

Targeting Lactylation Offers Therapy to Reverse Cell Death Resistance

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Abstract: Lactylation, a lactate-derived post-translational modification, emerges as a master metabolic regulator of resistance to regulated cell death (RCD) across pathologies including cancer, inflammatory disorders, and degenerative diseases. By dynamically modifying histones and non-histone proteins via lacyltransferases and delactylases, lactylation orchestrates convergent molecular pathways that suppress ferroptosis, cuproptosis, and apoptosis. This review synthesizes current understanding of lactylation as a central regulator of RCD resistance in diseases, especially in cancers. We dissect the molecular machinery through which lactylation subverts ferroptosis, cuproptosis, and apoptosis; evaluate its pathophysiological implications in diverse pathologies; and discuss emerging therapeutic strategies to disrupt lactylation-mediated cell death evasion. This metabolic-epigenetic crosstalk establishes a robust shield against RCD in disease microenvironments, promoting therapeutic resistance and pathological resilience. Targeting lactylation regulators (writers/erasers) or combining lactate modulation with RCD inducers represents a promising strategy to overcome treatment-refractory conditions in cancers.

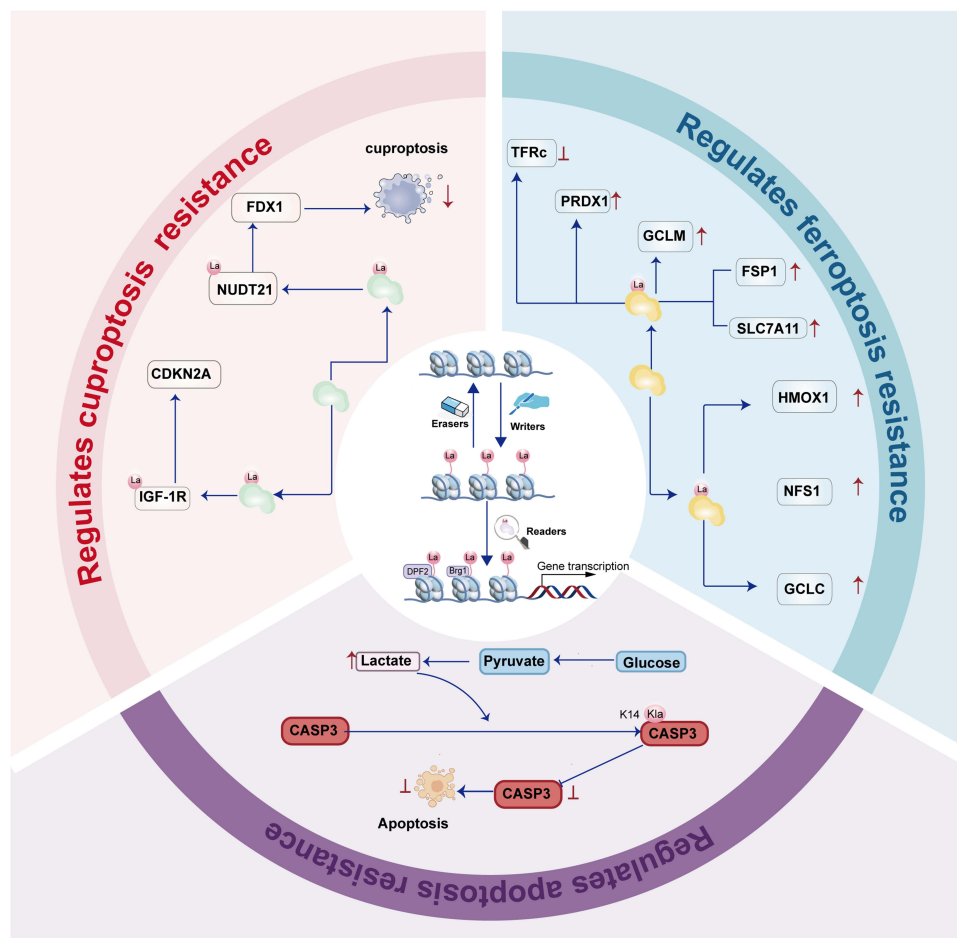
Keywords: lactylation, regulated cell death, ferroptosis, cuproptosis, apoptosis

Introduction

Metabolic reprogramming is a fundamental hallmark of diverse pathological states, driving the accumulation of metabolites like lactate that serve as precursors for novel post-translational modifications. Among these, lysine lactylation (Kla)—a lactate-derived epigenetic mark initially identified in macrophages—has emerged as a critical regulator of gene expression beyond immunomodulation. Elevated lactate levels, characteristic of inflammatory microenvironments, ischemic tissues, and metabolic disorders, provide the substrate for enzymatic lactylation catalyzed by acyltransferases such as p300 and KAT7. This modification directly links cellular metabolism to epigenetic and non-epigenetic reprogramming, enabling context-dependent adaptations in disease progression. Crucially, lactylation's influence extends to the regulation of fundamental cell death pathways, where it orchestrates resistance mechanisms that compromise tissue homeostasis and promote pathological resilience across cancer, neurodegenerative conditions, ischemic injuries, and autoimmune diseases.

The dysregulation of regulated cell death (RCD) pathways—including apoptosis, ferroptosis, and copper-dependent cuproptosis—represents a pivotal mechanism underlying treatment resistance and disease exacerbation. Ferroptosis, driven by iron-dependent lipid peroxidation, contributes to neurodegeneration, ischemia-reperfusion injury, and organ dysfunction; cuproptosis, mediated by mitochondrial copper toxicity, influences metabolic diseases and metal homeostasis disorders; while defective apoptosis underlies autoimmune pathologies and developmental abnormalities. Resistance to these RCD modalities

Graphical Abstract



enables pathological cell survival, fostering chronic inflammation, irreversible tissue damage, and therapeutic failure across multiple disease contexts.^{1–6} Emerging evidence reveals that lactylation subverts RCD execution through convergent molecular strategies: it epigenetically silences pro-death genes, stabilizes antioxidant transcripts via RNA methylation, enhances radical-trapping capacity, and disrupts metal ion homeostasis. By hijacking these effector mechanisms, lactylation establishes a robust shield against cellular demise in disease-perturbed environments.^{5,7,8}

Specifically, lactylation universally enables RCD evasion by rewiring cellular machinery: In ferroptosis, it upregulates glutathione synthesis via GCLM/GCLC lactylation,^{9,10} activates NRF2 through PRDX1 modification,¹¹ and reduces iron availability via histone-driven NFS1 expression.¹² For cuproptosis, lactylation of IGF-1R stabilizes the suppressor CDKN2A,¹³ while NUDT21 lactylation destabilizes FDX1 mRNA to disable copper toxicity.¹⁴ In apoptosis, caspase-3 lactylation directly impedes proteolytic activation.¹⁵ These findings position lactylation as a master metabolic switch that rewires epigenetic landscapes, metabolic fluxes, and stress-response networks to sustain pathological cell survival. Despite these advances, key knowledge gaps persist regarding tissue-specific “writer” enzymes, lactylation crosstalk with other PTMs, and context-dependent target selectivity dictating RCD sensitivity.^{16,17}

This review synthesizes current understanding of lactylation as a central regulator of RCD resistance across disease states. We dissect the molecular machinery through which lactylation subverts ferroptosis, cuproptosis, and apoptosis; evaluate its pathophysiological implications in diverse pathologies; and discuss emerging therapeutic strategies to disrupt

lactylation-mediated cell death evasion. By integrating advances in lactylome profiling, RCD modulation, and metabolic targeting, we aim to establish a unified framework for overcoming lactylation-driven resistance in refractory diseases.

Core Mechanisms of Lysine Lactylation

Similar to other PTMs, the protein lactylation process is a dynamic and reversible modification regulated by three types of enzymes: lactyltransferases (“writers”), delactylases (“erasers”), and lactylation binding proteins (“readers”) ^{10,17–22} (Figure 1 and Table 1). We define the enzymes mediating protein lactylation as lactylation regulators. Writers catalyze the addition of lactoyl groups (or lactyl moiety) to lysine residues on both histone and non-histone target proteins, while erasers remove these lactoyl modifications. Readers recognize lactylated proteins and translate this modification into diverse cellular functions by modulating downstream signaling pathways. ²³ Collectively, these enzymatic systems establish a sophisticated mechanism for the precise regulation of KLa, functioning as critical epigenetic regulators. ¹⁰

Writers

Current evidence indicates that typical lactylation writers, or lactyltransferases, are derived from lysine acetyltransferase (KAT) family enzymes. While these enzymes primarily catalyze lysine acetylation, recent research demonstrates their

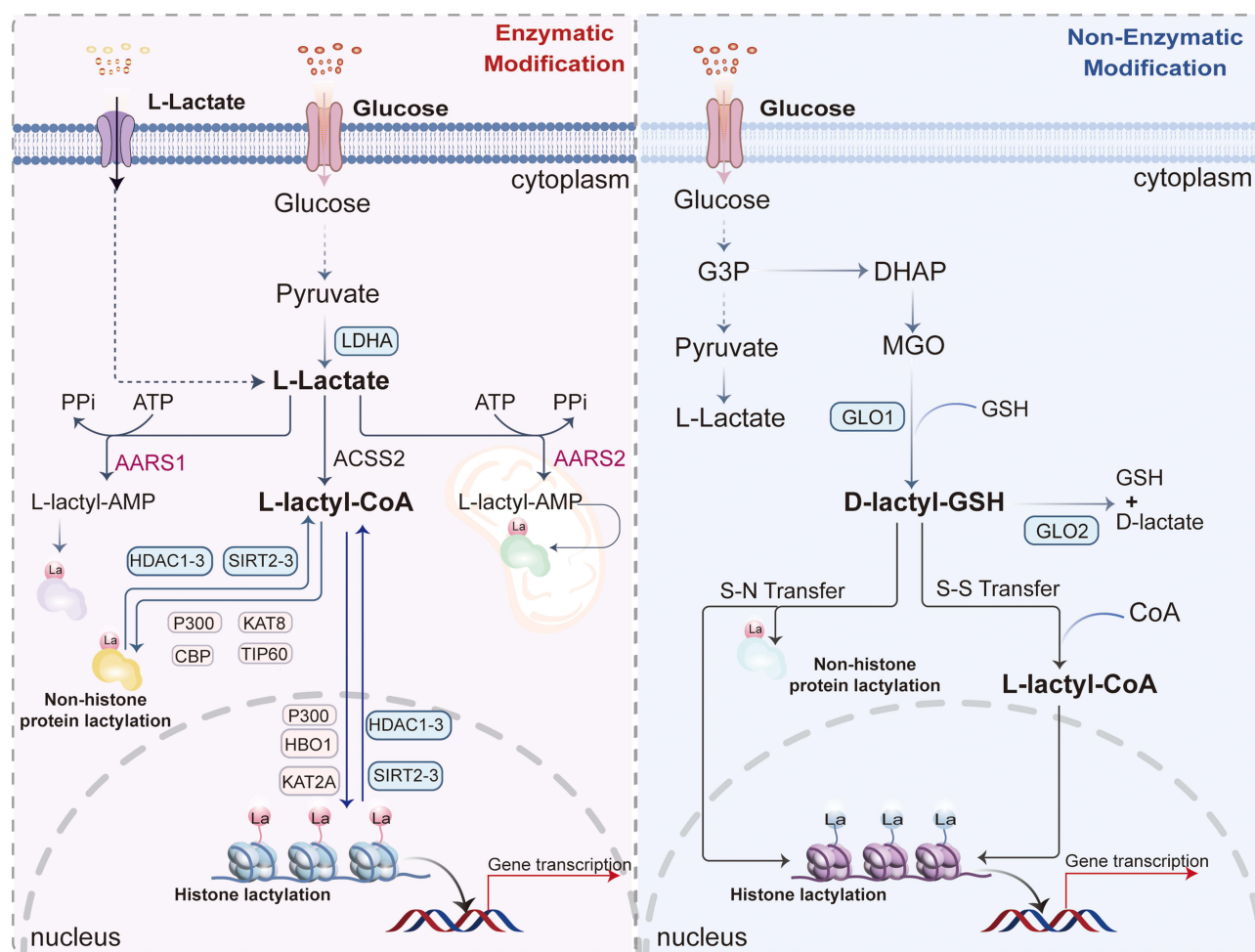


Figure 1 Core mechanisms of lactylation modification on histones and nonhistone proteins, including lactyl moiety sources and involved enzymes. Lactylation occurs via enzymatic reactions—mediated by diverse enzymes within the nucleus, cytoplasm, and mitochondrial matrix—or non-enzymatic reactions in the cytoplasm. Endogenous/exogenous L-lactate converts to L-lactyl-CoA, providing the L-lactyl moiety (La) for lysine lactylation (KLa) on target proteins. Identified KLa writers include acetyltransferases (p300, CBP, KAT8, KAT2A, TIP60, KAT7), while erasers comprise deacetylases (HDAC1-3, SIRT2-3). Alternatively, the glyoxalase intermediate S-D-lactylglutathione (D-lactyl-GSH) serves as a source for non-enzymatic D-lactyl group transfer to lysine residues. Parallel mechanisms include: AARS1/2 lactyltransferases catalyzing La transfer via L-lactyl-AMP complexes; and glyceraldehyde-3-phosphate (G3P) accumulation (following PKM2 inhibition) driving non-enzymatic S-lactylation of KEAP1 cysteine residues, thereby activating NRF2.

Table I The Function of Lysine Lactylation Regulator Proteins²⁴

Types	Lac Regulator	Full Names	Type	Localization	Modification Site	Reaction Substrate	Function	Ref
Writers	p300	–	KAT	Nucleus	H3K91a, H3K181a and H4K121a	Lactyl-CoA	Directly stimulate gene transcription	[25]
	GCN5 (KAT2A)	General control non-depressible 5 (Lysine acetyltransferase 2A)	KAT	Nucleus	H3K181a; H4K121a; H3K141a	Lactyl-CoA	Acetyltransferase	[16,26]
	CBP (KAT3A)	CREB-binding protein	KAT	Nucleus	K6731a	Lactyl-CoA	Acetyltransferase	[27,28]
	Tip60 (KAT5)	Tat-interacting protein 60 (Lysine acetyltransferase 5)	KAT	Nucleus	K388/K3561a	Lactyl-CoA	Acetyltransferase	[29,30]
	HBO1 (KAT7)	Histone acetyltransferase binding to ORC1 (Lysine acetyltransferase 7)	KAT	Nucleus	H3K91a	Lactyl-CoA	Acetyltransferase	[29]
	MOF (KAT8)	Lysine acetyltransferase 8	KAT	Nucleus	K4081a	Lactyl-CoA	Acetyltransferase	[31,32]
	NAA10	N-alpha-acetyltransferase 10	KAT	Nucleus	K5081a	Lactyl-CoA	Acetyltransferase	[33]
	AARS1	Alanyl-tRNA synthetase 1	Non-classical lactyltransferase	Cytoplasm	K90/K1081a; K120/K1391a	L-lactate	Converting L-lactate to L-lactyl-AMP	[34–36]
	AARS2	Alanyl-tRNA synthetase 2	Non-classical lactyltransferase	Mitochondrion matrix	K336/K4571a	L-lactate	Converting L-lactate to L-lactyl-AMP	[37]
	ACSS2	Acetyl-CoA Synthetase 2		Nucleus	Converting L-lactate to L-lactyl-CoA	Lactate	ERK-mediated phosphorylation of ACSS2 translocates to the nucleus to forms a complex with KAT2A, acting as a lactyltransferase, converting L-lactate to L-lactyl-CoA	[26]
Erasers	GTPSCS	Guanosine triphosphate -specific SCS	–	Nucleus	H3K181a	Lactate	Lactyl-CoA synthetase	[38]
	SIRT1	Sirtuin 1	Class 3 HDACs	Nucleus and cytoplasm	K2281a; K2071a; K18971a	–	NAD-dependent protein deacetylase sirtuin-1	[24,39,40]
	SIRT2	Sirtuin 2	Class 3 HDACs	Nucleus and cytoplasm	H3K181a, H4K81a, and H4K121a	–	–	[41,42]
	SIRT3	Sirtuin 3	Class 3 HDACs	Mitochondrion matrix	H4K161a; K348; K2281a;	–	NAD-dependent protein deacetylase	[39,43,44]
	SIRT3	Sirtuin 3	Class 3 HDACs	Mitochondrion matrix	H3K91a	–	Modulate gene transcription	[45]
	HDAC1	Histone deacetylases 1	Class I HDACs	Nucleus	H3K18, H4K5	–	Removes acetyl groups from histones	[46]
	HDAC2	Histone deacetylases 2	Class I HDACs	Nucleus and cytoplasm	H3K18, H4K5	–	Removing acetyl groups from histones	[46–48]
	HDAC3	Histone deacetylases 3	Class I HDACs	Nucleus and cytoplasm	H3K18, H4K5, K388	–	Class I histone deacetylases	[29,46,48]
Readers	HDAC8	Histone deacetylases 8	Class I HDACs	Nucleus and cytoplasm		–	–	[48]
	Brg1 (SMARCA4)	Brahma related gene 1 (SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4)	BD containing protein	Nucleus	H3K181a	–	Core component of the SWI/SNF chromatin remodeling complex	[49]
	DPF2	Decreased expression in fat 2	–	Nucleus	H3K141a	–	Modifying chromatin structure and control cell proliferation and differentiation	[50]

capacity to also mediate lysine lactylation (Kla). To date, the identified lactylation writers include, including p300 (lysine acetyltransferase 3B, KAT3B),²⁵ general control non-depressible 5 (GCN5; also named as lysine acetyltransferase 2A [KAT2A]),¹⁶ CREB-binding protein (CBP; also named as lysine acetyltransferase 3A[KAT3A]),²⁷ Tat-interacting protein 60 (Tip60; also named as lysine acetyltransferase 5[KAT5]),²⁹ histone acetyltransferase binding to ORC1 (HBO1; also named as lysine acetyltransferase 7[KAT7]),²⁹ males absent on the first (MOF; also named as lysine acetyltransferase 8 [KAT8]),³² and N-alpha-acetyltransferase 10 (NAA10).³³ Recent studies have been identified as a non-classical lactyltransferase, ie alanyl-tRNA synthetase 1/2 (AARS1/2), which directly utilize lactate as a lactyl group donor to catalyze Kla.^{34–36} The detailed role of these lactylation writers refer to recent excellent review.²³

Erasers

The histone deacetylases (HDACs) and sirtuins (SIRT) were originally associated with lysine residues deacetylation of lysine residues and have been revealed to implicate in regulating protein deacylases.²³ Several isozymes of histone deacetylases (HDACs) and sirtuins (SIRT) were identified as erasers, which catalyze the removal of other lysine acylations.²³ The erasers from HDACs include HDAC1,⁴⁶ HDAC2,^{46–48} HDAC3,^{29,46,48} and HDAC8.⁴⁸ The erasers from SIRT include SIRT1,^{24,39,40} SIRT2^{41,42} and SIRT3.^{39,43,44} The detailed role of these lactylation writers refer to recent excellent review.²³

Readers

Research on Kla-specific “readers” remains an emerging field with limited progress. To date, only a few readers have been identified, including brahma-related gene-1 (BRG1)⁴⁹ and decreased expression in fat 2 (DPF2).⁵⁰ BRG1 functions as a reader of H3K18la[31], while DPF2 recognizes H3K14la to modify chromatin structure and control cell proliferation and differentiation.⁵⁰ Currently, protein lactylation readers have not been unambiguously identified, and distinguishing their specific roles in lysine acetylation versus lactylation constitutes an ongoing research challenge.

Mitochondrial Influence on Lactylation and Cell Death Regulation

Beyond its well-established role as a product of cytoplasmic glycolysis, lactate production and its subsequent utilization for lactylation are intimately linked to mitochondrial function, creating a bidirectional regulatory axis that profoundly influences cell death susceptibility. Mitochondria themselves can contribute to the lactate pool. The mitochondrial lactate dehydrogenase (mLDHA) complex facilitates the conversion of pyruvate to lactate within the organelle, particularly under conditions of impaired electron transport chain (ETC) function or hypoxia.^{51,52} This mitochondrial-derived lactate can then contribute to both intra-mitochondrial and nuclear lactylation events. Furthermore, mitochondrial metabolism dictates the availability of key metabolites that influence lactylation. For instance, inhibition of the mitochondrial pyruvate carrier (MPC) reduces mitochondrial pyruvate import, potentially shunting pyruvate towards lactate production in the cytoplasm, thereby increasing the substrate for lactylation.⁵³

Crucially, lactylation directly targets a repertoire of mitochondrial proteins, thereby directly intervening in cell death pathways. As detailed in Non-Histone Lactylation Regulates Resistance to Cuproptosis, the core executor of cuproptosis, FDX1, is a mitochondrial protein, and its regulation via NUDT21 lactylation indirectly impacts mitochondrial copper toxicity.¹⁴ More directly, several mitochondrial enzymes and regulators are subject to lactylation, which can alter their function. For example, lactylation of the complex I subunit NDUFV1 has been shown to suppress its activity, leading to ETC dysfunction, increased ROS production, and altered apoptotic sensitivity.²⁸ Similarly, lactylation of the mitochondrial sirtuin SIRT3, a key deacetylase and delactylase, can impair its activity, leading to hyper-acetylation and hyper-lactylation of mitochondrial substrates, which disrupts oxidative metabolism and promotes a metabolic state resistant to certain cell death inducers.^{39,43} In the context of ferroptosis, mitochondrial lipid peroxidation is a key event, and lactylation-driven upregulation of NFS1, an iron-sulfur cluster biogenesis enzyme located in mitochondria, depletes the free iron necessary for propagating lipid peroxidation, thereby conferring resistance.¹²

This mitochondrial-lactylation axis creates a sophisticated feedback loop. Mitochondrial dysfunction (eg, ETC impairment, ROS overproduction) can promote lactate generation and subsequent lactylation. This lactylation, in turn, can either exacerbate mitochondrial dysfunction (eg, via NDUFV1 lactylation) or initiate adaptive survival programs (eg, via NFS1 upregulation or SIRT3 inhibition) that ultimately dictate cellular fate by modulating the threshold for

ferroptosis, cuproptosis, and apoptosis. Therefore, the mitochondrial influence on lactylation represents a fundamental layer of metabolic-epigenetic crosstalk that fine-tunes cellular stress responses and death signaling, emphasizing the need to consider the organelle's role for a fully integrated understanding of lactylation in pathophysiology.

Regulated Cell Death

Core Mechanism of Ferroptosis

Ferroptosis is a non-apoptotic, regulated cell death mechanism characterized by iron-dependent lipid peroxidation (LPO) and compromised antioxidant defenses^{1,3,6,54–56} (Figure 2). This process culminates in plasma membrane rupture driven by iron accumulation and lethal LPO,⁵⁷ with its induction precisely regulated through the balance of pro-ferroptotic factors and cellular defense systems mediated by specific inducers and inhibitors.² Core triggers include inhibition of the SLC7A11-GSH-GPX4 axis and intracellular free iron overload.^{58–60} Iron catalyzes LPO through both enzymatic and non-enzymatic pathways: non-enzymatically via Fe^{2+} -mediated Fenton reactions that convert H_2O_2 to hydroxyl radicals, initiating peroxidation of polyunsaturated fatty acid phospholipids (PUFA-PLs); enzymatically through Fe^{2+} acting as a cofactor for ALOXs/POR, oxidizing ACSL4-esterified and LPCAT3-incorporated PUFA-PLs into peroxidized

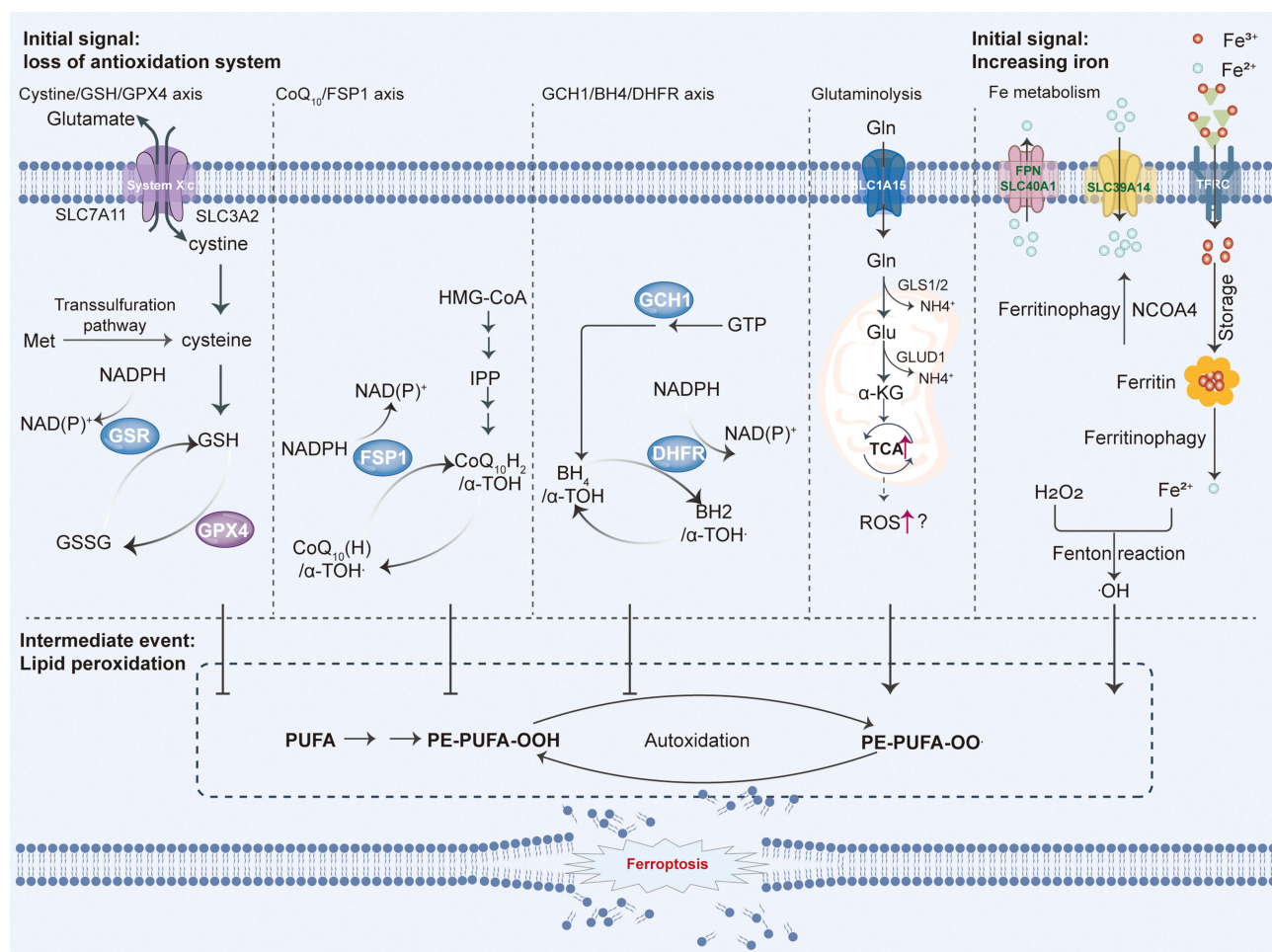


Figure 2 Core mechanisms of ferroptosis. Ferroptosis is initiated by iron-dependent peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids (PUFA-PLs). When pro-ferroptotic drivers—including PUFA-PL synthesis/peroxidation and dysregulated iron metabolism—overwhelm cellular antioxidant defenses, lethal accumulation of lipid peroxides ruptures cellular membranes, triggering ferroptotic cell death. Cells counteract ferroptosis through four major defense systems that detoxify lipid peroxides: the GPX4/xCT system (cytosolic and mitochondrial GPX4 isoforms); the FSP1/CoQ₁₀ system (plasma membrane); the DHODH/CoQ₁₀ system (mitochondria); the GCH1/BH₄ system. Mechanistically, ACSL4 and LPCAT3 mediate PUFA-PL synthesis, rendering membranes susceptible to peroxidation via enzymatic (eg, ALOXs, POR) and non-enzymatic (iron-dependent Fenton reaction) pathways. Iron further amplifies peroxidation as a cofactor for lipoxygenases. Ferroptosis ensues when pro-ferroptotic forces exceed the detoxification capacity of these defense systems, culminating in membrane-disrupting lipid peroxide accumulation and cell death.

derivatives (PUFA-PL-OOH).^{2,59,61–68} Critically, iron's redox activity enables radical propagation, as Fe^{2+} reacts with PUFA-PL-OOH to generate new radicals that perpetuate chain reactions.⁶⁹

Expansion of the labile iron pool is further driven by mechanisms such as ferritinophagy—a selective autophagic process that degrades ferritin to release stored iron—and enhanced mitochondrial Fe^{2+} transport, which amplifies iron availability for peroxidation reactions within mitochondria.^{66,70–75} Cellular susceptibility to ferroptosis is heightened by ferroportin suppression, ferritinophagy, increased transferrin uptake, or dysregulated mitochondrial iron handling. Cellular defenses against ferroptosis encompass both GPX4-dependent (GSH-reliant) and GPX4-independent systems, including the FSP1–CoQ₁₀, GCH1–BH₄, DHODH–CoQH₂, MBOAT1/2–MUFA, and SC5D–7–DHC axes that neutralize lipid peroxides. Given its mechanistic complexity and significant disease implications, ferroptosis represents a promising therapeutic target.^{24,76–85}

Cuproptosis

Tsvetkov et al in 2022 introduced the concept of cuproptosis.⁴ Prior research had established several key findings regarding copper's role in cell death: disulfiram (DSF) exhibits anticancer activity;⁸⁶ copper itself can induce cell death⁸⁷ and accelerate cancer cell death,⁸⁸ copper-based compounds induce cell death,⁸⁶ copper triggers non-apoptotic programmed cancer cell death,⁸⁶ elesclomol induces cancer cell apoptosis⁸⁶ by selectively transporting copper to mitochondria to kill cells;⁸⁹ copper enhances the anti-tumor activity of disulfiram;⁸⁶ and ferredoxin 1 (FDX1) and lipoyl synthase (LIAS) were identified as key regulators of copper toxicity.⁹⁰ These major findings on copper-induced cell death provided the foundation for understanding cuproptosis.

Cuproptosis represents a distinct form of cell death, differing mechanistically from necroptosis, apoptosis, pyroptosis, and ferroptosis (Figure 3). Copper, an essential micronutrient and trace metal,⁹¹ functions as a crucial structural and catalytic cofactor for numerous enzymes. It is indispensable for diverse biological processes—including biocompound synthesis, oxidative phosphorylation (OXPHOS), iron homeostasis, connective tissue cross-linking, reactive oxygen species (ROS) detoxification, and signal transmission—across nearly all organisms.^{92,93} However, copper can also be cytotoxic. Copper overload stimulates damaging ROS generation via copper-mediated Fenton reactions and disrupts iron-sulfur cofactors. Chronic copper exposure leads to toxicity, and elevated intracellular copper levels are implicated in various diseases, including cancer. Copper is also recognized as a crucial component for tumor growth and metastasis.⁹⁴

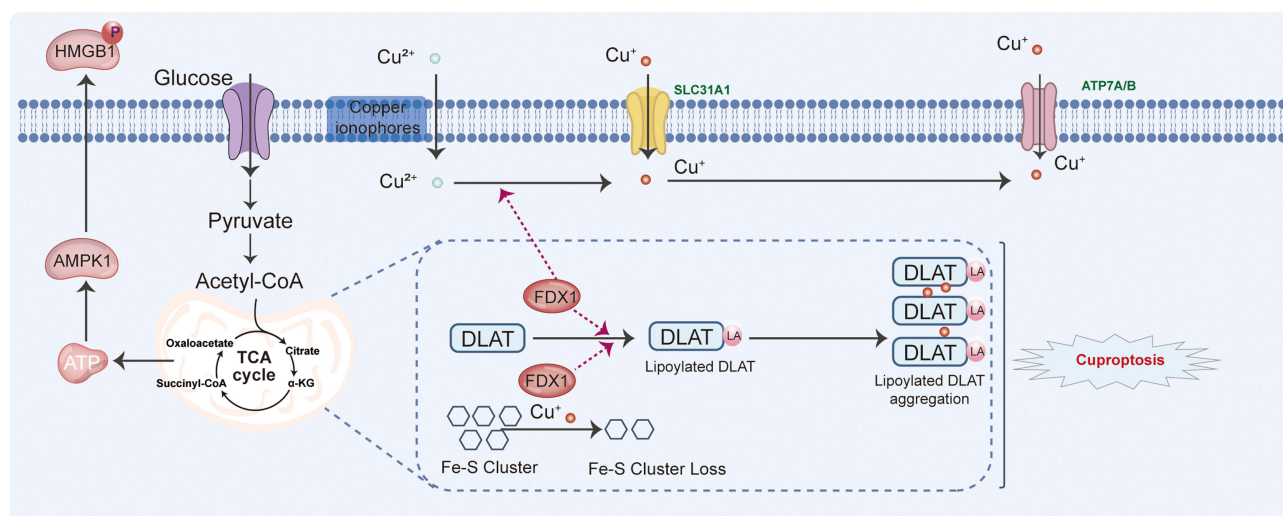


Figure 3 Core mechanisms of cuproptosis. Cuproptosis is initiated by the cellular uptake of Cu^{2+} , mediated by either the copper transporter SLC31A1 or copper ionophores. Intracellular Cu^{2+} selectively binds to lipoylated proteins within the tricarboxylic acid (TCA) cycle. This binding induces mitochondrial proteotoxic stress through two key events: copper-dependent oligomerization of the lipoylated proteins, and destabilization of iron-sulfur (Fe-S) cluster proteins. Together, these events lead to a toxic gain of function, ultimately resulting in cell death.

Abbreviations: ATP7B, ATPase copper transporting beta; DLAT, dihydrolipoamide S-acetyltransferase; FDX1, ferredoxin I; LA-DLAT, lipoylated DLAT; LIAS, lipoyl synthase; SLC31A1, solute carrier family 31 member 1; TCA, tricarboxylic acid.

Despite its importance, the precise molecular mechanisms underlying copper-induced toxicity and cell death remain elusive. Moreover, the known cellular machinery and enzymatic targets for copper do not fully explain cellular responses to copper toxicity. The discovery of cuproptosis emerged from efforts to understand how copper accumulation causes cellular toxicity.⁹⁰ Tsvetkov et al, in 2019, described copper-dependent death while investigating the anticancer mechanism of elesclomol (ES), a copper ionophore.⁹⁰ They demonstrated that ES sensitizes cancer cells to proteasome inhibitor-induced toxicity in a multiple myeloma mouse model. Mechanistically, ES-bound Cu^{2+} interacts with the mitochondrial enzyme ferredoxin 1 (FDX1), is reduced to Cu^+ , and consequently elevates ROS levels.^{90,95} Initial studies attributed ES lethality to lipid peroxidation.⁹⁶ Subsequently, in 2022, the same group formally named this unique copper-dependent cell death pathway “cuproptosis”, characterized by the aggregation of lipoylated mitochondrial enzymes and loss of iron-sulfur (Fe-S) cluster proteins.⁴ Tsvetkov et al’s study revealed that copper-induced toxicity involves the specific disruption of mitochondrial metabolic enzymes, significantly advancing our understanding of how copper overload impairs mitochondrial function.⁴ Excess intracellular Cu^{2+} can be delivered to mitochondria by ionophores. FDX1 then reduces Cu^{2+} to Cu^+ . The increased Cu^+ concentration directly binds to lipoylated dihydrolipoamide S-acetyltransferase (DLAT), causing aggregation of lipoylated proteins and destabilization of Fe-S cluster proteins. This leads to proteotoxic stress and ultimately, cuproptosis (Figure 4).⁴ Crucially, genetic or pharmacological inhibition of apoptosis, ferroptosis, and necroptosis failed to suppress ES-Cu complex-induced cell death across multiple cancer cell lines. Furthermore, other antioxidants, including N-acetylcysteine, α -tocopherol, ebselen, and JP4-039, could not rescue cells from ES-Cu-mediated growth inhibition, indicating that ROS (including mitochondrial ROS) are not required for cuproptosis. Interestingly, the hydrophilic antioxidant glutathione (GSH) inhibits ES-Cu-induced toxicity by chelating intracellular copper. These results strongly suggest that cuproptosis constitutes a novel cell death pathway distinct from previously identified mechanisms.⁴

Tsvetkov et al also established a strong link between mitochondrial metabolism and copper toxicity sensitivity. Lung cancer cells reliant on galactose-mediated mitochondrial respiration were nearly 1000-fold more sensitive to ES-Cu-induced growth inhibition than cells relying on glucose-induced glycolysis. Accordingly, inhibitors of mitochondrial respiration—rotenone and antimycin A (targeting complexes I and III, respectively), UK5099 (inhibiting mitochondrial pyruvate uptake), or genetic inhibition of complex I—all blocked cuproptosis. While ES-Cu did not affect basal or adenosine 5'-triphosphate (ATP)-linked respiration, hypoxia (1% O_2), which forces cells to rely on glycolysis rather than OXPHOS, reduced cancer cell sensitivity to cuproptosis. This metabolic dependency distinguishes cuproptosis from ferroptosis, which requires glucose uptake and pyruvate oxidation. Thus, cuproptosis and ferroptosis are associated with distinct alterations in energy metabolism and mitochondrial function. In summary, cuproptosis represents a novel form of regulated cell death that is copper-dependent, independent of oxidative stress, and initiated within the mitochondria.⁵

Apoptosis

The molecular machinery governing cell death was first characterized in *Caenorhabditis elegans*. Homologs of key *C. elegans* effector proteins—including caspases and BCL-2 family members—were subsequently identified in mammals. Mammalian apoptosis comprises two distinct pathways: extrinsic apoptosis, triggered by activation of plasma membrane-localized death receptors, and intrinsic apoptosis, which proceeds independently of death receptor signaling (Figure 4). These pathways diverge in their mechanisms for sensing and integrating apoptotic stimuli.⁹⁷

Intrinsic apoptosis is activated by cellular alterations including DNA damage, growth factor withdrawal, and mitochondrial damage (Figure 4). This pathway encompasses specialized forms such as anoikis, triggered by detachment from the extracellular matrix via loss of integrin-mediated adhesion.⁹⁸ The BCL-2 protein family serves as the principal upstream regulator of intrinsic apoptosis, with mammalian BCL-2—originally identified as an oncogene in follicular lymphomas with t(14;18) translocation—functioning as a survival promoter rather than a proliferation inducer.⁹⁹ Structurally defined by 1–4 BCL-2 homology (BH) domains,^{100,101} this family comprises both anti-apoptotic (eg, BCL-2, BCL-xL, MCL-1, BCL-W) and pro-apoptotic members, functionally analogous to the *C. elegans* CED-9/EGL-1 system.^{101,102} Elevated anti-apoptotic BCL-2 protein levels suppress apoptosis, and genetic ablation of these proteins causes lethality or severe developmental defects in mice,^{103–105} underscoring apoptosis’ essential role in development and homeostasis. BH domain-mediated interactions between pro- and anti-apoptotic members regulate

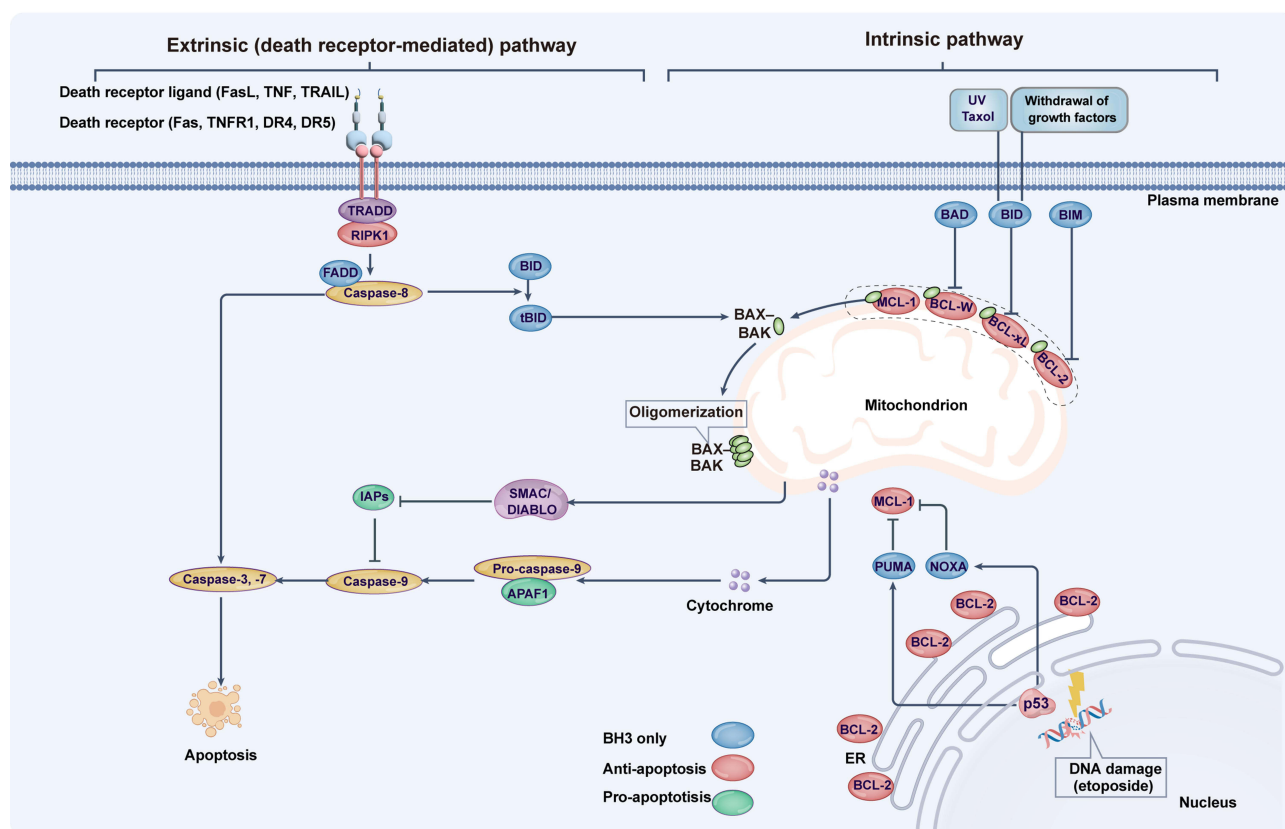


Figure 4 Core mechanisms of apoptosis. Extrinsic apoptosis (right) is triggered by the activation of plasma membrane death receptors—including TNFR1, Fas, and TRAIL receptors (DR4/DR5)—upon binding their cognate ligands (TNF, FasL, and TRAIL, respectively). In contrast, intrinsic apoptosis (left) can be initiated by growth factor withdrawal, mitochondrial or DNA damage, or chemotherapeutic agents like taxol. This pathway involves BH3-only BCL-2 family proteins (eg, p53-mediated transcriptional induction of NOXA/PUMA, post-translational modification of BAD /BIM, and caspase-8 cleavage of Bid), which neutralize pro-survival members (BCL-2, BCL-xL, MCL-1) and activate pro-death effectors BAX/BAK to oligomerize and disrupt mitochondria. Subsequent mitochondrial permeabilization releases cytochrome c and SMAC/DIABLO, driving APAF1-dependent caspase-9 activation. Caspase-9 then proteolytically processes executioner caspases-3 and -7 to execute apoptosis. These effector caspases further amplify the cascade through positive feedback activation of upstream caspases.

Abbreviations: ER, endoplasmic reticulum; UV, ultraviolet.

pathway activation. During cellular stress (DNA damage, oxidative stress, nutrient deprivation), transcriptional and post-translational activation of pro-apoptotic BCL-2 members—particularly BH3-only proteins (BIM, BID, BAD, NOXA, PUMA)—transduces death signals by neutralizing anti-apoptotic proteins while directly activating BAX/BAK. This triggers mitochondrial outer membrane permeabilization (Figure 4), releasing cytochrome c and SMAC/DIABLO to initiate caspase activation. Downstream, the APAF1 apoptosome (mammalian CED-4 homolog) activates caspase-9, which cleaves executioner caspases-3/7 to dismantle cellular structures.^{106–108} However, the traditional linear caspase cascade model requires refinement, as caspase-3/7 double-knockout delays mitochondrial damage and cell death,¹⁰⁹ suggesting apoptosis operates as a self-amplifying circular cascade.

Conventional cancer radiation therapies and chemotherapies rely on activating the intrinsic apoptosis pathway through DNA damage caused by agents like ionizing irradiation, etoposide, or taxol. However, research over the past decade has revealed significant redundancy in mammalian cell death mechanisms. Notably, cells or mice with double knockout of Bax and Bak ($Bax^{-/-}Bak1^{-/-}$) exhibit profound resistance to apoptosis,⁷ yet a small percentage of these mutant mice can still be born and survive for months.¹¹⁰ This observation strongly suggests that other cell death mechanisms may be activated or selected for in $Bax^{-/-}Bak1^{-/-}$ cells to eliminate unwanted cells when apoptosis fails during development. Furthermore, while DNA damage-induced cell death often proceeds through apoptosis by promoting mitochondrial damage and downstream caspase activation, it represents only part of the overall cell death response; severe DNA damage can also lead directly to cell death via mitotic catastrophe (discussed below). Consequently, when

the programmed cell death mechanism is blocked, the disruption of cellular homeostatic pro-survival mechanisms likely contributes to cell elimination in mammals.

Extrinsic apoptosis is initiated by the activation of plasma membrane-bound death receptors, characterized by an intracellular Death Domain (DD), such as Fas (CD95), TNFR1, TRAIL-R1 (DR4), and TRAIL-R2 (DR5), upon binding their cognate ligands.^{111,112} These pathways are clinically significant, as genetic defects in Fas or its ligand FasL cause autoimmune lymphoproliferative syndrome (ALPS) in humans—a rare autoimmune condition recapitulated in Fas- and FasL-deficient mouse models.^{113–116} During immune regulation, FasL expressed on activated T cells triggers apoptosis in target cells by engaging the Fas DD, thereby recruiting the adaptor protein FADD and activating caspase-8. Critically, ALPS-associated mutations in the Fas DD disrupt FADD recruitment and block caspase-8 activation, highlighting the indispensable role of caspase-8 in executing Fas-mediated extrinsic apoptosis.¹¹⁷

Lactylation Regulates Resistance to Regulated Cell Death

Lactylation Regulates Resistance to Ferroptosis

Lactylation functions as a master metabolic switch that universally enables ferroptosis resistance across malignancies. By hijacking histones, RNA modifiers, and antioxidant machinery, lactylation epigenetically activates cytoprotective genes, stabilizes key suppressors of lipid peroxidation, and rewires metabolic flux to synthesize radical-trapping molecules—collectively shielding cancer cells from iron-dependent death. Below, we dissect how lactylation of diverse substrates (H3K18, PRMT5, HDAC1, GCLM, SPRING, and others) orchestrates tissue-specific yet mechanistically convergent pathways to block ferroptosis execution, thereby sustaining tumor survival under therapeutic stress and microenvironmental challenges (Figure 5).

Histone Lactylation in Ferroptosis Resistance

Lactylation orchestrates ferroptosis resistance by hijacking m⁶A machinery through distinct mechanisms. Lactylation acts as a master switch that either activates m⁶A writers (METTL3) or inhibits m⁶A erasers (ALKBH5/FTO), driving hypermethylation of pro-survival transcripts (HIF1A, SLC7A11, FSP1). This m⁶A-dependent mRNA stabilization amplifies antioxidant (HMOX1), cystine transporter (SLC7A11), and radical-trapping (FSP1) pathways, collectively desensitizing cells to lipid peroxidation. Elevated histone lactylation, specifically H3K18la, in endometriotic stromal cells (EESCs) drives ferroptosis resistance by activating the METTL3-mediated HIF1A/HMOX1 signaling axis. Mechanistically, lactate accumulation from enhanced glycolysis promotes H3K18la enrichment at the METTL3 promoter, increasing METTL3 expression and m⁶A RNA modification; METTL3 stabilizes HIF1A mRNA via m⁶A methylation, leading to HIF1A-dependent transcriptional upregulation of the antioxidant gene HMOX1, which suppresses lethal lipid peroxidation.¹¹⁸ Consequently, inhibiting histone lactylation (via 2-DG) restores ferroptosis sensitivity by disrupting this pathway.¹¹⁸ In summary, histone lactylation epigenetically reinforces ferroptosis resistance by activating the METTL3/HIF1A/HMOX1 antioxidant axis to mitigate lipid peroxidation.¹¹⁸

Huang et al revealed that insufficient microwave ablation (IMWA) induces sublethal heat stress (HS) in hepatocellular carcinoma (HCC), triggering increased glycolysis and lactate accumulation. This lactate surge drives histone H3 lysine 18 lactylation (H3K18la).¹² Crucially, H3K18la enrichment at the promoter region epigenetically upregulates the expression of NFS1, a cysteine desulfurase essential for iron-sulfur cluster biosynthesis. Elevated NFS1 levels reduce intracellular free iron availability and subsequently suppress lipid peroxidation, the hallmark executioner of ferroptosis.¹² Consequently, this H3K18la-NFS1 axis confers significant resistance to ferroptosis in HCC cells, enabling their survival and promoting metastasis post-IMWA.¹² Knocking down NFS1 reverses this effect, increasing ferroptosis susceptibility and reducing metastasis. Furthermore, NFS1 deficiency synergizes with oxaliplatin (OXA) chemotherapy to enhance anti-tumor efficacy, partly by overcoming this ferroptosis resistance.¹² Histone lactylation (H3K18la) epigenetically upregulates NFS1 expression to reduce intracellular free iron and suppress lipid peroxidation, thereby conferring ferroptosis resistance in hepatocellular carcinoma¹² (Figure 5).

Histone lactylation, specifically at the H4K12 site (H4K12la), directly promotes chemoresistance in colorectal cancer stem cells (CCSCs) by inhibiting ferroptosis.¹¹⁹ Mechanistically, lactate-driven H4K12la, catalyzed by p300 and reversed by HDAC1, transcriptionally upregulates the expression of glutamate-cysteine ligase catalytic subunit (GCLC).¹¹⁹

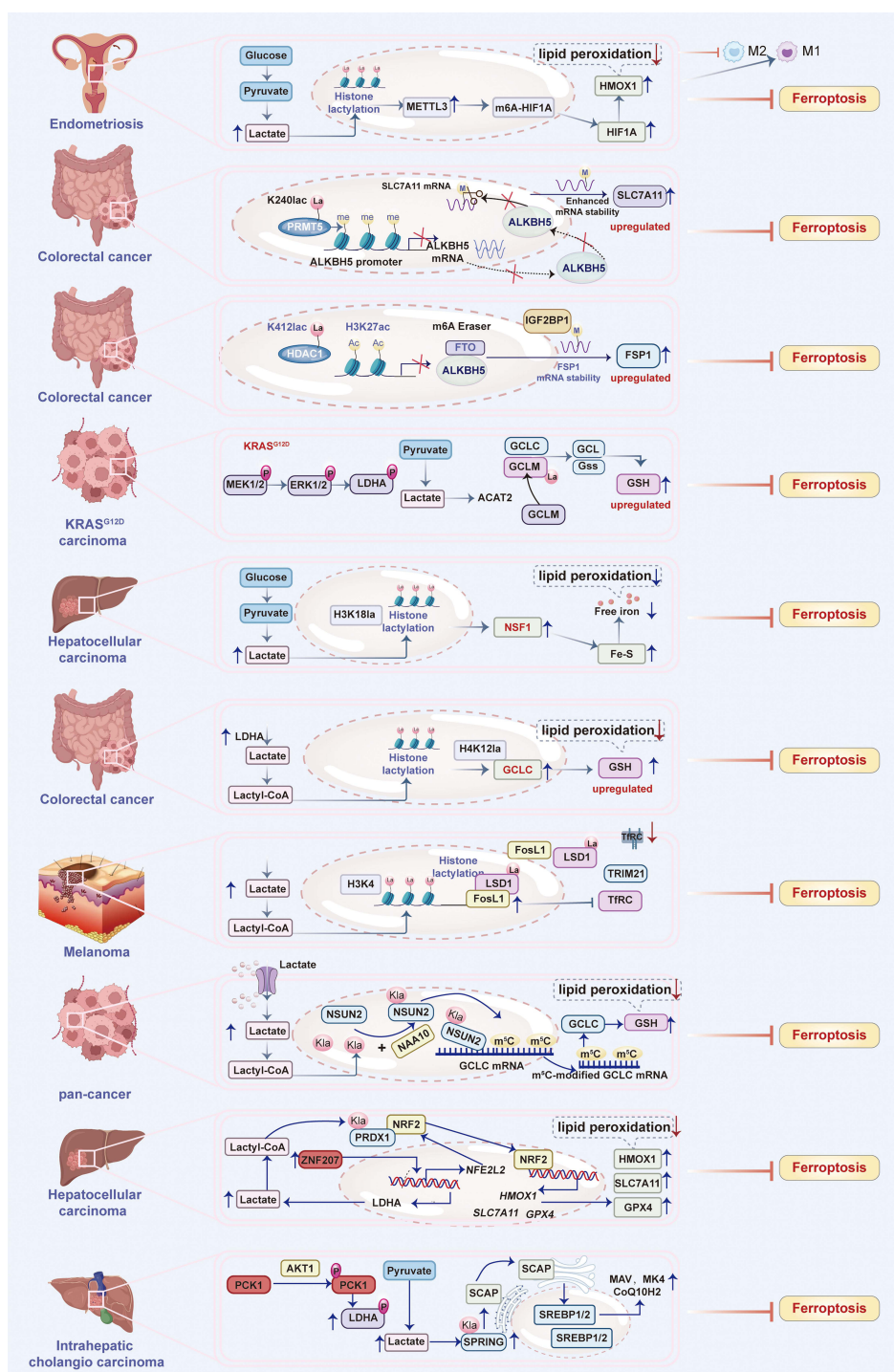


Figure 5 Lactylation regulates resistance to ferroptosis. Histone lactylation epigenetically reinforces ferroptosis resistance by activating the METTL3/HIF1A/HMOX1 antioxidant axis to mitigate lipid peroxidation in Endometriosis. Lactylation sustains ferroptosis resistance by enabling PRMT5 to epigenetically suppress ALKBH5 and stabilize SLC7A11 expression in colorectal cancer (CRC). Lactylation of HDAC1-K412la stabilizes FSP1 mRNA via m⁶A modification to confer ferroptosis resistance in CRC. Lactylation of GCLM by ACAT2 enhances GSH synthesis to scavenge lipid peroxides, directly enabling ferroptosis resistance in KRAS^{G12D}-driven cancer. Histone lactylation (H3K18la) epigenetically upregulates NFS1 expression to reduce intracellular free iron and suppress lipid peroxidation, thereby conferring ferroptosis resistance in hepatocellular carcinoma. Histone lactylation (H3K18la) epigenetically upregulates NFS1 expression to reduce intracellular free iron and suppress lipid peroxidation, thereby conferring ferroptosis resistance in hepatocellular carcinoma. Histone lactylation epigenetically activates GCLC to suppress ferroptosis, enabling chemoresistance in colorectal cancer stem cells. Histone lactylation epigenetically activates GCLC to suppress ferroptosis, enabling chemoresistance in colorectal cancer stem cells. Lactate-induced LSD1 epigenetically silences TFRC to inhibit ferroptosis, establishing a key mechanism of acquired resistance in melanoma. Lactylation confers ferroptosis resistance by activating the NSUN2-GCLC-GSH axis to suppress lethal lipid peroxidation. Lactate-induced NAA10-mediated lactylation of the RNA methyltransferase NSUN2 confers ferroptosis resistance by activating the GCLC-GSH axis to suppress lethal lipid peroxidation. Lactylation suppresses ferroptosis by enabling PRDX1-mediated activation of the NRF2 antioxidant pathway, promoting cancer cell survival under therapeutic stress. Lactylation of SPRING at K82, mediated by the pPCK1-pLDHA axis-induced lactate accumulation, activates the MVA pathway to synthesize radical-trapping antioxidants that suppress lipid peroxidation and confer ferroptosis resistance in AKT-hyperactivated intrahepatic cholangiocarcinoma (ICC).

Elevated GCLC enhances glutathione synthesis, thereby suppressing lipid peroxidation—the hallmark execution event of ferroptosis—and allowing CCSCs to survive chemotherapy-induced stress.¹¹⁹ Consequently, inhibition of the lactate-producing enzyme LDHA, the lactyltransferase p300, or GCLC itself (using BSO) restores ferroptosis sensitivity and overcomes chemoresistance.¹¹⁹ In summary, histone lactylation epigenetically activates GCLC to suppress ferroptosis, enabling chemoresistance in colorectal cancer stem cells¹¹⁹ (Figure 5).

Non-Histone Lactylation in Ferroptosis Resistance

Lactylation of the protein arginine methyltransferase PRMT5 at lysine 240 (PRMT5 K240lac) in colorectal cancer (CRC) cells promotes resistance to ferroptosis.¹²⁰ Mechanistically, lactylated PRMT5 represses transcription of the m⁶A demethylase ALKBH5 through histone modifications (H4R3me2s and H3R8me2s), which stabilizes SLC7A11 mRNA (encoding the cystine/glutamate antiporter xCT) and enhances its expression in an m⁶A-dependent manner.¹²⁰ Elevated SLC7A11 increases cystine uptake for glutathione synthesis, thereby suppressing lipid peroxidation and enabling CRC cells to evade ferroptosis.¹²⁰ Crucially, mutating the lactylation site (PRMT5 K240R) abolishes this protective effect. Lactylation sustains ferroptosis resistance by enabling PRMT5 to epigenetically suppress ALKBH5 and stabilize SLC7A11 expression¹²⁰ (Figure 5). Lactylation of HDAC1 at lysine 412 (HDAC1-K412la) drives ferroptosis resistance in colorectal cancer (CRC) by stabilizing the ferroptosis suppressor FSP1.¹²¹ Mechanistically, HDAC1-K412la enhances HDAC1-mediated suppression of the m⁶A erasers FTO and ALKBH5, leading to increased N⁶-methyladenosine (m⁶A) modification on FSP1 mRNA. This m⁶A enrichment recruits the reader protein IGF2BP1, which stabilizes FSP1 mRNA and boosts FSP1 protein expression, thereby inhibiting lipid peroxidation and ferroptosis.¹²¹ Critically, HDAC inhibitors (HDACi) like SAHA and TSA reduce HDAC1-K412la lactylation, destabilize FSP1 mRNA, and sensitize CRC to ferroptosis inducers.¹²¹ Lactylation of HDAC1-K412la stabilizes FSP1 mRNA via m⁶A modification to confer ferroptosis resistance in colorectal cancer¹²¹ (Figure 5). In conclusion, lactylation converges on m⁶A RNA modification to epigenetically and post-transcriptionally fortify antioxidant defenses, establishing a robust axis of ferroptosis resistance that spans histone, enzyme, and metabolic regulation. Critical gaps include how lactylation precisely recruits m⁶A regulators (eg, tissue-specific lactyltransferases targeting METTL3 vs PRMT5/HDAC1), whether lactylation-m⁶A crosstalk extends to other ferroptosis drivers (eg, GPX4, ACSL4), and if m⁶A readers (eg, YTHDFs) cooperate with lactylation to fine-tune mRNA stability. Future studies should: Develop dual-targeting inhibitors (eg, blocking lactyltransferases + m⁶A writers/readers); Map lactylation-m⁶A interactomes across cancer types to identify context-specific vulnerabilities; Explore lactate modulation (eg, LDHA inhibition) combined with m⁶A eraser activators to resensitize therapy-resistant tumors.

The oncogenic KRAS^{G12D} mutation drives lactate overproduction via MEK/ERK-mediated phosphorylation of LDHA, establishing a lactate-rich tumor microenvironment.⁹ Elevated lactate levels promote lactylation of the glutamate-cysteine ligase modifier subunit (GCLM) at lysine 34 (K34), catalyzed by the acetyltransferase ACAT2.⁹ GCLM lactylation enhances its interaction with the catalytic subunit GCLC, boosting glutamate-cysteine ligase (GCL) enzymatic activity. This increases glutathione (GSH) synthesis, which potently suppresses lipid peroxidation—a key executor of ferroptosis—thereby conferring resistance to ferroptosis inducers (eg, erastin, RSL3).⁹ Inhibition of ACAT2 or mutation of the GCLM K34 lactylation site ablates this protective effect, sensitizing KRAS^{G12D}-mutant cancers to ferroptosis. In summary, lactylation of GCLM by ACAT2 enhances GSH synthesis to scavenge lipid peroxides, directly enabling ferroptosis resistance in KRAS^{G12D}-driven cancers⁹ (Figure 5).

Li et al revealed that lactate accumulation in BRAF/MEK inhibitor (BRAFi/MEKi)-resistant melanoma drives lysine lactylation of the epigenetic regulator LSD1 at K503. Lactylated LSD1 forms a stable complex with the transcription factor FosL1, which recruits the LSD1/FosL1 complex to the promoter of the transferrin receptor gene TFRC.¹²² This recruitment facilitates LSD1-mediated demethylation of H3K4me2, leading to transcriptional repression of TFRC.¹²² Consequently, reduced TFRC expression diminishes cellular iron uptake, thereby suppressing ferroptosis—a critical vulnerability in therapy-resistant cells. Inhibition of LSD1 reverses TFRC repression, reactivates iron-dependent ferroptosis, and synergizes with anti-PD-1 immunotherapy to overcome resistance.¹²² Thus, lactate-induced LSD1 lactylation epigenetically silences TFRC to inhibit ferroptosis, establishing a key mechanism of acquired resistance in melanoma¹²² (Figure 5).

Niu et al showed that lactate-mediated lactylation of the RNA methyltransferase NSUN2 at lysine 508, catalyzed by the lactyltransferase NAA10, enhances NSUN2's enzymatic activity.³³ This activated NSUN2 specifically targets glutamate-cysteine ligase catalytic subunit (GCLC) mRNA, promoting m⁵C methylation at key cytosine sites (C13, C81, C972, C1135, C1136) which stabilizes GCLC mRNA and increases its expression.³³ Elevated GCLC protein boosts glutathione (GSH) synthesis, reducing lipid peroxidation and enabling cancer cells to resist ferroptosis induced by agents like doxorubicin (Dox) or RSL3 in an acidic tumor microenvironment. Lactylation confers ferroptosis resistance by activating the NSUN2-GCLC-GSH axis to suppress lethal lipid peroxidation³³ (Figure 5).

Lactylation of the antioxidant protein PRDX1 at lysine 67 (K67), driven by the transcription factor ZNF207, activates the NRF2 signaling pathway to suppress ferroptosis and confer resistance to the drug regorafenib in hepatocellular carcinoma (HCC).¹¹ Specifically, ZNF207 upregulates lactate production and lactate dehydrogenase A (LDHA), increasing intracellular lactate levels that catalyze PRDX1 lactylation.¹¹ Lactylated PRDX1 then facilitates NRF2 nuclear translocation and transcriptional activation of key antioxidant/ferroptosis-suppressing genes (SLC7A11, GPX4, HMOX1), thereby inhibiting lipid peroxidation and iron-dependent cell death.¹¹ Disrupting ZNF207, PRDX1 lactylation, or NRF2 activity restores ferroptosis sensitivity and overcomes regorafenib resistance.¹¹ In summary, lactylation suppresses ferroptosis by enabling PRDX1-mediated activation of the NRF2 antioxidant pathway, promoting cancer cell survival under therapeutic stress¹¹ (Figure 5).

Zhu et al identified a critical axis (pPCK1-pLDHA-SPRINGlac) linking lactylation to ferroptosis resistance in AKT-hyperactivated intrahepatic cholangiocarcinoma (ICC).¹²³ Phosphorylated PCK1 (pPCK1), driven by AKT hyperactivation, binds and phosphorylates LDHA at T248, enhancing glycolytic flux and lactate production. Elevated lactate activates KAT7, an acyltransferase that catalyzes lactylation of SPRING at K82 (SPRING lac).¹²³ This lactylation event promotes retrograde transport of SCAP from the Golgi to the endoplasmic reticulum, facilitating SREBP2 translocation to the nucleus and subsequent upregulation of the mevalonate (MVA) pathway.¹²³ The MVA pathway boosts synthesis of radical-trapping antioxidants (CoQ10H₂ and menaquinone-4), which suppress lipid peroxidation and confer ferroptosis resistance. Disrupting this axis—via SPRING K82R mutation (lactylation-deficient) or simvastatin (MVA inhibitor)—sensitizes ICC cells to ferroptosis and overcomes chemo-immunotherapy resistance.¹²³ In summary, lactylation of SPRING at K82, mediated by the pPCK1-pLDHA axis-induced lactate accumulation, activates the MVA pathway to synthesize radical-trapping antioxidants that suppress lipid peroxidation and confer ferroptosis resistance in AKT-hyperactivated ICC¹²³ (Figure 5).

Lactylation drives ferroptosis resistance across cancers via diverse mechanisms, i.e. epigenetic regulation, enzyme modulation, metabolic adaptation, and iron homeostasis. Histone lactylation (H3K18la, H4K12la) upregulates antioxidant genes (HMOX1, GCLC, NFS1) to suppress lipid peroxidation. Lactylation of PRMT5, HDAC1, and NSUN2 stabilizes ferroptosis suppressors (SLC7A11, FSP1, GCLC) via RNA methylation or epigenetic silencing. Lactylation of metabolic enzymes (GCLM, PRDX1, SPRING) enhances glutathione synthesis, activates NRF2 signaling, or boosts mevalonate pathway-derived antioxidants (CoQ10H₂), directly scavenging lipid peroxides. LSD1 lactylation represses TFRC to limit iron uptake, while NFS1 upregulation depletes free iron, jointly inhibiting ferroptosis execution. Key unresolved questions include the structural basis for lactylation's target specificity (eg, why H3K18la dominates in some cancers vs *PRMT5-K240lac* in others), the role of tissue-specific “writer/eraser” enzymes (eg, ACAT2 for GCLM vs KAT7 for SPRING), and whether lactylation cross-talks with other PTMs (eg, phosphorylation, acetylation) to fine-tune ferroptosis sensitivity. Future research should develop isoform-specific lactyltransferase inhibitors (eg, targeting KAT7, ACAT2, NAA10) to disrupt lactylation-driven antioxidant pathways; Map lactylomes in therapy-resistant tumors to identify novel targets; Explore lactate depletion (via LDHA inhibition) combined with ferroptosis inducers (eg, GPX4 inhibitors) in in vivo models; Investigate lactylation's role in regulating iron-sulfur cluster biogenesis (NFS1) and iron transport (TFRC) beyond antioxidant synthesis.

Non-Histone Lactylation Regulates Resistance to Cuproptosis

Lactylation, a lactate-derived post-translational modification, emerges as a master regulator of cuproptosis resistance across malignancies. By hijacking divergent signaling hubs—insulin-like growth factor receptor-1 (IGF-1R) in multiple myeloma and RNA processing factor NUDT21 in esophageal cancer—lactylation orchestrates molecular cascades that

disable copper-induced cell death. These pathways converge on either stabilizing endogenous suppressors of cuproptosis (eg, CDKN2A) or depleting essential executors (eg, FDX1), ultimately enabling cancer cells to evade metabolic toxicity. Below, we dissect how lactylation subverts cuproptosis through non-histone protein modifications (Figure 6).

Wang et al revealed that lactylation of insulin-like growth factor receptor-1 (IGF-1R) promotes proteasome inhibitor (PI) resistance in multiple myeloma (MM) by suppressing cuproptosis.¹³ Specifically, downregulation of MUC20 in PI-resistant MM cells increases IGF-1R lactylation (likely via elevated lactate levels), which activates the MET proto-oncogene.¹³ Activated MET phosphorylates and stabilizes cyclin-dependent kinase inhibitor 2A (CDKN2A), a known suppressor of cuproptosis, ultimately blocking copper-dependent cell death. Conversely, restoring MUC20 expression reduces IGF-1R lactylation, disrupts MET/CDKN2A signaling, and reinstates cuproptosis sensitivity.¹³ Extrachromosomal circular DNA (eccDNA) amplifies KIF3C to downregulate MUC20, initiating this resistance cascade. In summary, lactylation sustains cuproptosis resistance by stabilizing the IGF-1R/MET/CDKN2A signaling axis, enabling cancer cells to evade copper-induced death¹³ (Figure 6).

Lin et al revealed that L-lactate-induced lactylation of Nudix hydrolase 21 (NUDT21), a core component of the 3' end processing machinery at lysine 23 (K23), catalyzed by the “writer” enzyme AARS1 and reversed by the “eraser” HDAC2, reprograms alternative polyadenylation (APA) to promote resistance to cuproptosis in esophageal squamous cell carcinoma (ESCC).¹⁴ Specifically, NUDT21 lactylation enhances its interaction with CPSF6, facilitating CFIm complex formation and driving the selection of distal polyadenylation sites (dPAS) in the FDX1 transcript.¹⁴ This results in 3' UTR lengthening of FDX1 mRNA, which destabilizes the transcript and reduces FDX1 protein expression. Since FDX1 is essential for cuproptosis (by reducing Cu^{2+} to Cu^{+} and inducing mitochondrial protein lipoylation), its downregulation directly confers resistance to copper-induced cell death.¹⁴ Clinically, elevated NUDT21 lactylation correlates with reduced FDX1 and worse ESCC prognosis, and combined targeting of lactate production (via LDHA inhibitor stiripentol) and copper delivery (via ionophore elesclomol) synergistically overcomes this resistance.¹⁴ In summary,

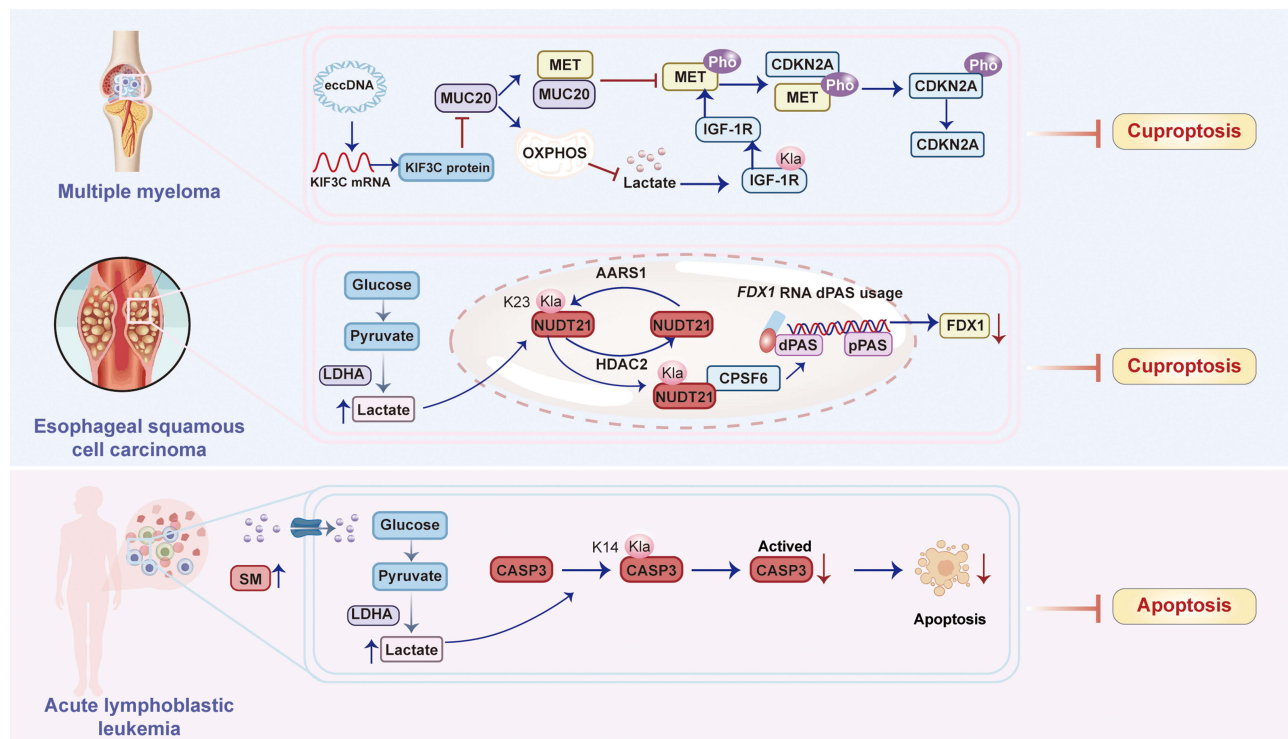


Figure 6 Lactylation regulates resistance to cuproptosis. Lactylation sustains cuproptosis resistance by stabilizing the IGF-1R/MET/CDKN2A signaling axis, enabling cancer cells to evade copper-induced death. Lactylation of Nudix hydrolase 21 (NUDT21) suppresses FDX1 expression through APA-mediated mRNA destabilization, thereby enabling cancer cells to evade cuproptosis in esophageal squamous cell carcinoma (ESCC). The sphingomyelin (SM)-driven lactate production mediates CASP3 K14 lactylation to prevent its proteolytic activation, conferring apoptosis resistance in leukemia.

lactylation of NUDT21 suppresses FDX1 expression through APA-mediated mRNA destabilization, thereby enabling cancer cells to evade cuproptosis¹⁴ (Figure 6).

Lactylation drives cuproptosis resistance via distinct mechanisms across cancers: in multiple myeloma (MM), IGF-1R lactylation stabilizes MET/CDKN2A signaling to suppress cuproptosis, while in esophageal squamous cell carcinoma (ESCC), lactylation of NUDT21 reprograms alternative polyadenylation to destabilize FDX1 mRNA—a core cuproptosis executor—thus conferring copper tolerance. Both pathways converge on metabolic adaptation, where elevated lactate fuels lactylation-mediated evasion of copper-induced death. However, unresolved questions include the precise structural impact of lactylation on IGF-1R/NUDT21 function, tissue-specific drivers selecting divergent lactylation targets (eg, IGF-1R vs NUDT21), and whether lactylation broadly regulates other cuproptosis components (eg, DLAT, LIAS). Future studies should develop lactylation-specific inhibitors (eg, blocking “writer” enzymes like AARS1) to disrupt resistance pathways. Map lactylation interactomes in cuproptosis-sensitive cancers to identify novel targets. Explore lactate modulation (eg, LDHA inhibition) combined with copper ionophores in *in vivo* models to overcome therapy resistance. Future work must address context-dependent regulatory networks and translate mechanistic insights into targeted therapies and investigate cross-talk between lactylation and other post-translational modifications in fine-tuning cuproptosis sensitivity.

Non-Histone Lactylation Regulates Resistance to Apoptosis

This study reveals that elevated sphingomyelin (SM) in acute lymphoblastic leukemia (ALL) reprograms glucose metabolism by enhancing SLC2A1-mediated glucose uptake and glycolysis, leading to increased lactate production¹⁵ (Figure 6). The accumulated lactate drives lactylation of caspase-3 (CASP3) specifically at lysine 14 (K14). This K14 lactylation physically impedes the proteolytic activation of CASP3, thereby disabling its apoptotic function and conferring apoptosis resistance to ALL cells.¹⁵ Critically, depletion of SM reduces lactate levels, decreases CASP3 K14 lactylation, restores CASP3 activation, and sensitizes cells to apoptosis. In summary, SM-driven lactate production mediates CASP3 K14 lactylation to prevent its proteolytic activation, conferring apoptosis resistance in leukemia.¹⁵

Link Lactylation to Autophagy-Mediated Resistance to Regulated Cell Death

Certainly, several recent studies have established a direct molecular link between lactylation, the induction of autophagy, and subsequent resistance to regulated cell death. Lactylation is emerging as a direct regulator of autophagy that promotes resistance to regulated cell death. Recent evidence demonstrates that lactate, a glycolysis byproduct, serves as a precursor for lactylation, a post-translational modification that directly activates core components of the autophagy machinery. Specifically, lactylation of the key autophagy regulator Vps34 at lysine residues 356 and 781 enhances its lipid kinase activity by strengthening its interaction with regulatory subunits like Beclin-1.^{30,124,125} This Vps34 hyperlactylation significantly promotes autophagic flux and the endolysosomal degradation pathway.¹²⁵ In the context of cellular stress, this lactate-driven autophagy can suppress cell death. For instance, in models of spinal cord injury, lactate-mediated lactylation of the Ran protein facilitates astrocyte polarization and survival by promoting STAT3 nuclear transport.¹²⁶ Conversely, inhibiting this lactylation pathway reverses the protective autophagy and increases susceptibility to cell death. Furthermore, in stressed melanoma cells, the acidic microenvironment created by lactic acid was shown to suppress glucose deprivation-induced autophagic cell death.¹²⁴ Therefore, lactylation functions as a critical metabolic switch that links glycolytic activity to pro-survival autophagy, conferring resistance to various forms of regulated cell death.

Targeting Lactylation Overcome Resistance to Regulated Cell Death Against Ferroptosis Resistance

Inhibiting histone lactylation (via 2-DG) restores ferroptosis sensitivity by disrupting this pathway.¹¹⁸ Deoxy-D-glucose (2-DG) functions as a competitive glycolytic inhibitor by mimicking glucose structure yet lacking the 2-hydroxyl group essential for further glycolysis. This non-metabolizable glucose analog enters cells via glucose transporters (GLUTs) and undergoes phosphorylation by hexokinase to form 2-DG-6-phosphate. Unlike glucose-6-phosphate, this metabolite

cannot be isomerized or further processed in glycolysis, resulting in intracellular accumulation that allosterically inhibits hexokinase activity and blocks glycolytic flux. In endometriotic stromal cells (EESCs), 2-DG significantly reduces lactate production by disrupting the Warburg effect—a hallmark metabolic shift in endometriosis where cells prioritize glycolysis over oxidative phosphorylation even under normoxic conditions.¹¹⁸ The consequent depletion of lactate, the substrate for histone lactylation, directly reduces global lysine lactylation (pan-Kla) and specifically diminishes histone H3 lysine 18 lactylation (H3K18la).¹¹⁸ This epigenetic modulation occurs via reduced enrichment of H3K18la at the promoter of METTL3, a key RNA methyltransferase, leading to decreased METTL3 expression and subsequent reduction of N6-methyladenosine (m6A) RNA modifications.¹¹⁸ Through this cascade, 2-DG disrupts the METTL3-regulated HIF1 α /HMOX1 antioxidant signaling axis, thereby impairing cellular defenses against ferroptosis.¹¹⁸ Phenotypically, 2-DG treatment sensitizes EESCs to ferroptosis inducers (eg, erastin) by depleting glutathione (GSH), increasing lipid peroxidation (elevated MDA and Liperflu staining), and accumulating intracellular Fe²⁺.¹¹⁸ In vivo, 2-DG synergizes with erastin to suppress endometriotic lesion growth in mice, demonstrating its therapeutic potential. This synergy arises from 2-DG's dual role: metabolic disruption of lactate-dependent pathways and epigenetic silencing of pro-survival genes, ultimately overcoming ferroptosis resistance in endometriosis¹¹⁸ (Figure 7 and Table 2).

Critically, HDAC inhibitors (HDACi) like SAHA and TSA reduce HDAC1-K412la lactylation, destabilize FSP1 mRNA, and sensitize CRC to ferroptosis inducers. Lactylation of HDAC1-K412la stabilizes FSP1 mRNA via m6A modification to

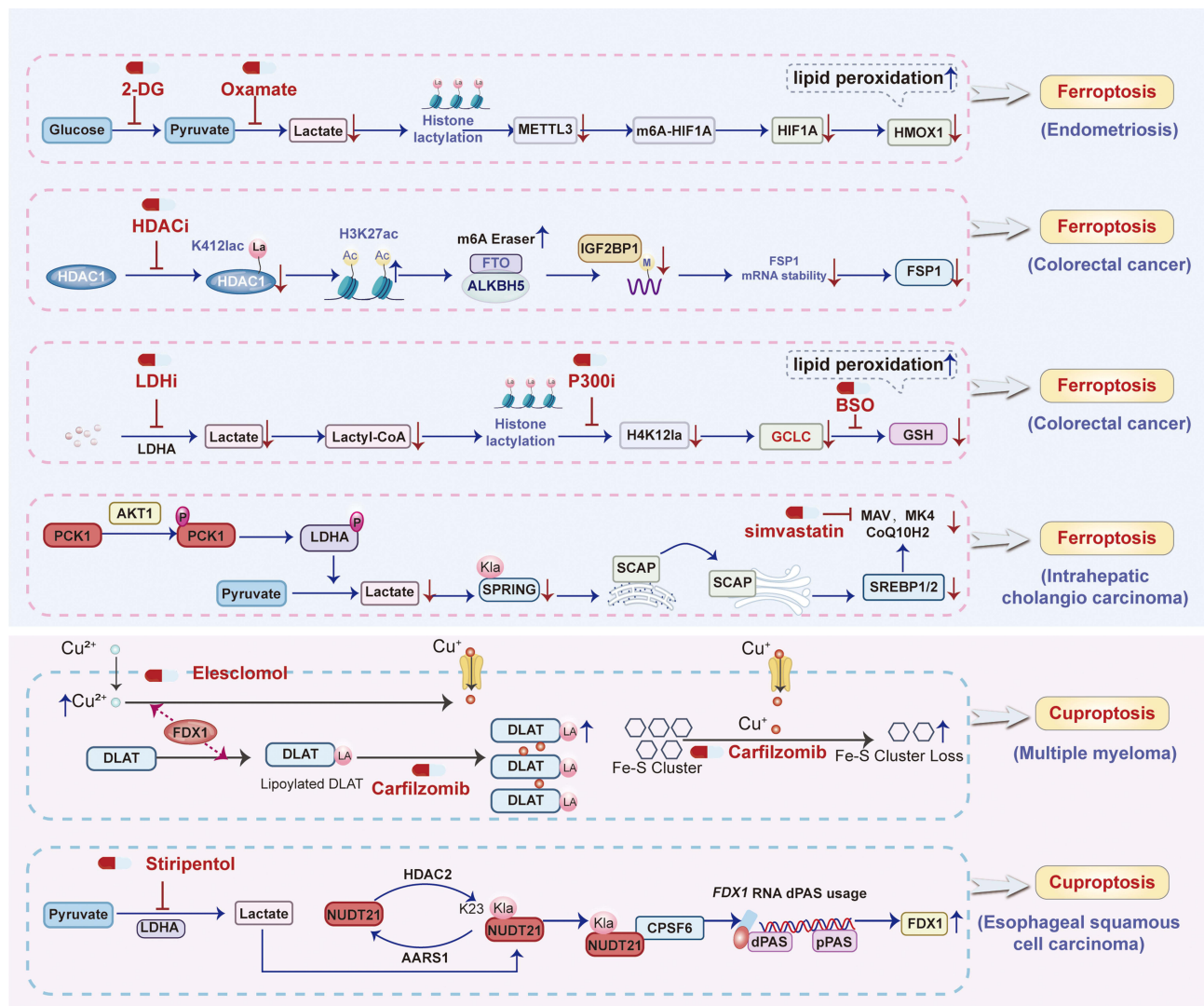


Figure 7 Pharmacologically targeting lactylation overcome resistance to ferroptosis and cuproptosis.

Table 2 Therapeutic Strategies Targeting Lactylation to Overcome Resistance to Regulated Cell Death (RCD)

Therapeutic Agent	Molecular Target/ Class	Mechanism of Action in Overcoming RCD Resistance	Targeted RCD Pathway	Ref
2-Deoxy-D-Glucose (2-DG)	Glycolysis/Hexokinase	Inhibits glycolysis, reduces lactate production and subsequent histone lactylation (eg, H3K18la), disrupting pro-survival signaling (eg, ETTL3/HIF1 α /HMOX1 axis).	Ferroptosis	[118]
Vorinostat (SAHA), Trichostatin A (TSA)	HDAC1 (Delactylase)	Reduces HDAC1-K412la lactylation, upregulates m6A erasers (FTO, LKBH5), destabilizes FSP1 mRNA, and sensitizes to ferroptosis inducers.	Ferroptosis	[121]
LDHA Inhibitors (eg, Oxamate, Stiripentol)	Lactate Dehydrogenase A (LDHA)	Reduces lactate production, the substrate for lactylation, thereby suppressing lactylation-driven resistance mechanisms (eg, GCLC upregulation, NUDT21 lactylation).	Ferroptosis, Cuproptosis	[14,119]
Buthionine Sulfoximine (BSO)	Glutamate-Cysteine Ligase Catalytic Subunit (GCLC)	Directly inhibits GCLC, depletes glutathione (GSH), and overrides lactylation-enhanced GSH synthesis, leading to lethal lipid peroxidation.	Ferroptosis	[119]
Simvastatin	HMG-CoA Reductase (HMGCR)	Inhibits the mevalonate (MVA) pathway, depleting radical-trapping antioxidants (CoQ10H2, MK4), and counteracts SPRING lactylation-mediated ferroptosis resistance.	Ferroptosis	[123]
Elesclomol	Copper Ionophore	Shuttles copper into mitochondria, directly inducing cuproptosis; overcomes resistance by bypassing lactylation-stabilized suppression (eg, CDKN2A) or restoring FDX1 dependency.	Cuproptosis	[13,14]
Tetrathiomolybdate (TTM)	Copper Chelator	Chelates copper ions, thereby suppressing cuproptosis; used as a mechanistic tool to confirm copper dependency of cell death.	Cuproptosis	[13]
Carfilzomib (CFZ)	Proteasome	Induces cuproptosis in sensitive cells; efficacy is compromised in PI-resistant cells with lactylation-driven resistance (eg, IGF-1R/MET/CDKN2A axis).	Cuproptosis	[13]

confer ferroptosis resistance in colorectal cancer¹²¹ (Figure 7 and Table 2). Vorinostat (SAHA) and Trichostatin A (TSA) both pan-histone deacetylase inhibitors (HDACis), exert their primary pharmacological action by selectively inhibiting HDAC1, a key epigenetic regulator.¹²¹ Their mechanism in sensitizing colorectal cancer (CRC) to ferroptosis involves a multi-step pathway initiated by the reduction of lactylation at lysine 412 (K412) on HDAC1 itself—a novel post-translational modification identified in this study. This diminished lactylation impairs HDAC1's deacetylase function, leading to increased acetylation of histone H3 at lysine 27 (H3K27ac) specifically at the promoter regions of two critical RNA demethylases, FTO and ALKBH5.¹²¹ Consequently, the enhanced H3K27ac promotes transcriptional upregulation of FTO and ALKBH5. These enzymes, acting as m⁶A erasers, then reduce N⁶-methyladenosine (m⁶A) methylation on the mRNA of ferroptosis suppressor protein 1 (FSP1), a key defender against lipid peroxidation-driven cell death.¹²¹ The decreased m⁶A modification destabilizes FSP1 mRNA, accelerating its degradation and ultimately suppressing FSP1 protein expression. Since FSP1 maintains cellular resistance by regenerating the antioxidant ubiquinol (CoQH₂) to neutralize lipid radicals, its downregulation cripples the CRC's anti-ferroptosis defense system.¹²¹ This renders cancer cells profoundly vulnerable to ferroptosis inducers (eg, RSL3, erastin, IKE), causing synergistic cell death through accumulated lipid peroxidation. Importantly, SAHA and TSA demonstrate superior efficacy in reducing HDAC1[K412] lactylation compared to other HDAC1 inhibitors, correlating directly with their potency in ferroptosis sensitization. Pharmacologically, while both agents share this core mechanism, their clinical relevance is amplified by the finding that combining sublethal doses of these HDACis with ferroptosis inducers achieves potent antitumor effects in vivo (demonstrated in xenograft and AOM/DSS models) while potentially mitigating the dose-limiting toxicities (eg, myelosuppression, gastrointestinal effects) associated with higher doses of HDACis or conventional chemotherapy like 5-FU+oxaliplatin.¹²¹ Thus, their pharmacological role extends beyond traditional HDAC inhibition to encompass the regulation of lactylation-dependent epigenetic-to-RNA modification crosstalk, positioning them as strategic agents for combination therapy in ferroptosis-resistant CRC.¹²¹

Inhibition of the lactate-producing enzyme LDHA, the lactyltransferase p300, or GCLC itself (using BSO) restores ferroptosis sensitivity and overcomes chemoresistance¹¹⁹ (Figure 7). LDHA inhibitor (eg, oxamate) pharmacologically

targets lactate dehydrogenase A (LDHA), a key enzyme in glycolysis that converts pyruvate to lactate. By inhibiting LDHA, LDHi reduces intracellular lactate production, which serves as the substrate for histone lactylation. This reduction in lactate availability decreases histone H4 lysine 12 lactylation (H4K12la) in colorectal cancer stem cells (CCSCs).¹¹⁹ Lower H4K12la levels diminish transcriptional activation of the ferroptosis-related gene GCLC (glutamate-cysteine ligase catalytic subunit), a critical enzyme in glutathione (GSH) synthesis.¹¹⁹ Consequently, impaired GSH biosynthesis weakens cellular antioxidant defenses, leading to accumulation of lipid peroxides and sensitization to ferroptosis.¹¹⁹ This mechanism enhances the efficacy of chemotherapeutic agents like oxaliplatin by overcoming CCSC chemoresistance, as validated both *in vitro* and *in vivo* through suppressed tumor growth and increased ferroptosis markers (eg, lipid ROS, MDA).¹¹⁹ Trichostatin A (TSA), an HDAC1 inhibitor, functions as a delactylase antagonist.¹¹⁹ By inhibiting HDAC1—identified as a histone delactylase—TSA increases global histone lactylation, including H4K12la, in CCSCs. Elevated H4K12la promotes GCLC transcription, enhancing GSH synthesis and inhibiting ferroptosis.¹¹⁹ Paradoxically, this confers chemoresistance; however, TSA's pharmacological utility lies in its role as a tool to elucidate lactylation dynamics. When combined with lactate-depleting agents (eg, LDHi), TSA's pro-lactylation effects are counteracted, indirectly supporting strategies to sensitize CCSCs to chemotherapy.¹¹⁹ Buthionine sulfoximine (BSO) directly inhibits GCLC, the rate-limiting enzyme in GSH synthesis. By depleting GSH, BSO disrupts the cellular redox balance, leading to uncontrolled lipid peroxidation and ferroptosis.¹¹⁹ Pharmacologically, BSO overrides the lactylation-driven GCLC upregulation in CCSCs, effectively reversing chemoresistance.¹¹⁹ *In vitro*, BSO synergizes with oxaliplatin to induce ferroptosis (evidenced by elevated lipid ROS/MDA); *in vivo*, it significantly suppresses tumor growth in xenograft models.¹¹⁹ This positions BSO as a therapeutic adjuvant to standard chemotherapy, particularly in GCLC-overexpressing, oxaliplatin-resistant CCSCs.¹¹⁹ Collectively, these agents target interconnected nodes of the lactylation-GCLC-ferroptosis axis: LDHi mitigates lactate-driven histone lactylation to suppress GCLC. TSA validates HDAC1's role as a lactylation eraser but requires combinatorial use to avoid resistance. BSO directly inhibits GCLC to induce ferroptosis, offering a clinically translatable strategy to enhance chemosensitivity in colorectal cancer.¹¹⁹

Disrupting this axis—via SPRING K82R mutation (lactylation-deficient) or simvastatin (MVA inhibitor)—sensitizes ICC cells to ferroptosis and overcomes chemo-immunotherapy resistance.¹²³ In summary, lactylation of SPRING at K82, mediated by the pPCK1-pLDHA axis-induced lactate accumulation, activates the MVA pathway to synthesize radical-trapping antioxidants that suppress lipid peroxidation and confer ferroptosis resistance.¹²³

Simvastatin's inhibition of HMGCR reverses this resistance by depleting CoQ10H₂ and MK4, sensitizing ICC cells to ferroptosis.¹²³ This effect is mechanistically validated by rescue experiments where exogenous MVA supplementation (MVA-Li) restores ferroptosis resistance, confirming the specificity of Simvastatin's action on the MVA pathway.¹²³ In preclinical models, Simvastatin synergizes with CIT by amplifying lipid peroxidation (increased MDA levels), enhancing CD8⁺ T-cell infiltration and activation (elevated TNF α +/IFN γ + CD8⁺ T cells), and suppressing tumor growth in both subcutaneous and hydrodynamic ICC mouse models.¹²³ Simvastatin's ability to target this axis positions it as a rational adjunct therapy, particularly in AKT-hyperactivated ICC subtypes. This pharmacological strategy leverages statins' established safety profile to overcome metabolic reprogramming-driven therapy resistance, offering a translatable approach to improve clinical outcomes.¹²³

Against Cuproptosis Resistance

Carfilzomib (CFZ) functions as a second-generation proteasome inhibitor, core to MM treatment.¹³ It induces cell death in PI-sensitive MM cells primarily by triggering cuproptosis, a copper-dependent form of programmed cell death (Figure 7). Mechanistically, CFZ promotes the aggregation of lipoylated proteins (eg, DLAT) and loss of iron-sulfur cluster proteins, leading to proteotoxic stress.¹³ However, in PI-resistant MM cells, CFZ fails to elicit cuproptosis due to downregulated MUC20 and dysregulated downstream pathways (MET/CDKN2A). At concentrations of 10–20 nM, CFZ inhibits proteasome activity but only reduces viability in sensitive cells, highlighting its dependence on intact cuproptosis machinery.¹³

Tetrathiomolybdate (TTM) acts as a high-affinity copper chelator, disrupting cuproptosis by sequestering copper ions. Pharmacologically, TTM (at 50 nM) completely reverses CFZ-induced cell death in PI-sensitive MM cells, confirming copper's essential role in this process. In rescue experiments, TTM neutralizes the pro-cuproptotic effects of MUC20

overexpression in resistant cells, demonstrating its utility in dissecting copper-dependent mechanisms. Its efficacy is dose-dependent, with 50 nM sufficient to abrogate cuproptosis without off-target cytotoxicity¹³ (Figure 7).

Elesclomol operates as a copper ionophore that complexes with extracellular copper (Cu^{2+}) and shuttles it into cells.¹³ At 50–150 nM, elesclomol potently restores cuproptosis in PI-resistant MM cells by overwhelming endogenous copper homeostasis. It synergizes with CFZ, significantly reducing proliferation and increasing programmed cell death (PCD) in resistant lines. In vivo, elesclomol (25 mg/kg) combined with CFZ suppresses tumor growth in xenograft models, validating its role in re-sensitizing resistant MM to PI therapy via copper delivery¹³ (Figure 7). This study revealed a dynamic balance wherein CFZ efficacy depends on functional cuproptosis, compromised in resistance. TTM and elesclomol serve as mechanistic tools: TTM suppresses cuproptosis by copper depletion, while elesclomol induces it by copper overload. Critically, elesclomol overcomes PI resistance by bypassing MUC20 deficiency and directly forcing copper-dependent cell death. This supports targeting copper metabolism as a strategy to overcome PI resistance, with elesclomol emerging as a promising adjuvant to proteasome inhibitors in refractory MM.¹³

Stiripentol, clinically approved for Dravet syndrome, functions as a potent inhibitor of lactate dehydrogenase A (LDHA), a key enzyme in the glycolytic pathway responsible for converting pyruvate to lactate. By inhibiting LDHA, stiripentol effectively reduces intracellular lactate production, thereby diminishing the substrate available for the lactylation modification catalyzed by AARS1¹⁴ (Figure 7). This reduction in lactate levels consequently attenuates the lactylation of NUDT21 at lysine 23 (K23), a critical post-translational modification identified in the study.¹⁴ The suppression of NUDT21 lactylation disrupts its enhanced interaction with CPSF6 and the subsequent formation of the CFIm complex. Consequently, this prevents the NUDT21-mediated shift towards distal polyadenylation site (dPAS) usage in the FDX1 gene, leading to the restoration of FDX1 protein expression.¹⁴ FDX1 is essential for cuproptosis, as it reduces Cu^{2+} to the more toxic Cu^+ and facilitates mitochondrial protein lipoylation, ultimately triggering copper-dependent cell death.¹⁴ Therefore, stiripentol's primary pharmacological action in this context is metabolic reprogramming, sensitizing esophageal squamous cell carcinoma (ESCC) cells to copper-induced stress by reversing lactylation-driven resistance mechanisms.¹⁴

Elesclomol operates as a copper ionophore, forming a stable 1:1 complex with extracellular Cu^{2+} ions (eg, in the form of elesclomol- Cu^{2+}). This complex facilitates the active transport and intracellular delivery of copper, specifically targeting mitochondria. Once inside the mitochondria, the released copper ions directly bind to lipoylated components of the tricarboxylic acid (TCA) cycle. This binding induces proteotoxic stress through the aggregation of lipoylated mitochondrial proteins and subsequent disruption of iron-sulfur cluster proteins, culminating in a unique form of regulated cell death termed cuproptosis. The efficacy of elesclomol is critically dependent on functional FDX1, which reduces the delivered Cu^{2+} to Cu^+ , the redox-active form responsible for initiating the lipoylated protein aggregation. Thus, elesclomol's core pharmacological mechanism is the targeted induction of copper-dependent cytotoxicity via mitochondrial copper overload¹⁴ (Figure 7). The study demonstrated a powerful synergistic interaction between stiripentol and elesclomol in suppressing ESCC tumor growth in vivo.¹⁴ This synergy arises from their complementary mechanisms targeting the lactate-NUDT21-FDX1-cuproptosis axis. Stiripentol, by inhibiting lactate production and NUDT21 lactylation, restores FDX1 expression and removes the block to cuproptosis sensitivity.¹⁴ Elesclomol, concurrently, provides the cytotoxic copper payload. By overcoming lactylation-mediated resistance (via stiripentol) and effectively delivering the copper death signal (via elesclomol), the combination therapy achieves significantly greater anti-tumor efficacy than either agent alone.¹⁴ This synergistic effect highlights the therapeutic potential of co-targeting the metabolic adaptation (lactate/LDHA) and the cell death pathway (copper/cuproptosis) in cancers like ESCC characterized by elevated glycolysis, lactate, and NUDT21 expression. The combination was reported to be well-tolerated in the preclinical models described.¹⁴

Conclusions and Perspectives

This review consolidates the paradigm-shifting role of lysine lactylation (Kla) as a master metabolic regulator orchestrating resistance to regulated cell death (RCD) across diverse pathologies, particularly cancer. By dynamically modifying histones and non-histone proteins, lactylation establishes a robust shield against ferroptosis, cuproptosis, and apoptosis. The

convergence of elevated lactate—a hallmark of pathological microenvironments—and specific lactyltransferases drives the reprogramming of epigenetic landscapes, RNA stability, metabolic fluxes, and metal homeostasis to sustain cell survival.

Lactylation epigenetically upregulates antioxidant genes (HMOX1, GCLC, NFS1), stabilizes suppressors (SLC7A11, FSP1) via RNA methylation, enhances glutathione synthesis (GCLM lactylation), activates NRF2 signaling (PRDX1 lactylation), and disrupts iron availability (LSD1-mediated TFRC repression; NFS1 upregulation). IGF-1R lactylation stabilizes the CDKN2A suppressor, while NUDT21 lactylation reprograms alternative polyadenylation to destabilize FDX1 mRNA, disabling mitochondrial copper toxicity. Caspase-3 lactylation directly impedes proteolytic activation, blocking apoptotic execution. These findings position lactylation as a central metabolic-epigenetic switch that rewires cellular stress responses to promote pathological resilience and therapeutic resistance. However, critical outstanding questions remain unresolved. What dictates the selective targeting of lactylation “writers” (eg, ACAT2 in KRAS-mutant cancer vs KAT7 in cholangiocarcinoma) and their substrate preferences in different disease contexts? How does lactylation integrate with other post-translational modifications (eg, acetylation, phosphorylation, ubiquitination) to fine-tune RCD sensitivity? Does lactylation compete with or reinforce these modifications? What is the precise structural impact of lactylation on enzyme function (eg, conformational changes in caspase-3 or IGF-1R) and how does lactylation alter reader protein engagement? Does lactylation regulate additional RCD components (eg, GPX4, DLAT, BCL-2 family members) or novel RCD modalities beyond the three discussed?

Future research directions should focus on translating these mechanistic insights into therapeutic strategies. Develop isoform-specific inhibitors of lactyltransferases (eg, KAT7, ACAT2, NAA10) or delactylases to disrupt lactylation-driven RCD resistance. Combinatorial approaches—pairing lactate depletion (via LDHA inhibitors) with RCD inducers (eg, ferroptosis inducers, copper ionophores)—hold promise for overcoming therapy-refractory diseases. Systematically map the “lactylome” across disease states and therapy-resistant niches to identify context-specific vulnerabilities. Integrate lactylation data with transcriptomic, metabolomic, and proteomic datasets to decipher regulatory networks. Investigate how lactate from stromal cells, immune infiltrates, or microbiota fuels lactylation in tumor cells, and whether modulating the microenvironment sensitizes cells to RCD. Establish genetically engineered models (eg, lactylation-site mutants) to rigorously test the causal role of lactylation in RCD resistance *in vivo*. Explore lactylation’s impact on antitumor immunity and its synergy with immunotherapy. Evaluate lactylation levels (eg, H3K181a, lactylated PRDX1) as prognostic markers or predictors of treatment response in clinical cohorts.

In conclusion, lactylation represents a fundamental link between cellular metabolism and cell fate determination. Targeting this axis offers a transformative strategy to dismantle the shield of RCD resistance, paving the way for novel therapies against cancer and other lactate-rich pathological conditions. Unlocking the full potential of lactylation modulation requires concerted efforts to address its contextual complexity and harness its therapeutic promise.

Highlights

- Lactylation serves as a master metabolic switch for regulated cell death (RCD) resistance.
- Diverse molecular mechanisms confer ferroptosis resistance.
- Lactylation subverts cuproptosis and apoptosis.
- Targeting lactylation regulators or combining lactate modulation with RCD inducers lactylation-mediated RCD resistance.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

Funding

This work was supported in part by the Beijing Natural Science Foundation (No. 7252174), Wu Jieping Medical Foundation (320.6750.2024-13-59), Natural Science Foundation of Inner Mongolia Autonomous Region (2025MS08029), Talent development plan for the future in Medical-Engineering Integration by BRA-CDCHE and ZTA (MBRC0012025029; MBRC0012025011), Science Foundation of ASCH (YN202305; YN202402; YN202423; YN202503), and the Science Foundation of AMHT (2024YK04; 2024YK05).

Disclosure

The authors declare no conflict of interest.

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