Dual role of lactate in ferroptosis: Mechanisms, pathophysiology and therapeutic opportunities (Review)

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Abstract. Ferroptosis, an iron-catalyzed form of regulated cell death driven by lipid peroxidation-induced membrane rupture, has emerged as a critical determinant of cellular fate across diverse physiological and pathological contexts. Simultaneously, lactate has undergone a notable conceptual transformation, evolving from being regarded as merely a glycolytic waste product to being recognized as a key signaling metabolite that modulates iron homeostasis, lipid dynamics, cellular redox balance and the immune response. This metabolic renaissance has revealed an intricate lactate-ferroptosis regulatory network with implications for human disease. Notably, lactate exhibits diametrically contrasting effects on ferroptosis susceptibility: Promoting cell death in certain contexts while conferring protection in others. This apparent paradox, particularly evident when contrasting tumor and normal cell responses, suggests sophisticated context-dependent regulatory mechanisms that are yet to be fully elucidated. The present review explores the molecular basis of both ferroptosis execution and lactate signaling, synthesizing recent advances that illuminate their dynamic interplay. Crucially, the present review discusses putative key contextual determinants, including the metabolic state, pH tolerance and antioxidant capacity, which may govern divergent roles of lactate in ferroptosis regulation. Furthermore, understanding these context-specific mechanisms promises to unlock new therapeutic strategies for diseases ranging from cancer to neurodegeneration, where the lactate-ferroptosis axis represents both a vulnerability and an opportunity.

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Contents

1. Introduction

Ferroptosis, first described by Dixon in 2012 as an iron-dependent regulated form of cell death, has emerged as a critical determinant of cellular fate across diverse physiological and pathological contexts (1). This unique mode of cell death is primarily driven by phospholipid peroxidation and iron overload, extending from decades of research that recognized the cytotoxic consequences of iron and lipid peroxidation (2,3). The elucidation of antioxidant defense systems in ferroptosis regulation has advanced our integrated understanding of the interplay between iron metabolism and oxidative stress in regulated cell death. Emerging evidence further indicates that ferroptosis significantly contributes to tumor suppression, immune regulation and the maintenance of metabolic homeostasis (4).

Concurrently, lactate has undergone a profound conceptual transformation from a metabolic waste product to a sophisticated signaling molecule. Once considered merely a metabolic waste product associated with hypoxic stress

and detrimental effects, subsequent research has revealed that lactate is actively produced and utilized even under aerobic conditions (5). The lactate shuttle hypothesis further revealed its pivotal roles in oxidative substrate transport and cellular signaling via monocarboxylate transporters (MCTs), leading to its recognition as a potent signaling metabolite, particularly through its receptor GPR81 (6-8). subsequent discoveries have revealed the epigenetic functions of lactate through histone lysine lactylation (Kla), a post-translational modification analogous to acetylation and succinylation (9,10). This modification impacts transcriptional regulation and extends to non-histone proteins, thereby regulating enzyme activities (11,12). However, a paradox has emerged: Lactate exhibits opposing effects on ferroptosis, promoting cell death in certain contexts while conferring protection in others, particularly when comparing tumor vs. normal cells. To the best of our knowledge, no relevant articles currently summarize and explain these contradictory observations.

The present review elucidates the molecular mechanisms underlying the lactate-ferroptosis axis, examining how lactate influences ferroptosis through lactylation-independent and -dependent pathways that modulate iron homeostasis, lipid metabolism, redox balance and the immune response. Meanwhile, the 'dual role' refers to the context-dependent, bidirectional regulation of ferroptosis by lactate. In non-tumor tissues, lactate tends to promote ferroptosis, potentially accelerating disease progression. Conversely, in tumor microenvironments, lactate tends to inhibit ferroptosis, facilitating cancer cell survival and therapeutic resistance. Furthermore, the present review highlights the key contextual determinants that may dictate the divergent roles of lactate. Understanding these context-specific mechanisms promises new therapeutic strategies targeting a broad spectrum of diseases ranging from cancer to neurodegeneration.

Unless otherwise specified, the term 'lactate' throughout the present review refers to L-lactate, the predominant enantiomer produced by mammalian lactate dehydrogenase (LDH). By contrast, D-lactate, though present in trace amounts from bacterial metabolism and certain metabolic disorders, has not yet been systematically investigated in ferroptosis contexts.

2. Ferroptosis: Molecular mechanisms

Ferroptosis is mediated by multiple mechanisms including lipid peroxidation, iron overload and dysfunction of the antioxidant system (Fig. 1). A hallmark of ferroptotic initiation and execution is the upregulated peroxidation of phospholipid-bound polyunsaturated fatty acids (PUFAs) within cellular membranes, a process facilitated by labile iron pools (LIPs) and amplified through autocatalytic radical reactions (13,14). In this context, redox-active iron, principally existing as ferrous (Fe^{2+}) ions, serves as a critical cofactor, driving Fenton reactions that generate reactive oxygen species (ROS). These ROS abstract hydrogen atoms from bis-allylic positions within PUFA chains, producing lipid radicals that react with molecular oxygen to yield lipid peroxyl radicals. This initiates a self-perpetuating cascade of membrane lipid peroxidation, ultimately compromising membrane integrity and triggering cell death (14).

This process of lipid peroxidation is regulated by a complex network of metabolic and enzymatic regulators. Glutathione peroxidase 4 (GPX4) plays a central role in counteracting ferroptosis by reducing membrane lipid hydroperoxides to their corresponding alcohols, utilizing glutathione (GSH) as a reducing substrate (15). Perturbation of this axis, either through direct GPX4 inhibition or GSH depletion via impaired cystine import (for example, via system Xc^- inhibition), markedly sensitizes cells to ferroptotic death (1,16). In parallel, ferroptosis suppressor protein 1 (FSP1)/ubiquinol (CoQH2), dihydroorotate dehydrogenase/CoQH2 and GTP cyclohydrolase 1 (GCH1)/tetrahydrobiopterin have been identified as independent systems that scavenge free radicals to exert their antioxidative effects and suppress ferroptosis (17-21).

The execution of the Fenton response is dependent on iron availability. Cellular iron metabolism is exquisitely regulated, with transferrin-mediated uptake, ferritin-based storage and transferrin-transferrin receptor (TFRC)-mediated export collectively maintaining intracellular iron homeostasis (22). Perturbations that expand the LIP, whether through increased iron import, mobilization from stores or diminished export, potentiate ferroptosis by providing increased substrate levels for lipid peroxidation reactions (1,23). In addition, the membrane susceptibility to ferroptotic damage is modulated by its lipidomic composition, with phospholipids enriched in PUFAs, particularly arachidonic acid (AA) and adrenic acid (AdA), being especially prone to peroxidation, thereby rendering membrane vulnerability to ferroptosis (24).

3. Lactate metabolism and regulation

Recently, a growing body of evidence has demonstrated that lactate is not merely a metabolic by-product but also serves as a key energy source and a critical signaling molecule involved in memory formation, neuroprotection, modulation of inflammatory responses, wound healing, ischemic injury repair, as well as tumor growth and metastasis (5,25-27). In this section, a comprehensive overview of the metabolic pathways of lactate is presented and its specific mechanistic roles, with particular emphasis on its dual role in regulating ferroptosis, are examined (Fig. 2).

Lactate biosynthesis and metabolism. When cellular energy demands exceed the capacity of aerobic metabolism, as occurs during intense exercise or infection, lactate is generated via glycolysis to serve as an alternative energy source. Under hypoxic conditions, cytoplasmic glucose is metabolized into pyruvate through a series of enzymatic reactions. However, instead of being transported into mitochondria for oxidative metabolism, pyruvate is converted into lactate by LDHA, coupled with $NADH/NAD^+$ interconversion (5). This reaction is reversible: Under sufficient oxygen availability, lactate can be reconverted into pyruvate by LDHB, which is then subsequently oxidized to acetyl-CoA by pyruvate dehydrogenase (PDH) and enters the tricarboxylic acid cycle (TCA) for efficient energy production (5). Furthermore, an electrochemical gradient driving ATP synthesis is created as electrons shuttle through $NAD^+/NADH$ and $FAD/FADH_2$ to the electron transport chain (28).

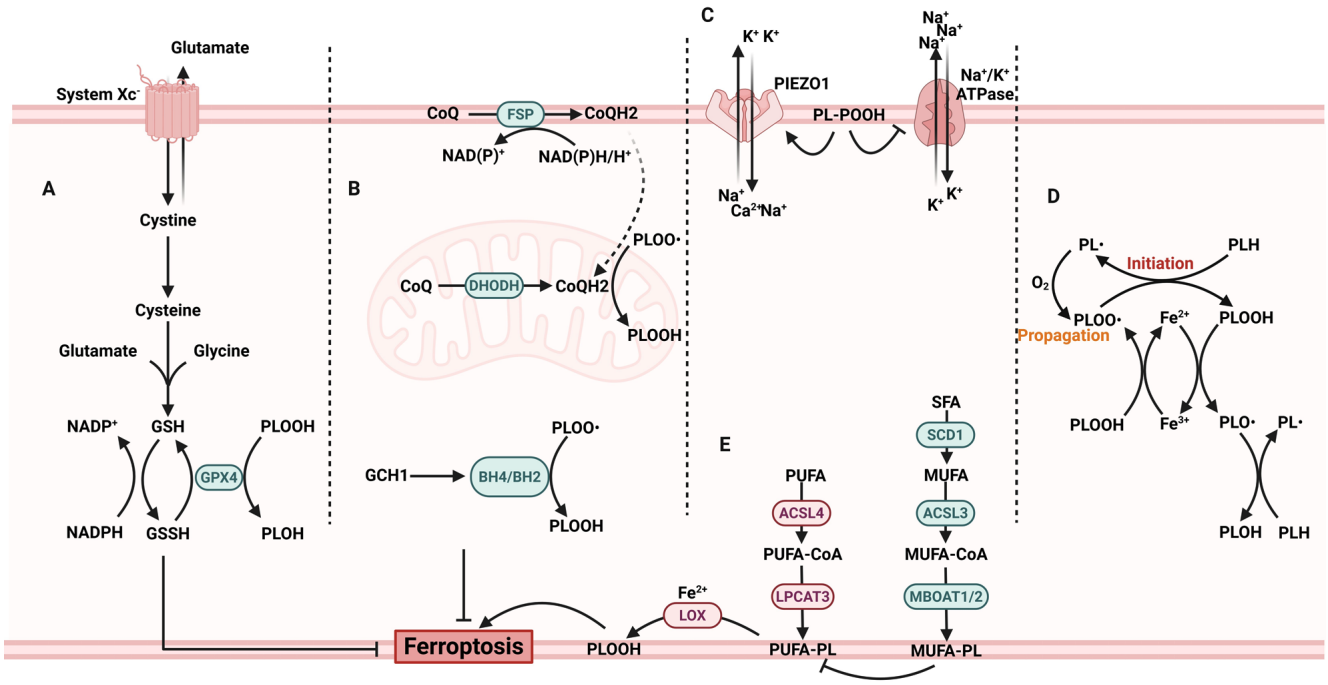

Figure 1. Molecular mechanism of ferroptosis. (A) The canonical ferroptosis-regulating axis involves cystine uptake via system Xc^-, GSH biosynthesis and GPX4-mediated reduction of PLOOH into their corresponding alcohols (PLOH). NADPH provides electrons for recycling GSSG. (B) The FSP1/CoQ10, DHODH/CoQ10 and GCH1/BH4/BH2 system serves as parallel pathways to inhibit lipid peroxidation and ferroptosis. (C) The peroxidation of phospholipids in the plasma membrane activates PIEZO1, leading to the influx of Ca^{2+} and Na^+. This process, combined with the inactivation of the Na^+/K^+ ATPase, results in the efflux of K^+. (D) The initiation and propagation of PLOOH form a chain reaction with positive feedback. (E) PUFA and MUFA metabolic pathways promote and inhibit lipid peroxidation, respectively. GSH, glutathione; PLOOH, phospholipid hydroperoxides; PLOH, phospholipid alcohol; GSSG, oxidized glutathione; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; DHODH, dihydroorotate dehydrogenase; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin; BH2, dihydrobiopterin; PIEZO1, piezo-type mechanosensitive ion channel component 1; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; PL, phospholipid; SFA, saturated fatty acid. Created with BioRender.com.

Studies have highlighted that the conversion of glucose to lactate by cells constitutes a tightly regulated metabolic state, which may confer advantages during periods of heightened biosynthetic demand (29,30). By channeling excess pyruvate toward lactate production, proliferating cells effectively prevent cytosolic NADH accumulation and prevent excessive ATP generation. This regulation ensures the continuation of cytosolic glucose metabolism without feedback inhibition from mitochondrial ATP overproduction. Furthermore, glucose-6-phosphate derived from glycolysis can be diverted into branching metabolic pathways, such as the pentose phosphate pathway (PPP), where it is partially oxidized to generate NADPH (28). This NADPH serves as a critical reducing equivalent for fatty acid synthesis and other anabolic processes. Additionally, isotope tracing studies have demonstrated that lactate functions as a major fuel in the TCA cycle, where ^{13}C-lactate labeled TCA intermediates in every tissue of the body, even in tumors (31,32). However, the accumulation of lactate carries significant risks to the human body. Elevated serum lactate levels can result in lactic acidosis, a condition that poses a greater physiological threat compared with other metabolic intermediates (33).

In addition to glycolysis, other biochemical pathways, such as glutamine metabolism, contribute significantly to lactate production *in vivo* particularly in cancer cells (34). Under the regulation of the oncogene c-Myc, glutamine is metabolized through the TCA cycle to generate pyruvate, which is subsequently converted into lactate by LDH (35). This process provides an alternative and critical source of lactate in rapidly proliferating cells, supporting energy production and biosynthesis.

Hypoxia-induced lactate accumulation. Hypoxia represents a hallmark of pathological conditions, including tumors, infections, ischemia-reperfusion injury (IRI) and inflammation (36); it occurs when cells experience reduced oxygen availability and activate an adaptive response to cope with it. In response to reduced oxygen availability, cells activate adaptive signaling cascades mediated by hypoxia-inducible factor-1α (HIF-1α). Under this condition, HIF-1α becomes stabilized and subsequently translocates to the nucleus, where it binds to hypoxia-responsive elements within target genes, thereby promoting metabolic programming, notably the upregulation of anaerobic glycolysis (37,38). Under hypoxic conditions, the reduced oxygen availability diminishes the activity of prolyl hydroxylase domain enzymes (PHDs), which typically employ oxygen and α-ketoglutarate as substrates to hydroxylate HIF-1α, thereby targeting it for degradation. Consequently, the decreased PHD activity leads to HIF-1α stabilization (39).

Cellular adaptation to hypoxia involves an enhanced glycolytic flux, primarily mediated by HIF-dependent transcriptional upregulation of genes encoding glucose transporters and glycolytic enzymes. This metabolic shift is accompanied by an active suppression of mitochondrial pyruvate oxidation and respiratory activity (40-43). These biochemical adaptations result in a metabolic reprogramming that promotes lactate

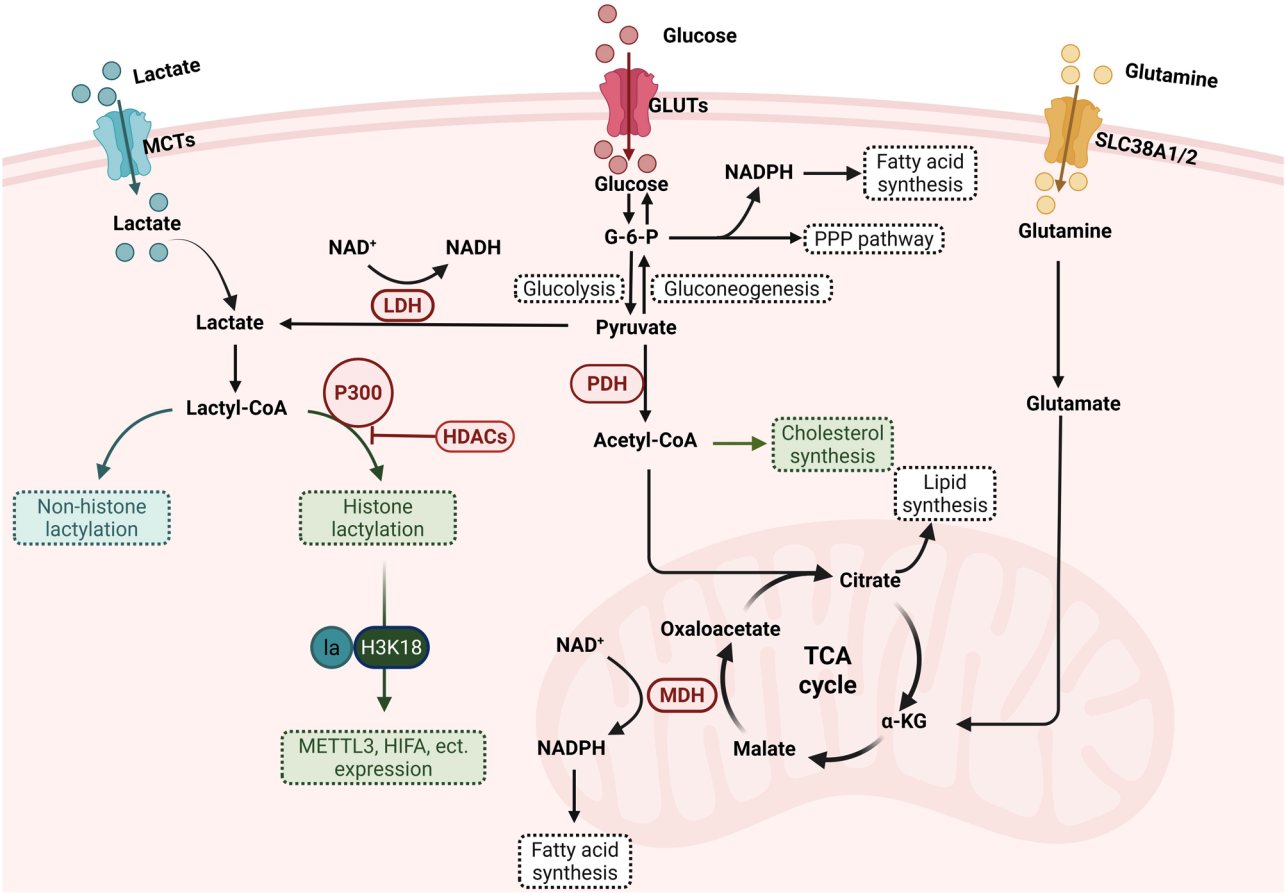

Figure 2. Lactate metabolism, lactylation and the pathways involved in cells. Lactate is transported into cells via MCTs and is generated through glycolysis or glutamine decomposition in the cytoplasm. Once oxidized to pyruvate, pyruvate can be metabolized through two major pathways: i) Entering mitochondria for metabolism via the TCA cycle; or i) being converted to glucose via gluconeogenesis. Intermediate products of glycolysis and gluconeogenesis contribute to NADPH production through the PPP. Malate can be converted to oxaloacetate via MDH, generating NADPH, which supports fatty acid synthesis and GSSG recycling. Citrate, another key metabolite, serves as a precursor for lipid synthesis. Additionally, lactate can be converted into lactyl-CoA, facilitating the lactylation of histone and non-histone proteins, linking metabolism to epigenetic regulation. MCTs, monocarboxylate transporters; TCA cycle, tricarboxylic acid cycle; PPP, pentose phosphate pathway; MDH, malate dehydrogenase; GSSG, oxidized glutathione; GLUTs, glucose transporters; LDH, lactate dehydrogenase; HDACs, histone deacetylases; PDH, pyruvate dehydrogenase; METTL3, methyltransferase like 3; HIFA, hypoxia-inducible factor α; MDH, malate dehydrogenase; SLC38a1/2, solute carrier family 38 member a 1/2. Created with BioRender.com.

production and accumulation, thereby reinforcing the hypoxic cellular response.

LDHA/B. LDHA and LDHB constitute the subunits of the catalytically active LDH enzyme, which has long been recognized for its pivotal role in ATP generation and energy homeostasis under both anaerobic and aerobic glycolytic conditions (44). LDHA possesses a higher affinity for pyruvate and preferentially catalyzes its reduction to lactate, thereby sustaining anaerobic glycolysis. By contrast, LDHB catalyzes the reverse reaction (oxidizing lactate to pyruvate) which subsequently fuels mitochondrial oxidative phosphorylation (44). However, accumulating evidence suggests that all LDH isoforms retain the inherent capacity to mediate pyruvate-to-lactate conversion accompanied by NAD^+ regeneration, and that LDHA and LDHB can functionally compensate for each other under metabolic stress (44,45). By regulating the NAD^+/NADH ratio, mitochondrial function and ROS levels, LDH isoforms indirectly modulate ferroptosis susceptibility. For instance, LDHA has been demonstrated to promote tumor cell survival by mitigating oxidative stress, whereas LDHB deficiency induces mitochondrial dysfunction and oxidative damage, ultimately leading to neurodegeneration in the adult mouse brain (46,47). More recently, non-canonical roles of LDHA and LDHB have been identified, with both isoforms contributing to ferroptosis resistance in IRI and cancer through mechanisms associated with GPX4 activity or GSH availability (48,49).

MCTs and GPR81/HCAR1. MCTs serve as the principal mediators of lactate transport across cell membranes. By coupling lactate translocation with proton co-transport, these transporters help maintain acid-base balance and cellular metabolic stability (7). For instance, inhibition of MCT1 disrupts lactate homeostasis and impairs both glycolytic flux and GSH biosynthesis in MYC-driven cancer, resulting in reduced glucose uptake and depletion of ATP, NADPH and GSH (50). Furthermore, extracellular lactate must enter cells through MCTs before contributing to lactylation reactions, which have been demonstrated to modulate ferroptosis through multiple mechanisms (51).

GPR81/HCAR1 is a cell-surface G protein-coupled receptor that recognizes lactate as its endogenous ligand and coordinates metabolic signaling across diverse tissues (8).

In adipocytes, GPR81 acts synergistically with insulin to lower intracellular cyclic adenosine monophosphate (cAMP) levels, thereby suppressing postprandial lipolysis (52). Beyond adipose tissue, GPR81 is abundantly expressed in skeletal muscle, kidney, brain, heart and various cancer types (8). Elevated extracellular lactate, a defining feature of the tumor microenvironment, predicts poor outcomes, and high GPR81 expression correlates with poorer survival (8,53,54). Analogous to its role in adipocytes, GPR81 activation in cancer cells decreases intracellular cAMP and suppresses proteinkinase A (PKA) activity, thereby modulating lipid remodeling (55,56).

Elevated lactate concentrations within the tumor microenvironment can activate GPR81 receptors located on the cytoplasmic membrane of cells, subsequently facilitating MCT1-mediated lactate uptake (57,58). Through this pathway, lactate disrupts AMPK signaling, which in turn downregulates sterol regulatory element-binding protein 1 (SREBP1) and its downstream target stearoyl-CoA desaturase 1 (SCD1). Consequently, cells produce more anti-ferroptotic monounsaturated fatty acids (MUFAs), thereby suppressing lipid peroxidation. Simultaneously, long-chain acyl-CoA synthetase 4 (ACSL4) expression decreases, reducing the availability of oxidizable PUFAs, although the exact mechanism underlying this remains unclear. Notably, blocking lactate transport by inhibiting MCT1 or GPR81 promotes ferroptosis primarily through alterations in lipid metabolism rather than through conventional ferroptosis regulators, as evidenced by unchanged GPX4 and FSP1 levels (57). Additionally, other research has demonstrated that intracellular lactate accumulation following MCT inhibition may lead to end-product inhibition of LDH, thereby impairing NAD^+ regeneration capacity (59). This sustained disruption of glycolysis can result in the depletion of ATP, NADPH and GSH (50). These findings suggest that therapeutic strategies targeting the function of MCTs could prove effective against both oxidative and hypoxic tumors.

4. Dual roles of lactate in ferroptosis

Accumulating evidence indicates that lactate metabolism modulates ferroptosis through both lactylation-independent and dependent pathways. Notably, this regulation exhibits context-dependent effects. The lactylation-independent mechanisms, including the iron handling, lipid remodeling, redox regulation and immune responses in ferroptosis, are summarized in this section. Additionally, evidence supporting lactylation-dependent mechanisms has been compiled.

Lactate regulates iron homeostasis in ferroptosis

Lactate-hepcidin axis in ferroptosis. Clinical and experimental evidence has consistently demonstrated a robust association between hyperlactatemia and anemia, indicating a functional interconnection between lactate metabolism and systemic iron homeostasis (60). For instance, in endurance athletes, repeated bouts of exercise induces transient elevations in plasma lactate concentrations, which have been correlated with the development of iron-restrictive anemia in 10-15% of individuals, particularly among those engaging in >10 h of training per week (61). Hepcidin, a peptide hormone predominantly synthesized by hepatocytes, regulates iron homeostasis by binding to ferroportin (FPN), the sole identified cellular iron exporter. This interaction triggers FPN internalization and degradation, consequently restricting iron efflux and leading to the elevation of intracellular iron pools. Concurrently, it limits systemic iron availability by reducing intestinal iron absorption, ultimately resulting in decreased serum iron concentrations (62) (Fig. 3).

Liu *et al* (63) recently elucidated the molecular mechanism by which lactate regulates hepcidin expression and, consequently, systemic iron homeostasis. Their findings revealed that lactate, transported into cells via MCT1, directly interacts with soluble adenylyl cyclase, resulting in elevated cAMP levels. This, in turn, activates the PKA-Smad1/5/8 signaling cascade, ultimately upregulating hepcidin transcription (63). Further investigation demonstrated that lactate administration in mice induced hepcidin expression, leading to reduced FPN levels. This resulted in increased splenic iron sequestration, diminished duodenal iron absorption and, consequently, decreased serum and tissue iron content accompanied by attenuation of oxidative stress (63,64). Although tissue-specific differences in hepcidin sensitivity, along with variations in critical thresholds, time kinetics and the compensatory capability of cellular antioxidant defense systems, may modulate iron accumulation and ferroptotic outcomes, existing evidence supports a pro-ferroptotic role of hepcidin in Kupffer cells, neurons and hepatocytes (65-67).

Although current evidence supports a sophisticated mechanistic framework linking lactate-mediated hepcidin induction to ferroptosis, the tissue- and cell-type-specific effects of elevated lactate levels induced by diverse physiological and pathophysiological processes on iron homeostasis and ferroptosis throughout the body warrant further investigation.

Lactate regulates iron via the TFRC. Iron can be imported into the cell via the TFRC system. In this process, Fe^{3+}-transferrin complexes are internalized through TFRC and eventually trafficked to and liberated within the acidic environment of the lysosome mediated by nuclear receptor coactivator 4 (NCOA4) (2). TFRC silencing and NCOA4 disruption reduce ferroptotic sensitivity by restricting iron retrieval from ferritin and thereby limiting the LIP (68,69). Lactylation of histones or non-histone proteins involved in iron autophagy-related pathways can modulate iron handling, thereby regulating ferroptosis (70-72). Notably, this regulatory effect appears to be context-dependent; for instance, H3K14 lactylation has been demonstrated to promote ferroptosis in endothelial cells exposed to lipopolysaccharide (LPS) by transcriptionally upregulating the TFRC (73). Conversely, lactylation of lysine-specific demethylase 1 (LSD1) in melanoma promotes its interaction with Fos-like antigen 1 (FosL1), resulting in repression of TFRC-mediated iron uptake and conferring resistance to ferroptosis (70). However, at present, there is no direct evidence demonstrating that histone lactylation regulates the TFRC in tumor cells. Notably, ferroptotic susceptibility is determined not only by iron overload but also by the lipid ratio and the capacity of antioxidant defense systems.

Lactate-lipid remodeling in ferroptosis. Beyond its established roles in energy metabolism and immune modulation within the tumor microenvironment, lactate serves as a crucial metabolic substrate that supports the TCA cycle in major organs under physiological conditions (31). Tracer studies employing

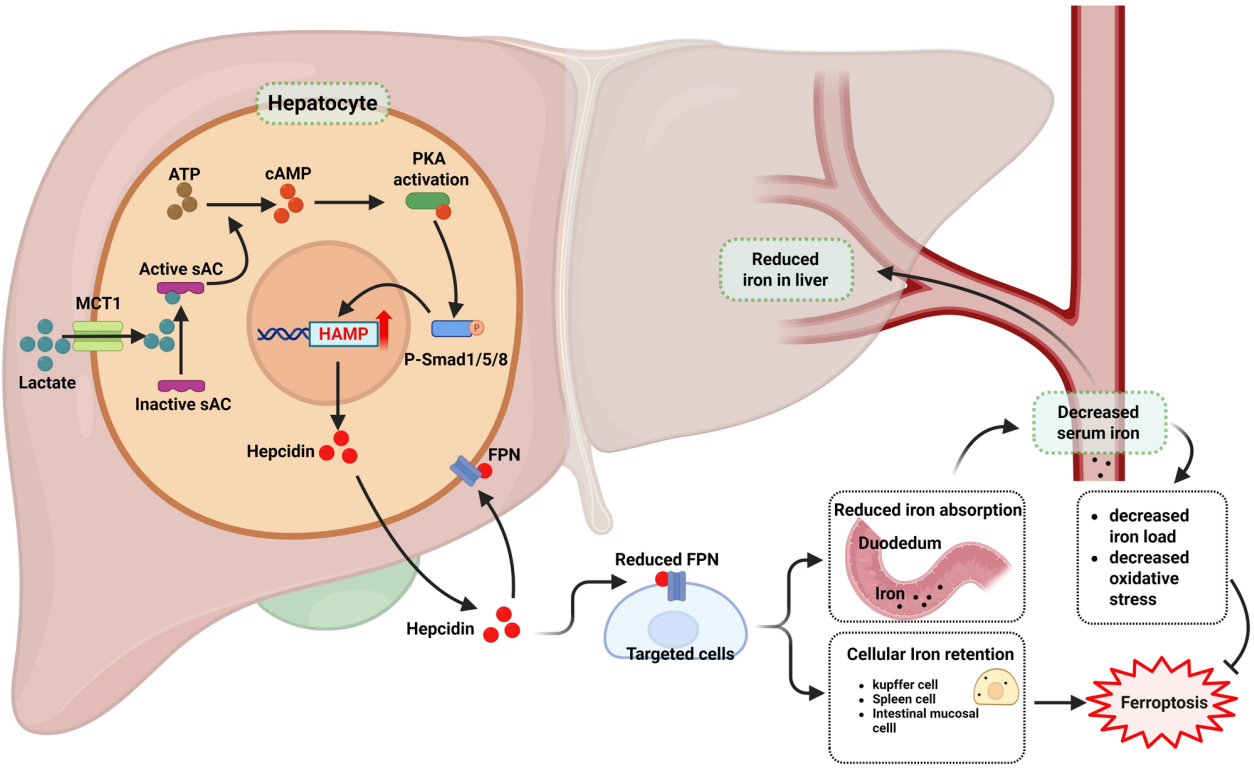

Figure 3. Lactate-hepcidin axis regulates iron homeostasis. Lactate enters cells via MCT1 and binds sAC, triggering its conversion of ATP to cAMP. The cAMP activates PKA, which enhances SMAD signaling. Activated SMAD upregulates HAMP transcription, increasing hepcidin, the master regulator of iron homeostasis. Hepcidin then binds FPN, causing its internalization and degradation, which promotes cellular iron retention and lowers circulating iron. MCT1, monocarboxylate transporter 1; sAC, soluble adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; HAMP, human hepcidin gene; FPN, ferroportin 1. Created with BioRender.com.

^{13}C-labeled lactate have demonstrated robust incorporation of lactate-derived carbon into TCA intermediates across a wide array of tissues, encompassing both healthy and malignant cells (31,32).

Mechanistically, lactate contributes to the intracellular acetyl-CoA pool through its conversion to pyruvate, followed by subsequent metabolism (74). Acetyl-CoA carboxylase (ACC) then catalyzes the rate-limiting carboxylation of acetyl-CoA to malonyl-CoA, a critical intermediate in fatty acid biosynthesis (75). Fatty acid synthase subsequently utilizes malonyl-CoA to synthesize palmitic acid (C16:0), which can be elongated to stearic acid (C18:0) through the action of elongation-of-very-long-chain-fatty acids 6 (Fig. 4). SCD1 then introduces a double bond at the Δ9 position, converting these saturated fatty acids to palmitoleic and oleic acids, respectively. Malonyl-CoA also plays a vital role in PUFA synthesis, where dietary linoleic acid undergoes sequential desaturation and elongation reactions catalyzed by fatty acid desaturase (FADS)2, ELOVL5 and FADS1, leading to the formation of AA (C20:4, ω-6), which can be further elongated by ELOVL2/4 to generate AdA (C22:4, ω-6) (76). These interconnected pathways highlight the pivotal role of ACC-derived malonyl-CoA in fatty acid metabolism, with ACC inhibition potentially attenuating lipid peroxidation and ferroptosis (77-79). Additionally, lactate metabolism enhances cellular NADPH availability through a glucose-sparing mechanism: When cells use lactate as their primary fuel source, glucose is redirected towards the PPP, which generates NADPH essential for fatty acid biosynthesis (28).

A study by Zhao *et al* (57) demonstrated that lactate-enriched hepatocellular carcinoma (HCC) cells exhibit enhanced resistance to ferroptotic damage induced by RAS-selective lethal 3 (RSL3) and Erastin. The authors elucidated a mechanism wherein MCT1-mediated lactate uptake promotes ATP production, leading to AMPK deactivation and subsequent upregulation of SREBP1 and SCD1, enhancing the production of MUFAs that confer protection against ferroptosis (57). Corroborating these findings, Yang *et al* (58) demonstrated that lactate-induced alterations in SCD1/ACSL4 expression and ferroptosis resistance are correlated with lactate production levels in esophageal squamous cell carcinoma (ESCC). The conservation of this lactate/SCD1 regulatory axis across diverse tissue types has been substantiated by multiple studies (80,81). ACSL4 is an enzyme that esterifies CoA into specific PUFAs, such as AA and AdA, contributing to ferroptosis execution by triggering phospholipid peroxidation. In sepsis, lactate promotes ferroptosis via GPR81-mediated upregulation of methyltransferase like 3 (METTL3), which may mediate ACSL4 mRNA stability via N6-methyladenosine (m6A) modification in pulmonary epithelial cells (82).

Although regulating the MUFA/PUFA ratio by lactate through the SCD1/ASCL4 pathway does affect membrane lipid peroxidation sensitivity, this protective effect against ferroptosis may be more highly dependent on the state of the intracellular antioxidant system (83).

Lactate-redox regulation in ferroptosis. Disruptions in redox balance, whether toward excessive oxidation or reduction, are generally deleterious to cellular function. Lactate acts as a

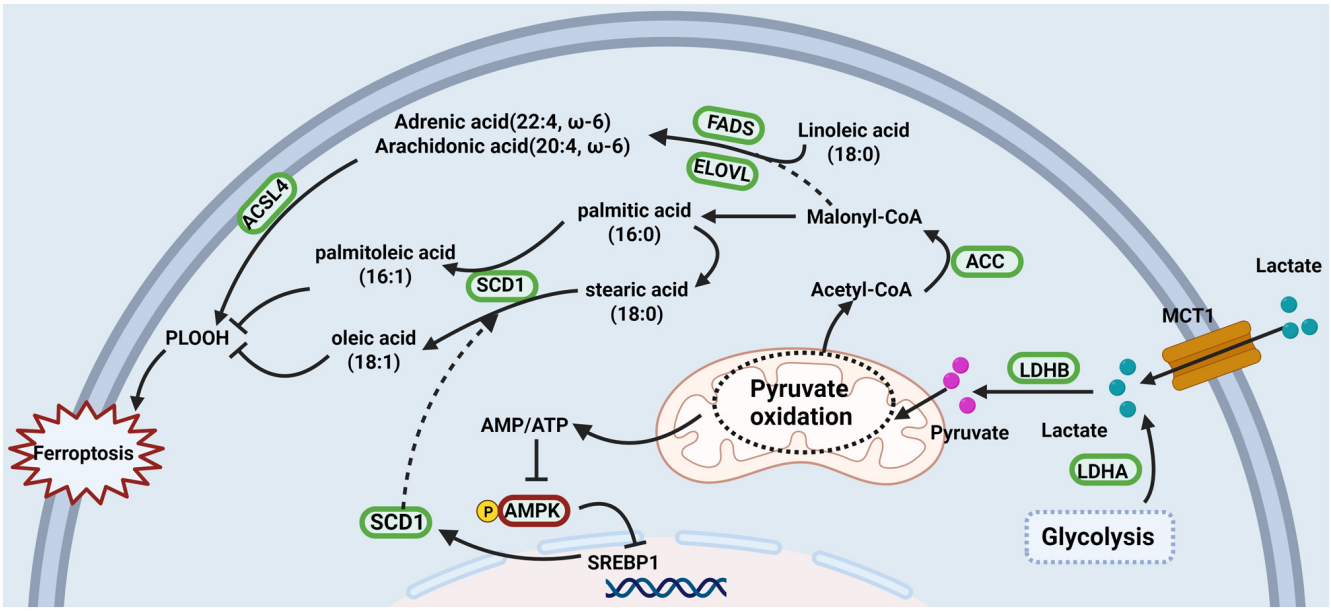

Figure 4. Lactate promotes lipid remodeling in cells. Lactate is taken up via MCT1 and converted by LDH to pyruvate and acetyl-CoA, which fuels *de novo* lipogenesis through ACC, FASN, SCD1, FADS and ELOVL under the control of the AMPK-SREBP1 axis. The resulting balance between MUFAs and PUFAs, and their ACSL4-dependent incorporation into membranes, governs lipid peroxidation and cellular susceptibility to ferroptotic cell death. MCT1, monocarboxylate transporter 1; LDH, lactate dehydrogenase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SCD1, stearyl-CoA desaturase 1; FADS, fatty acid desaturases; ELOVL, elongation of very long-chain fatty acid; AMPK, AMP-activated protein kinase; SREBP1, sterol regulatory element-binding protein 1; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; ACSL4, acyl-CoA synthetase long-chain family member 4. Created with BioRender.com.

redox buffer by modulating the NAD(P)H/NAD(P)$^+$ ratio and serves as a signaling molecule that regulates the activity of antioxidant enzymes involved in ROS metabolism.

NADH/NAD$^+$ balance in lactate-ferroptosis crosstalk. The interconversion of lactate and pyruvate, catalyzed by LDHA/B, is closely coupled to the NAD$^+$/NADH redox pair, thereby modulating cellular redox balance in a context-dependent manner (84,85). Elevated lactate concentrations have been demonstrated to increase the NADH/NAD$^+$ ratio, leading to the inhibition of key glycolytic enzymes such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and phosphoglycerate dehydrogenase, ultimately suppressing both glycolysis and mitochondrial respiration (85). When the cellular demand for NAD$^+$ to sustain oxidation exceeds the rate of ATP turnover, particularly in cells exhibiting active aerobic glycolysis, NAD$^+$ regeneration becomes a limiting factor under conditions of compromised mitochondrial respiration. In such circumstances, cells preferentially rely on glycolysis, resulting in an elevated NAD$^+$/NADH ratio. Under these conditions, activation of PDH facilitates pyruvate oxidation, attenuates lactate accumulation and restores the NAD$^+$/NADH equilibrium (86). Conversely, when lactate is oxidized to pyruvate and enters mitochondrial oxidative pathways, it can indirectly elevate ROS production through electron leakage from the respiratory chain (87-89). In adipocytes, lactate exposure transiently elevates the NADH/NAD$^+$ ratio, which normalizes after 24 h due to elevated NAD$^+$ levels associated with increased mitochondrial membrane potential and enhanced ROS production (90). Similarly, Jia *et al* (91) reported that elevated neuronal lactate uptake augments ROS production and mitochondrial oxidative metabolism, thereby disrupting the balance between ROS generation and detoxification, impairing ATP synthesis and ultimately leading to peripheral axonal degeneration. The mitochondrial enzyme nicotinamide nucleotide transhydrogenase further modulates redox status by catalyzing the reversible conversion of NADH and NADP$^+$ into NAD$^+$ and NADPH, the latter serving as a crucial factor for GSH reductase-mediated recycling of reduced GSH (92). Unlike observations in normal cells, lactate uptake in melanoma cells via MCT1 elevates NADH, NADPH, GPX4 and FSP1 levels, thereby conferring resistance to ferroptosis (93). The net effect of lactate on redox status is governed by the balance between reducing equivalents of NADH and ROS production, which may differ between normal and cancer cells due to variations in oxidative phosphorylation activity and NADH-processing pathways. This apparent contradiction may reflect a critical evolutionary adaptation in which cancer cells reprogram lactate metabolism to attain dual benefits (enhanced metabolic flexibility coupled with augmented oxidative stress resistance) thereby facilitating survival under adverse microenvironmental conditions.

NADPH/NADP$^+$ balance in lactate-ferroptosis. Within glucose metabolism, glucose-6-phosphate generated either through glycolysis or via gluconeogenesis from lactate can enter the PPP, where it is partially oxidized to generate NADPH (94,95). Moreover, lactate metabolism contributes to NADPH production through TCA cycle-linked pathways, particularly those catalyzed by malic enzyme 1 (ME1) and isocitrate dehydrogenase 1 (IDH1) (94,96). Similar to NADH, NADPH fulfills dual roles in cellular redox regulation: It is indispensable for antioxidant defense by facilitating GSH reduction yet simultaneously serves as a substrate for NADPH oxidases that generate ROS production (97). Under glucose-deprived conditions, the knockout of IDH1 or ME1

significantly reduces the NADPH/$NADP^+$ and GSH/oxidized GSH ratios, leading to elevated ROS levels and increased cell death in cancer cells (94). Conversely, excessive NADPH accumulation can induce reductive stress, leading to the upregulation of NADPH oxidase 4 through activation of the PI3K/Akt signaling pathway, thereby promoting ROS generation, as observed in osteoarthritis (96).

Collectively, cellular redox homeostasis is maintained by a delicate equilibrium between NAD(P)H-dependent antioxidant defense mechanisms and NAD(P)H-mediated reductive stress. By engaging in NAD(P)H/$NAD(P)^+$ redox cycling, lactate functions as a dynamic redox buffer that modulates cellular responses to oxidative and reductive stress.

Antioxidant enzymes in lactate-ferroptosis. Under physiological conditions, lactate indirectly regulates cellular antioxidant systems through modulation of the NAD(P)H/$NAD(P)^+$ redox balance. Specifically, uncontrolled elevated intracellular lactate concentrations disrupt the NADH/NAD^+ ratio, thereby impairing the activity of key glycolytic enzymes, particularly GAPDH due to NAD^+ depletion (50,57). This metabolic perturbation, coupled with lactate-mediated feedback inhibition of phosphofructokinase-1, ultimately impairs cellular ATP homeostasis and compromises GSH biosynthesis, the predominant intracellular antioxidant (50). GPX4 plays a pivotal role in counteracting ferroptosis. A recent investigation has demonstrated that intracellular lactate accumulation under ischemic conditions can inactivate the AMPK/GPX4 axis to promote myocardial ferroptosis (98). Conversely, emerging evidence indicates that lactate can paradoxically potentiate antioxidant defense mechanisms through alternative signaling cascades. Metabolically reprogrammed lactate has been demonstrated to augment GPX4 expression and confer resistance to ferroptosis via activation of the p38-serum glucocorticoid-regulated kinase 1 signaling axis. This pathway mitigates GPX4 ubiquitination and subsequent degradation in non-small cell lung cancer (NSCLC) cells (99). Furthermore, an additional study has elucidated that lactate activates antioxidant defense and pro-survival pathways, including the unfolded protein response and nuclear factor erythroid 2-related factor 2 (NRF2) signaling cascades, by inducing mild oxidative stress in neuroblastoma cells (100). Notably, lactate has also been shown to alleviate oxidative stress-induced cell death through autophagy activation in retinal pigment epithelial cells (101).

Lactate-ferroptosis axis in immunometabolism. The immunomodulatory properties of lactate significantly influence ferroptosis susceptibility within both inflammatory conditions and the tumor microenvironment, carrying notable therapeutic relevance (102,103).

Inflammatory response and sepsis. Sepsis-induced metabolic reprogramming drives increased lactate accumulation and systemic oxidative stress, triggering multiple cell death pathways in both immune and parenchymal cells (82,104). In septic lung injury, elevated lactate levels exacerbate alveolar epithelial cell ferroptosis through lactylated histone H3 lysine 18 (H3K18la)-mediated upregulation of METTL3, which enhances m6A modification of ACSL4, ultimately contributing to the development of acute respiratory distress syndrome (82). Lactate further augments neutrophil functions, including chemotaxis, phagocytosis, oxidative burst and neutrophil extracellular trap formation, via energy provision and PI3K/Akt signaling, which may exacerbate tissue cell ferroptosis (105). Nevertheless, lactate simultaneously exerts immunomodulatory effects in sepsis; it suppresses LPS-induced pro-inflammatory cytokine production in macrophages and promotes M2 polarization through MCTs and HIF-1α activation (106). Moreover, lactate-induced histone lactylation drives macrophages toward a reparative phenotype characterized by reduced pro-inflammatory cytokine expression, thereby potentially constraining excessive inflammation (107,108). This dual role of lactate in modulating ferroptosis and inflammation may account for the inconsistent therapeutic outcomes associated with hypertonic sodium lactate administration in sepsis, as these effects appear to be highly dependent on factors such as timing of intervention, dosage and the specific experimental animal models employed (104,109).

Tumor immunity context. The lactate-ferroptosis axis influences anti-tumor immunity through multifaceted mechanisms that reshape the tumor microenvironment. Lactate accumulation within the tumor microenvironment suppresses effector T cell proliferation and cytotoxic activity via GPR81-mediated signaling and metabolic competition, while simultaneously polarizing tumor-associated macrophages toward an immunosuppressive M2 phenotype that promotes tumor progression (8). Notably, ferroptosis induction in cancer cells can trigger immunogenic cell death (ICD), leading to the release of damage-associated molecular patterns that activate dendritic cells and stimulate antitumor T cell responses (110). However, lactate-mediated ferroptosis resistance through SCD1 upregulation and enhanced antioxidant capacity diminishes this immunogenic potential, effectively creating an immune-evasive tumor phenotype (57,58). Recent evidence demonstrates that targeting the lactate-ferroptosis axis can reprogram the immunosuppressive tumor microenvironment. Specifically, the combination of MCT4 inhibition with ferroptosis inducers not only depletes lactate accumulation but also enhances $CD8^+$ T cell infiltration and ferroptosis-driven ICD, thereby synergistically improving checkpoint blockade efficacy (111). This immunometabolic reprogramming represents a promising approach to convert 'cold' tumors into 'hot' tumors that are more responsive to immunotherapy.

Epigenetic regulation via protein lactylation. Kla was initially identified as an enzymatically catalyzed post-translational modification, wherein lactyl groups derived from lactate are covalently attached to lysine residues (9). Originally identified on histones, Kla has been indicated to accumulate at gene promoters in response to diverse stimuli, including hypoxia, interferon-γ, LPS exposure and bacterial infections. This modification directly modulates transcriptional activity and gene expression, thereby establishing a mechanistic link between cellular metabolism and transcriptional regulation (107,108). Subsequent investigations have expanded the functional repertoire of Kla, demonstrating its presence on non-histone proteins, particularly metabolic enzymes (11,12). The lactylation of these enzymes regulates cellular metabolism by modulating enzymatic activity, notably through feedback mechanisms that regulate glycolytic flux (108,112). However, the precise enzymatic machinery responsible for Kla deposition and removal remains incompletely characterized

and the relative contributions of enzymatic vs. non-enzymatic lactylation pathways warrant further clarification.

Histone lactylation. Nuclear Kla is predominantly observed at H3K18, with p300-mediated H3K18la at gene promoters serving as a key determinant of transcriptional regulation. For instance, H3K18la enrichment at the METTL3 promoter upregulates METTL3 expression, subsequently augmenting m6A modification of ACSL4 mRNA (82). This cascade stabilizes ACSL4 transcripts, elevates ACSL4 protein levels and promotes mitochondrial ROS accumulation, ultimately driving ferroptosis in alveolar epithelial cells during sepsis (82). Furthermore, H3K18la facilitates ACSL4 expression through direct promoter engagement and activation of the HIF-1α signaling pathway (113,114). Under hypoxic conditions, elevated lactate levels stimulate H3K18la at the HIF-1α promoter, leading to upregulation of HIF-1α expression (115). This signaling cascade subsequently elevates ACSL4 expression, driving lipid peroxidation and ferroptosis through the ACSL4/lysophosphatidylcholine acyltransferase 3/arachidonate lipoxygenase 15 axis, as demonstrated in both *in vitro* and *in vivo* models of severe acute pancreatitis (114). Paradoxically, Kla modifications can also confer cytoprotective effects in specific cancer contexts. In triple-negative breast cancer, cancer-associated fibroblasts exhibit elevated H3K18la levels, which enhance zinc finger protein 64 expression and subsequently activate the transcription of GCH1 and FTH. This cascade facilitates iron sequestration and protects cells from doxorubicin-induced ferroptosis (71). Similarly, in colorectal cancer stem cells, p300-mediated H4K12la upregulates glutamate-cysteine ligase catalytic subunit (GCLC), thereby expanding the GSH pool and conferring ferroptosis resistance (116). Furthermore, H3K18la enhances the transcriptional activity of NFS1 cysteine desulfurase, a cysteine desulfurase essential for iron-sulfur cluster biosynthesis, consequently reducing the susceptibility of HCC to ferroptosis following microwave ablation (117). These findings underscore the notable tissue-specific and context-dependent nature of histone Kla function. However, the molecular determinants underlying this functional dichotomy remain poorly understood, and the systematic frameworks capable of predicting whether Kla will promote or suppress ferroptosis within specific cellular contexts are still lacking.

Non-histone lactylation. Beyond its role in chromatin regulation, Kla also influences the activity and stability of various non-histone proteins, including key metabolic and RNA-modifying enzymes that regulate ferroptosis. Notably, lactate-primed lysine acetyltransferase 8 directly lactylates mitochondrial phosphoenolpyruvate carboxykinase 2 at K100, thereby enhancing its kinase activity and reprogramming mitochondrial fatty-acid synthesis to promote ferroptotic processes (118). Additionally, Kla of METTL3 stabilizes the protein and promotes m6A modifications on ACSL4 and TFRC transcripts, thereby accelerating ferroptosis in PC12 cells (72). In the context of Alzheimer's disease, reduced lactylation of tau at K677 inhibits ferroptosis by disrupting ferritinophagy, resulting in dysregulated iron metabolism and increased resistance to cell death (119). Similarly, decreased lactylation of malate dehydrogenase 2 at K241, coupled with reduced lactate production, leads to elevated levels of GSH and GPX4, thereby alleviating ferroptosis and improving mitochondrial function in myocardial IRI (120). By contrast, lactylation of LSD1 in melanoma promotes its interaction with FosL1, resulting in repression of TFRC-mediated iron uptake and thereby conferring resistance to ferroptosis (70). Similarly, lactylation of NOP2/Sun RNA methyltransferase 2 enhances its catalytic activity and stabilizes GCLC mRNA via m5C modifications, leading to increased intracellular GSH levels and ferroptosis resistance in gastric cancer cells (121). These findings underscore the versatility of Kla as a regulatory mechanism capable of either promoting or inhibiting ferroptotic cell death through modulation of enzymatic activity.

The bidirectional influence of Kla on ferroptosis is of significant therapeutic interest. In cancer, Kla-driven modulation of ferroptosis has been implicated in developing resistance to chemotherapy and radiation. For example, evodiamine has been found to inhibit histone lactylation at the HIF-1α promoter, suppressing angiogenesis and programmed death-ligand 1 expression while inducing ferroptosis in prostate cancer cells (122). This highlights the potential of targeting Kla 'writers', 'erasers' or 'readers' to selectively induce ferroptosis in cancer cells, thereby enhancing the efficacy of cancer therapies while minimizing damage to normal tissues. Conversely, Kla manipulation could also hold promise in treating degenerative diseases and ischemic injury by reducing ferroptotic damage (123). However, the clinical translation of Kla-targeted therapies faces notable challenges, including the lack of specific inhibitors, potential off-target effects and the complex tissue-specific functions of lactylation.

In summary, Kla represents a critical metabolic regulator integrating cellular metabolic status with ferroptotic outcomes. Although the context-dependent, bidirectional modulation of ferroptosis by Kla presents promising therapeutic avenues, notable barriers remain between current mechanistic insights and clinical implementation. This underscores the need for more rigorous investigations into tissue-specific regulatory networks and the development of targeted therapeutic strategies.

5. Putative context-dependent mechanisms

The seemingly contradictory roles of lactate in ferroptosis (its capacity to both promote and inhibit this regulated form of cell death) highlight the complex interplay among cellular metabolism, redox homeostasis and iron regulation. In the previous section, the factors that determine whether lactate functions in a pro-ferroptotic or anti-ferroptotic manner within specific cellular contexts were systematically examined (Fig. 5). In pathological conditions such as sepsis (73,82), neurodegeneration (91,119), osteoarthritis (96), pancreatitis (114), IRI (120), intracerebral hemorrhage (72) and adipocytes browning (90), lactate promotes ferroptosis. Conversely, in various malignancies, including HCC (57,117), ESCC (58), melanoma (70), NSCLC (99), neuroblastoma (100), breast cancer (71), colorectal cancer (116), gastric cancer (121) and prostate cancer (122), lactate suppresses ferroptosis. Table I summarizes recent *in vitro* studies examining the role of lactate in ferroptosis regulation. In this section, three potential mechanisms underlying this context-dependent regulation are discussed: Differences in metabolic enzyme expression, pH homeostatic capacity and antioxidant defense systems (Fig. 6).

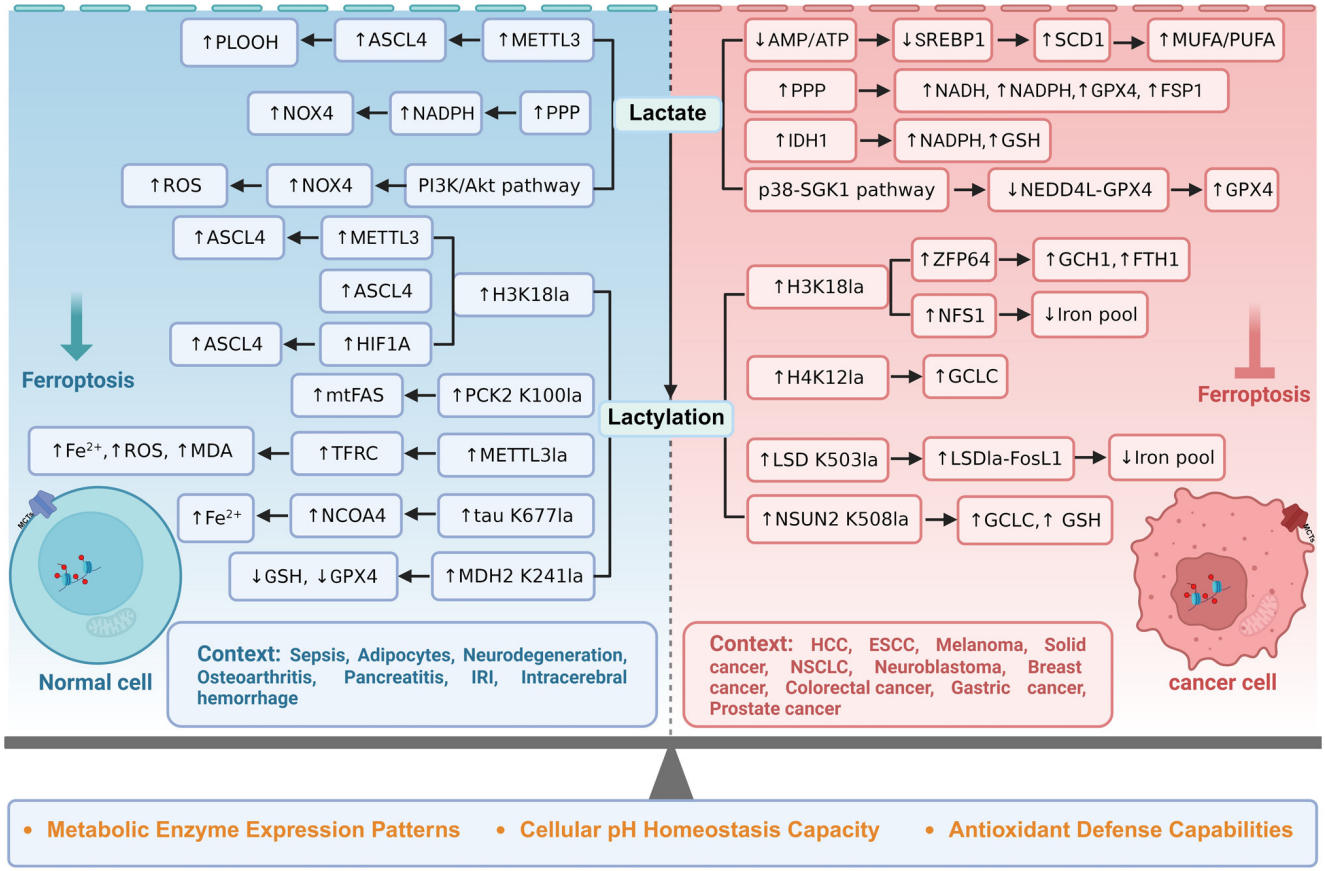

Figure 5. Dual roles of lactate and lactylation in ferroptosis regulation across cellular contexts. Lactate and lactylation exhibit contrasting regulatory effects on ferroptosis in normal vs. tumor cells through both lactylation-dependent and -independent mechanisms. In lactylation-independent pathways, lactate modulates cellular metabolism and redox homeostasis via MCTs and GPR81 receptor signaling, with contrasting outcomes observed between normal and malignant cell populations. In lactylation-dependent pathways, lactate similarly demonstrates contrasting effects in normal vs. tumor cell contexts through post-translational protein modifications. PLOOH, phospholipid hydroperoxides; ACSL4, acyl-CoA synthetase long-chain family member 4; METTL3, methyltransferase like 3; NOX4, NADPH oxidase 4; PPP, pentose phosphate pathway; ROS, reactive oxygen species; SREBP1, sterol regulatory element-binding protein 1; SCD1, stearoyl-CoA desaturase 1; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; IDH1, isocitrate dehydrogenase 1; GSH, glutathione; SGK1, serum- and glucocorticoid-inducible kinase 1; NEDD4L, neural precursor cell expressed developmental downregulated protein; PCK2, phosphoenolpyruvate carboxykinase 2; mtFAS, mitochondrial fatty acid synthesis; TFRC, transferrin-transferrin receptor; MDA, malondialdehyde; NCOA4, nuclear receptor coactivator 4; MDH2, malate dehydrogenase 2; ZFP64, zinc finger protein 64; GCH1, GTP cyclohydrolase 1; FTH1, ferritin heavy chain 1; NFS1, NFS1 cysteine desulfurase; GCLC, glutamate-cysteine ligase catalytic subunit; LSD1, lysine-specific demethylase 1; FosL1, Fos-like antigen 1; NSUN2, NOP2/Sun RNA methyltransferase family member 2; IRI, ischemia-reperfusion injury; HCC, hepatocellular carcinoma; ESCC, esophageal squamous cell carcinoma; NSCLC, non-small cell lung cancer; MCT (1,4), monocarboxylate transporter (1,4); GPR81, G protein-coupled receptor 81. Created with BioRender.com.

Metabolic enzyme expression patterns. Cancer cells characterized by the Warburg effect demonstrate elevated expression of MCT1 and MCT4, which promote enhanced lactate uptake and consequent metabolic reprogramming. Notably, identical lactate concentrations exert diametrically contrasting effects on ferroptosis susceptibility in malignant lung cancer cells compared with their normal epithelial counterparts, highlighting fundamental differences in lactate metabolism between these cellular contexts (82,99). Although LDHA has been extensively characterized as a tumor survival factor through its role in mitigating ROS, targeted depletion via small interfering RNA or pharmacological inhibition (GSK2837808A or R-GNE-140) fails to sensitize A549 cells to ferroptosis inducers, including RSL3 or erastin (49). This observation necessitates the existence of LDHA-independent anti-ferroptosis mechanisms. In KRAS-driven NSCLC, LDHB has been identified as a key regulator of GSH-dependent ferroptosis resistance through STAT1 signaling, although the precise molecular mechanisms underlying LDHB-mediated STAT1 activation remain incompletely elucidated (49). A recent investigation propose that LDHB mediates a complex three-step reaction cycle, wherein reducing equivalents are transferred from lactate to reduced CoQH2, with NAD^+ serving as a cycling cofactor (124). The markedly elevated NAD^+ concentrations observed in tumor cells compared with normal tissues may provide enhanced substrate availability for LDHB-mediated lactate oxidation cycles (125). Given that CoQH2 serves as an alternative anti-ferroptosis system operating in parallel with GPX4, the differential metabolic environments between malignant and normal cells likely contribute to the divergent effects of lactate on ferroptosis sensitivity observed across these cellular contexts. Nevertheless, this proposed mechanism lacks direct biochemical validation and relies heavily on circumstantial evidence from functional studies. Despite these limitations, this finding provides an important avenue for subsequent research.

Table I. *In vitro* evidence of lactate regulating ferroptosis.

Authors, year	Cell type	Lactate concentration	Phenotype	Mechanism	Disease context	Reduce/promote ferroptosis	(Refs.)
Zhao *et al*, 2020	Hep3B and Huh-7	20 mM	MUFAs↑	SCD1↑	Hepatocellular carcinoma	Reduce	(57)
Yang *et al*, 2024	EC109	20 μM	MUFAs↑	SCD1↑	Esophageal cancer	Reduce	(58)
Jia *et al*, 2021	Primary spinal and DRG neuron	1 and 10 mM	mtROS↑	Alters energy metabolism	Neurodegenerative disease	Promote	(91)
Huang *et al*, 2023	Chondrocyte	10, 20 and 40 mM	ROS↑	NADPH/NOX4, GPR81/NOX4	Osteoarthritis	Promote	(96)
Lin *et al*, 2022	COMM-SUS	10 and 30 mM	NADPH↑, NADH↑	PPP activation	Melanoma	Reduce	(93)
Bauzá-Thorbrügge *et al*, 2023	Adipocyte	25 mM	ROS↑	NADH↑	Adipose tissue	Promote	(90)
Cheng *et al*, 2023	H1229 and A549	5, 10, 15 and 25 mM	GPX4↑	Inhibits GPX4 ubiquitination by inactivating the E3 ubiquitin ligase NEDD4L	NSCLC	Reduce	(99)
Tauffenberger *et al*, 2019	SH-SY5Y	20 mM	UPR↑, NRF↑	ROS burst	Neuroblastoma	Reduce	(100)
Zou *et al*, 2023	ARPE-19	20 mM	ROS↓	Activate autophagy pathway	A cell line derived from the retina	Reduce	(101)
Wu *et al*, 2024	MLE12	10 mM	GPX4↓, GSH/GSSG↓, ACSL4↑	GPR81/H3K18la/ METTL3/ACSL4	Mouse lung epithelial cells in sepsis	Promote	(82)
Zhang *et al*, 2025	AR42J	5, 10, 15 and 25 mM	ACSL4↑, LPCAT3↑, ALOX15↑	H3K18la in HIF-1α promoter	Pancreatitis	Promote	(114)
Zhang *et al*, 2025	DOX-resistant TNBC	25 mM	GCH1↑, FTH1↑	H3K18la in ZFP64 promoter	TNBC	Reduce	(71)
Deng *et al*, 2025	LoVo, SW-620 and HCT-116	5, 10 and 15 mM	ROS↓, MDA↓, GPX4↑	GCLC↑	Colorectal cancer	Reduce	(116)
Huang *et al*, 2025	MHCC-97H and Huh7.	5 and 10 mM	ROS↓, free iron↓	H3K18la in NFS1 promoter	Hepatocellular carcinoma	Reduce	(117)

Table I. Continued.

Authors, year	Cell type	Lactate concentration	Phenotype	Mechanism	Disease context	Reduce/promote ferroptosis	(Refs.)
Yuan *et al*, 2025	THLE2	5, 10 and 20 mM	GPX4↓, COX2↑, TFRC↑	Lactylation in PCK2 (K100) induces mtFAS remodeling, potentiation of oxidative phosphorylation and the tricarboxylic acid cycle	Human liver epithelial cell line	Promote	(118)
She *et al*, 2024	H9c2	10, 20 and 50 mM	GSH↓, GPX4↓, MDA↑, iron↑	Lactylation in MDH2 (K241)	Cardiomyocyte cell lines from the rat heart	Promote	(120)
Niu *et al*, 2025	HEK293T and MKN45	10 and 20 mM	GSH↑, Lipid perioxidation↓	Lactylation in NSUN2 (K508) stabilizes GCLC mRNA via promoting m5C modification	Gastric cancer	Reduce	(121)
Yu *et al*, 2023	DU145	10 mM	ROS□, iron↓	H3K18la in HIF-1α promoter	Prostate cancer	Reduce	(122)

MUFA, monounsaturated fatty acid; mtROS, mitochondrial reactive oxygen species; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; UPR, unfolded protein response; NRF, nuclear factor erythroid 2-related factor; GSH, glutathione; GSSG, glutathione disulfide; ACSL4, acyl-CoA synthetase long chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; ALOX15, arachidonate 15-lipoxygenase; GCH1, GTP cyclohydrolase 1; FTH1, ferritin heavy chain 1; MDA, malondialdehyde; COX2, cyclooxygenase-2; TFRC, transferrin receptor; SCD1, stearoyl-CoA desaturase 1; NOX4, NADPH oxidase 4; PPP, pentose phosphate pathway; NEDD4L, NEDD4-like E3 ubiquitin protein ligase; GPR81, G-protein coupled receptor 81; H3K18la, histone H3 lysine 18 lactylation; METTL3, methyltransferase like 3; HIF-1α, hypoxia-inducible factor 1α; ZFP64, zinc finger protein 64; GCLC, glutamate-cysteine ligase catalytic subunit; PCK2, phosphoenolpyruvate carboxykinase 2; mtFAS, mitochondrial fatty acid synthesis; MDH2, malate dehydrogenase 2; NSUN2, NOP2/Sun RNA methyltransferase family member 2; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer; DRG, dorsal root ganglion; m5C, 5-methylcytosine.

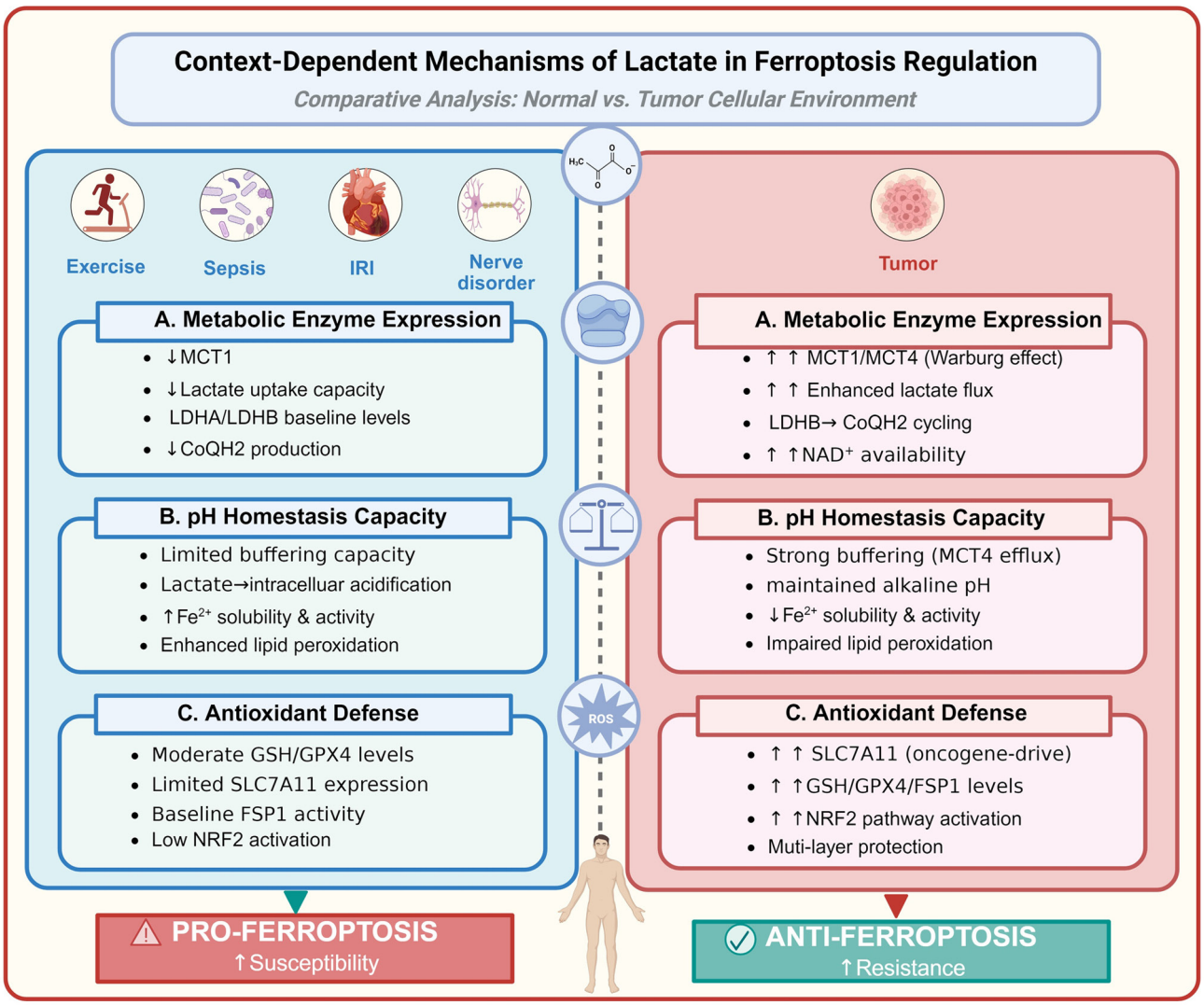

Figure 6. Context-dependent mechanisms of lactate in ferroptosis regulation. The context-dependent mechanisms of lactate in ferroptosis regulation include: (A) Differential metabolic enzyme expression profiles, (B) distinct cellular pH homeostasis capacities and (C) varying antioxidant defense capabilities. These mechanisms may underlie the distinct effects of the context-dependent lactate-ferroptosis axis. IRI, ischemia-reperfusion injury; MCT (1,4), monocarboxylate transporter (1,4); LDHA/B, lactate dehydrogenase A/B; CoQH2, ubiquinol; GSH, glutathione; GPX4, glutathione peroxidase 4; SLC7A11, cystine/glutamate antiporter solute carrier family 7 member 11; FSP1, ferroptosis suppressor protein 1; NRF2, nuclear factor erythroid 2-related factor 2. Created with BioRender.com.

Cellular pH homeostasis capacity. The differential expression of MCTs between normal and malignant cells provides a mechanistic framework for understanding lactate-mediated modulation of ferroptosis susceptibility. Normal cells predominantly express MCT1, which confers a relatively limited capacity for lactate transport (126). By contrast, cancer cells typically co-express MCT1 and MCT4, facilitating highly efficient lactate efflux that preserves intracellular pH homeostasis even within the acidic tumor microenvironment (127). This enhanced acid-extruding capacity enables tumor cells to sustain intracellular pH at neutral or slightly alkaline levels, potentially exceeding those observed in normal cells under comparable conditions (128). The pH dependence of Fe^{2+}-catalyzed lipid peroxidation constitutes a critical determinant of ferroptotic sensitivity, proceeding efficiently under acidic conditions but being markedly impaired at neutral or basic pH due to reduced Fe^{2+} solubility. Consequently, the efficacy of ferroptosis-inducing therapies may be limited in alkaline cytoplasmic environments (129). However, the proposed lactate-acidification-ferroptosis axis warrants careful evaluation in light of emerging contradictory evidence. An early study by Jackson and Halestrap (130) documented lactate-induced intracellular acidification in rat hepatocytes, whereas Bozzo *et al* (131) observed only modest pH reductions following 5 mM lactate treatment in mouse neurons. These findings suggest that normal cells possess notable buffering capacity against lactate-induced acidification, challenging the assumption that lactate uniformly acidifies the cytoplasm across diverse cell types. Moreover, LDHA-mediated lactate accumulation has been reported to promote ferroptosis resistance in a pH-dependent manner in tumors, a mechanism that may involve inhibition of Piezo1 in an acidic environment (132-134). Accordingly, the mechanistic link between lactate-mediated pH changes and iron-dependent ferroptosis remains inadequately characterized.

Antioxidant defense capabilities. Tumor cells have developed intricate adaptive mechanisms to evade ferroptosis, a key tumor-suppressive process. In response to the heightened oxidative stress associated with malignant transformation, cancer cells activate a comprehensive antioxidant defense pathway that, paradoxically, shields them from ferroptotic cell death (4). At the core of this protective adaptation lies the upregulation of cystine/glutamate antiporter solute carrier family 7 member 11 (SLC7A11), driven by the inactivation of key tumor suppressors including TP53, BRCA1 associated protein 1 and alternate reading frame (16,135). This dysregulation fundamentally alters the cellular redox balance, conferring ferroptosis resistance while simultaneously promoting tumor proliferation and survival. The oncogenic KRAS signaling cascade further amplifies this effect by directly upregulating SLC7A11 expression, thereby establishing a robust anti-ferroptotic defense that is particularly pronounced in lung adenocarcinoma progression (136). Beyond cystine import, the ferroptosis evasion machinery encompasses the upregulation of critical antioxidant enzymes, notably GSH and GPX4, which are consistently upregulated across multiple tumor types (137,138). Complementing these classical antioxidant systems, cancer cells also exploit radical-trapping antioxidant mechanisms mediated by FSP1 and GCH1, both of which are frequently upregulated in diverse malignancies and markedly contribute to ferroptosis resistance (21,139). Furthermore, NRF2 activation, a hallmark of numerous cancer types, serves as both a driver of tumor progression and a coordinator of therapy resistance. Through its transcriptional control of ferroptosis-regulatory components, including SLC7A11, GPX4 and FSP1, NRF2 creates a unified resistance program that simultaneously promotes tumor progression and confers therapeutic resistance (140).

Notably, this mechanism of ferroptosis evasion may be closely associated with altered lactate metabolism in tumor cells. While lactate has been reported to promote ferroptosis in normal cellular contexts by modulating iron homeostasis and lipid peroxidation, tumor cells appear to exploit lactate signaling pathways to reinforce their anti-ferroptotic defenses. This metabolic rewiring suggests that the Warburg effect and ferroptosis evasion may be mechanistically linked, representing complementary adaptive strategies that collectively support malignant transformation and tumor progression.

6. Crosstalk between the lactate-ferroptosis axis and other cell death modalities

The lactate-ferroptosis axis does not function independently but rather integrates with other forms of programmed cell death, constituting a complex regulatory network that modulates therapeutic outcomes. Growing evidence suggests that lactate metabolism exerts regulatory control over multiple cell death modalities, with the dominant pathway contingent upon the specific cellular context and magnitude of stress stimuli.

Lactate-mediated coordination of ferroptosis and apoptosis. In cancer cells, increased lactate concentrations have been reported to suppress apoptosis through HIF-1α-mediated upregulation of anti-apoptotic proteins, including BCL-2 and survivin, while concurrently promoting ferroptosis resistance via SCD1 upregulation (58,141). This coordinated suppression of apoptotic and ferroptotic pathways confers a metabolic survival advantage under stress conditions. Conversely, in certain therapeutic contexts, lactate depletion strategies have been demonstrated to induce a synergistic activation of both apoptotic and ferroptotic pathways. For instance, MCT1 inhibition in glycolytic tumors induces a metabolic catastrophe that triggers caspase-dependent apoptosis alongside GSH depletion-mediated ferroptosis, thereby yielding enhanced antitumor efficacy relative to the activation of either pathway alone (142). A study has demonstrated that GPX4 inhibition can simultaneously activate the caspase-8-mediated apoptotic pathway and ferroptosis, suggesting shared upstream signaling mechanisms (143). Furthermore, the tumor suppressor p53 serves as a critical node connecting these pathways as it can promote ferroptosis via SLC7A11 repression while simultaneously regulating apoptotic gene expression (144).

Autophagy as a double-edged sword in lactate-ferroptosis. The interplay between lactate, autophagy and ferroptosis is notably intricate. Lactate has been reported to induce protective autophagy in retinal pigment epithelial cells, mitigating oxidative stress and cell death through AMPK activation (101,145). However, in the context of ferroptosis, selective autophagy pathways such as ferritinophagy (autophagic degradation of ferritin) and lipophagy (degradation of lipid droplets) can paradoxically facilitate ferroptosis by elevating the LIP and releasing PUFAs for peroxidation (146,147). Studies have demonstrated that lactate-induced autophagy activation can dictate cellular fate between survival and ferroptotic death based on the iron-handling capacity and antioxidant reserve of specific cell types (101,119,148). In Alzheimer's disease, diminished tau lactylation suppresses ferritinophagy, resulting in iron accumulation and altered susceptibility to ferroptosis, highlighting the complex interplay among lactate metabolism, autophagy and iron homeostasis (119). Additionally, clockophagy (selective degradation of aryl hydrocarbon receptor nuclear translocator-like protein 1, a core clock gene) has been reported to enhance ferroptosis sensitivity by disrupting the circadian regulation of lipid metabolism and antioxidant defenses (149).

7. Therapeutic approaches in lactate-ferroptosis

As the role of lactate in disease progression becomes increasingly evident, strategies aimed at modulating lactate metabolism are receiving growing attention in conditions including neurodegenerative disorders, IRI, sepsis and cancer. These approaches encompass systemic administration of lactate-enriched solutions to provide metabolic support, as well as interventions aimed at inhibiting lactate production or transport as well as promoting its depletion to disrupt metabolic symbiosis in tumors, highlighting the dual therapeutic potential of lactate (150,151).

Lactate in therapeutic contexts

Neurodegenerative diseases and IRI. Increasing evidence implicates ferroptosis in the pathogenesis of major neurodegenerative disorders, including Alzheimer's disease,

Parkinson's disease, Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis (152). In these chronic conditions, persistent elevations in lactate are associated with oxidative stress and disrupted iron homeostasis, collectively promoting ferroptotic neuronal death (153-155). Similarly, lactate accumulation during prolonged ischemia or late reperfusion has detrimental effects. Sun *et al* (98) demonstrated that intracellular lactate overload under prolonged ischemia inactivates the AMPK/NRF2/GPX4 protective axis, thereby promoting myocardial ferroptosis and exacerbating cardiac injury. By contrast, lactate exhibits striking neuroprotective properties in acute ischemic stroke. Intraventricular administration following reperfusion markedly reduces infarct volume and ameliorates neurological deficits (156). This protective action is attributed to the role of lactate as an alternative energy substrate, whereby its conversion to pyruvate enables mitochondrial oxidation once oxygen is restored (157). However, lactate accumulated during the ischemic phase itself, when oxygen tension is absent, cannot fuel oxidative metabolism. Instead, it drives protein lactylation in ischemic tissues, a post-translational modification that exacerbates cellular injury (158).

The neuroprotective effects of exogenous lactate are highly dependent on both dose and timing. Following oxygen-glucose deprivation, 4 mM lactate markedly attenuates hippocampal neuronal death, whereas 20 mM exerts neurotoxic effects (159). Optimal neuroprotection is observed at ~10 mM, with concentrations below this threshold insufficient to alleviate the metabolic crisis associated with cerebral ischemia (160). Similarly, perfusion of isolated mouse hearts with 20 mmol/l L-lactate for only 15 min at reperfusion onset reduced infarct size from 44.74 to 21.46% (161). Clinical and preclinical studies suggest that lactate-enriched solutions confer notable benefits in traumatic brain injury and myocardial ischemia, including reductions in cognitive deficits, improvements in cerebral blood flow and attenuation of reperfusion injuries through mechanisms such as anti-inflammatory effects and provision of alternative energy substrates (156,162). Moreover, lactate-enriched solutions exhibit promising effects by producing a positive inotropic response in both healthy individuals and patients with acute heart failure, and they may further mitigate reperfusion injuries following myocardial ischemia (163-165). Collectively, these findings underscore the context-dependent duality of lactate: It acts as a metabolic burden in chronic neurodegeneration and hypoxic conditions; however, it serves as a therapeutic asset during reperfusion when oxidative capacity is restored.

Sepsis. Elevated serum lactate levels serve as a prognostic indicator in sepsis, with higher concentrations correlating with increased mortality (166). A mechanistic study has further implicated lactate in ferroptosis-mediated lung injury during sepsis progression (82). However, Besnier *et al* (104) reported that hypertonic sodium lactate solutions protected against cardiac dysfunction, microcirculatory impairment and vascular leakage in septic animals, while simultaneously attenuating inflammation and promoting ketogenesis. This paradox, wherein lactate exhibits context-dependent anti-inflammatory effects while promoting ferroptosis, represents a significant challenge for its clinical translation.

Targeting lactate therapy in tumor

Lactate production inhibition. Given its role in catalyzing the conversion of pyruvate to lactate in glycolytic cancer cells and the observation that LDHA deficiency results in only relatively mild symptoms, such as exertional myopathy, LDHA represents a pivotal and safe therapeutic target (150,167). Inhibitors, including gossypol (AT-101) and its derivative FX-11, have demonstrated efficacy in preclinical and early clinical studies, while other molecules, such as galloflavin, oxamate, quinoline derivatives and N-hydroxyindole-based compounds, demonstrate potential in suppressing tumor progression (168-173). Despite these promising findings, challenges, including isoform-specific expression (LDHA vs. LDHB) and tumor metabolic plasticity, have limited their broader application (174). Targeting other metabolic enzymes, including hexokinase 2 and PDH kinase 1, using agents such as 2-deoxy-D-glucose and dichloroacetate (DCA), has demonstrated potential in reducing lactate production and suppressing tumor growth (175,176).

Nanomedicines, owing to their nanoscale size and multifunctional design, facilitate precise tumor targeting, controlled drug release and enhanced bioavailability, thereby offering innovative solutions to modulate tumor lactate metabolism and amplify antitumor efficacy (150). For example, Zhang *et al* (177) developed PMVL, a lonidamine-loaded nanoplatform that enhances ferroptosis and immune activation through dual inhibition of glycolysis and the PPP, effectively reducing lactate production.

Lactate clearance enhancement. Lactate oxidase provides a direct strategy by catalyzing lactate oxidation to pyruvate and H_2O_2, reducing lactate levels, exacerbating tumor hypoxia and increasing oxidative stress (150). This approach enhances antitumor immune responses and activates hypoxia-sensitive prodrugs. A recent study reported that an engineered biohybrid of DH5α *Escherichia coli* with hypoxia-inducible lactate oxidase and iron-doped zeolitic imidazolate framework-8 nanoparticles enables targeted lactate depletion, immune activation and ferroptosis, significantly inhibiting tumor growth and metastasis (178). However, systemic administration of lactate oxidase carries the risk of off-target H_2O_2 toxicity, underscoring the need for tumor-specific delivery systems to improve safety and therapeutic outcomes.

MCT-mediated transport inhibition. Inhibiting MCT-mediated lactate transport offers another avenue to disrupt tumor metabolic symbiosis. MCT1 inhibition compels cancer cells to compete for glucose, thereby inducing apoptosis in hypoxic cancer cells, while MCT4 inhibition triggers intracellular acidosis under hypoxic conditions (142). Early inhibitors (hydroxycinnamate and lonidamine) lacked isoform selectivity, limiting their clinical potential (179,180). However, next-generation inhibitors, such as AZD3965, AR-C155858, SR13800 and VB124, demonstrate improved specificity, with AZD3965 progressing to phase I trials (111,181-183). Additionally, CD147-targeting therapies, including anti-CD147 antibodies, modulate MCT1/4 surface expression, although off-target effects remain a concern (184). Certain statin drugs demonstrate MCT4 inhibitory activity, with lipophilic statins exhibiting greater potency compared with their hydrophilic counterparts (185,186). Recently, Chen *et al* (187) developed a folic acid-decorated, manganese dioxide-coated mesoporous

Table II. Targeting lactate in tumor therapeutic strategies.

Targeted drugs	Mechanism	Research development	(Refs.)
A, Targeting lactate production			
AT-101	Inhibits LDH	Phase II clinical trials	(168)
FX-11	Inhibits LDHA	Preclinical research	(169)
Oxamate	Inhibits LDHA	Preclinical research	(170)
Galloflavin	Inhibits LDHA	Preclinical research	(171)
LDHA short interfering RNA	Suppresses LDHA expression	Preclinical research	(204)
N-hydroxyindole-based compounds	Inhibits LDHA activity	Preclinical research	(172)
Quinoline derivatives	Inhibits LDHA	Preclinical research	(173)
2-DG	Inhibits HK2	Phase I clinical trials	(175)
DCA	Inhibits PDK1	Preclinical research	(176)
B, Targeting lactate transport			
AZD3965	Blocks MCT1	Phase I clinical trials	(181)
AR-C155858	Blocks MCT1	Preclinical research	(182)
SR13800	Blocks MCT1	Preclinical research	(183)
VB124	Inhibits MCT4	Preclinical research	(111)
Fluvastatin Sodium	Inhibits MCT4	Preclinical research	(185)
Lonidamine	Inhibits MCT activity	Preclinical/early clinical research	(179,180)
C, Enhancing lactate depletion			
Lactate oxidase	Catalyzes lactate oxidation	Preclinical research	(205)
Biohybrid Materials (e.g., iron-doped ZIF-8 nanoparticles)	Enables targeted lactate depletion via lactate oxidase delivery	Animal models	(178)

LDH(A), lactate dehydrogenase(A); HK2, hexokinase 2; PDK1, pyruvate dehydrogenase kinase 1; MCT (1,4), monocarboxylate transporter (1,4); 2-DG, 2-deoxyglucose; DCA, dichloroacetate.

silica nanoparticle to co-deliver fluvastatin sodium (MCT4 inhibitor) and metformin, effectively targeting tumor lactate metabolism by promoting lactate production and inhibiting lactate efflux, thereby exacerbating intracellular acidosis and inducing cancer cell death. This nanomedicine demonstrated enhanced antitumor efficacy, suppressed tumor cell migration and suppressed metastasis by disrupting the MCT4-mediated lactate shuttling in breast cancer models. Targeting lactate metabolism has therefore emerged as a promising therapeutic approach in oncology, and the aforementioned strategies are summarized in Table II.

Targeting lactate therapy in neurodegenerative diseases, IRI and sepsis. Therapeutic approaches aimed at modulating lactate metabolism have demonstrated some potential in regulating ferroptosis in neurodegenerative diseases, IRI and sepsis. However, their effectiveness is critically context-dependent, varying according to the metabolic characteristics of the specific tissues and cell types (48,188,189). Approaches that suppress lactate production, such as using PDK inhibitors (DCA and thiamine), have been demonstrated to alleviate organ damage and mitigate ferroptosis in sepsis by reversing the pathological Warburg effect-like state, thereby improving mitochondrial function and reducing ROS accumulation (189,190). Conversely, in myocardial IRI, activation of LDHA has been found to phosphorylate and stabilize the ferroptosis-suppressing enzyme GPX4 via its kinase activity, suggesting that direct inhibition of LDHA could be detrimental (48).

Enhancing lactate clearance has also emerged as a promising strategy in sepsis, as increased lactate elimination has been positively correlated with improved clinical outcomes in patients with sepsis (191). Beyond merely correcting metabolic acidosis, this approach also restricts lactate-driven histone

lactylation, which influences the epigenetic regulation of TFRC expression and ferroptosis susceptibility (73,192). By contrast, controlled utilization of lactate, such as lactate post-conditioning, has been demonstrated to exert neuroprotective effects in cerebral IRI (156).

Inhibition of MCT-mediated lactate shuttling has demonstrated cell-type-specific therapeutic potential. For instance, blocking lactate efflux via MCT4, using agents such as VB124, can redirect pyruvate toward mitochondrial oxidation, thereby conferring cardioprotection in myocardial IRI (193). Meanwhile, MCT1 inhibitors, including AZD3965, have been revealed to regulate immune responses and significantly reduce mortality in septic mice by promoting neutrophil apoptosis (194). However, MCT1-mediated lactate transport remains crucial for sustaining energy homeostasis and preserving tissue health in neurons and pulmonary epithelial cells under comparable conditions (195,196).

In summary, modulation of lactate metabolism represents a promising avenue for managing ferroptosis in disease. Nevertheless, future translational studies must focus on developing drugs with high tissue specificity and isoform-selective activity to account for the metabolic duality inherent to lactate biology.

8. Conclusions and perspectives

Regulated cell death and metabolic homeostasis constitute fundamental determinants of cellular development and growth. In the present review, comprehensive analysis revealed a particularly intriguing phenomenon: Lactate exhibits diametrically contrasting effects on ferroptosis, promoting cell death in normal cells while conferring protection in tumor cells. This apparent paradox, largely attributed to context-dependent mechanisms, has remained incompletely understood.

Several critical research gaps remain to be addressed. The molecular mechanism underlying lactate-induced downregulation of ACSL4 via MCT1 remains incompletely elucidated, although accumulating evidence suggests a potential involvement of the lactate-induced STAT3 signaling pathway (197,198). Notably, MCT1 blockade in HCC cells promotes ferroptosis without observable alterations in GPX4 and FSP1 expression levels, while lactate uptake in melanoma cells via MCT1 elevates NADH, NADPH, GPX4 and FSP1. This paradox may be explained by enzymatic dysfunction rather than transcriptional downregulation. In neurodegenerative contexts, the notable metabolic differences between immature and mature neurons indicate that the lactate-ferroptosis axis during neurogenesis is largely unexplored, with potential implications for neurodevelopmental disorders (199-201). Similarly, in IRI and sepsis, studies lack systematic investigation of temporal exposure windows, a critical limitation given that prolonged lactate exposure may trigger adaptive responses or cumulative toxic effects. While Wu *et al* (202) recently addressed lactate-regulated ferroptosis in cancer contexts and acknowledged the context-dependent nature of this phenomenon, their analysis did not elucidate the mechanistic determinants underlying this differential regulation. The present review addresses this knowledge gap by identifying three key context-dependent mechanisms governing the dual role of lactate: Metabolic enzyme expression patterns, pH homeostasis capacity and antioxidant defense capabilities. Additionally, the present review explored the therapeutic potential of lactate in non-tumor diseases and elucidated its crosstalk with other cell death pathways. Although lactylation modifications have been demonstrated to regulate ferroptosis across diverse experimental models, it remains unclear whether these mechanisms are restricted to the specific disease contexts and models studied or can be universally extended to all cellular systems.

The therapeutic implications are profound yet complex. Strategies aimed at disrupting lactate-mediated ferroptosis resistance in tumors while reducing lactate-mediated ferroptosis in sepsis may offer selective therapeutic windows. However, in IRI, the dual nature of lactate, providing a protective effect through energy supply while simultaneously promoting ferroptotic damage, poses significant challenges for its clinical application. In the nervous system, interventions harnessing the neuroprotective properties of lactate while mitigating pro-ferroptotic effects offer novel approaches (203).

Future research directions must prioritize three key directions: First, investigating the triggering factors of lactate-ferroptosis interactions across diverse biological contexts to enable the design of tissue-specific lactate-targeting therapeutic interventions; second, developing spatiotemporally resolved analytical techniques to identify predictive biomarkers that can distinguish between different ferroptotic responses; and third, leveraging advanced imaging technologies, metabolomics approaches and novel biosensors to provide essential tools for tracking lactate-ferroptosis dynamics *in vivo*.

In conclusion, the lactate-ferroptosis network represents a sophisticated cellular regulatory mechanism that integrates metabolic status with cell fate determination. Translating these mechanistic insights into targeted therapeutic strategies across diverse disease contexts, from cancer to neurodegeneration, constitutes a pivotal future challenge, requiring interdisciplinary collaboration and innovative experimental approaches.

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QY and HY discussed the structure of the article and completed the manuscript; YK, JH and LY provided technical and material support and completed the manuscript. XL provided suggestions for revision. All authors read and approved the final version of the manuscript. Data authentication is 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, artificial intelligence tools (Claude 4.5 Sonnet) to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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