Role of protein lactylation in pulmonary and cardiovascular diseases: Current research and future perspectives (Review)

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Abstract. The cardiopulmonary system is highly coupled in structure and function. Metabolic and epigenetic disturbances constitute the common pathological basis for the progression of cardiopulmonary diseases and their comorbidities. Aberrant metabolic reprogramming triggers lactate accumulation. As a novel post-translational modification, protein lactylation participates in the regulation of inflammatory responses, cell death and fibrotic remodeling, thereby mediating cardiopulmonary dysfunction. Existing studies have separately illustrated the roles of lactylation in isolated pulmonary and cardiac disorders. Nevertheless, most investigations are confined to a single-organ perspective, lacking systematic summaries of common mechanisms for cardiopulmonary crosstalk and comorbidities. The present review summarized research advances of lactylation in various cardiopulmonary diseases, generalized its potential comorbid mechanisms, identified existing research gaps and translational obstacles for targeted therapy and collected lactylation-targeted intervention compounds with potential therapeutic effects reported in basic studies. The present review further outlined prospective research directions focused on spatiotemporal regulation of lactylation, metabolic-immune-epigenetic crosstalk that shapes disease progression, and the identification of specific targets in cardiopulmonary comorbidities, with the aim of providing a theoretical foundation for developing precise, broad-spectrum, co-targeted therapeutic strategies for cardiopulmonary diseases.

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1. Introduction

Under hypoxic conditions, glucose is converted into lactate in the cytoplasm. Lactate, long regarded as a metabolic waste product (1), is now understood to play a more complex role. In 1985, Brooks proposed the lactate shuttle hypothesis, which posits that lactate can be shuttled between cells and tissues, functioning as both an energy substrate and a signaling molecule (2). In addition, lactate exhibits autocrine, paracrine and endocrine-like effects, serving as a redox signaling molecule that facilitates inter-cellular and inter-tissue communication (3,4).

In 2019, Zhang *et al* (5) first discovered the non-metabolic function of lactate, namely lysine lactylation (Kla), which represents a novel post-translational modification (PTM), sparking widespread enthusiasm in the academic community. Kla refers to the process through which lactate acts as a lactyl donor, attaching a lactyl group to proteins. It was initially identified as an epigenetic mark on histones, and similar to other epigenetic marks, histone Kla can directly regulate gene expression, thereby expanding the implications of the Central Dogma (6). Of note, a recent study revealed that Kla also occurs in non-histone proteins. For example, lactylomic profiling of a prospective cohort of hepatitis B-related HCC identified a total of 9,275 Kla sites, the vast majority of which are located on non-histone proteins (7). Using the YnLac chemical probe, a study demonstrated that lactylation of PARP1 regulates its ADP-ribosylation activity (7). Lactate accumulated during sepsis promotes the lactylation of cold-inducible RNA-binding protein (CIRP) in macrophages, leading to CIRP release and subsequent mediation of pyroptosis, apoptosis and necroptosis (PANoptosis) in pulmonary endothelial cells, exacerbating acute lung injury (ALI) (8). In summary, studies on lactylation modifications in both histones and non-histone proteins demonstrate that lactylation broadly participates in transcriptional regulation and the modulation of protein structure and function, providing

novel insights into the role of lactate in physiological and pathological processes.

Studies have demonstrated that lactate and lactylation modification regulate cellular metabolism, inflammation, cell death and tissue remodeling, and are extensively involved in the occurrence and progression of multiple-organ diseases (9-12). The cardiopulmonary system is highly coupled in structure and function. The heart and lungs are anatomically coupled via the pulmonary circulation and coexist within the closed thoracic cavity, rendering their functions highly interdependent (13). For example, in acute respiratory distress syndrome, acidemia and elevated transpulmonary pressure during mechanical ventilation increase pulmonary vascular resistance and right ventricular afterload. Cardiac dysfunction aggravates pulmonary edema and impairs gas exchange, creating a vicious cycle that complicates cardiopulmonary management (14). Meanwhile, cardiopulmonary interactions can be used to predict fluid responsiveness in mechanically ventilated patients (15).

Exploring the regulatory mechanisms of lactylation is of significance for elucidating the common pathogenic features of cardiopulmonary diseases and the pathogenetic rules underlying cardiopulmonary crosstalk. The present review systematically summarized the regulatory factors and signaling pathways of lactylation as well as its biological roles in cardiac and pulmonary diseases and discussed the potential shared molecular mechanisms through which it drives the progression of cardiopulmonary lesions. Meanwhile, lactylation-targeted compounds with potential therapeutic value were compiled, and current research limitations and translational bottlenecks were analysed, with the aim of providing theoretical references for further elucidating cardiopulmonary comorbidity mechanisms and developing precise intervention strategies (Fig. 1).

2. Enzymes that specifically regulate lactate modification

Despite numerous studies indicating that the levels of protein lactylation in cells are sensitive to lactate, the enzymes directly regulating reversible lactylation have not yet been fully identified and confirmed. The potential regulatory enzymes involved in lactylation modification have been summarized below.

'Writers' are primarily a class of acyltransferases that catalyze the interaction between the lactyl-coenzyme A (CoA) group and lysine residues (9), including p300 (5), aminoacyl-tRNA synthetase (AARS) (10), general control nonderepressible 5 (GCN5) (11), histone acetyltransferase binding to ORC1 (12), tat-interactive protein 60 (16), CREB-binding protein (CBP) (17), YiaC acyltransferase (18), lysine acetyltransferase 8 (KAT8) (19) and NOP2/Sun RNA methyltransferase family member 2 (20), among others. 'Readers' are mainly responsible for reading and transmitting information to influence the expression of related genes, including Brahma-related gene 1 (21) and Y-box binding protein 1 (20). After lactylation modification has taken effect, the 'erasers' responsible for removing the lactyl group and terminating the modification are engaged, including histone deacetylases (HDACs) (1-3,8), sirtuins (SIRT)1-3 (22), CobB deacetylase (18) and others.

Among these enzymatic molecules, p300 has been extensively studied. p300 is primarily localized in the nucleus and contains a central histone acetyltransferase domain that can catalyze the transfer of the acetyl group from acetyl-CoA to the lysine side chain of proteins (23). Andrographolide can inhibit H3Kla by interfering with p300, thereby alleviating calcific aortic valve disease (CAVD) (24). p300 can cooperate with guanosine triphosphate to synergistically regulate the expression of histone H3K18 lactylation (H3K18la) and growth differentiation factor 15, promoting glioma proliferation and radioresistance (25). A recent study has found that p300 can act as a crossroads for multiple PTMs. p300-mediated H3K18 lactylation drives radiation-induced pulmonary fibrosis via VIRMA-dependent m^6A modification of GATA3 (26).

Moreno-Yruela *et al* (22) conducted pioneering research. The authors discovered that *in vitro* HDAC1-3 and SIRT1-3 are delactylases with site-specific delactylation activity in cells. These findings have supported that histone Kla modification is a regulated and dynamic epigenetic mechanism, rather than a spontaneous chemical reactivity. SIRT2 is the most effective 'eraser' among HDACs in the process of inhibiting the proliferation and migration of neuroblastoma cells through lactylation modification (27). Research on HDACs is relatively well-developed in the context of acetylation, but lacks systematic studies in lactylation modification, and the specificity and selective mechanisms of HDACs at different lactylation sites have not yet been fully elucidated.

Subsequently, several teams almost simultaneously confirmed that AARS1/2 can act as moonlighting proteins to regulate lactylation modification. Unlike the aforementioned enzymes that use lactyl-coenzyme A lactyl-CoA as the donor, AARS1/2 employ lactyl-adenosine monophosphate as an intermediate donor for co-translational modification (28). AARS1/2 are considered sensors for L-lactate, capable of directly binding to L-lactate and catalyzing the ATP-dependent conjugation of L-lactate with lysine (10). AARS1 senses intracellular lactate and translocates to the nucleus to lactylate and activate the Yes-associated protein-TEA domain transcription factor complex, promoting the proliferation of gastric cancer cells and associating with poor prognosis (29). Moreover, AARS1 acts on tumor protein p53 (p53) to enhance systemic lactylation, leading to tumor cell proliferation and metastasis (28). AARS1 senses intracellular lactate and translocates into the nucleus, where it activates the YAP-TEAD complex of the Hippo pathway via lactylation modification. Meanwhile, AARS1 is a target gene of YAP-TEAD, and they form a positive feedback loop that promotes the proliferation of gastric cancer cells (29). Under hypoxia, AARS2 accumulates and catalyzes lactylation of PDHA1 (K336) and CPT2 (K457/8), which inactivates both enzymes and thereby suppresses oxidative phosphorylation; SIRT3 can erase these lactylation marks to restore oxidative phosphorylation activity (30).

Reports on the remaining lactylation 'writers', 'erasers' and 'readers' are relatively scarce (31). In addition, the regulatory molecules of lactylation overlap with those of other types of histone modifications, rendering the regulation of lactylation less specific and prone to multiple responses. For example, a genome-wide analysis of H3K18la was performed in T-cell acute lymphoblastic leukemia (T-ALL), revealing that H3K18la exhibits synergistic and divergent crosstalk with

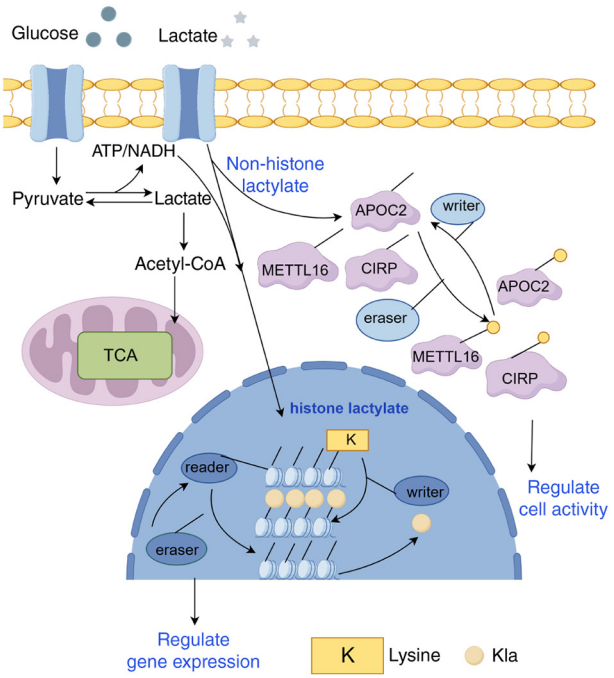

Figure 1. Process of lactate metabolism and lactylation in cells. There are two ways accumulate lactate in cytoplasm. Pyruvate, produced during glycolysis, enters the mitochondria and is metabolized through the TCA, which can also be converted to lactate by the action of lactate dehydrogenase. In the other pathway, lactate can be transported by membrane protein into cytoplasm. Histones and nonhistone proteins are lactylated by lactyl-CoA, which is derived from lactate. Figure created on figdraw.com. ATP, adenosine triphosphate; NADH, nicotinamide adenine dinucleotide; APOC2, apolipoprotein C-II; METTL16, methyltransferase-like protein 16; CIRP, cold-inducible RNA-binding protein; TCA, tricarboxylic acid cycle; Kla, lysine lactylation.

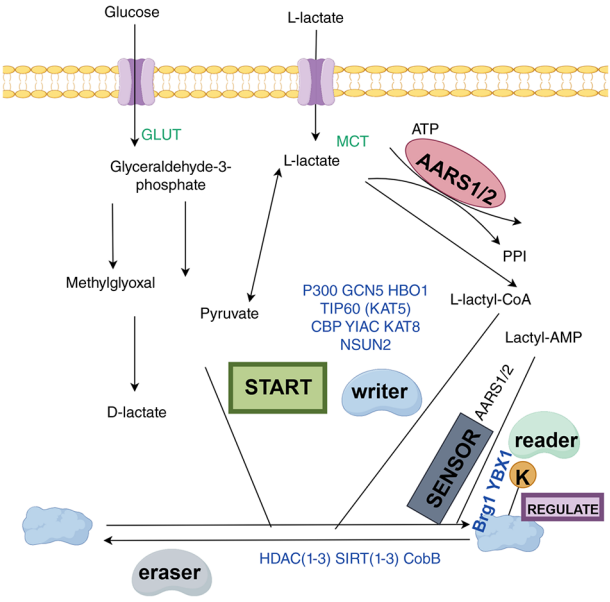

Figure 2. Process of histone lactylation and non-histone lactylation. Increased lactate levels, produced by pyruvate or transported by MCT, lead to the lactylation of histone or non-histone proteins, which subsequently affects chromatin structure and gene expression. The 'writer' catalyzes the binding of the lactyl-CoA group to lysine residues. The 'reader' is responsible for reading and transmitting information to affect the expression of related genes. The 'eraser' is responsible for removing the lactyl group, terminating the effect of lactylation modification. Figure created on figdraw.com. MCT, monocarboxylate transporter; L-lactyl-CoA, lactyl-coenzyme A; lactyl-AMP, lactyl-adenosine monophosphate; GLUT, glucose transporter; ATP, adenosine triphosphate; AARS1/2, aminoacyl-tRNA synthetase 1/2; PPI, peptidyl-prolyl isomerase; P300, E1A-associated protein p300; GCN5 HBO1, histone acetyltransferase binding to ORC1; TIP60, Tat-interactive protein 60 kDa; CBP, CREB-binding protein; YIAC, GNAT-family lysine acetyltransferase; NSUN2, NOP2/Sun RNA methyltransferase family member 2; HDAC, histone deacetylase; SIRT, sirtuin; CobB, CobB deacetylase; Brg1, Brahma-related gene 1; YBX1, Y-box binding protein 1.

H3K27 acetylation (H3K27ac) (32). The gradual discovery of lactylation regulatory enzymes has greatly promoted the exploration of functional Kla events, which are precisely orchestrated to regulate various biological processes (Fig. 2).

3. Physiological coupling and pathological interaction of the cardiopulmonary unit

Under physiological conditions, the heart and lungs constitute a highly integrated 'cardiopulmonary unit' through anatomical adjacency and hemodynamic series connection (33). Mechanical interaction serves as the physical basis for cardiopulmonary coupling: Respiratory fluctuations in intrathoracic pressure are directly transmitted to the cardiac chambers, resulting in increased right ventricular preload and reduced left ventricular filling during inspiration, whereas the opposite changes occur during expiration (15). Under conditions of elevated metabolic demand such as exercise, the respiratory and circulatory systems work synergistically via a 'series pump' mechanism. Respiratory muscle contraction stabilizes blood gas homeostasis, while cardiac output increases synchronously to guarantee systemic oxygen delivery (34). In addition to the classical mechanical and hemodynamic coupling, metabolic coupling has emerged as a novel dimension of cardiopulmonary interaction. Lactate is no longer merely regarded as a terminal glycolytic metabolite but acts as a crucial signaling molecule linking cellular metabolism and gene expression. By initiating protein lactylation, lactate translates the energetic status of cardiopulmonary tissues into epigenetic signals, thereby mediating metabolic interorgan crosstalk between the heart and lungs.

When physiological homeostasis is disrupted, cardiopulmonary interaction manifests as multi-level pathological crosstalk. Hemodynamic decoupling represents the core pathological feature. Increased pulmonary vascular resistance elevates right ventricular afterload and induces right ventricular-pulmonary artery (RV-PA) decoupling. Through ventricular interdependence, right ventricular pressure overload further alters left ventricular geometry and impairs diastolic function, forming a vicious cycle of progressive cardiopulmonary injury (35,36). Neurohumoral and immune crosstalk further exacerbates this pathological process. Catecholamines released by the sympathetic nervous system modulate pulmonary inflammatory responses and endothelial barrier integrity through adrenergic receptors. In addition, renin-angiotensin system imbalance, particularly the activation of the angiotensin II/angiotensin II type-1 receptor axis, has been verified as a critical driver of myocardial hypertrophy and persistent pulmonary inflammation (37).

Mechanistically, immune-mediated inter-organ communication has attracted increasing attention in cardiopulmonary research. Immune cells and their secreted soluble mediators

act as essential signaling carriers between the heart and lungs, participating in the progression of multiple cardiopulmonary diseases, including pulmonary arterial hypertension, acute respiratory distress syndrome and pneumonia (38). Hypoxia-stimulated pulmonary artery endothelial cells can release specific microRNA-enriched exosomes, which are transported through the circulation to the right ventricle, modulate mitochondrial function and apoptotic programs in cardiomyocytes, and ultimately facilitate right ventricular remodeling (39). Genetically, accumulating evidence has demonstrated shared genetic basis between cardiac and pulmonary disorders. Marked genetic overlap exists between chronic obstructive pulmonary disease (COPD) and major cardiovascular diseases, including hypertension, coronary heart disease and heart failure, providing genetic evidence for the high comorbidity of cardiopulmonary diseases (40,41).

Clinical evidence has highlighted the prognostic value of cardiopulmonary coupling indicators. RV-PA coupling serves as an independent prognostic biomarker across multiple cardiovascular diseases. In patients with aortic stenosis, tricuspid regurgitation or acute myocardial infarction (MI), a reduced tricuspid annular plane systolic excursion/pulmonary artery systolic pressure ratio, reflecting impaired cardiopulmonary adaptation, is notably associated with all-cause mortality and an increased risk of major adverse cardiovascular events (42-44). Therapeutic strategies have gradually shifted from simple vasodilation to holistic restoration of cardiopulmonary homeostasis. Novel 'coupling-targeted agents', such as sotatercept, simultaneously reverse pulmonary vascular remodeling and improve right ventricular adaptation, representing a promising therapeutic direction for cardiopulmonary comorbidities (33) (Fig. 3).

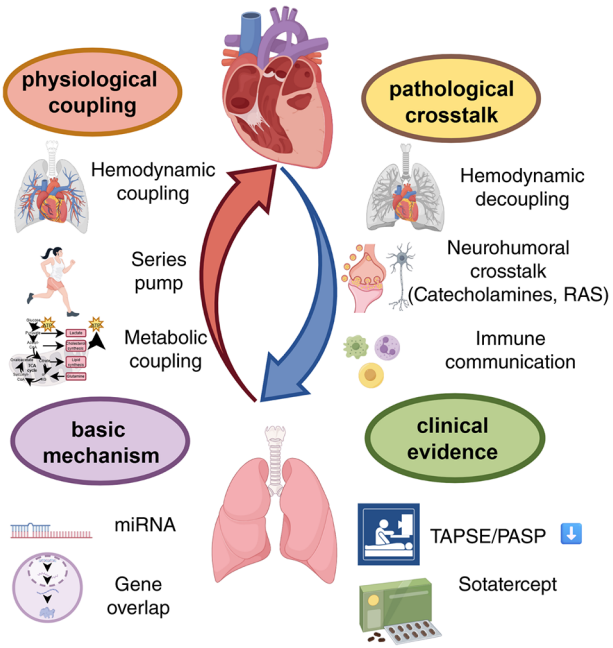

Figure 3. Multidimensional crosstalk of the integrated cardiopulmonary unit under physiological and pathological conditions. Physiological cardiopulmonary homeostasis is maintained by hemodynamic coupling, exercise-related "series-pump" adaptation, and lactate-driven metabolic coupling via protein lactylation. Homeostasis disruption triggers pathological crosstalk including hemodynamic decoupling, neurohumoral activation (catecholamines, RAS), and immune-mediated interorgan communication, leading to progressive cardiopulmonary injury. Exosomal miRNA transfer and shared genetic susceptibility underlie cardiopulmonary comorbidities. Clinically, reduced TAPSE/PASP serves as a prognostic biomarker, and sotatercept represents a promising coupling-targeted therapy. Figure created on figdraw.com. miRNA, microRNA; RAS, renin-angiotensin system; TAPSE/PASP, tricuspid annular plane systolic excursion/pulmonary artery systolic pressure.

4. Role and mechanisms of lactylation in respiratory and cardiovascular diseases

Lactylation in respiratory diseases. Respiratory diseases, which are characterized by ventilation impairment, defective gas exchange and pulmonary circulatory disturbances, frequently induce systemic metabolic perturbations (45). In this pathological context, cells within the pulmonary niche and the circulating compartment undergo metabolic reprogramming, predominantly manifested as a compensatory enhancement of glycolytic flux and consequent lactate accumulation (46). Beyond its role as a metabolic intermediate, lactate serves as a critical signaling molecule that bridges metabolic alterations and epigenetic regulation by inducing both histone and non-histone lactylation. Emerging evidence underscores lactylation as a pivotal pathogenic mechanism across a spectrum of respiratory diseases. Lactylation is not a unitary pro-inflammatory or pro-fibrotic signal, but rather exerts multifaceted effects contingent upon disease type, cell status and microenvironmental cues (47). Deciphering the tissue- and cell-type-specific regulatory networks of lactylation may offer novel avenues for precision intervention in respiratory diseases.

Pulmonary hypertension (PH). Excessive proliferation of pulmonary arterial smooth muscle cells (PASMCs) leads to medial hypertrophy and luminal stenosis of the pulmonary arteries, markedly increasing pulmonary vascular resistance. This heightened resistance imposes a severe afterload on the right ventricle, ultimately precipitating decompensated heart failure, and constitutes a core pathological basis of PH (48). Metabolic reprogramming is a key metabolic driver of lactylation modification in PH; upregulation of pyruvate dehydrogenase kinases (PDK1/2) enhances glycolysis and lactate accumulation, and the resultant histone lactylation at H3K18 and H4K5 sites promotes PASMC proliferation (49). Mechanistically, aldolase B at K87 lactylation facilitates SUMO-specific protease 3-dependent dynamin-related protein 1 (DRP1) deSUMOylation, which recruits DRP1 to the mitochondria to trigger mitochondrial fission, and further aggravates PASMC proliferation, migration and phenotypic transformation (50). In addition, lactate-induced Twist-related protein 1 (Twist1) lactylation enhances its binding to p300/CBP, promotes Twist1 nuclear translocation, upregulates transforming growth factor β1 transcription and activates Smad2 signaling, ultimately driving endothelial-to-mesenchymal transition and thereby contributing to PASMC proliferation and vascular remodeling in PH (51). Beyond intrinsic metabolic disorder, external environmental stimuli and comorbid conditions also mediate PH progression through lactylation: Microplastic exposure intensifies hexokinase 2-dependent glycolysis and elevates histone lactylation at tumor necrosis factor receptor superfamily member 11B and serum/glucocorticoid-regulated kinase 1 promoters to drive endothelial-to-mesenchymal transition (EMT) in human

pulmonary arterial endothelial cells (52), while lactate accumulation in obstructive sleep apnea-associated PH enhances phosphodiesterase 4B (PDE4B) promoter lactylation to activate PDE4B transcription, regulate fused in sarcoma activity and upregulate angiotensinogen expression, thereby accelerating PH development (53). Conversely, the super-enhancer-derived long non-coding RNA UNC5B antisense RNA 1 exerts protective effects by limiting glycolysis and reducing global lactylation in PASMCs, which reverses abnormal switching of PASMCs from contractile to synthetic phenotype and suppresses vascular inflammatory responses by reducing H3K18la enrichment at the promoters of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (54).

Pulmonary fibrosis. Histone lactylation acts as a crucial epigenetic force driving pulmonary fibrosis progression through multi-layered inter-cellular crosstalk. In immune cells, elevated histone lactylation facilitates M1 macrophage polarization and nitric oxide synthase 2 upregulation via H3K18la modification (55). Meanwhile, it activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome to promote IL-1β production, which further enhances 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3-dependent glycolysis through IL-1 receptor signaling. This process forms a positive glycolysis-lactylation feedback loop, enriches H3K18la at the transcription start site to upregulate SIX1 expression, and ultimately promotes EMT (56). Lactylation also exerts regulatory effects at the post-transcriptional level: p300-mediated H3K18la activates vir-like m6A methyltransferase associated transcription and stabilizes GATA-binding protein 3 mRNA in an m6A-dependent manner, thereby driving EMT and extracellular matrix deposition (26); lipopolysaccharide-induced H3K18la elevates METTL3-mediated m6A modification to promote peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) degradation, resulting in mitochondrial dysfunction and fibroblast activation (57). In structural cells, lactylation directly and indirectly triggers fibroblast activation; histone H4 K12 lactylation (H4K12la) promotes fibrotic progression by activating the phosphoinositide-3-kinase regulatory subunit 2/phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) signaling axis (58). In addition, mitochondrial pyruvate dehydrogenase E1 subunit α 1 K83 acetylation-initiated H4K12la is enriched in the super-enhancer region of the NUAK family kinase 2 (NUAK2) locus, which robustly induces NUAK2 expression and drives myofibroblast activation and extracellular matrix accumulation (59).

ALI. Metabolic reprogramming and aberrant lactylation constitute a central regulatory hub for inflammatory amplification and tissue destruction during ALI. Enhanced glycolysis and subsequent lactate accumulation initiate multiple deleterious cascades: Yin Yang 1 K183 lactylation suppresses PGC-1α transcription, disrupting mitochondrial homeostasis and impairing alveolar epithelial barrier integrity (60). Meanwhile, H3K18la upregulates insulin-like growth factor 2 mRNA-binding protein 2 expression, which stabilizes myristoylated alanine-rich C-kinase substrate-like 1 mRNA in an m6A-dependent manner and further activates NF-κB-mediated inflammatory signaling (61). Lactylation extensively modulates immune cell effector functions in ALI. In neutrophils, H3K18la enhances autophagy-related protein 7 transcription to trigger non-degradative secretory autophagy, facilitating robust IL-1β release and contributing to pulmonary microvascular endothelial dysfunction (62). In macrophages, platelet-derived growth factor-associated protein 1 lactylation acts as a core metabolic switch to activate the NLRP3 inflammasome. Combined with the loss of PDZ and LIM domain protein 1-mediated molecular restriction on NF-κB, this modification bridges metabolic stress and oxidative damage via the nuclear factor erythroid 2-related factor 2/GPX4-dependent ferroptotic pathway (63). In addition, lactylation of S100A9 at the K4/K94 sites promotes its nuclear translocation, cooperates with the transcription factor CCAAT/enhancer-binding protein β, and potentiates IL-1β transcription to amplify pulmonary inflammation (64). At the level of cell fate regulation, H3K18la increases caspase-8 promoter activity and sensitizes AECs to TNF-α-induced apoptosis (65). In pulmonary microvascular endothelial cells, H3K18la exacerbates ferroptosis and vascular hyperpermeability through a dual mechanism: It promotes acyl-CoA synthetase long-chain family member 4 (ACSL4) transcription to enhance lipid peroxidation and upregulates microtubule-associated protein 1 light chain 3 and nuclear receptor coactivator 4 to accelerate ferritin autophagy (66). Furthermore, pyruvate dehydrogenase kinase 4-driven lysophosphatidylcholine acyltransferase 2 K375 lactylation inhibits signal transducer and activator of transcription 1a (STAT1) acetylation while enhancing STAT1 phosphorylation, thereby repressing solute carrier family 7 member 11 transcription, impairing glutathione synthesis and aggravating epithelial ferroptosis (67). Platelet endothelial aggregation receptor 1 (PEAR1) promotes AARS1-mediated hypoxia-inducible factor 1 (HIF-1α)-α K172 lactylation, which enhances HIF-1α nuclear translocation and glycolysis. The glycolysis-derived lactate drives H3K18la enrichment at the PEAR1 promoter to upregulate PEAR1 expression, forming a self-reinforcing circuit that increases pulmonary microvascular endothelial permeability and exacerbates lung injury (68). Of note, multiple positive feedback loops sustained by lactylation further exacerbate ALI progression. Histone H3 K14 lactylation (H3K14la) enrichment at the transferrin receptor and solute carrier family 40 member 1 promoters remodel endothelial iron distribution and accelerates ferroptotic injury (69). Lysine acetyltransferase 2B-mediated early growth response protein 1 (EGR1) K364 lactylation facilitates EGR1 nuclear translocation, elevates heparinase expression and induces endothelial glycocalyx degradation (70). Extracellular release of lactylated CIRP from macrophages competitively blocks tripartite motif-containing protein 32-mediated Z-DNA-binding protein 1 (ZBP1) ubiquitination and degradation via TLR4 internalization, stabilizes ZBP1 and triggers receptor-interacting serine/threonine-protein kinase 3-dependent PANoptosis to aggravate endothelial damage (71). In AECs, extracellular lactate sensing by GPR81 activates the H3K18la/METTL3/m6A/ACSL4 axis to stabilize ACSL4 mRNA, ultimately reinforcing ferroptotic cell death (72).

COPD. In the pathological progression of COPD, aberrant glycolytic reprogramming and lactylation represent one of the important molecular mechanisms contributing to pulmonary tissue injury. Pathological stimuli can upregulate lactate dehydrogenase A (LDHA) and LDHB expression,

boost glycolytic metabolism and lactate accumulation, and facilitate p53 transcriptional activation through H3K14la modification, thereby triggering cell-cycle arrest and senescence in pulmonary epithelial cells (73). Benzo[a] pyrene metabolite benzo[a]pyrene-7,8-diol-9,10-epoxide cooperates with pathological stimuli to increase LDHB-driven lactate production, leading to H4K12la enrichment at the p53 promoter. This event activates the p53/p21/p16 signaling cascade and induces senescence-associated secretory phenotype (SASP), which participates in COPD-related pathological damage (74). Lactylation modulates cellular senescence through metabolic-epigenetic crosstalk: H4K12la depletes cellular nicotinamide adenine dinucleotide (oxidized form, NAD^+) pools by enhancing cluster of differentiation 38 (CD38) transcription and consequently promotes senescence in alveolar type II cells (75). For epithelial barrier regulation, H3K14la activates the low-density lipoprotein receptor-related protein 5/β-catenin pathway, down-regulates tight-junction proteins Occludin and zonula occludens-1 and disrupts airway epithelial barrier homeostasis (76). Furthermore, cigarette-smoke exposure elevates AARS1 expression in $CD8^+$ T cells, mediates runt-related transcription factor 3 (RUNX3) K193 lactylation and blocks the autophagic degradation of RUNX3. This sustains $CD8^+$ T-cell activation and cytotoxicity, further aggravating emphysematous lesions (77).

Asthma. In the pathological progression of asthma, aberrant glycolytic reprogramming and lactylation serve as an important molecular hub participating in airway inflammation and remodeling. Pathological-stimulus-induced lactate accumulation triggers the dual-site lactylation of ATPase H^+-transporting V1 sector subunit B2 at K108/K109, which inactivates lysosomal V-ATPase and leads to lysosomal alkalinization and lysosomal membrane permeabilization. The subsequent leakage of cathepsin B provokes massive mitochondrial reactive oxygen species burst and initiates the atypical caspase-8/3/gasdermin E-dependent pyroptotic pathway (78). At the adaptive immunity level, H3K18la promotes T helper 17 cell differentiation by activating dipeptidyl peptidase-4 transcription and induces EMT in bronchial epithelial cells to drive airway remodeling (79). Lactylation amplifies inflammatory responses through crosstalk among multiple PTMs: The succinylation of phosphoenolpyruvate carboxykinase 2 (PCK2)-K100 increases PCK2 protein stability and establishes a positive-feedback loop for lactate production. It further induces polyglutamine-binding protein 1-K223 lactylation to suppress protein arginine n-methyltransferase 5 activity, erases the repressive Histone H4 arginine-3 symmetric demethylation mark on the promoters of pro-inflammatory genes, and relieves transcriptional repression of mitogen-activated protein kinase (MAPK)-pathway-related genes (80). Furthermore, H3K18la enrichment at the colony-stimulating factor 1 receptor (CSF1R) promoter enhances its transcription, constructing an autocrine positive-feedback axis of CSF1/CSF1R/MAPK. This renders airway epithelial cells an upstream driver and inflammatory amplifier of allergic airway inflammation (81).

Lactylation in cardiovascular diseases. As a critical bridge linking cardiac metabolic reprogramming and epigenetic regulation, lactylation has regulatory effects across a spectrum of cardiovascular disorders and attracted substantial research interest in cardiovascular studies over the years. This lactate-driven PTM not only mirrors cellular energy status but also modulates diverse cardiac pathophysiological processes by altering the functions of histones and non-histone proteins (82). Its biological outcomes are not unidirectional; instead, it acts as a double-edged sword that either facilitates repair or aggravates injury, contingent upon cell types and disease stages (83). Although preliminary advances have been made in deciphering its molecular mechanisms, precisely dissecting its context-specific functions in distinct cardiac diseases remains a central research challenge (84). In this section, the recent research progress of lactylation in several major cardiac diseases has been discussed.

MI. Abnormal lactate accumulation following MI contributes to disease progression by triggering myocardial dysfunction through lactylation-dependent mechanisms. In conventional MI models, lactate is transported into endothelial cells through the monocarboxylate transporter (MCT) system. It promotes the binding of CBP/p300 to snail family transcriptional repressor 1 (Snail1) to induce Snail1 lactylation, further activates the TGF-β/Smad2 signaling cascade, disturbs endothelial homeostasis and induces mesenchymal-like phenotypic transition, which ultimately aggravates myocardial injury (85). Distinct from ordinary MI, diabetic MI exhibits a unique protective lactylation-related mechanism. Extracellular lactate is imported into cardiac microvascular endothelial cells through MCT1 and triggers acetyl-CoA acetyltransferase 1-dependent Isocitrate dehydrogenase 2 (IDH2) K272 lactylation. This modification strengthens the interaction between IDH2 and caveolin-1 (Cav1) and relieves the Cav1-mediated suppression of endothelial nitric oxide synthase, thereby facilitating endothelial proliferation, migration and angiogenesis. Consequently, it improves post-infarction left-ventricular function and confers cardioprotective effects (86). In parallel, a distinct protective axis operates in monocytes through GCN5-mediated H3K18la. Wang *et al* (11) demonstrated that monocytes undergo early glycolytic reprogramming and MCT1-dependent lactate uptake post-MI, driving IL-1β-dependent GCN5 recruitment and H3K18la at promoters of reparative genes (leucine-rich α-2-glycoprotein 1, vascular endothelial growth factor A, IL-10), thereby conferring anti-inflammatory and pro-angiogenic activities to macrophages and improving cardiac function.

Myocardial hypertrophy and pathological cardiac remodeling. In pressure-overload and hypertrophic cardiomyopathy models, aberrant lactylation drives the progression of myocardial hypertrophy, fibrosis and heart failure through multi-layered epigenetic regulatory networks. Pressure overload enhances myocardial glycolysis and lactate accumulation. On the one hand, p300/GCN5-dependent H3K18la is enriched at the transforming growth factor β-2 (TGFB2) promoter to activate the TGFB2-PI3K/AKT/mTOR cascade, triggering myocardial hypertrophy and heart failure (87). On the other hand, elevated H3K18la potentiates the transcriptional activity of GATA4 and markedly upregulates hypertrophy-associated genes, including atrial natriuretic peptide, B-type natriuretic peptide and β-myosin heavy chain, thus promoting pathological cardiac remodeling (88). From the perspective of delactylation regulation, METTL7B modulates ubiquitin-specific peptidase

38 (USP38) mRNA stability through m6A modification. Upregulated USP38 stabilizes HDAC3 protein and reinforces the erasure of histone lactylation, which reduces global histone lactylation, represses cardioprotective gene expression and accelerates heart failure, indicating that the METTL7B-histone lactylation axis serves as a potential therapeutic target for heart failure (89). Conversely, insufficient protective lactylation can also drive heart failure. In failing hearts, the lactylation of α-myosin heavy chain (α-MHC) at K1897 is decreased, which impairs the interaction between α-MHC and titin and leads to structural and functional cardiac deterioration, highlighting the direct role of metabolic-lactate modification in regulating sarcomere structure (90).

Bidirectional regulatory roles of lactylation in myocardial ischemia-reperfusion injury (MIRI). Lactylation exhibits prominent bidirectional regulatory features during MIRI. Lactylation occurring on distinct proteins and different sites can mediate either cardioprotective or detrimental effects. Regarding protective mechanisms, ischemia-reperfusion induces serpin family A member 3K K351 lactylation in fibroblasts, which improves protein stability and paracrine function, and suppresses cardiomyocyte apoptosis by activating the RISK and SAFE survival signaling pathways (91). Exercise intervention exerts cardioprotection by reducing global protein lactylation, inhibiting YTH N6-methyladenosine RNA-binding protein F2 (YTHDF2) function and upregulating Ras-GTPase-activating protein-binding protein 1 expression to alleviate cardiomyocyte apoptosis (92). Notably, in cardiomyocytes, HSPA12A preserves aerobic glycolysis by stabilizing HIF-1α to sustain protective histone H3 lactylation, thereby alleviating cell death and cardiac dysfunction (93).

By contrast, most aberrant lactylation modifications markedly exacerbate reperfusion injury. LDHA-driven lactate accumulation triggers NLRP3 K245 lactylation, which stabilizes the inflammasome and activates pyroptosis (94). Lactate upregulates mitochondrial calcium uptake protein 3 expression through two pathways, namely H3K18la-dependent epigenetic activation and AARS1-catalyzed protein lactylation. This event promotes mitochondria-endoplasmic reticulum contact, mitochondrial calcium overload, neutrophil extracellular trap (NET) release and microvascular injury (95). Histone lactylation derived from excessive glycolysis activates transient receptor potential cation channel subfamily M member 7 transcription, facilitating calcium influx and cardiomyocyte apoptosis (96). IDH2 K275 lactylation represses the AMP-activated protein kinase pathway and aggravates mitochondrial dysfunction, whereas SIRT3 reverses that damage through delactylation (97). Furthermore, lactate accumulation amplifies ischemia-reperfusion injury through multiple dimensions: It drives ferroptosis through the dual-site lactylation of GPX4 and lactate-induced YTHDF2 lactylation (which promotes its binding to FTH1 mRNA in an m6A-dependent manner) (98,99). In addition, it enhances neutrophil infiltration and myocardial toxicity through S100 calcium-binding protein A9 K26 lactylation, promoting their nuclear translocation and NET formation (100). Collectively, lactylation acts as a core epigenetic-metabolic target governing MIRI and holds value for targeted therapeutic intervention.

Vascular diseases. Lactylation is extensively involved in the pathological progression of vascular remodeling-related disorders including atherosclerosis, aortic aneurysm and dissection, and mediates vascular structural destruction and functional abnormalities through distinct epigenetic regulation. In atherosclerosis, TNF receptor-associated protein 1 boosts glycolysis and lactate accumulation, inhibits HDAC3 and elevates H4K12la to trigger the SASP-driven senescence program, thereby driving vascular smooth muscle cell senescence and atherosclerosis progression (101). In aortic aneurysm and dissection, dysregulated membrane-associated RING-CH protein 2-pyruvate kinase M2 axis facilitates lactate accumulation. H3K18la activates p53-dependent apoptotic transcriptional responses and aggravates vascular smooth muscle cell apoptosis and aortic wall destruction (102). Meanwhile, lysine acetyltransferase 7-catalyzed H4K16la forms a positive-feedback loop by modulating PDK1 transcription, which further sustains glycolytic disturbance and pathological vascular remodeling (103). For CAVD, lumican activates inflammatory signaling and enhances glycolysis-dependent lactate accumulation. It further triggers specific histone lactylation including H3K14la and H3K9la, upregulates calcification-related genes Runx2 and bone morphogenetic protein 2, induces osteogenic differentiation of valvular interstitial cells and accelerates aortic valve calcification (104).

Metabolic cardiomyopathy and drug-induced cardiac injury. Lactylation exerts complex regulatory functions in diabetic cardiomyopathy and drug-triggered myocardial injury, contributing to myocardial metabolic disturbance and cardiac dysfunction. Lactylation displays prominent functional heterogeneity with both protective and detrimental effects in diabetic cardiomyopathy. AARS2-dependent thioredoxin reductase 2 (TrxR2) K340 lactylation strengthens mitochondrial TrxR activity and eliminates reactive oxygen species. It protects cardiac microvascular function and alleviates myocardial damage through modulating mitochondrial autophagy and ferroptosis pathways (105). By contrast, nucleophosmin-related protein 3-mediated H3K18la/H3K27la lactylation activates fatty acid synthase transcription to promote fatty-acid synthesis and trigger cardiomyocyte necroptosis (106). Acyl-CoA thioesterase 1 physically interacts with Sterol regulatory element-binding protein 1c (SREBP1c) and promotes Kla of SREBP1c under high lactate conditions, which drives SREBP1c nuclear translocation and enhances its transcriptional activity, leading to the upregulation of CD36. The CD36-mediated uptake of free fatty acids is increased, resulting in myocardial lipid accumulation and lipotoxic injury, which ultimately promotes ventricular hypertrophy and diastolic dysfunction (107). In drug-induced cardiac injury, doxorubicin-provoked cardiotoxicity relies on GCN5-mediated KAT8 K145 lactylation with SIRT6 serving as the deacetylase that reverses this modification to facilitate pro-apoptotic complex assembly, which further activates the p53-Bcl-2-associated X protein/p53-upregulated modulator of apoptosis apoptotic cascade, induces cardiomyocyte apoptosis and gives rise to cardiac dysfunction (108).

Potential common pathogenic mechanisms of lactylation underlying cardiopulmonary crosstalk. The lactylation modifications involved in the pathogenesis of cardiopulmonary diseases are summarized in Table I. In cardiovascular diseases, the lactate-lactylation axis exerts double-edged-sword effects. On the one hand, it promotes the expression of

Table I. Overview of lactylation modifications involved in the pathogenesis of cardiopulmonary diseases.

Disease category	Substrate protein and modification site	Regulatory enzymes	Downstream pathway	Pathological consequence
Pulmonary hypertension	ALDOB K87	Sirtuin 1	sentrin/SUMO/DRP1	Mitochondrial fragmentation (50)
	H3K18la/H4K5a	/	mROS/HIF-1α/PDK1/2	PASMC proliferation (49)
	Twist1	p300/CBP	TGFB1/Smad2	EndoMT (51)
	H3K18la	/	PDE4B/FUS/AGT	PASMC proliferation (53)
	H3K18la	/	FOXP3/UNC5B-AS1	Inflammatory phenotypic (54) transition
Pulmonary fibrosis	H3K18la	p300	VIRMA/GATA3	EMT (26)
	PIK3R2/H4K12la	/	PI3K/AKT/mTOR	Fibroblast activation and (58) proliferation
	H3K18la	SIRT3	NOS2	Macrophage M1 polarization (55)
	H3K18la	p300	SIX1	EMT (56)
Acute lung injury	YY1 K183la	Tip60	PGC-1α	Mitochondrial homeostasis (60) disorder
	H3K18la	EP300	IGF2BP2/MARCKSL1/NF-κB	Inflammatory cascade (61)
	HIF-1α K172la	AARS1	PEAR1	Increased pulmonary micro- (68) vascular endothelial cell permeability
	H3K18la	p300	ATG7	Endothelial dysfunction (62)
	PDAP1	/	IL-1β	Inflammatory cascade (63)
	S100A9 K9/K4	/	CCAAT/CEBPB/IL-1β	Sepsis (64)
	H3K18la	/	Caspase-8	AECs apoptosis (65)
	H3K18la	/	ACSL4	Excessive lipid peroxidation (66)
	H3K18la	/	LC3/GATA2/NCOA4	Ferroptosis (66)
	LPCAT2 K375la	AARS1/HDAC9	STAT1/SLC7A11	Ferroptosis (67)
	H3K14la	/	TFRC□SLC40A1	Ferroptosis (69)
	EGR1 K364la	KAT2B (GCN5)	importin-α	Endothelial barrier dysfunction (70)
	CIRP	/	TLR4/ZBP1/TRIM32	PANoptosis (8)
	H3K18la	p300	METTL3/ACSL4	Ferroptosis (72)
Chronic obstructive pulmonary disorder	H3K14la	/	p53	Cellular senescence (73)
	H4K12la	/	p53/p21/p16/SASP	Cellular senescence (74)
	H4K12la	p300/CBP	CD38/NAD	Cellular senescence (41135106)
	H3K14la	/	LRP5/β-catenin	Disruption of airway epithelial barrier integrity (76)
	RUNX3 K193la	AARS1	/	Escape from autophagy (77)
Asthma	ATP6V1B2 K108/K109la	/	Caspase-8/3/GSDME	Pyroptosis (78)
	H3K18la	/	DPP4	EMT of bronchial epithelial cells (79)
	PQBP1 K223la	/	PRMT5/WDR77	Airway inflammation (80)
	H3K18la	p300	CSF1/MAPK	Airway inflammation (81)
Myocardial infarction	Snail1	CBP/p300	TGF-β/Smad2	EndoMT (85)
	IDH2 K272la	ACAT1/HDAC1	IDH2/Cav1/eNOS	Compensatory angiogenesis (86)
	H3K18la	GCN5	LRG1, VEGF-A, IL-10	Activate transcription of reparative genes (11)

Table I. Continued.

Disease category	Substrate protein and modification site	Regulatory enzymes	Downstream pathway	Pathological consequence
Cerebral ischemia-reperfusion injury	Histone H3	/	/	Improving cardiomyocyte survival (93)
	NLRP3 K245la	/	NLRP3	Pyroptosis (94)
	SERPINA3K K351la	/	SERPINA3	Reduce cardiomyocyte apoptosis (91)
	H3K18la, MICU3	AARS1	MICU3/VDAC1	Exacerbate myocardial injury (95)
	GPX4 K218la, K228la	/	/	Ferroptosis (98)
	S100a9 K26la	DLAT	/	Neutrophil infiltration (100)
	YTHDF2	/	FTH1	Ferroptosis (99)
	IDH2 K275la	SIRT3	AMPK	Exacerbate mitochondrial injury (97)
Atherosclerosis	H4K12la	HDAC3	SASP	VSMC senescence (101)
Aortic valve calcification	H3K14la/H3K9la	/	Runx2, BMP2	Osteogenic differentiation of VICs (104)
Aortic aneurysm/ dissection	H3K18la	/	p53	VSMC apoptosis (102)
	H4K16la	KAT7	PDK1	VSMC phenotypic dysregulation (103)
Atrial fibrillation	H3K18la	p300	TGF-β1	Atrial fibrosis (119)
Diabetic cardiomyopathy	TrxR2 K340la	AARS2	SCP2/ACSL4	Facilitates mitochondrial protection/ Endothelial ferroptosis resistance (105)
	H3K18la, H3K27la	NPM3	FASN	Cell necroptosis (106)
	SREBP1c	/	CD36	Myocardial lipid accumulatio (107)
Doxorubicin-induced cardiotoxicity	KAT8 K145la	GCN5/SIRT6	KAT8-TIP60/p53	Cardiomyocyte apoptosis (108)
Cardiac hypertrophy	H3K18la	p300/GCN5	TGFB2/PI3K/ AKT/mTOR	Cardiac hypertrophy (87)
	H3K18la	/	GATA4	Cardiac hypertrophy (88)
Heart failure	α-MHC K1897la	p300/SIRT1	Titin	Maintenance of sarcomere structure (90)
	H3K9la	/	/	Myocardial fibrosis (118)

AARS, Alanyl-tRNA synthetase; ACSL4 Acyl-CoA synthetase long-chain family member 4; ACAT1, Acetyl-CoA acetyltransferase 1; AECs, alveolar epithelial cells; AGT, angiotensinogen; AKT, protein kinase B; ALDOB, aldolase B; AMPK, AMP-activated protein kinase; ATG7, autophagy related 7; ATP6V1B2, ATPase H+ transporting V1 subunit B2; BMP2, bone morphogenetic protein 2; Cav1, caveolin 1; CEBPB, CCAAT/enhancer binding protein beta; CBP, CREB-binding protein; CSF1, colony stimulating factor 1; CIRP, cold-inducible RNA-binding protein; DLAT, dihydrolipoamide S-acetyltransferase; EGR1, early growth response 1; EndoMT, endothelial-to-mesenchymal transition; EP300, E1A binding protein p300; EMT, epithelial-mesenchymal transition; FASN, fatty acid synthase; FOXP3, forkhead box P3; FTH1, ferritin heavy chain 1; GATA, GATA binding protein; GCN5, lysine acetyltransferase 2B; GPX4, glutathione peroxidase 4; GSDME, gasdermin E; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1 alpha; H4K5a, H4 lysine 5 acetylation; H4K12la, H4 lysine 12 lactylation; H4K16la, H4 lysine 16 lactylation; H3K9la, H3 lysine 9 lactylation; H3K14la, H3 lysine 14 lactylation; H3K18la, H3 lysine 18 lactylation; H3K27la, H3 lysine 27 lactylation; IDH2, isocitrate dehydrogenase 2; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; IL-1β, interleukin 1 beta; KAT, lysine acetyltransferase; LC3, microtubule-associated protein 1 light chain 3; LRG1, leucine-rich alpha-2-glycoprotein 1; LRP5, low-density lipoprotein receptor-related protein 5; MAPK, mitogen-activated protein kinase; MARCKSL1, MARCKS-like 1; METTL3, methyltransferase-like 3; mROS, mitochondrial reactive oxygen species; mTOR, mechanistic target of rapamycin kinase; MICU3, mitochondrial calcium uptake 3; NAD, nicotinamide adenine dinucleotide; NLRP3, nuclear factor kappa B; NOS2, nitric oxide synthase 2; NCOA4, nuclear receptor coactivator 4; p16, cyclin-dependent kinase inhibitor 2A; p21, cyclin-dependent kinase inhibitor 1A; p300, E1A binding protein p300; PDK, pyruvate dehydrogenase kinase; PDAP1, PDGFA associated protein 1; PDE4B, phosphodiesterase 4B;

Table I. Continued.

PEAR1, platelet endothelial aggregation receptor 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphatidylinositol 3-kinase; PIK3R2, phosphatidylinositol 3-kinase regulatory subunit beta; PQBP1, polyglutamine binding protein 1; PRMT5, protein arginine methyltransferase 5; RUNX, Runt-related transcription factor; S100A9, S100 calcium binding protein A9; SASP, senescence-associated secretory phenotype; SCP2, sterol carrier protein 2; SERPINA3K, serpin family A member 3 variant K; SIX1, sine oculis homeobox homolog 1; SIRT, sirtuin; SLC7A11, solute carrier family 7 member 11; SLC40A1, solute carrier family 40 member 1; SREBP1c, sterol regulatory element binding transcription factor 1c; STAT1, signal transducer and activator of transcription 1; SUMO, small ubiquitin-like modifier; TGFB, transforming growth factor beta; TFRC, transferrin receptor; Tip60, lysine acetyltransferase 5; TLR4, toll-like receptor 4; TRIM32, tripartite motif containing 32; TrxR2, thioredoxin reductase 2; UNC5B-AS1, UNC5B antisense RNA 1; VDAC1, voltage dependent anion channel 1; VEGF-A, vascular endothelial growth factor A; VICs, valve interstitial cells; VIRMA, VIRMA N6-methyladenosine methyltransferase complex subunit; VSMC, vascular smooth muscle cell; WDR77, WD repeat domain 77; YTHDF2, YTH N6-methyladenosine RNA binding protein F2; ZBP1, Z-DNA binding protein 1; α-MHC, alpha-myosin heavy chain.

repair-related genes, drives anti-inflammatory cell polarization and preserves myocardial structural integrity. On the other hand, aberrant lactylation aggravates inflammatory responses, facilitates fibrosis, triggers cell death and induces vascular calcification (83,109). Such context-dependent dual effects are also observed in pulmonary diseases. Moderate lactylation confers pulmonary protective benefits: It triggers macrophage polarization toward an anti-inflammatory phenotype, induces the expression of damage-repair-related genes, maintains the alveolar-capillary endothelial barrier, and alleviates excessive pulmonary inflammatory injury (110). By contrast, pathologically elevated lactylation produces detrimental outcomes. It amplifies pulmonary inflammatory cascades, promotes fibroblast activation and proliferation, drives fibrotic remodeling in lung tissues, modulates immune-cell death programs, and exacerbates parenchymal and vascular lung injury (111).

Among multiple cardiopulmonary comorbidity models, the multi-organ injury mechanism governed by lactylation has been best characterized and most extensively investigated in sepsis-associated multiple-organ dysfunction. Sepsis-provoked systemic metabolic disturbance and uncontrolled inflammation markedly boost glycolysis and trigger aberrant protein lactylation across multiple organs. Through epigenetic regulation, lactylation modulates downstream gene transcription and inflammatory-cytokine release, contributing to functional and structural damage of vital organs including the lung, heart, brain and liver. In sepsis, lactylation broadly shapes immune-cell functions. It participates in macrophage phenotypic switching, aberrant NET formation, myeloid-derived suppressor cell activation and dysregulated T-cell differentiation, serving as one of the core epigenetic-metabolic mechanisms underlying immune imbalance and simultaneous cardiopulmonary injury (112).

In sepsis-induced myocardial dysfunction, lactylation plays a vital role via histone-dependent epigenetic regulation. Enhanced myocardial glycolysis during sepsis leads to lactate accumulation. Lysine acetyltransferase 2A-catalyzed H3K14la facilitates the binding of histone H3 to promoters of inflammatory and apoptotic genes and activates their transcription (113). Meanwhile, MOF-dependent H4K16la upregulates chemokines C-X-C motif chemokine ligand 8 and C-C motif chemokine ligand 2 to drive myocardial inflammation (114). Furthermore, KAT5-dependent H3K27la accumulates at pro-inflammatory gene promoters and further enhances their transcriptional activation (115).

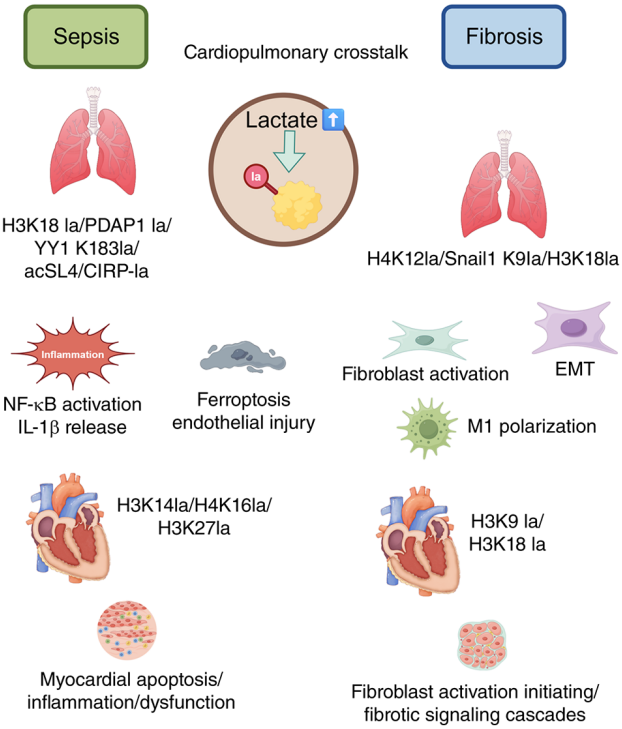

Figure 4. Lactylation-mediated molecular mechanisms underlying cardiopulmonary crosstalk in sepsis-and fibrosis-related cardiopulmonary injury. Elevated lactate induces protein lactylation to propagate cardiopulmonary injury through cardiopulmonary crosstalk. During sepsis, lung-enriched lactylation modifications (H3K18la, PDAP1la, YY1 K183la) activate NF-κB-mediated inflammation, IL-1β secretion, ferroptosis and endothelial damage. Cardiac H3K14la/H4K16la/H3K27la further contribute to myocardial apoptosis, inflammation and dysfunction. Under fibrotic stimuli, H4K12la, Snail1 K9la and H3K18la drive pulmonary fibroblast activation, EMT and M1 macrophage polarization. Cardiac H3K9la/H3K18la triggers fibroblast activation and fibrotic cascades, aggravating cardiopulmonary fibrotic lesions. Figure created on figdraw.com. H3K18la, histone H3 lysine-18 lactylation; PDAP1la, PDGFA-associated protein 1 lactylation; YYY1, yin yang 1; K183la, lysine-183 lactylation; acSL4, acyl-CoA synthetase long-chain family member 4; CIRPla, cold-inducible RNA-binding protein lactylation; H4K16la, histone H4 lysine-16 lactylation; Snail, snail family transcriptional repressor 1; K9la, lysine-9 lactylation; EMT, epithelial-mesenchymal transition; CoA, co-enzyme A.

Beyond acute inflammatory injury, cardiopulmonary fibrotic remodeling represents another key shared process modulated by lactylation in cardiopulmonary comorbidities. Pathologically enhanced glycolysis in cardiac and pulmonary tissues supplies sufficient energy for fibroblast activation,

Table II. Pharmacological interventions targeting lactylation and their protective effects in cardiopulmonary diseases.

Disease category	Targeting strategies/small molecules	Substrate protein and modification site	Regulatory enzymes	Downstream pathway	Protection effects
Pulmonary hypertension	Indotecan	/	/	TOP1/AKT/mTORC1	Decreased PASMC proliferation (125)
Pulmonary fibrosis	Wogonoside	Snail1 K9la	/	TGF-β	Inhibited fibroblast activation (126)
Acute lung injury	ALA	H3K14la	/	PARK7/BMP/FADS1/2	Alleviated lipid peroxidation and ferroptosis (127)
	Dunhuang Daxiefei Decoction	H3K18la	/	/	Restrained MI-driven inflammatory amplification (128)
	Ma Xing Shi Gan Decoction	HMGB1	/	/	Reduced autophagosome accumulation (129)
	Glycyrrhizin	YY1 K183	/	PGC-1α	Restored mitochondrial function (60)
Asthma	Flavonoid astragalin	H4K12la	/	Sirt6/LDHA/CXCL1/2	Reduced neutrophil infiltration (130)
	Veratramine	CREB1 K122la	/	SMAD7/TGF-β	Attenuated airway remodeling (131)
	Ephedrine	ACSL4	/	PKM2	Inhibited ferroptosis (132)
Aortic valve calcification	Andrographolide	H3Kla	p300	Runx2	Alleviated aortic valve calcification (24)
	Jatrorrhizine	ALDOA K42la	KAT5	Runx2	Inhibited osteogenic differentiation (133)
	Gastrodin	H3K9la		BMP2	Inhibited osteogenic differentiation (134)
Cerebral ischemia-reperfusion injury	Dexmedetomidine	MDH2 K239la	/	NR3C1/PDK	Inhibited ferroptosis (135)
Radiation-Induced Heart Disease	Aloe-emodin	P4HB K311la	/	GOT2/PTGS2/SH3GLB1/NDP52	Protected mitochondrial function (136)
Myocardial infarction	Astragaloside IV	Snail1	/	TGF-β	Alleviated cardiomyocyte injury (137)
	Asprosin	/	/	PI3K/AKT-HIF-1α/VEGF/TIMP1	Inhibited cellular senescence (138)
SIMD	Gastrodin	H3K14la	KAT2A	CDT2/KAT2A	Suppressed transcription of inflammatory/apoptotic genes (113)
	Ailanthone	H4K16la	MOF (KAT8)	CXCL8/CCL2	Suppressed inflammation (114)
	Eupatilin	H3K27la	KAT5	/	Suppressed transcription of inflammatory genes (115)
Diabetic Cardio-myopathy	Dihydroartemisinin	H3K18la, H3K27la	NPM3	FASN	Alleviated necroptosis (106)

Table II. Continued.

Disease category	Targeting strategies/small molecules	Substrate protein and modification site	Regulatory enzymes	Downstream pathway	Protection effects
Doxorubicin-induced myocardial injury	Vericiguat	/	/	RELB	Alleviated inflammation and oxidative stress (139)

ACSL4, acyl-CoA synthetase long-chain family member 4; AKT, protein kinase B; ALA, alpha-lipoic acid; ALDOA, aldolase A; BMP2, bone morphogenetic protein 2; CCL2, C-C motif chemokine ligand 2; CDT2, chromatin licensing and DNA replication factor 2; CREB1, cAMP responsive element binding protein 1; CXCL, C-X-C motif chemokine ligand; FADS, fatty acid desaturase; FASN, fatty acid synthase; GOT2, glutamic-oxaloacetic transaminase 2; HMGB1, high mobility group box 1; HIF-1α, hypoxia-inducible factor 1 alpha; KAT, lysine acetyltransferase; LDHA, lactate dehydrogenase A; MDH2, malate dehydrogenase 2; MI, myocardial ischemia; MOF, lysine acetyltransferase 8; mTORC1, mechanistic target of rapamycin complex 1; NDP52, nuclear dot protein 52; NPM3, nucleophosmin 3; NR3C1, nuclear receptor subfamily 3 group C member 1; PARK7, Parkinson disease protein 7; PASMC, pulmonary artery smooth muscle cell; PDK, pyruvate dehydrogenase kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKM2, pyruvate kinase M2 isoform; P4HB, prolyl 4-hydroxylase subunit beta; PTGS2, prostaglandin-endoperoxide synthase 2; RELB, RELB proto-oncogene, NF-κB subunit; Runx2, runt-related transcription factor 2; SH3GLB1, SH3 domain containing GRB2 like, endophilin B1; SIMD, sepsis-induced myocardial dysfunction; SMAD7, SMAD family member 7; Sirt6, sirtuin 6; TIMP1, tissue inhibitor of metalloproteinases 1; TOP1, DNA topoisomerase I; VEGF, vascular endothelial growth factor.

proliferation and migration. Beyond its metabolic function, lactate acts as a functional signaling molecule to initiate and propagate fibrotic progression. Protein lactylation directly couples cellular metabolic reprogramming with epigenetic control of fibrosis-related genes at the transcriptional level and plays a central regulatory role in both cardiac and pulmonary fibrosis (116). Myocardial fibrosis is a hallmark secondary pathological alteration following MI. Excessive and persistent myocardial fibrosis reduces myocardial compliance, impairs cardiac systolic-diastolic function, induces ventricular structural remodeling and ultimately progresses to irreversible heart failure (117).

Specific mechanistic studies on myocardial fibrosis have further uncovered molecular pathways for lactylation-driven cardiac remodeling. Hexokinase 1 (HK1) maintains intracellular lactate homeostasis to promote histone H3K9 lactylation, thereby activating pro-fibrotic gene transcription and triggering abnormal cardiac fibroblast activation. The clinical relevance of the interferon regulatory factor 7-HK1 axis has been validated in human heart samples. This axis drives fibroblast activation and myocardial fibrosis through metabolic-epigenetic reprogramming and provides new mechanistic insights (118). Other studies focusing on atrial fibrosis have revealed that abnormal lactate accumulation elevates global lactylation and specifically increases H3K18la in atrial fibroblasts. Mechanistically, P300-mediated H3K18la strongly activates TGF-β1 transcription, initiates fibrotic signaling cascades, and aggravates atrial fibrotic lesions (119). Collectively, existing evidence identifies lactylation as a shared core mechanism mediating fibrotic injury in both heart and lung. Targeting aberrant lactylation may constitute a general therapeutic strategy to intervene in cardiopulmonary damage and halt the progression of fibrotic cardiopulmonary comorbidities (Fig. 4).

5. Prospects and outlook

Since lactylation was identified in 2019, this novel metabolic-epigenetic modification has become a research hotspot and offered new insights into disease mechanisms and targeted therapies. Lactylation-related studies have covered multiple-system diseases, and its critical roles in regulating inflammatory disorders, cell death and organ remodeling have been separately validated in cardiac and pulmonary diseases (120-122). Nevertheless, most existing investigations focus on either cardiac or pulmonary disorders alone. Mechanisms underlying lactylation-mediated cardiopulmonary crosstalk and comorbidities remain poorly documented, which hinders our comprehensive understanding of synergistic cardiopulmonary injury and partly accounts for conflicting experimental observations.

Targeted translational research on lactylation still faces considerable limitations. Current drugs targeting glycolysis and lactate metabolism generally suffer from poor specificity and off-target toxicities (123,124). The present article summarizes compounds with proven therapeutic efficacy against the lactylation pathway in basic research, as listed in Table II (24,60,106,113-115,125-139). Furthermore, lactylation can occur in a non-enzymatic manner and exhibits intricate crosstalk with acetylation, ubiquitination and other post-translational modifications, posing substantial challenges for precise intervention (140).

Artificial-intelligence-based predictive models facilitate mechanistic exploration and target screening for lactylation (141-143). Future studies should adopt a cardiopulmonary-crosstalk perspective, integrate multi-omics and bioinformatics analyses to clarify the specific functions of lactylation and its modification crosstalk in cardiopulmonary comorbidities, identify highly specific therapeutic targets and advance the translation of lactylation crosstalk

in cardiopulmonary comorbidities. Besides, future research should systematically assess how lactate concentration, cell type, disease stage and microenvironmental factors influence lactylation function under standardized experimental models and conditions.

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Authors' contributions

Literature search, drafting and preparation of the initial manuscript was performed by ZP. Literature screening, drawing and critical revision of the manuscript was performed by LT. ZW was responsible for conceptualization and design of the review, supervision of the literature review process, critical revision of all sections for intellectual content and final approval of the version to be published. All authors contributed to the editorial changes in the manuscript. All authors 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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