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Review Article

Lactylation in Gynecological Malignancies: A Bridge between Lactate Metabolism and Epigenetic Therapy

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Abstract

Lactate exerts regulatory effects on both cellular homeostasis and disease progression, far beyond being a mere metabolic waste product. As lactate accumulates, the level of lactylation increases significantly. Lactylation, a novel type of post-translational modification, bridges metabolic reprogramming and epigenetic regulation in malignant tumors, including gynecological malignancies. Both lactate and lactylation play critical roles in the tumor microenvironment, ultimately promoting tumor proliferation, metastasis, and drug resistance. Therapies targeting lactate production and transport show considerable anticancer potential, particularly through the inhibition of lactate dehydrogenase and monocarboxylate transporters. These inhibitors can also act as immunotherapy potentiators, producing a synergistic therapeutic effect when combined with immunotherapy. This review emphasizes how lactate and lactylation drive the malignant progression of gynecological cancers and explores promising perspectives on potential therapeutic targets.

Introduction

Gynecological malignancies pose a significant threat to female health and survival. Ovarian cancer (OC), cervical cancer (CC), and endometrial cancer (EC) are common gynecological malignancies worldwide, placing a particularly high disease burden on low-resource regions. OC is the eighth most common cancer in women, accounting for an estimated 3.7% of cases and 4.7% of cancer deaths in 2020.[1] In the same year, an estimated 604,127 new cases of CC were reported globally, resulting in 341,831 deaths.[2] Meanwhile, EC has become the most common gynecological cancer in developed countries,[3,4] with its incidence steadily rising in China, where it now ranks as the leading reproductive system malignancy in urban areas.

Lactate secretion is a well-established metabolic hallmark of cancer, most commonly referred to as the Warburg effect.[5] This metabolic reprogramming describes the tendency of cancer cells to rely on glycolysis for energy production even in the presence of sufficient oxygen. Lactic acid is an organic acid with the chemical formula C3H6O3.[6] When lactic acid dissolves in water, it can lose a hydrogen ion (proton), resulting in lactate ($C_3H_5O_3^-$). Lactylation is a recently discovered post-translational modification of proteins, characterized by the covalent addition of lactyl groups to amino acid residues.[7] This modification occurs not only in histones but also widely in non-histone proteins, playing important roles in both tumor cells and immune cells. Lactate serves as an alternative carbohydrate fuel, buffers cellular redox homeostasis, and modulates amino acid and fatty acid metabolism.[8] In tumor cells, lactate can disrupt glycolytic processes and elevate lactylation levels. Accumulating evidence demonstrates that lactate and lactylation can drive malignant progression and therapy resistance in gynecological malignancies.[9–12] Therapeutic strategies targeting lactate and lactylation, including agents such as irinotecan, have shown promising results in patients.[13]

Consequently, targeting lactate metabolism and lactylation represents a novel and promising therapeutic approach for gynecological malignancies. In this review, we aim to summarize the key roles of lactate metabolism and lactylation in the occurrence and progression of gynecological cancers, explore potential therapeutic targets, and discuss future directions and challenges.

Keywords: Lactate; Lactylation; Gynecological malignancies; Post-translational modification; Epigenetics; Targeted therapy.

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Table 1. Enzymes involved in lactylation

Types	Enzyme	Mechanism	Related research
Writer	GNAT,[23] MYST[24] and p300-CBP, YiaC[25]	Enzymes that catalyze histone lysine lactylation modifications transfer lactate moieties to specific sites, regulating gene expression and cellular functions	Through overexpression/ knockdown experiments, p300 was confirmed to regulate histone lactylation levels via a p53-dependent catalytic mechanism[7]
Eraser			
	HDACs[26]	Zinc ion-dependent deacetylases dynamically regulate lysine lactylation modifications	p300 and HDAC1/3 dynamically orchestrate lysine lactylation modifications through complementary regulatory functions[27]
	SIRTs	NAD^+-dependent deacetylases modulate substrate specificity in lactylation modifications	SIRT1/SIRT3 knockout studies reveal HDACs' substrate-specific regulation: selective deacetylation of histone vs. non-histone Kla targets[28]
Reader	Smarca4[29]	Proteins with specialized structural domains recognize lactylation modification sites to govern gene expression and cellular processes	Brg1 was first identified as a histone lactylation reader protein in iPSC reprogramming research

CBP, CREB-binding protein; GNAT, Gcn5-related N-acetyltransferase; HDACs, histone deacetylases; iPSC, induced pluripotent stem cell; MYST, MOZ, Ybf2/Sas3, Sas2, TIP60; NAD, nicotinamide adenine dinucleotide; SIRTs, sirtuins; Smarca4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4.

Lactate metabolism and biological function

Glucose serves as the primary energy substrate in humans, undergoing glycolysis to produce pyruvate, an essential step in cellular respiration. Under normal aerobic conditions, pyruvate enters the mitochondria and is metabolized via the tricarboxylic acid cycle, generating carbon dioxide, water, and substantial adenosine triphosphate, which are critical energy substrates for life. However, during intense physical exertion or under anaerobic conditions, pyruvate is reduced to lactate intracellularly via lactate dehydrogenase (LDH). This lactate is subsequently released into circulation, serving as an alternative energy substrate for various tissues. Conversion of glutamine to lactate (glutaminolysis) can supply carbon skeletons for both pyruvate and lactate biosynthesis, revealing a novel lactate source in tumor environments.[14] Chemotherapy downregulates glucose transporter expression and impairs cellular glucose uptake, thereby enhancing malate enzyme 2 activity to drive glutamine-derived lactate production. This malate enzyme 2-synthesized lactate promotes chemoresistance in cancer cells during prolonged treatment cycles, principally through lactylation modification of homologous recombination (HR) repair proteins.[15] While lactate is primarily generated in skeletal muscle, erythrocytes, and brain tissue, it is also produced microbiologically (e.g., by *Lactobacillus* spp. in the vaginal environment).[16] Additionally, metabolic disorders in the tumor microenvironment (TME) are important contributors to lactate production.[17]

Lactate was once regarded as a metabolic waste product; however, an increasing number of studies have recently demonstrated its crucial role in normal physiological activities. It serves as an alternative cerebral energy substrate, helping to maintain cognitive activity.[18] In pancreatic and lung cancer models, lactate contributes more significantly than glucose to the TME.[19] Lactate also acts as a redox buffer by regulating the lactate-pyruvate equilibrium and the cellular NAD^+/NADH ratio, influencing respiratory and glycolytic functions.[20] Ultimately, lactate affects reactive oxygen species (ROS) generation and cellular stability. In addition, lactate has been found to promote fatty acid synthesis in immune cells.[21]

The process of lactylation

In the 1920s, Warburg's research revealed that tumor tissues exhibit elevated anaerobic glycolysis despite adequate oxygen availability—a metabolic paradox now known as the Warburg effect.[22] This phenomenon is potentially attributable to aberrant expression of glycolysis-associated enzymes in the tumor cells. Post-translational modifications represent a means of genetic regulation in cells, with the most common including methylation and phosphorylation. In 2019, lysine lactylation (Kla) was first detected in MCF-7 cells through histone profiling. Further studies expanded this observation, identifying 28 conserved Kla sites on core histones across human cervical carcinoma (HeLa) cells and mouse bone marrow-derived macrophages,[7] revealing Kla's potential as a regulatory mechanism linking metabolism to epigenetic reprogramming.

Kla is a conserved and reversible process that involves specific activities of glycolytic enzymes, including writers, erasers, and readers. These enzymes add or remove lactate and identify lactylation sites (Table 1).[7,23–29]

Alanyl-tRNA synthetases AARS1 and AARS2 (AARS1/2) act as intracellular L-lactate sensors required for lactate to stimulate the lysine lactylome.[30] Previous studies have shown that AARS1 can mediate global lysine lactylation in tumor cells.[31] AARS1 binds lactate and catalyzes the formation of lactate-AMP, followed by transfer of lactate to lysine residues. P53 is one AARS1 target, with lysines 120 and 139 in the DNA-binding domain being lactylated. AARS1 expression and P53 lactylation correlate with poor prognosis in patients carrying wild-type P53.[32] However, AARS1 activity has also been associated with inhibition of tumor growth and reduced P53 cleavage through β-alanine, providing experimental evidence for targeting lactate sensors and lactyltransferases.

Lactylation sites are present not only on histones but also on non-histone proteins across various cell types, significantly impacting tumor progression. Histones, the main protein components of chromatin, interact with DNA and regulate transcription. Histone H3K18 lactylation (H3K18la),[33–35] histone H4K5l lactylation,[36] and histone H3K14 lactylation (H3K14la) have shown significant effects on tumor progression and drug resistance.[37,38] Inactive von Hippel-Lindau-triggered histone lactylation contributes to clear cell renal cell carcinoma progression by activating transcription of platelet-derived growth factor receptor β (PDGFR-β), establishing a positive feedback loop between histone lactylation and PDGFRβ signaling.[39] Royal jelly acid inhibits hepatocellular carcinoma development by

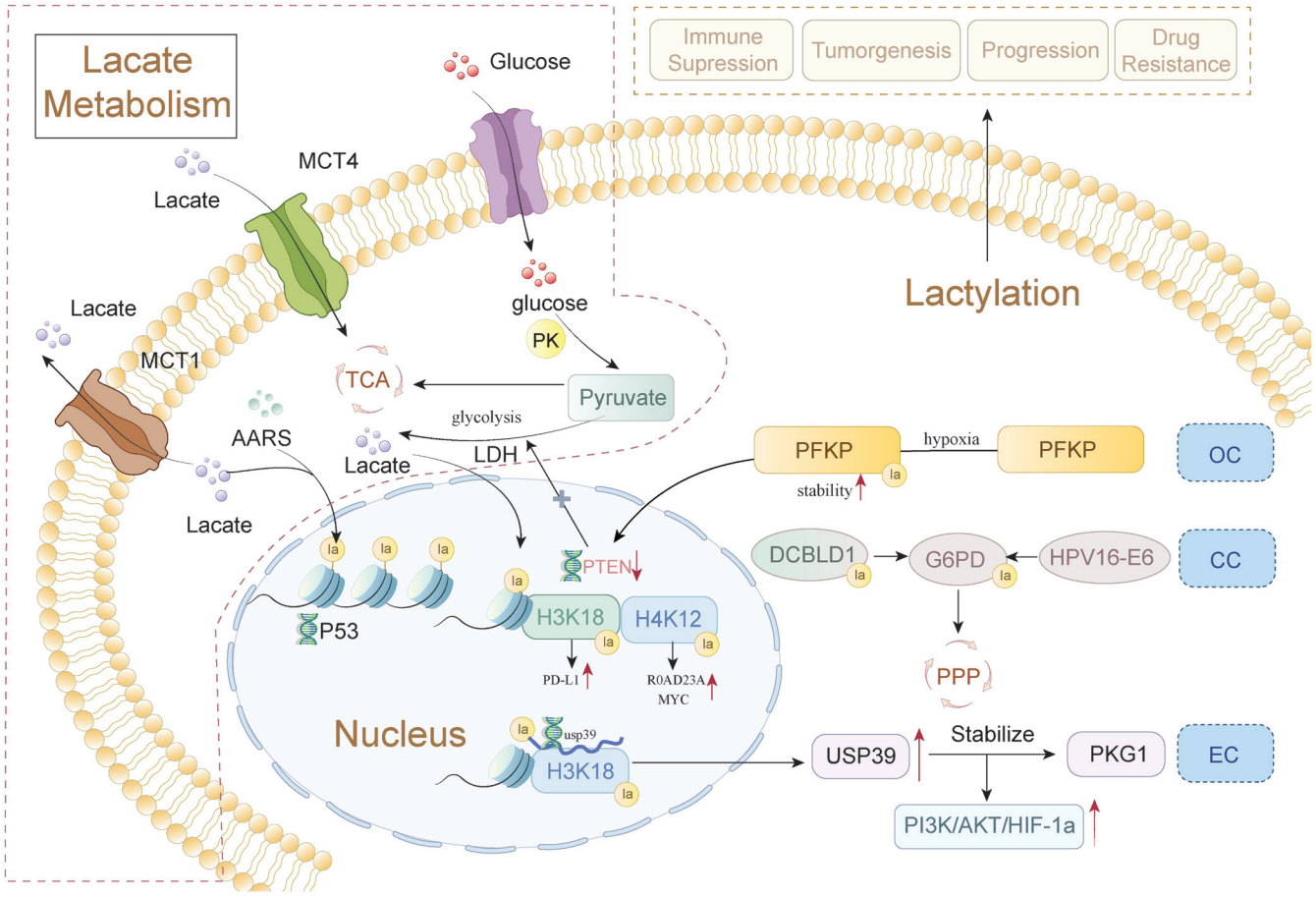

Fig. 1. Role of lactate metabolism and lactylation in gynecological malignancies. AARS, Alanyl-tRNA synthetase; AKT, protein kinase B; CC, cervical cancer; DCBLD1, discoidin, CUB, and LCCL domain-containing protein 1; EC, endometrial cancer; G6PD, glucose-6-phosphate dehydrogenase; H3K18, histone H3 lysine 18; H4K12, histone H4 lysine 12; HIF-1α, hypoxia-inducible factor-1α; HPV16-E6, human papillomavirus type 16 E6 protein; LDH, lactate dehydrogenase ; MCT, monocarboxylate transporter; MYC, myelocytomatosis viral oncogene homolog; OC, ovarian cancer; P53, tumor protein 53; PD-L1, programmed cell death ligand 1; PFKP, phosphofructokinase platelet-type; PI3K, phosphatidylinositol-3 kinase; PK, pyruvate kinase; PKG1, Protein kinase G1; PPP, pentose phosphate pathway; PTEN, phosphatase and tensin homolog; TCA, trichloroacetic acid; USP39, ubiquitin-specific peptidase 39.

interfering with lactate production and suppressing histone lactylation at H3K9la and H3K14la.[37] Under low-glucose conditions, Treg cells actively absorb lactate and promote nuclear factor of activated T cells 1 translocation into the nucleus, thereby increasing H3K18la levels and activating immune checkpoints.[40] Additionally, histone lactylation plays important roles in wound healing and homeostasis.[7] Histone lactylation further promotes tumorigenesis by upregulating YT521-B homology domain 2. This discovery establishes a novel mechanistic link between histone modifications and RNA regulation,[41] providing new research directions to investigate metabolism-epigenetics crosstalk in oncology.

With advances in integrative lactylation and proteome analysis, numerous non-histone lactylation sites have been identified. Notably, non-histone lactylation preferentially targets metabolic enzymes, particularly those involved in the tricarboxylic acid cycle and carbohydrate, amino acid, fatty acid, and nucleotide metabolism. Lactylation at K28 inhibits adenylate kinase 2, facilitating the proliferation and metastasis of hepatocellular carcinoma cells.[42] Vps34 lactylation (lysine-356 and lysine-781) enhances Vps34 lipid kinase activity, promoting autophagic flux and endolysosomal trafficking.[43] METTL16 lactylation significantly improves the therapeutic efficacy of the copper ionophore elesclomol, inducing gastric cancer cuproptosis.[44] Additionally, non-histone lactylation can promote tumor therapy resistance by facilitating HR repair and enhancing DNA damage response pathways.[45,46] Lactylation at METTL3 effectively induces the immunosuppressive function of tumor-infiltrating myeloid cells.[47]

Role of lactylation in gynecological malignancies

Accumulating evidence demonstrates that lactate and lactylation drive malignant progression and therapy resistance in gynecological malignancies (Fig. 1).[48] This review investigates the role of lactylation modifications in gynecological cancers (Table 2).[9–12,49–56] Analysis of public datasets confirms frequent lactylation on glycolytic enzymes in these malignancies.[67] H3K18la levels correlate with advanced International Federation of Gynecology and Obstetrics staging and shortened platinum-free intervals in OC, serving as an independent prognostic biomarker.[48] Serum lactate levels have also been observed to associate with the staging of OC patients.[49] Concurrently, lactate metabolism disorders critically influence the homeostasis of the tumor immune microenvironment.

Table 2. Lactylation in gynecological malignancies

Gynecological malignancies	Mechanisms	Modification sites	Supplementary
OC	H3K18la upregulates CCL18 to regulate M2 polarization and T cells[49]	H3K18	Treatment with the anti-CCL18 antibody can reverse these effects
	Lactylation of PFKP promoted glycolysis by regulating PTEN[50]	PFKP at the K392 residue	PFKP is highly expressed in OC tissues and cells
	LDHB modulated lactate production and the histone lactylation on the PD-L1 promoter[12]	H3K18	Overexpression of PD-L1 abolished the immune activation effects induced by siLDHB
	RAD51 lactylation enhances HR repair efficiency[9]	RAD51K73	Correlating with platinum resistance and poor prognosis
	H4K12la elevates R0AD23A expression and MYC transcription factor level[10]	H4K12	Promoting niraparib resistance
CC	Lactylation upregulates GPD2 thereby promoting M2 macrophage polarization[53]	H3K18	GPD2 knockdown reversed lactate induction in M2 macrophages
	DPF2 can bind to H3K14la and colocalize with it on promoters of oncogenic genes[54]	H3K14	Disrupting the DPF2-H3K14la interaction blunts cancer-related gene expression
	Lactylation stabilizes DCBLD1, activating the PPP to promote cancer progression[51]	DCBLD1 K172	6-An can mediate the inhibition of G6PD enzyme activity, inhibiting tumor proliferation
	HPV-16 E6 can inhibit G6PD lactylation[11]	G6PD K45A	The inhibition of G6PD enzyme activity with 6-An or the re-expression of G6PD K45T inhibited tumor proliferation
EC	H3K18la stimulated USP39 expression to stabilize PGK1[52]	H3K18	2-DG and oxamate treatment could decrease the level of lactylation
	PFKM lactylation regulates glycolysis[55]	PFKM K-678	Transfection of Ishikawa cells with mutant PFKM K678R plasmids can significantly reduce the invasiveness of the EC cells
	CAP modulates HDAC3 mediated the histone H3K18[56]	H3K18	Resulting in upregulation of p53, driving cell ferroptosis

2-DG, 2-deoxy-D-glucose; 6-An, 6-aminonicotinamide; CAP, cold atmospheric plasma; CC, cervical cancer; CCL18, C-C motif ligand 18; DCBLD1, discoidin, CUB, and LCCL domain-containing protein 1; DPF2, double plant homeodomain; EC, endometrial cancer; G6PD, glucose-6-phosphate dehydrogenase; GPD2, glycerol-3-phosphate dehydrogenase 2; H3K18la, histone H3 lysine 18 lactylation; H4K12, histone H4 lysine 12; HPV-16, human papillomavirus-16; HR, homologous recombination; LDHB, lactate dehydrogenase; MYC, myelocytomatosis viral oncogene homolog; OC, ovarian cancer; PD-L1, programmed cell death ligand 1; PFKM, phosphofructokinase muscle-type; PFKP, phosphofructokinase platelet-type; PGK1, phosphoglycerate kinase 1; PPP, pentose phosphate pathway; PTEN, phosphatase and tensin homolog; RAD51, Recombination protein RAD51; siLDHB, siRNA targeting lactate dehydrogenase B; USP39, ubiquitin-specific peptidase 39.

In OC, K392 lactylation of phosphofructokinase platelet-type (hereinafter referred to as PFKP) enhances glycolysis by modulating phosphatase and tensin homolog activity.[50] K172 lactylation of discoidin, CUB, and LCCL domain-containing protein 1 (hereinafter referred to as DCBLD1) promotes its overexpression. Elevated DCBLD1 suppresses autophagic degradation of glucose-6-phosphate dehydrogenase, activating the pentose phosphate pathway to drive cervical carcinogenesis.[51] Histone lactylation stimulates ubiquitin-specific peptidase 39 expression, which interacts with and stabilizes phosphoglycerate kinase 1, activating phosphatidylinositol-3 kinase (PI3K)/ protein kinase B (AKT)/ hypoxia-inducible factor-1α (HIF-1α) signaling to promote glycolysis and invasion.[52] These results suggest that histone lactylation plays a critical role in EC progression by enhancing the malignant behavior of EC cells, offering potential therapeutic targets for EC.

Lactate also regulates chemokine C-C motif ligand 18 expression via H3K18la, thereby promoting M2 macrophage polarization and tumorigenesis in OC.[49] In OC, LDHB modulates lactate production and drives histone lactylation at the programmed cell death ligand 1 (PD-L1) promoter, upregulating PD-L1 expression and facilitating immune escape.[12] Lactate secreted by CC cells elevates glycerol-3-phosphate dehydrogenase 2 expression via H3K18la, driving M2 polarization of macrophages in the TME.[53] These findings provide new insights into the role of histone lactylation in macrophage polarization during the malignant transformation of gynecological cancers.

Lactylation also promotes therapy resistance in gynecological malignancies. In platinum-resistant OC, H3K9la levels are significantly elevated, directly activating RAD51 and BRCA2 expression to enhance HR repair. Concurrently, RAD51 lactylation at RAD51K73la further increases HR efficiency. Both modifications correlate with platinum resistance and poor prognosis.[9] In niraparib-resistant models, RAD23A is markedly upregulated. Lactate accumulation in OC drives histone H4K12 lactylation, aberrantly elevating RAD23A expression and myelocytomatosis viral oncogene homolog (MYC) transcription factor levels, thereby promoting niraparib resistance.[10]

Epigenetic therapy

Current research on chemotherapy resistance in gynecological malignancies explores diverse mechanisms, such as exosomes and

metabolic reprogramming.[58–60] Lactate accumulation and protein lactylation drive malignant progression and confer resistance to platinum-based agents and poly ADP-ribose polymerase inhibitors, positioning lactate metabolism and lactylation as promising therapeutic targets. Lactylation-regulated genes significantly influence responses to gemcitabine and cisplatin.[61] Bevacizumab is commonly administered in OC, particularly in BRCA-mutant cases receiving combination chemotherapy. However, H3K18la induces RUN domain and cysteine-rich domain-containing Beclin 1-interacting protein-like expression, promoting bevacizumab resistance in cancer cells,[33] while targeted inhibition of H3K18la restores cisplatin sensitivity in resistant bladder epithelial cells.[35] In platinum-resistant OC, H3K9la levels are significantly elevated. This histone modification directly activates RAD51 and BRCA2 expression, promoting HR repair. Concurrently, RAD51 lactylation at RAD51K73la enhances HR repair efficiency. Both modifications correlate with platinum resistance and poor prognosis.[9] In niraparib-resistant models, RAD23A is markedly upregulated. Lactate accumulation in OC drives histone H4K12 lactylation, which aberrantly elevates RAD23A expression and MYC transcription factor levels, thereby promoting niraparib resistance.[10]

Metabolic interference

Pharmacological targeting of glycolytic pathways reduces lactate production and lactylation modifications. 2-deoxy-D-glucose (2-DG) exerts its effect on hexokinase (hereinafter referred to as HK), a glycolytic rate-limiting enzyme. It functions by depleting the energy of cancer cells and increasing ROS production, leading to cell death. However, its efficacy in treating tumors is limited; thus, it is used in combination with other pharmaceuticals or chemotherapy to enhance antitumor effects.[62] Cell function experiments suggest that 2-DG may act through glycolysis and the Wnt/β-catenin signaling pathway.[63]

Tanshinone I reduces glycolysis by downregulating glycolytic enzymes (HK2, PFKP, enolase 2, lactate dehydrogenase A (LDHA)), decreasing lactate production and H3K18la levels.[64] It also downregulates the oncogenes threonine tyrosine kinase protein kinase and PDGFR-β, reversing the immunosuppressive TME in OC and exerting inhibitory effects. Enolase 1 (ENO1) mAb specifically blocks ENO1 on the cell membrane and inhibits ENO1 glycolytic activity inside tumor cells, providing therapeutic benefits against CC.[65] The SLC16A1/3 inhibitor gallic acid-iron-Embelin delivery system targets the cancerous cell marker SLC16A1/3, promoting lactic acid accumulation, inducing redox imbalance, and disrupting glycolysis. In conjunction with photothermal therapy, it modulates glycolysis and glycolysis-related redox processes, providing a novel therapeutic approach for malignant CC.[66]

Lactate transporter inhibitors

Monocarboxylate transporters 1/4 (MCT 1/4) regulate lactate movement into and out of cells. Targeting lactate shuttling has emerged as a validated anticancer strategy.[67] Syrosingopine and AZD3965 are potent dual inhibitors of MCT1 and MCT4.[68] Syrosingopine sensitizes cancer cells to metformin and its more potent derivative, phenformin, at doses far below each compound's toxic threshold. Thus, combining syrosingopine with co-drugs is a promising therapeutic strategy for clinical application.[69] Additionally, CD147 regulates MCT1/4 membrane trafficking via Akt-FoxO3-NF-κB signaling,[70] which may serve as a potential pharmaceutical target for drugs designed to impede MCT function on the cell membrane.

Immunotherapeutic strategies

Immune checkpoint inhibitors, such as anti- programmed death 1 receptor (PD-1)/PD-L1 antibodies, represent breakthrough cancer therapies.[71] Signal transducer and activator of transcription 5 overexpression in acute myeloid leukemia enhances lactate production via glycolytic upregulation. This lactate accumulation drives histone lactylation, directly activating PD-L1 transcription. Consequently, acute myeloid leukemia patients exhibiting signal transducer and activator of transcription 5-mediated hyperglycolysis and lactate accumulation may respond better to PD-1/PD-L1 blockade therapy.[72] In OC, LDHB modulates lactate production and drives histone lactylation at the PD-L1 promoter, upregulating PD-L1 expression to facilitate immune evasion.[12] Combining PD-L1 inhibitors with lactate dehydrogenase inhibitors or MCT inhibitors has shown superior efficacy compared with lactate dehydrogenase inhibitors alone.[73] In CC, hyperactivation of the N-Acetyltransferase-like protein 10 / N4-acetylcytidine / forkhead box P1 axis enhances glycolytic metabolism and sustained lactate hypersecretion. Genetic ablation of this axis potentiates PD-L1 blockade-mediated tumor regression, identifying it as a promising target for combinatorial immunotherapy.[74] Resveratrol inhibits glucose uptake and metabolism, reducing glycolytic ROS production and lowering lactate levels in the TME, which attenuates Treg-mediated immunosuppression.[75] Concurrently, resveratrol induces autophagy,[76] counteracting IL-6-driven OC progression.

Other therapeutic targets

LDH inhibitors disrupt lactate metabolism, reducing lactylation-mediated DNA repair and immunosuppressive pathways. Oxamate, a small-molecule LDHA inhibitor, induces protective autophagy in gastric cancer cells by suppressing the Akt- mammalian target of rapamycin axis. In CC cells, LDHA inhibition induces cell cycle arrest and apoptosis primarily via the c-Jun N-terminal kinase signaling pathway.[77] Lactate production inhibitors not only reprogram glucose metabolism in cancer stem cells but also modulate macrophage immunophenotypes via H3K18la-mediated epigenetic remodeling, reducing tumor-infiltrating Tregs and potentiating PD-L1 inhibitor efficacy.[78] However, LDH's essential roles in systemic metabolism and current inhibitors' poor tissue selectivity raise safety concerns, as nonspecific LDH inhibition may disrupt physiological lactate metabolism.[79] Developing tissue-specific or isoform-selective LDH inhibitors remains a critical pharmacological challenge. Metformin, a classic antidiabetic agent, inhibits CC cell proliferation, induces apoptosis and cell cycle arrest, and enhances natural killer cell cytotoxicity via PI3K/AKT-mediated regulation.[80] When combined with nelfinavir, metformin triggers Sirtuin 3 (SIRT3)-dependent autophagy via mitochondrial ROS generation, reducing protein lactylation levels.[81] This dual-agent approach synergizes with immunotherapy to suppress tumor growth. Dichloroacetate and metformin together significantly enhance ovarian tumor suppression in xenograft models.[82] Cold atmospheric plasma (CAP) is a promising therapy that shows anti-tumor effect in several gynecologic cancer cell lines.[83] CAP suppresses cancer cell migration and proliferation by inducing ferroptosis. Mechanistically, CAP downregulates USP49, enhancing HDAC3 ubiquitination and reducing HDAC3-mediated H3K18la. This epigenetic shift upregulates p53 expression, driving ferroptotic cell death.[56]

Challenges and future research directions

The Warburg effect leads to lactate accumulation, which in turn promotes lactylation, forming a core axis of "lactate–lactylation–

functional protein/signaling pathway". Lactate and lactylation now serve as key integrators linking metabolic reprogramming and epigenetic regulation, transforming lactate from a metabolic waste product into a functionally central molecule. This mechanism facilitates tumor proliferation and immune evasion, thereby impairing therapeutic efficacy and patient prognosis.

Ongoing lactylation-targeted clinical trials (NCT05163505, NCT04889716) have provided preliminary evidence of therapeutic benefits, indicating the potential of targeting lactylation in cancer treatment. Current research focuses on limiting lactate production—for instance, using 2-DG to inhibit glycolytic enzymes, which modulates immunosuppression by decreasing H3K18la levels.[84] The LDH inhibitor stiripentol can inhibit NBS1 K388 lactylation, reduce DNA repair efficacy, and overcome chemotherapy resistance.[85] Nowadays, MCT inhibitors have also emerged as promising targets. However, many therapeutic candidates remain in the preclinical stage. Although targeting lactate metabolism holds promise, the broad involvement of lactate in metabolic and signaling pathways poses challenges for drug specificity, raising concerns about potential adverse effects. There is a compelling need to improve the specificity and effectiveness of these inhibitors to selectively disrupt lactate production and lactylation while minimizing toxicities. Recent studies also suggest that AARS1 may act as a bridge connecting lactate metabolism and lactylation, indicating that disrupting this interaction could offer a novel treatment avenue. BLM is highly lactylated at Lys24 by AARS1 in response to chemotherapy. A single-arm phase I study (NCT06766266) indicated that irinotecan shows synergistic effects and safety in alleviating anthracycline resistance by targeting BLM lactylation and suppressing HR repair in pancancer models.[13] Based on current research, the role of LDH inhibitors has gained broad recognition, and further studies are aimed at enhancing their targeting specificity. Meanwhile, direct targeting of lactylation sites and modulation of PD-L1 lactylation show substantial research potential, as they influence cancer therapy through upstream signaling pathways and immune regulation, respectively. Notably, disrupting the DPF2-H3K14la interaction via structure-guided mutation blunts cancer-related gene expression and decreases cell survival.[54] Future directions may also include direct intervention targeting the enzymes of lactylation—"writers", "erasers", and "readers".

Kla modification sites are critical for advancing research. Integrated proteomic and metabolomic screening should be deployed to discover gynecological malignancy-specific Kla sites, followed by systematic functional validation of their pathological significance. Building upon conventional mass spectrometry, researchers have employed automated machine learning approaches to achieve rapid and accurate prediction of lactylation sites in gastric cancer models.[86] Leveraging multi-omics databases combined with single-cell analyses, it is now possible to construct lactylation-associated prognostic models for gynecological malignancies.[87] ALDH1A1 and S100A4 have been confirmed and characterized as potentially associated with chemoresistance in OC.[88]

It must be acknowledged that this field has certain limitations. Lactylation is a recently discovered and rapidly evolving area of study, and current basic and clinical research in gynecological oncology remains limited. By drawing insights from studies in other cancers, we provide valuable references for future research in gynecological malignancies. Additionally, current therapies targeting lactylation sites are not first-line treatment options, and most related drugs are still in the preclinical stage. These limitations highlight both the challenges and the promising research potential of lactate metabolism and lactylation modifications in the future.

Conclusions

In this review, we elucidate the relationship between lactate metabolism and lactylation in gynecological malignancies. We comprehensively demonstrate that lactate accumulation and lactylation are closely associated with tumor progression and chemotherapy resistance. Several epigenetic therapies targeting this pathway, including glycolytic metabolism interference, lactate transport inhibition, immunotherapeutic strategies, and other therapeutic targets, have shown therapeutic potential. Therefore, exploring emerging therapies based on lactate metabolism and lactylation remains a promising direction in the treatment of gynecological malignancies.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Interpretation, drafting of the article (YH, ZY), study conception (LC, YZ), critical revision of the article, and final approval of the version to be published (YH, ZY, LC, YZ).

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