, as well as regulation of cellular metabolism. The specific role of histone lactylation in gene targeting is well established; however, the function of non-histone lactylation is still largely unexplored and remains unclear. Preliminary research suggests that non-histone lactylation also plays an important part in protein function consisting of protein activity modulation, influencing protein-DNA/protein interactions and regulation of protein stability. Nevertheless, further research is required to comprehend the full spectrum of its functions and mechanisms.

Recent research developments have underscored the relationship between metabolic reprogramming and pulmonary diseases. In this context, the accumulation of lactate within structural and immune cells is not merely a consequence of these diseases; it also plays a significant role in their progression (122-124). For instance, in bronchial epithelial cells and PASMCs, altered lactate metabolism heavily contributes to their pathological remodeling by stimulating aberrant inflammatory responses, structural changes and cell proliferation (125,126). Furthermore, lactate can

impair the bactericidal activity of neutrophils and stimulate macrophages to produce pro-inflammatory cytokines, exacerbating inflammation and tissue damage (127). Although our understanding of the roles and functions of lactylation in pulmonary diseases is only nascent, several studies have implicated lactylation in diverse neoplastic and inflammatory pulmonary diseases, including NSCLC, malignant pleural effusion, pulmonary fibrosis, acute lung injury and asthma. In general, histone lactylation, particularly H3K18la and non-histone lactylation of SOX9/VPS34, have harmful effects on lung tumors by increasing glycolysis in lung cancer cells, which in turn increases lactate levels and eventually leads to a vicious cycle (16,62,94,95). Furthermore, histone lactylation could promote lung fibrosis via modulating the expression of profibrotic genes in macrophages or mediating m6A methylation of *Nrep* mRNA (11,64,117). Research on chronic inflammatory diseases such as asthma has revealed only a limited correlation between elevated lactate levels and subsequent lactylation, while the underlying mechanisms have yet to be thoroughly investigated (120). In other lung diseases, research regarding lactylation is currently scarce, yet this field holds immense potential for future studies. For instance, during acute exacerbations of chronic obstructive pulmonary disease, an increase in lactate levels is frequently noted. Elevated lactate may indicate excessive β2-agonist treatment and warrants further investigation as a potential biomarker (128). Furthermore, lactate also exhibits a range of immunomodulatory effects both within the context of tuberculosis and in other conditions (129). In all cases of plastic bronchitis in children, lactate dehydrogenase levels increased to different degrees (130). Given the potential of lysine lactylation as a biomarker and therapeutic target, future research is promising. Investigating the reversible nature of lactylation may unveil novel treatment strategies by targeting specific molecular pathways. However, a robust understanding of its clinical mechanism remains imperative. Future research should explore the functions of lactylation in various cellular environments and disease conditions, examine its interactions with other post-translational modifications and assess the broader implications for pulmonary health. Ultimately, expanding the knowledge in this domain could revolutionize therapeutic approaches, offering new hope for targeting pulmonary diseases at a molecular level. As research progresses, the insights gained from studying lysine lactylation could have wide-ranging applications, not just in pulmonary medicine but across the spectrum of systemic diseases affected by metabolic dysregulation and epigenetic modification.

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Not applicable.

**Authors' contributions**

SW and HZ wrote and revised the manuscript, organized the tables and drew the figures. JZ and JX critically conceptualized and supervised the study and reviewed the manuscript. All authors have read and approved the final 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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