Lactylation-mediated ferroptosis: A novel mechanism and therapeutic prospects in human diseases (Review)

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Abstract. Lysine lactylation (Kla), an emerging post-translational modification, bidirectionally regulates cell fate decisions through epigenetic reprogramming and the direct modification of key ferroptosis proteins. It drives disease progression or mediates therapeutic resistance in inflammation, neurodegenerative diseases, cancer and ischemia-reperfusion injury, with its regulatory direction being disease-type-dependent. The present review discusses the functions of the Kla-ferroptosis regulatory network, unraveling the role of Kla-ferroptosis in diseases and its therapeutic implications. The present review aimed to provide novel perspectives for the treatment of human diseases.

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Abbreviations: Kla, lysine lactylation; PTMs, post-translational modifications; GSH, glutathione; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; ACSL4, acyl-CoA synthetase long-chain family member 4; PUFAs, polyunsaturated fatty acids; LDH, lactate dehydrogenase; HIF1A, hypoxia-inducible factor 1-alpha; METTL3, methyltransferase-like 3; m^6A, N6-methyladenosine; FTH1, ferritin heavy chain 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; NCOA4, nuclear receptor coactivator 4; FSP1, ferroptosis suppressor protein 1; HDAC1, histone deacetylase 1; SLC7A11, solute carrier family 7 member 11; IREB2, iron-responsive element-binding protein 2; NRF2, nuclear factor erythroid 2-related factor 2; HMOX1, heme oxygenase 1; HMGB1, high-mobility group box 1; HDACi, HDAC inhibitor; MCT4, monocarboxylate transporter 4

Key words: lysine lactylation, ferroptosis, metabolic-epigenetic regulation, therapeutic target, drug resistance

1. Introduction

Post-translational modifications (PTMs) increase proteomic functional diversity by covalently adding functional groups, regulating the proteolytic cleavage of subunits or the degradation of entire proteins. These include glycosylation, ubiquitination, small ubiquitin-like modification, acetylation, phosphorylation and palmitoylation, affecting nearly all aspects of cell biology and pathology (1-5). Lactate, once considered a waste product of glucose metabolism, has been revealed in recent years as not only a key circulating energy substrate, but also as a signaling molecule. Notably, it profoundly regulates gene expression and cell fate through a novel PTM, lysine lactylation (Kla) (6-10). In 2019, Zhang *et al* (11) first reported histone Kla in Nature, inaugurating a new era in lactate biology research. Kla has rapidly emerged as a research hotspot in life sciences, with its mechanisms and pathological significance providing transformative insights in fields such as cancer, immunology and neurological diseases (11-16). Kla involves the transfer of a lactyl group to the amino group of lysine residues, a process regulated by a series of enzymes and metabolites, including lactate, 'writer' enzymes, 'reader' proteins and 'eraser' enzymes (17). Lactate accumulation is the core trigger for Kla, with its level being positively associated with the degree of Kla modification (18,19). Under the action of 'writers', L-lactyl-CoA derived from lactate is transferred to proteins, initiating Kla. Erasers remove L-lactyl-CoA from proteins to terminate Kla, while 'reader' proteins recognize Kla and transduce signals to downstream targets (20-23).

The concept of ferroptosis was first proposed in 2012, referring to a unique form of programmed cell death triggered by iron-dependent lipid peroxidation pathways. It participates in multiple physiological and pathological processes and is prevalent in various diseases (24-28). In recent years, significant progress has been made in understanding the mechanisms of ferroptosis, including iron homeostasis imbalance, lipid peroxidation and the disruption of antioxidant systems (29-33).

Furthermore, numerous factors regulate cellular sensitivity to ferroptosis under pathological conditions, thereby influencing disease progression (27). System xCT is an antiporter, with solute carrier family (SLC)7A11 as a key component, responsible for transporting cysteine and glutamate. It increases cellular cysteine uptake, which is converted to glutathione (GSH) under the action of thioredoxin reductase 1. Glutathione (GSH) peroxidase 4 (GPX4) relies on GSH as a substrate to enhance its activity, promoting the conversion of phospholipid hydroperoxides (PL-OOH) to lipid alcohols. Thus, system xCT prevents ferroptosis by reducing PL-OOH accumulation. Erastin and RAS-selective lethal 3 (RSL3, a ferroptosis inducer), as inhibitors of system xCT and GPX4, respectively, promote ferroptosis (34-36). An imbalance in iron homeostasis is another classical pathway in ferroptosis, primarily regulated by a network involving transferrin receptor 1 (TFR1), iron regulatory protein (IRP)1 and IRP2, affecting cellular iron uptake, storage and release (30,37,38). Reactive oxygen species (ROS) generation and phospholipid peroxidation require numerous metabolic enzymes, with iron acting as their catalyst and essential element. Iron-dependent Fenton reactions rapidly amplify PL-OOH and generate various reactive radicals, inducing ferroptosis in cancer cells (39-41). Unrestricted lipid peroxidation is a hallmark of ferroptosis. Acyl-CoA synthetase long-chain family member 4 (ACSL4) is a key enzyme converting polyunsaturated fatty acids (PUFAs) to phospholipids (PUFA-PEs). PUFA-PEs promote intracellular lipid peroxide accumulation under the action of various enzymes. Phospholipids rich in PUFAs in cell membranes and phospholipid peroxidation are considered the direct executors of ferroptosis (42,43).

Lactate is the driver of lactylation and is associated with lactylation levels (11). Lactate production and removal maintain electron flux through specific pathways, including NADH conversion to NAD^+ and H^+, and lactate dehydrogenase (LDH)-mediated lactate conversion. These reduced coenzymes generate electrons upon oxidation via mitochondrial respiration or lactate fermentation, maintaining redox balance (44,45). Lactate accumulation can also promote intracellular fatty acid synthesis by activating key enzymes and supplying precursors (46,47). Studies have also demonstrated that cellular redox imbalance and fatty acid metabolism are associated with ferroptosis (48,49). Increasing evidence indicates that lactylation regulates ferroptosis either by mediating gene transcription via histone modifications or by directly modifying key ferroptosis enzymes, altering their activity and inducing ferroptosis, thereby influencing disease pathogenesis. Notably, lactylation exhibits significantly higher dynamics than other PTMs, with its level directly regulated by microenvironmental lactate concentration. This characteristic renders Kla a crucial hub connecting cellular metabolic state and epigenetic regulation, particularly in diseases with active glycolysis (e.g., tumors and inflammation). However, a systematic description of the Kla-ferroptosis axis is currently lacking. Therefore, the present review discusses the regulation of ferroptosis by lactylation and summarizes its impact on diseases, including inflammation, degenerative diseases, cancer and ischemia-reperfusion (I/R) injury. The present review aimed to provide insight for future research and disease treatment.

2. Molecular mechanisms of lactylation-mediated ferroptosis

Kla was initially discovered as a process modifying histone lysine residues, thereby altering binding to target gene promoters and activating transcription to exert biological effects. Subsequently, it expanded to non-histone lactylation. In ferroptosis, lactylation primarily involves Kla on histones H3 and H4, binding to promoter regions of target genes to alter transcriptional activity. On the other hand, Kla can directly modify non-histone lysine residues to mediate ferroptosis, demonstrating the multifaceted nature of Kla in regulating ferroptosis. Furthermore, Kla is subject to a complex interplay of upstream signals. A key determinant involves the participating lactyltransferases ('writers') and delactylases. EP300/p300/CREB-binding protein (CBP) are well-established 'writers' of histone lactylation (50-52), while other transferases such as lysine acetyltransferase (KAT), acetyl-CoA acetyltransferase 2 (ACAT2) and N-alpha-acetyltransferase 10 (NAA10) are emerging as modifiers of non-histone substrates (53-55). By contrast, histone deacetylase 1 (HDAC1) and HDAC3 have been identified as possessing delactylase activity (56,57). Their substrate specificity is influenced by expression patterns, spatial localization and interactions with specific factors in different cellular microenvironments. Additionally, metabolic status serves as a fundamental upstream signal. Lactate accumulation can directly drive lactyltransferase-catalyzed lactylation (55,58,59). Local pH in microenvironments, such as tumors, can also influence enzyme kinetics and substrate accessibility (60). Finally, crosstalk with other PTMs creates a regulatory network; for instance, prior acetylation or phosphorylation at or near lysine residues may competitively inhibit or cooperatively promote subsequent lactylation (56). This intricate network, comprising writers, metabolic signals and competitive PTMs, ultimately determines whether lactylation at specific sites on given proteins promotes or suppresses ferroptosis under particular pathophysiological conditions.

Histone lactylation regulates ferroptosis via epigenetic reprogramming. The nucleosome, consisting of a core histone octamer (two each of H2A, H2B, H3 and H4) and wrapped DNA, is the fundamental unit of chromatin. Typically, PTMs are key mechanisms dynamically regulating chromatin structure and DNA templating processes such as gene transcription (61,62). Lactylation modifications at histone H3 lysine 18 (H3K18la), lysine 14 (H3K14la) and histone H4 lysine 8 (H4K8la), and lysine 12 (H4K12la) alter histone function by the covalent addition of a lactyl group, mediating epigenetic reprogramming to regulate ferroptosis. The effect is dependent on the modification site, target gene and disease microenvironment (Fig. 1).

H3K18la is the most extensively studied histone lactylation site in ferroptosis. One of its core regulatory targets is the key fatty acid metabolism enzyme, ACSL4; elevated ACSL4 protein levels can induce transient mitochondrial activation, ROS accumulation and lipid peroxidation, ultimately driving ferroptosis. Notably, H3K18la plays context-dependent dual roles in regulating ACSL4. However, despite differing regulatory directions in different diseases, the outcome consistently promotes disease progression. In inflammatory

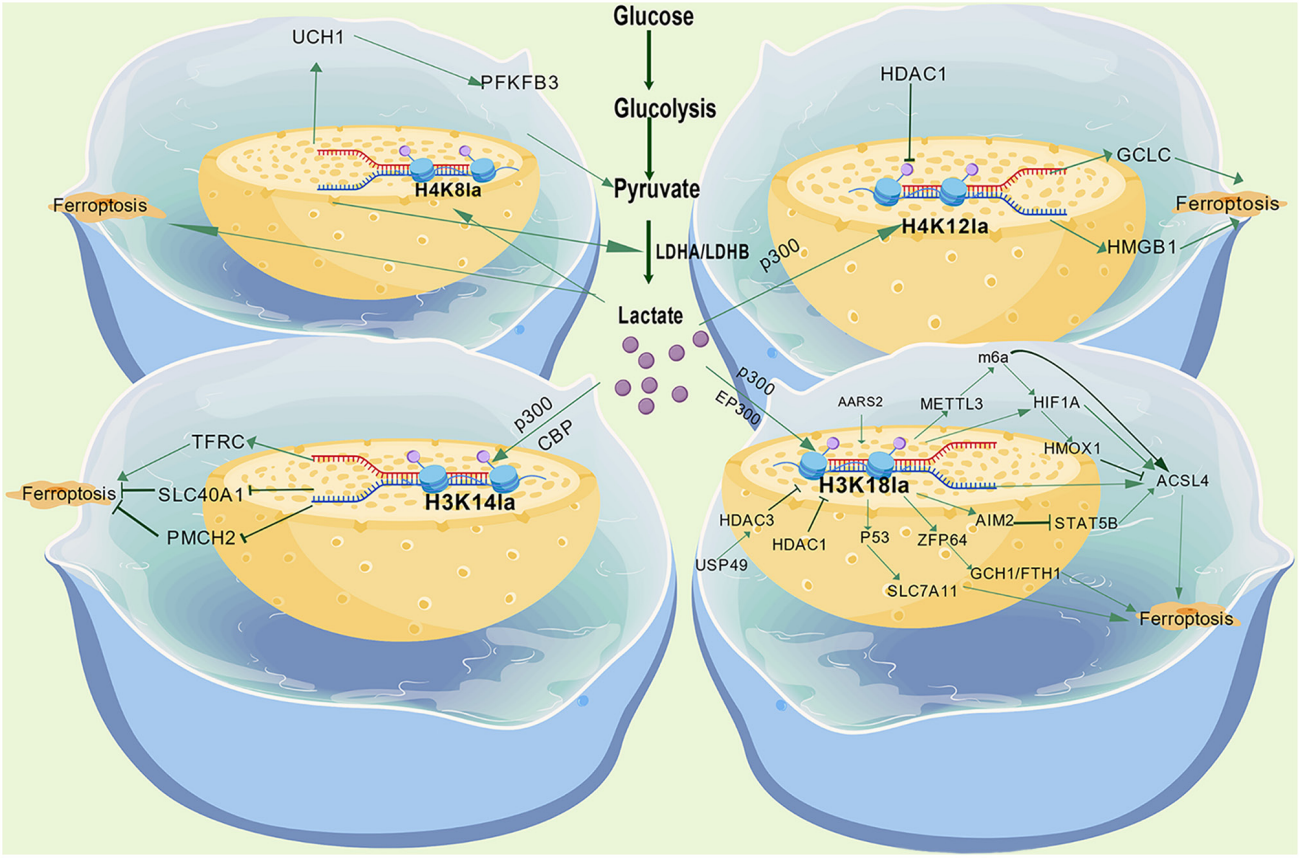

Figure 1. Histone lactylation regulates cellular ferroptosis by affecting transcription of target genes. Glycolysis leads to lactate accumulation, promoting histone lactylation modification under the action of writer enzymes. This acts on promoter regions to regulate target gene transcription, thereby mediating ferroptosis. AARS2, alanyl-tRNA synthetase 2; AIM2, absent in melanoma 2; CBP, CREB-binding protein; GCLC, glutamate-cysteine ligase catalytic subunit; H3K13la, histone H3 lysine 13 lactylation; HDAC1, histone deacetylase 1; HIF1A, hypoxia-inducible factor 1 subunit alpha; HMGB1, high mobility group box 1; HMOX1, heme oxygenase 1; LDHA, lactate dehydrogenase A; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PMCH2, pro-melanin-concentrating hormone 2; SLC40A1, solute carrier family 40 member 1 (Ferroportin); STAT5B, signal transducer and activator of transcription 5B; TFRC, transferrin receptor; UCHL1, ubiquitin C-terminal hydrolase L1; USP49, ubiquitin specific peptidase 49; ZFP64, zinc finger protein 64.

diseases, lactate accumulation upregulates ACSL4 via H3K18la, promoting ferroptosis-mediated disease progression. The mechanisms involved include H3K18la enrichment in promoter regions, which enhances hypoxia-inducible factor (HIF)1A transcriptional activity, thereby transcriptionally activating ACSL4. Additionally, H3K18la can directly bind the ACSL4 gene promoter region to increase transcription (53,54). Simultaneously, in sepsis-mediated lung injury, H3K18la upregulates methyltransferase-like 3 (METTL3) by enhancing its promoter activity, increasing ACSL4 mRNA stability via N^6-methyladenosine (m6A) RNA methylation modification and reader protein YTH domain-containing protein 1 dependency, leading to an elevated protein expression of ACSL4 (63). Conversely, in cancer, H3K18la suppresses ACSL4 expression, enhancing ferroptosis resistance and promoting disease progression. In endometriosis, H3K18la binds the promoter of methyltransferase METTL3, promoting its expression, which subsequently stabilizes HIF1A mRNA via m6ARNA methylation and upregulates heme oxygenase 1 (HMOX1), ultimately downregulating ACSL4 (64). H3K18la binding to the promoter region significantly enhances absent in melanoma 2 (AIM2) transcription, downregulating ACSL4 expression by promoting ubiquitin-mediated degradation of transcription factor STAT5B. This leads to decreased cellular lipid peroxidation, reduced GSH depletion and limited ferrous iron (Fe^{2+}) accumulation, ultimately inhibiting ferroptosis (65). Furthermore, H3K18la can influence ferroptosis by regulating other key genes. H3K18la binding promotes transcription of zinc finger protein (ZFP)64, which directly binds the promoter regions of ferroptosis-related genes GTP cyclohydrolase 1 (GCH1) and ferritin heavy chain 1 (FTH1), promoting their transcription. GCH1 reduces ROS accumulation by inhibiting lipid peroxidation, while FTH1 reduces iron-dependent lipid peroxidation triggered by sequestering intracellular free Fe^2; both synergistically inhibit ferroptosis (60). The reduced expression of H3K18la specifically decreases ferroptosis driver genes [activating transcription factor (ATF3), ATF4 and ChaC glutathione specific gamma-glutamylcyclotransferase 1 (CHAC1)], thereby inhibiting ferroptosis (66). H3K18la enrichment at the promoter region of the key iron-sulfur cluster synthesis enzyme NSF1 cysteine desulfurase (NFS1) enhances its transcription. NFS1 inhibits lipid peroxidation and ferroptosis by maintaining iron ion homeostasis (67).

H3K14la represents lactylation at another H3 site, K14, and is a clear signal promoting ferroptosis. H3K14la transcriptionally activates transferrin receptor (TFRC) and suppresses ferroportin SLC40A1 expression by binding the promoter regions of ferroptosis-related genes, leading to intracellular

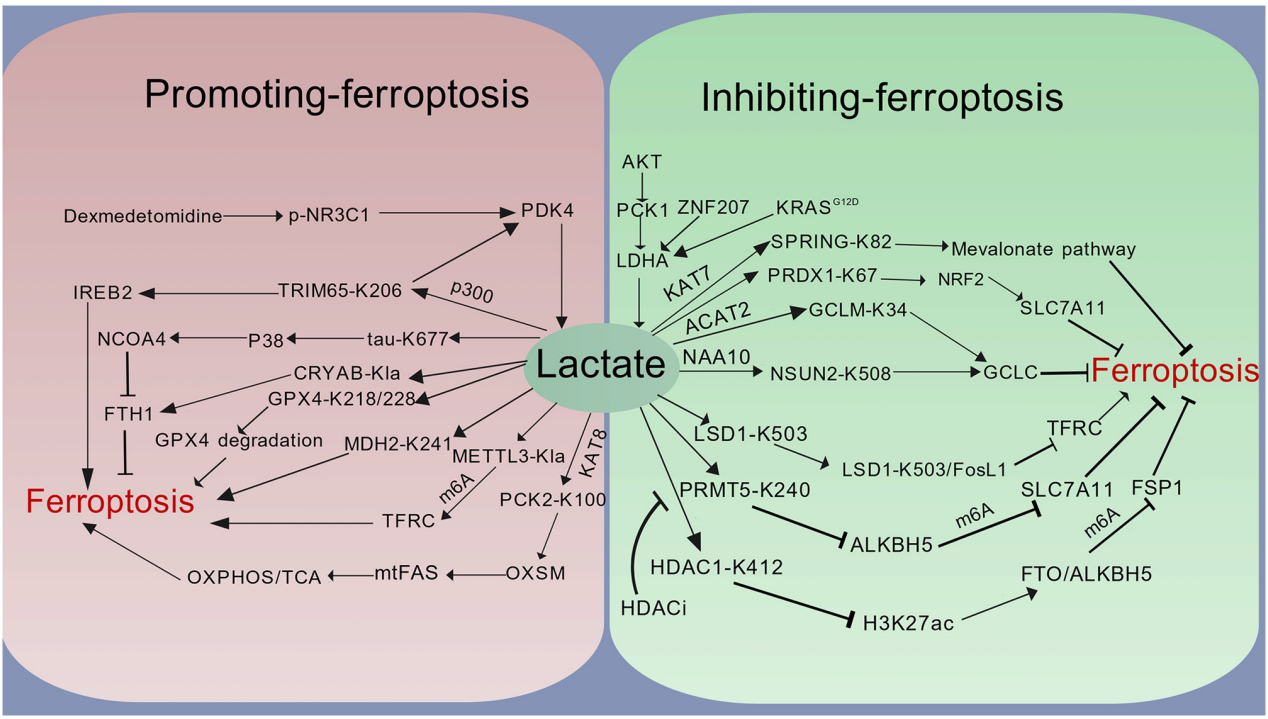

Figure 2. Non-histone lactylation regulates cell fate by modifying key ferroptosis effector molecules. Glycolysis leads to lactate accumulation. Under the action of writer enzymes, it regulates ferroptosis through pathways including direct targeting of key ferroptosis effectors, remodeling cellular metabolic pathways and reprogramming the epigenetic landscape. ACAT2, acetyl-CoA acetyltransferase 2; AKT, AKT serine/threonine kinase; ALKBH5, AlkB homolog 5; FTH1, ferritin heavy chain 1; FSP1, ferroptosis suppressor protein 1; FTO, fat mass and obesity-associated protein; FosL1, FOS like 1, AP-1 transcription factor subunit; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, GCL modifier subunit; GPX4, glutathione peroxidase 4; HDAC1, histone deacetylase 1; H3K27ac, histone H3 lysine 27 acetylation; IREB2, iron-responsive element-binding protein 2; KRAS, KRAS proto-oncogene, GTPase; LDHA, lactate dehydrogenase A; LSD1, lysine-specific demethylase 1; METTL3, methyltransferase-like 3; mtFAS, mitochondrial fatty acid synthesis; NAA10, N-alpha-acetyltransferase 10; NCOA4, nuclear receptor coactivator 4; NR3C1, nuclear receptor subfamily 3 group C member 1; NRF2, nuclear factor erythroid 2-related factor 2; NSUN2, NOP2/Sun RNA methyltransferase 2; OXPHOS, oxidative phosphorylation; OXSM, mitochondrial 3-oxoacyl-ACP synthase; P38, p38 mitogen-activated protein kinase; P300, E1A binding protein p300; PCK1, phosphoenolpyruvate carboxykinase 1; PCK2, p PDK4, pyruvate dehydrogenase kinase 4; PRDX1, peroxiredoxin 1; PRMT5, protein arginine methyltransferase 5; SLC7A11, solute carrier family 7 member 11; SPRING, SREBP pathway regulator in Golgi; TCA, tricarboxylic acid; TFRC, transferrin receptor; TRIM65, tripartite motif-containing protein 65; YAP1, Yes-associated protein 1; ZNF207, zinc finger protein 207.

iron overload, lipid peroxidation and mitochondrial damage, ultimately triggering endothelial cell ferroptosis (52).

H4K8la represents lactylation at histone H4 K8. Its core mechanism involves tight coupling with glycolysis. 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), a key glycolytic rate-limiting enzyme, is stabilized by deubiquitinase ubiquitin C-terminal hydrolase L1 (UCHL1), cleaving its K48-linked ubiquitin chains, promoting lactate production. Increased lactate levels further induce H4K8la modification, forming a positive feedback loop that activates UCHL1 and glycolytic-related genes [e.g., LDHA, pyruvate kinase M2 (PKM), MYC and Yes-associated protein 1], amplifying the inhibition of ferroptosis (68).

H4K12la, catalyzed by lactyltransferase p300 at histone H4 lysine 12, is enriched at the glutamate-cysteine ligase catalytic subunit (GCLC) promoter region, enhancing glutathione synthesis, inhibiting lipid peroxide accumulation and ultimately blocking the ferroptosis pathway (51).

Non-histone lactylation regulates cell fate by modifying key ferroptosis effectors. Beyond histones, Kla precisely regulates cell fate by directly modifying key ferroptosis enzymes. This regulation operates through three core mechanisms: By directly targeting key ferroptosis effectors, remodeling cellular metabolic pathways and reprogramming the epigenetic landscape, collectively constituting a dynamic hub for ferroptosis regulation in response to metabolic stress (Fig. 2).

At the level of the direct targeting of key molecules, lactylation acts directly on core ferroptosis proteins, altering their stability or functional activity to regulate cellular antioxidant capacity and iron metabolism, thereby influencing ferroptosis progression. GPX4 is a key inhibitor of oxidative stress-induced ferroptosis. Lactate-driven lactylation at lysines 218 and 228 (K218/K228) of GPX4 significantly reduces its protein stability, impairing its ability to clear lipid peroxides and enhancing ferroptosis sensitivity (69,70). FTH1 alters intracellular iron homeostasis by influencing iron storage and release, and iron imbalance is a major trigger for ferroptosis (71,72). Tau protein lactylation at K677 upregulates nuclear receptor coactivator 4 (NCOA4) expression by activating p38 phosphorylation signaling, subsequently lowering FTH1 levels and inducing ferroptosis (73). Conversely, alpha-crystallin B chain (CRYAB), via lactylation, directly binds and stabilizes the FTH1 protein to enhance ferroptosis resistance (74).

Metabolic reprogramming constitutes the second major mechanism by which lactylation regulates ferroptosis, driving lipid peroxidation by intervening in mitochondrial energy metabolism and lipid synthesis pathways. The lactylation of the mitochondrial phosphoenolpyruvate carboxykinase 2 (PCK2) protein at K100 competitively inhibits E3 ubiquitin ligase

Parkin-mediated ubiquitination and degradation of mitochondrial 3-oxoacyl-ACP synthase (OXSM), the rate-limiting enzyme of mitochondrial fatty acid synthesis (mtFAS). This promotes mtFAS pathway metabolic reprogramming, exacerbating ferroptosis (75). The inhibition of lactylation at K241 of malate dehydrogenase 2 (MDH2) maintains MDH2 catalytic activity, sustaining the tricarboxylic acid (TCA) cycle and blocking ferroptosis (76). Lactylation at K82 of sterol regulatory element-binding protein (SREBP) pathway regulator in Golgi (SPRING) protein activates the SREBP2-driven mevalonate pathway, ultimately conferring ferroptosis resistance to cancer cells through enhanced antioxidant capacity (53).

Epigenetic reprogramming forms the third pillar of lactylation-mediated ferroptosis regulation. It dynamically affects the transcription and mRNA stability of ferroptosis-related genes by modifying epigenetic regulators, such as RNA methylation enzymes and histone modifiers. In the epitranscriptome, m6A methylation bidirectionally regulates ferroptosis by increasing mRNA stability. On the one hand, lactylation of the m6A writer, METTL3, increases m6A methylation on TFRC mRNA, promoting TFRC mRNA stability, accelerating cellular iron uptake and inducing ferroptosis (77). De-lactylation at K412 of HDAC1 activates the transcription of the m6A erasers, fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), suppressing m6A modification on ferroptosis suppressor protein 1 (FSP1) mRNA and accelerating its degradation, thereby enhancing ferroptosis sensitivity (56). Conversely, lactylation at K240 of protein arginine methyltransferase 5 inhibits the transcription of the m6A eraser ALKBH5, leading to increased m6A modification and enhanced stability of solute carrier family 7 member 11 (SLC7A11) mRNA, conferring resistance to ferroptosis (78). m5C methylation is another way to regulate mRNA stability. Lactylation at K508 of NOP2/Sun RNA methyltransferase 2 (NSUN2) catalyzes m5C formation, maintaining GCLC mRNA stability, promoting GCLC-dependent glutathione synthesis and avoiding ferroptosis in cancer cells within the acidic tumor microenvironment (55). Furthermore, in epigenomics, lactylation can regulate gene transcription through key proteins beyond histones. For instance, lactylation at K503 of lysine-specific demethylase 1 (LSD1) enhances the formation of a stable complex with transcription factor FosL1, specifically enriching at the ferroportin receptor TFRC promoter region to suppress TFRC transcription, reduce iron uptake and enhance ferroptosis resistance (79).

3. Role of lactylation-regulated ferroptosis in diseases and therapeutic prospects

As an emerging metabolic-epigenetic regulatory mechanism, Kla plays a core role in reshaping cell fate by targeting ferroptosis in inflammatory injury, neurodegenerative diseases, cancer and I/R injury, altering disease outcomes through actions on key targets. This section integrates the latest research progress on Kla-mediated ferroptosis in diseases, discusses the underlying pathological mechanisms and explores translational therapeutic potential (Table I).

Infectious and inflammatory diseases. Lactylation drives pro-ferroptotic pathways promoting disease progression. Previous studies have suggested that the inhibition of ferroptosis holds broad prospects for the prevention and treatment of inflammatory diseases. Lactate, the end product of glycolysis, accumulates in the extracellular environment, and the resulting acidosis is a hallmark of inflammatory diseases. Lactate in the microenvironment promotes inflammatory disease progression via Kla-mediated ferroptosis, rendering the inhibition of glycolysis and ferroptosis a promising therapeutic approach (7,80-82). Sepsis is a major cause of mortality in infectious diseases, and among organs susceptible to its harmful effects, the lungs are most frequently affected (83,84). Research indicates that lactylation-mediated ferroptosis promotes sepsis-associated lung injury. In sepsis-associated acute respiratory distress syndrome, H3K14la in pulmonary vascular endothelial cells transcriptionally activates TFRC and suppresses ferroportin SLC40A1, leading to iron overload and mitochondrial-damaging ferroptosis, promoting disease progression. Oxamate, an LDHA inhibitor reducing lactate production, lowers H3K14la modification levels, subsequently downregulating TFRC transcription, reducing iron uptake and alleviating endothelial cell ferroptosis (52). Sepsis-induced lung injury further reveals the core role of the H3K18la-METTL3-ACSL4 axis, inducing mitochondrial fatty acid oxidation-dependent ferroptosis; the METTL3 inhibitor, STM2457, effectively blocks this pathway (63). Severe acute pancreatitis (SAP) and non-alcoholic steatohepatitis (NASH) are non-infectious inflammatory diseases. In SAP, aberrant glycolysis causes lactate accumulation, enhancing HIF1A promoter activity via histone H3K18 lactylation, which transcriptionally activates the ACSL4/lysophosphatidylcholine acyltransferase 3/arachidonate lipoxygenase pathway, inducing pancreatic acinar cell ferroptosis and ultimately exacerbating organ damage. As previously demonstrated, combining a glycolysis inhibitor with a ferroptosis inducer (Ferrostatin-1) significantly alleviates organ damage (85). Previous research has also confirmed that Qing Xia Jie Yi Formula granules alleviate acute pancreatitis by inhibiting the glycolysis pathway (86). In NASH, irisin (TEC) recruits HDAC1 via tRF-31R9J to clear H3K18la, suppressing ferroptosis driver genes such as ATF3/CHAC1, protecting hepatocytes from ferroptosis and providing a novel intervention target for metabolic liver disease (66). These findings establish the 'lactylation-pro-ferroptosis gene activation' axis as a hub in the inflammatory cascade. The inhibition of glycolysis and lactylation may thus be a strategy for the treatment of infectious and inflammatory diseases.

Degenerative diseases: Inhibition of lactylation-mediated ferroptosis as a therapeutic target. Ferroptosis is a critical factor in degenerative diseases and its pharmacological inhibition is a therapeutic target for these conditions (87-89). Lactylation is a novel mechanism regulating ferroptosis, and modulating this process provides new hope for treatment. In degenerative diseases, one disease-promoting mechanism involves lactylation-mediated iron overload to trigger ferroptosis by regulating key genes in iron homeostasis. Research on Alzheimer's disease has found that tau protein de-lactylation (K677R mutation) inhibits p38 phosphorylation, downregulates NCOA4 and reduces ferritinophagy-dependent free iron release, thereby alleviating neuronal ferroptosis and

Table I. Summary of mechanisms mediated by lactylation in ferroptosis.

A, Histone lactylation

Modification site	Target/pathway	Effect on ferroptosis	Related disease	Therapeutic strategy	(Refs.)
H3K18la	Transcriptional activation of ACSL4 → ↑Lipid peroxidation	Promotes	Intervertebral disc degeneration	Glycolysis inhibitor (2-DG)	(91)
	Activation of ACSL4/LPCAT3/ALOX15 pathway via HIF1A	Promotes	Severe acute pancreatitis	HIF1A inhibitor + Ferroptosis inhibitor (Ferrostatin-1)	(85)
	Enhanced ACSL4 mRNA stability via m6A modification	Promotes	Sepsis-induced lung Injury	METTL3 inhibitor (STM2457)	(63)
	Suppression of STAT5B → Downregulation of ACSL4	Inhibits	Lung cancer	Shikonin (inhibits PKM2/AIM2)	(65)
	Activation of GCH1/FTH1 → Inhibition of lipid peroxidation	Inhibits	Triple-negative breast cancer	Lactate production inhibitor (Oxamate)	(60)
	Downregulation of ferroptosis driver genes	Inhibits	Nonalcoholic steatohepatitis	Irisin (TEC) activates HDAC1 for de-modification	(66)
	Maintenance of iron homeostasis	Inhibits	Liver cancer metastasis	NFS1 knockdown + Oxaliplatin	(67)
	HIF1A/HMOX1 → Downregulation of ACSL4	Inhibits	Endometriosis	2-DG + Erastin combination	(64)
	Accelerated SLC7A11 mRNA degradation via m6A modification	Promotes	Coronary artery disease	METTL3 inhibitor	(50)
	Activation of p53 → Inhibition of SLC7A11/GPX4	Promotes	Endometrial cancer	Cold atmospheric plasma	(57)
	Promotion of ACSL4 expression	Promotes	Osteoarthritis	LDHB inhibitor (Oxamate)	(90)
	Increased HIF1A expression	Inhibits	Prostate cancer	Inhibition of MCT4 and GPX4 (Evodiamine)	(103)
	Transcriptional activation of ACSL4	Promotes	Intestinal ischemia injury	AARS2 inhibitor	(93)
H3K14la	Iron overload → Mitochondrial damage	Promotes	Sepsis-induced ARDS	Glycolysis inhibitor (Oxamate)	(52)
	Inhibition of calcium efflux → Calcium overload	Promotes	Intracerebral hemorrhage	p300 inhibitor	(77)
H4K8la	Enhancement of glycolysis positive feedback loop	Inhibits	Spinal cord injury	UCHL1 activator	(68)
H4K12la	Enhanced glutathione synthesis	Inhibits	Colorectal cancer	p300 inhibitor + BSO	(51)
	Activation of HMGB1 → ↑ACSL4/↓GPX4	Promotes	Intestinal ischemia-reperfusion injury	PKM2 dimer inhibitor (ML265)	(59)

B, Non-histone lactylation

Modification site	Target/pathway	Effect on ferroptosis	Related disease	Therapeutic strategy	(Refs.)
GPX4 (K218/K228)	Decreased protein stability	Promotes	Myocardial ischemia-reperfusion injury	Dexmedetomidine (inhibits lactate)	(70)

Table I. Continued.

B, Non-histone lactylation

Modification site	Target/pathway	Effect on ferroptosis	Related disease	Therapeutic strategy	(Refs.)
MDH2 (K241)	TCA cycle dysfunction	Promotes	Myocardial ischemia-reperfusion injury	Dexmedetomidine (restores metabolism)	(76)
PCK2 (K100)	Stabilization of OXSM → ↑Mitochondrial lipid synthesis	Promotes	Liver ischemia-reperfusion injury	KAT8 inhibitor (MC4033)	(75)
Tau (K677)	Activation of p38 → ↑NCOA4 → Ferritinophagy	Promotes	Alzheimer's disease	tau K677R mutant	(73)
NSUN2 (K508)	Enhanced GCLC mRNA stability via m5C modification	Inhibits	Multiple cancers	NSUN2 inhibitor	(55)
LSD1 (K503)	Inhibition of TFRC transcription	Inhibits	Melanoma drug resistance	LSD1 inhibitor	(79)
HDAC1 (K412)	Activation of FTO/ALKBH5 → Degradation of FSP1 mRNA	Promotes	Colorectal cancer	SAHA/TSA	(56)
SPRING (K82)	Activation of SREBP2-MVA pathway	Inhibits	Cholangiocarcinoma	Statins	(70)
GCLM (K34)	Enhanced GCL activity → ↑GSH synthesis	Inhibits	KRAS-mutant pancreatic cancer	ACAT2 inhibitor	(103)
PRMT5 (K240)	Inhibition of ALKBH5 → ↑SLC7A11 mRNA stability	Inhibits	Colorectal cancer	PRMT5 inhibitor	(73)
TRIM65 (K206)	Inhibition of E3 activity → ↑PDK4/IREB2	Promotes	Diabetic nephropathy	SGLT2 inhibitor	(58)
PRDX1 (K67)	Promotion of NRF2 nuclear translocation & regulation of NF207-PRDX1 axis	Inhibits	Liver cancer drug resistance	PRDX1 K67 blocker	(102)
ACSL4 (K412)	Promotion of dimerization → Activation of enzymatic activity	Promotes	Intervertebral disc degeneration	SIRT3 activator	(91)
METTL3	Enhanced TFRC mRNA stability	Promotes	Intracerebral hemorrhage	Silencing METTL3	(77)
Unknow	Maintenance of FTH1 stability	Inhibits	Osteoporosis	Sodium lactate (maintains modification)	(74)

2-DG, 2-deoxy-D-glucose; AARS2, alanyl-tRNA synthetase 2; ACSL4, acyl-CoA synthetase long-chain family member 4; AIM2, absent in melanoma 2; ALOX15, arachidonate lipoxygenase; ALKBH5, AlkB homolog 5; ARDS, acute respiratory distress syndrome; BSO, Buthionine sulfoximine; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; FTO, fat mass and obesity-associated protein; GCH1, GTP cyclohydrolase 1; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, GCL modifier subunit; GPX4, glutathione peroxidase 4; GSH, glutathione; HDAC, histone deacetylase; HIF1A, hypoxia-inducible factor 1-alpha; HMGB1, high-mobility group box 1; HMOX1, heme oxygenase 1; IREB2, iron-responsive element-binding protein 2; KAT, lysine acetyltransferase; KRAS, KRAS proto-oncogene, GTPase; LDHB, lactate dehydrogenase B; LPCAT3, lysophosphatidylcholine acyltransferase 3; MCT, monocarboxylate transporter; MDH2, malate dehydrogenase 2; METTL3, methyltransferase-like 3; m5C, 5-methylcytosine; m6A, N6-methyladenosine; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; NSUN2, NOP2/Sun RNA methyltransferase 2; PCK2, phosphoenolpyruvate carboxykinase 2; PDK4, pyruvate dehydrogenase kinase 4; PRDX1, peroxiredoxin 1; PRMT5, protein arginine methyltransferase 5; SGLT2, sodium-glucose cotransporter 2; SAHA, Suberoylanilide hydroxamic acid (Vorinostat); SIRT3, Sirtuin 3; SLC7A11, solute carrier family 7 member 11; SPRING, SREBP pathway regulator in Golgi; SREBP2, sterol regulatory element-binding protein 2; STAT5B, signal transducer and activator of transcription 5B; TCA, tricarboxylic acid; TFRC, transferrin receptor; TRIM65, tripartite motif-containing protein 65; UCHL1, ubiquitin C-terminal hydrolase L1; ZNF207, zinc finger protein 207.

improving cognitive function (73). Breakthrough research in osteoporosis (OP) revealed significantly downregulated CRYAB/FTH1 expression in patients with OP. CRYAB de-lactylation promotes ferroptosis in bone marrow-derived mesenchymal stem cells and inhibits osteogenic differentiation (74). These studies highlight the impact of lactylation on

cell survival and disease progression via iron homeostasis regulation. Promoting ACSL4 expression via lactylation is another key mechanism regulating ferroptosis in degenerative diseases. LDHB promotes H3K18la and ACSL4 expression by increasing microenvironment lactylation levels, inducing chondrocyte ferroptosis and further promoting osteoarthritis development; inhibiting glycolysis alleviates osteoarthritis (90). During inflammation-induced human intervertebral disc degeneration, the shift from aerobic to anaerobic metabolism produces lactate that not only promotes H3K18la and ACSL4 transcription, but also increases ACSL4 lactylation at K412. Concurrently, lactate reduces the expression of sirtuin 3 (a Kla eraser), suppressing the clearance of ACSL4 lactylation. These factors increase cellular ferroptosis and promote disease progression (91).

I/R injury: Lactylation bidirectionally regulates ferroptosis. Ferroptosis is recognized as a cause of reperfusion injury and organ failure, and the development of ferroptosis modulators provides novel opportunities for the treatment of I/R injury (92). Lactate accumulation is a hallmark of ischemia, and lactate-driven ferroptosis is often a key factor in disease progression. The inhibition of lactylation-mediated ferroptosis has been shown to exert positive effects in various studies on diseases. Research indicates that lactate accumulation upregulates METTL3 expression via EP300-mediated H3K18la, subsequently accelerating SLC7A11 mRNA degradation in an m6A modification- and YTH N6-methyladenosine RNA binding protein F2-dependent manner, ultimately inducing macrophage ferroptosis and promoting coronary heart disease progression (50). In myocardial I/R, enhanced glycolysis and lactate accumulation promote the lactylation of GPX4 at K218 and K228, destabilizing GPX4 and enhancing cardiomyocyte sensitivity to ferroptosis, exacerbating injury (70). Dexmedetomidine provides a novel cardioprotective strategy by inhibiting lactate production, blocking MDH2 K241 lactylation, restoring TCA cycle function and upregulating GPX4 (76). In intestinal ischemia, mitochondrial alanyl-tRNA synthetase 2 epigenetically upregulates ACSL4 transcriptional activity by enhancing H3K18la, driving lipid peroxidation and ferroptosis to worsen intestinal injury (93). In mice with intestinal I/R injury and intestinal epithelial cells subjected to hypoxia-reoxygenation, the nuclear translocation of pyruvate kinase M2 (PKM2) dimers promotes the expression of glycolytic key enzymes (GLUT1/enolase 1/LDHA) and lactate accumulation. Lactate drives histone modifier p300 to specifically catalyze H4K12la, enriching at the promoter region to significantly enhance high-mobility group box 1 (HMGB1) transcription. This disrupts the ferroptosis regulatory balance (ACSL4↑/GPX4↓), promoting intestinal damage. Targeting PKM2 dimerization (ML265) or HMGB1 (Gly-cyrrhizin) blocks this pathway and alleviates tissue injury (59). Research on liver I/R has revealed that lactate activates PCK2 K100 lactylation, stabilizing mitochondrial fatty acid synthase OXSM, and promoting lipid peroxidation and ferroptosis. KAT8 inhibitors or adeno-associated virus-short hairpin RNA targeting PCK2 significantly reduce liver injury (75). Intracerebral hemorrhage causes lactate accumulation and an acidic microenvironment within neurons. Lactate, mediated by histone acetyltransferases p300/CBP, specifically promotes lactylation at the H3K14 site. H3K14la functions as an epigenetic mark, directly inhibiting the transcription of the calcium pump plasma membrane Ca^{2+} ATPase 2 gene, hindering intracellular calcium efflux, causing calcium overload and exacerbating neuronal ferroptosis. The elevated lactate microenvironment induces the lactylation of METTL3 protein, increasing m6A methylation on TFRC mRNA, accelerating cellular iron uptake, leading to Fe^{2+} accumulation, elevated ROS and malondialdehyde levels, and ultimately inducing ferroptosis (77,94). In diabetic nephropathy, a high-lactate microenvironment inhibits the E3 ubiquitin ligase activity of tripartite motif-containing protein 65 (TRIM65) via p300-mediated lactylation at K206, preventing the degradation of its two key substrates, glycolytic kinase pyruvate dehydrogenase kinase 4 and iron regulatory protein iron-responsive element-binding protein 2. This promotes glycolytic flux and induces iron overload and lipid peroxidation, activating ferroptosis. Targeting the TRIM65-K206 lactylation site or reducing lactate production via sodium-glucose cotransporter 2 inhibitors restores the dual inhibition of ferroptosis and glycolysis by TRIM65 (58). However, lactate accumulation is not always detrimental to tissue injury. In spinal cord injury, deubiquitinase UCHL1 stabilizes the key glycolytic enzyme PFKFB3 by cleaving its K48-linked ubiquitin chains, enhancing glycolysis and lactate production in astrocytes. The produced lactate serves as an energy substrate for neurons and inhibits neuronal ferroptosis. Furthermore, elevated lactate levels induce H4K8la in astrocytes, promoting UCHL1 and glycolytic gene (e.g., PKM and LDHB) transcription, forming a positive feedback loop that amplifies the protective effect (62).

Neoplastic diseases: Inhibition of lactylation-mediated ferroptosis provides new hope for cancer therapy. Under both hypoxic and aerobic conditions, tumor cells prefer glycolysis over oxidative phosphorylation as their primary energy source to meet rapid growth and proliferation demands, resulting in high glycolytic flux, massive lactate production and an acidic tumor microenvironment (94-98). Lactate accumulation in the tumor microenvironment promotes tumor cell invasion, metastasis and drug resistance by facilitating lactylation (12,79,99-101). Lactylation regulates key ferroptosis molecules through diverse targets, serving not only as a survival strategy for tumor cells to adapt to the microenvironment, but also as a crucial mechanism to evade therapeutic pressure.

Lactate is considered the initiator of lactylation-regulated ferroptosis. Therefore, reducing lactate production by inhibiting key glycolytic enzymes can suppress tumor growth. Aberrant glycolysis in lung cancer cells causes lactate accumulation, inducing histone H3K18 lactylation at the AIM2 gene promoter region, significantly enhancing AIM2 transcription. This promotes the ubiquitin-mediated degradation of the transcription factor STAT5B, downregulating its downstream target gene ACSL4 and ultimately inhibiting ferroptosis. The natural compound Shikonin can target and inhibit PKM2 (a key glycolytic enzyme) and AIM2 expression, reversing histone lactylation-mediated AIM2 activation (65). Cancer-associated fibroblasts enhance histone H3K18 lactylation by secreting lactate, activating ZFP64, which promotes GCH1 and FTH1 transcription. GCH1 reduces ROS accumulation by inhibiting

lipid peroxidation, and FTH1 reduces iron-dependent lipid peroxidation triggered by sequestering free Fe^{2+}; both synergistically inhibit ferroptosis, enhancing tumor cell drug resistance. The lactate production inhibitor Oxamate can reverse this resistant phenotype (60). ZNF207 increases lactate levels by upregulating LDHA expression, inducing lactylation at lysine 67 (K67 lactylation) of antioxidant protein peroxiredoxin 1 (PRDX1). Lactylated PRDX1 binds the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) and promotes its nuclear translocation, activating the NRF2 antioxidant pathway and upregulating ferroptosis inhibitor genes, such as SLC7A11, GPX4 and HMOX1, ultimately causing drug resistance in hepatocellular carcinoma (HCC) cells. Knockdown of ZNF207, blocking PRDX1 lactylation at K67, or inhibition of NRF2 activity, restore regorafenib sensitivity and induce ferroptosis (102).

The inhibition of the lactylation of key ferroptosis proteins is considered an effective anti-cancer strategy, as it can promote ferroptosis and suppress tumor growth. Lactate maintains GCLC mRNA stability via the NAA10-mediated lactylation of NSUN2 K508, evading cancer cell ferroptosis in the acidic tumor microenvironment (55). The re-activation of glycolysis causes lactate re-accumulation, inducing lactylation at lysine 503 of LSD1, blocking TRIM21-mediated LSD1 degradation and altering its genomic localization. The inhibition of H3K4me2 modification suppresses TFRC transcription, reducing cellular iron uptake, inhibiting ferroptosis and promoting the survival of resistant cells. Inhibition of LSD1 activates ferroptosis and effectively suppresses tumor growth (79). HDAC inhibitors reduce the lactylation of HDAC1 at K412, which in turn activates the transcription of the m6A demethylases, FTO and ALKBH5 via H3K27ac. This reduces m6A modification on ferroptosis suppressor protein FSP1 mRNA, accelerating its degradation and ultimately enhancing lipid peroxide accumulation and sensitivity to ferroptosis. Vorinostat (SAHA) and Trichostatin A (TSA) both significantly reduce HDAC1 K412 lactylation and inhibit tumor growth (56). As previously demonstrated, following incomplete microwave ablation, a sublethal temperature zone forms in the residual tumor area, triggering enhanced glycolysis and lactate accumulation in HCC cells, specifically upregulating H3K18la. This enhances NFS1 transcription, suppressing lipid peroxidation and ferroptosis by maintaining iron ion homeostasis, thereby enhancing the metastatic capacity of HCC cells. NFS1 deletion combined with oxaliplatin (OXA) synergistically inhibits HCC metastasis and overcomes resistance to OXA (67). Evodiamine inhibits monocarboxylate transporter 4 (MCT4) function to block lactate signaling, directly reducing H3K18la to restore Semaphorin 3A transcription and suppress programmed cell death ligand 1. It also downregulates GPX4, inducing ferroptosis, and ultimately inhibiting tumor growth (103).

Lactate enhances the resistance of tumor cells to ferroptosis through lactyltransferase-mediated lactylation. Therefore, the inhibition of lactyltransferase activity to promote ferroptosis is a potential strategy for cancer therapy. Driven by AKT hyperactivation, phosphorylated PCK1 interacts with LDHA, enhancing glycolytic activity and lactate production, promoting the KAT7-mediated lactylation of SPRING at K82. This subsequently activates the SREBP2-driven mevalonate pathway, promoting resistance to ferroptosis (53). Lactyltransferase p300 catalyzes H4K12la, which transcriptionally activates GCLC, enhancing glutathione synthesis, inhibiting lipid peroxide accumulation and ultimately blocking the ferroptosis pathway. The inhibition of p300, LDHA or GCLC enhances sensitivity to chemotherapy (51). KRAS G12D mutation enhances LDHA phosphorylation via the MEK/ERK pathway, promoting glycolysis and lactate generation. This induces the ACAT2-mediated lactylation of glutamate-cysteine ligase modifier subunit (GCLM) at K34, elevating GCL activity, increasing GSH synthesis and conferring ferroptosis resistance to KRASG 12D-mutant cancer cells. Inhibiting ACAT2 or mutating GCLM-K34R restores the sensitivity of cancer cells to ferroptosis inducers (e.g., erastin/RSL3) and significantly suppresses tumor growth (54).

4. Detection methods for lactylation

As an emerging epigenetic regulatory mechanism, the precise detection of lactylation is crucial for elucidating its functions in physiological and pathological processes. The detection of lactylation primarily relies on mass spectrometry and specific antibody-based detection. Mass spectrometry, particularly liquid chromatography-tandem mass spectrometry, serves as the core method, enabling the highly sensitive identification of specific sites and quantification of modification levels. This method involves digesting protein samples with proteases to generate a mixture of peptides. These peptides are then separated by liquid chromatography and are subjected to precise mass detection and sequence analysis via mass spectrometry. This allows for the unbiased identification of specific lactylation sites and their absolute or relative quantification. However, challenges include potential misidentification due to the similar chemical properties of lactylation and acetylation, and the need for higher-resolution instruments due to low modification abundance (11,100,104-107). Specific antibody-based detection utilizes antibodies targeting specific modification sites. Techniques such as western blot analysis for quantification, immunofluorescence for observing intranuclear distribution and co-immunoprecipitation for exploring protein interactions enable the *in situ* and intuitive observation of the subcellular localization and tissue distribution characteristics of lactylation. This approach provides advantages, such as operational simplicity and high sensitivity; however, it is associated with risks of non-specific binding and the limited availability of commercial antibodies (108-112). The comprehensive application of these methods provides key technical support for elucidating the role of lactylation in tumorigenesis and development, laying the foundation for its clinical translation.

5. Therapeutic translation

The intricate interplay between lactylation and ferroptosis has positioned the Kla-ferroptosis axis as an attractive novel therapeutic frontier across a broad spectrum of human diseases. Although basic research continues to uncover the enzymatic regulation, site-specific functions and context-dependent outcomes of this axis, its translational potential demands focused exploration. Looking ahead, clinical development

targeting this axis may proceed through the following strategies: First, directly targeting lactylation regulatory mechanisms holds significant promise. Developing inhibitors of specific lactyltransferases ('writers') or activators of delactylases ('erasers') could enable precise control over pro-ferroptotic or anti-ferroptotic lactylation events (17,20). For example, p300/CBP inhibitors (e.g., SGC-CBP30, A-485) and KAT8 inhibitors (KAT8-IN-1/MC4033) may disrupt lactylation that drives disease progression (51,75). Conversely, deacetylase inhibitors (SAHA, TSA and TEC) can modulate lactylation and sensitize cells to ferroptosis, highlighting the therapeutic feasibility of targeting 'erasers' (56,66). Second, regulating lactate metabolism provides a broader, yet effective strategy with which to indirectly modulate the entire Kla-ferroptosis axis (7,101). Inhibiting key glycolytic enzymes (Oxamate, 2-DG, Shikonin and Simvastatin) or disrupting lactate transport via monocarboxylate transporters (MCTs), e.g., using Syrosingopine to inhibit MCT4, can effectively deplete lactate, the fundamental driver of lactylation (60,65,103). This approach is particularly attractive in tumors and inflammatory microenvironments characterized by a high glycolytic flux (12,82).

To date, to the best of our knowledge, no clinical studies have been designed with 'direct regulation of protein lactylation' as the primary endpoint. However, some drugs targeting lactylation-regulating enzymes and lactate metabolism-related proteins have entered clinical trials. Among them, the most advanced is CCS1477 (inobrodib). It is a highly effective p300/CBP bromodomain inhibitor. Its phase I/IIa clinical trials in advanced solid tumors and hematological malignancies have been initiated (NCT04068597) (113,114). In patients with metastatic castration-resistant prostate cancer (mCRPC), CCS1477 monotherapy was shown to reduce the expression of key oncogenic protein MYC and proliferation marker Ki-67 in tumor tissues (113). In trials for relapsed/refractory acute myeloid leukemia and multiple myeloma, the drug demonstrated the ability to induce leukemia cell differentiation and significantly reduce myeloma-related serum/urine biomarkers. Notably, in the hematological malignancy cohort, about one-third of heavily pretreated patients responded to CCS1477 monotherapy. Some of these patients had progression-free survival exceeding 12 months (114). Another potent p300/CBP bromodomain inhibitor, FT-7051, has also shown early clinical progress. Early results from an open-label phase I trial in patients with mCRPC indicated that its monotherapy achieved the effective exposure threshold predicted by pharmacokinetic/pharmacodynamic models. However, safety concerns exist. Approximately 80% of patients experienced mild to moderate treatment-related adverse events, including hyperglycemia (115). NEO2734 (EP31670) is a dual bromodomain inhibitor targeting both p300/CBP and bromodomain and extra-terminal motif proteins. Due to its broader mechanism, it has entered a phase I trial. This trial aims to treat patients with advanced cancer, including those with metastatic nuclear protein in testis midline carcinoma and refractory mCRPC (NCT05488548); the results are not yet available. Furthermore, drug development targeting HDAC has advanced significantly. Currently, five HDAC inhibitors are approved for clinical use in hematological malignancies. These include Vorinostat and Romidepsin for cutaneous T-cell lymphoma, Belinostat for peripheral T-cell lymphoma, Panobinostat for relapsed/refractory multiple myeloma and Tucidinostat for peripheral T-cell lymphoma (116-119). In solid tumors, HDAC inhibitor monotherapy shows limited efficacy. However, combination strategies with other agents hold promise. For example, the selective HDAC inhibitors Tucidinostat and Entinostat combined with endocrine therapy (e.g., Exemestane) improved progression-free survival and the objective response rate in hormone receptor-positive breast cancer trials (120,121). Combining HDAC inhibitors with immune checkpoint inhibitors also demonstrated synergistic anti-tumor activity in various solid tumors, such as melanoma and colorectal cancer (122,123). Challenges and failures exist in this field. Some trial results did not meet primary endpoints. For instance, Mocetinostat monotherapy was ineffective in urothelial carcinoma. Entinostat combined with Atezolizumab did not significantly prolong progression-free survival in advanced triple-negative breast cancer (124). Additionally, HDAC inhibitor applications are expanding into non-oncological areas. Romidepsin is being explored for HIV latency reversal (125), and Givinostat and Ricolinostat show potential in clinical studies for Duchenne muscular dystrophy and diabetic neuropathic pain, respectively (126,127). Overall, further development of HDAC inhibitors in solid tumors still faces toxicity issues. Future efforts should focus on optimizing combination strategies and developing more subtype-selective inhibitors to enhance their therapeutic value.

Research on lactate metabolism-related proteins remains limited. Glycolysis is the primary source of lactate. 2-deoxy-D-glucose (2-DG) is a broad-spectrum glycolysis inhibitor. Intranasal administration of 3.5% 2-DG was safe and well-tolerated in healthy volunteers. Systemic exposure was almost negligible. Local nasal concentrations reached effective anti-viral levels *in vitro* (NCT05314933) (128). LDHA is a key enzyme for lactate production in glycolysis. Its inhibitors show extensive pre-clinical evidence across multiple cancers. They can inhibit glycolysis, reduce lactate and acidification, suppress invasion and metastasis, and enhance chemo/radiotherapy sensitivity. However, most findings are still at the pre-clinical stage (129). For lactate transmembrane transport inhibition, only one MCT-targeting drug, AZD3965 (an MCT1 inhibitor), has entered clinical trials. It aims to evaluate safety and preliminary efficacy in patients with advanced cancer (NCT01791595). Preliminary results indicate manageable safety (130-132). Specific MCT4 inhibitors are mostly in pre-clinical development. However, dual inhibition or combination with LDH/GLUT inhibitors appears more promising. This approach may sustainably reduce lactate supply, improve the acidic microenvironment and restore sensitivity to ferroptosis (133).

In summary, clinical interventions directly regulating lactylation are still emerging. However, drugs targeting its key nodes have established a considerable clinical and translational foundation. Based on metabolic resistance mechanisms and solid tumor treatment experience, it may be recommended to prioritize combination therapies that integrate metabolic-epigenetic-ferroptosis signaling. This should be accompanied by biomarker stratification and optimized administration strategies, such as intranasal delivery for high lesion exposure and low systemic exposure. These steps will help accelerate the clinical translation of the Kla-ferroptosis axis.

6. Future prospects

Notably, the cross-regulatory mechanisms between lactylation and other programmed cell death pathways are increasingly becoming a focus of research. Beyond ferroptosis, Kla may modulate processes such as necroptosis, apoptosis and autophagy by modifying key proteins, forming a complex network governing cell fate decisions (134). For instance, preliminary studies suggest that lactate accumulation can influence the activity of receptor interacting serine/threonine kinase 3, a core necroptosis protein, via lactylation, thereby modulating cell death patterns in inflammatory diseases (135). In tumor models, Kla may promote cell survival and resistance to therapy by inhibiting apoptotic signaling pathways (e.g., BCL-2 family proteins) or enhancing the stability of autophagy-related proteins (e.g., light chain 3) (136,137). Such cross-regulation not only reveals the central role of metabolic-epigenetic networks in multiple death pathways, but also provides new insight for developing combination therapies targeting lactylation. Future studies are required to systematically elucidate the site-specific functions of Kla in necroptosis, apoptosis and autophagy, and clarify the dynamic interactions among these pathways to more comprehensively evaluate the therapeutic potential of targeting Kla.

However, the field still faces multiple challenges: Structural similarities between lactylation-regulating enzymes and other acyltransferases/deacetylases necessitate highly specific drugs to avoid off-target effects on PTMs such as acetylation; the dual role of the Kla-ferroptosis axis in diseases (e.g., promoting injury in sepsis while exerting protection in spinal cord injury) calls for cell- and microenvironment-specific targeted delivery systems; notably, dynamic detection technologies for lactylation remain underdeveloped, requiring novel *in vivo* imaging probes to facilitate patient stratification and treatment monitoring (108,112,138). Further studies are thus required to focus on designing highly specific modulators, constructing intelligent delivery systems and validating dynamic lactylation biomarkers. This may broaden the understanding of cell fate regulation mechanisms and may provide novel paradigms for the treatment of cancer, as well as inflammatory, degenerative and ischemic diseases.

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Authors' contributions

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors used Grammarly (app.grammarly.com) for the purpose of checking and correcting spelling, grammar, and punctuation errors.

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