Am J Cancer Res 2025;15(12):5168-5182
www.ajcr.us /ISSN:2156-6976/ajcr0168787

Review Article

Decoding protein lactylation in the pathogenesis and progression of gynecological cancer

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Received September 13, 2025; Accepted December 14, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Gynecological tumors represent a significant health burden worldwide. Protein lactylation has emerged as a novel post-translational modification (PTMs) that directly links metabolic reprogramming to epigenetic and functional regulation. Lactylation occurs when lactate covalently modifies the lysine residues of proteins. Initially discovered on histones, lactylation was shown to influence gene transcription; however, accumulating evidence reveals its broader impact on nonhistone proteins, affecting diverse processes. Elevated lactate levels in the tumor microenvironment increase protein lactylation. Evidence suggests a dynamic interplay between tumor metabolism and cancer progression. In this review, we provide an overview of the fundamental aspects of protein lactylation, including the key enzymes that catalyze the addition and removal of lactyl groups. We further emphasize recent discoveries on how lactylation influences the development and progression of gynecological malignancies. Finally, we explore the potential of targeting protein lactylation as an emerging therapeutic strategy in the management of gynecological cancers.

Keywords: Lactylation, cervical cancer, ovarian cancer, endometrial cancer, treatment

Introduction

Gynecological tumors are a group of common malignancies that originate in the female reproductive system [1]. Gynecological cancers are categorized based on their site of origin, including cervical, ovarian, endometrial, vulvar, and vaginal cancers [2]. Gynecological cancer patients exhibit irregular intermenstrual bleeding or discharge, pelvic pain, dyspareunia, and vulvar itching or burning. Various strategies have been implemented for prevention and early detection, such as routine pelvic examinations, HPV vaccination, and evaluation of family history [3-5]. Moreover, inherited susceptibility contributes importantly to the onset of certain gynecologic malignancies [6, 7]. Current treatment options include surgical intervention, chemotherapy, radiation therapy, molecular targeted agents, immune-based treatments, or integrated multimodal approaches [8-10].

Post-translational modifications (PTMs) refer to chemical changes that occur in proteins once they have been synthesized by ribosomes [11]. Typical PTMs include ubiquitination, methylation, glycosylation, phosphorylation, acetylation, nitrosylation, and lipidation [12-14]. PTMs influence protein function by regulating their enzymatic activity, structural stability, and localization within cells through the addition or removal of functional groups or by modifying amino acid structures [15]. PTMs are fundamental to the modulation of numerous cellular functions, such as metabolism, differentiation, proliferation, cell cycle progression, apoptosis, immune responses, and metastasis [16]. Consequently, perturbation of PTMs is tightly connected to the pathogenesis of various diseases, including cancer [17, 18].

In 2019, Zhang et al. reported that lactate-derived histone lactylation functions as a novel epigenetic modification that regulates gene transcription, which links the Warburg effect and various broader pathophysiological processes [19]. In recent years, research on pro-

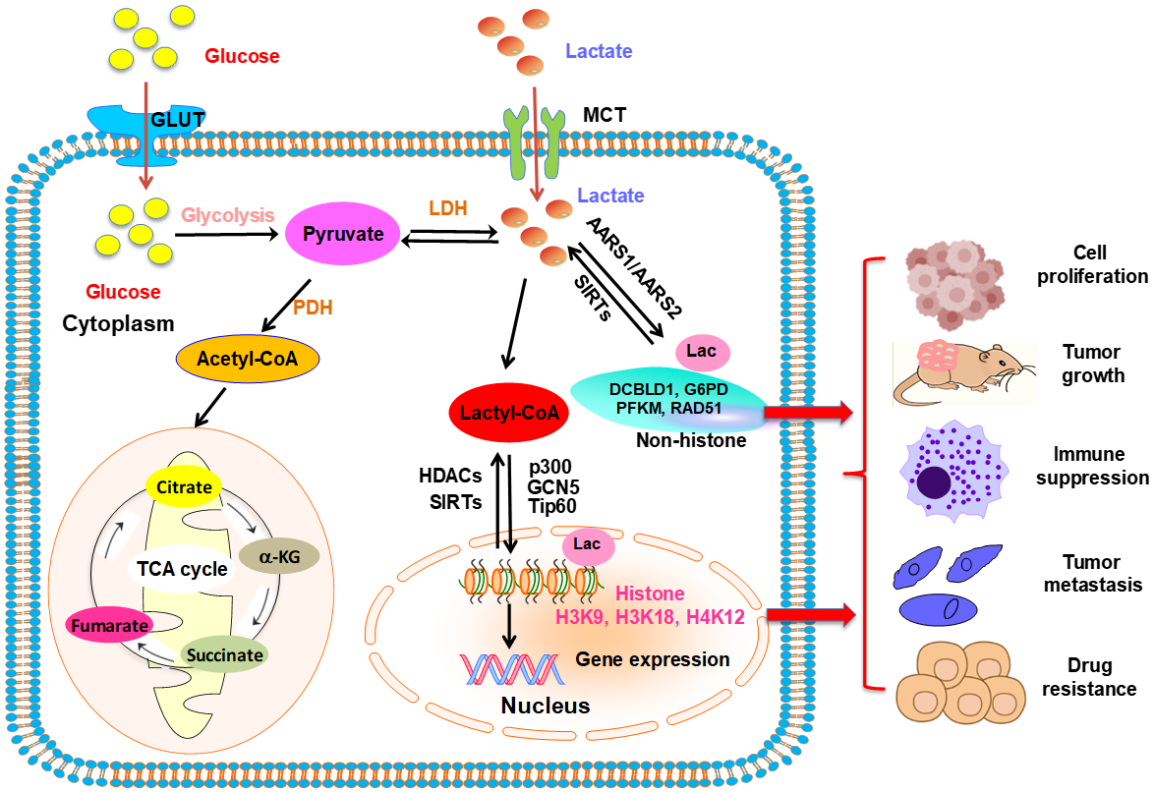

Figure 1. Schematic overview of the protein lactylation process. Glucose metabolism via glycolysis produces pyruvate, which is converted into lactate by lactate dehydrogenase (LDH). Lactate is transported by monocarboxylate transporters (MCTs) and used to produce lactyl-CoA. Lactyl-CoA serves as a donor for histone and nonhistone protein lactylation mediated by acyltransferases, thereby influencing gene expression. Conversely, histone deacetylases (HDACs) and sirtuins (SIRTs) remove lactylation marks, suggesting the dynamic and reversible feature of this modification. Abnormal lactylation regulates cell proliferation, tumor metastasis, drug resistance, and immune evasion in human cancer.

tein lactylation has increased rapidly, with numerous studies demonstrating its important role in a broad range of illnesses, including cardiovascular abnormalities [20, 21], neurodegeneration [22, 23], and cancers [24-26]. Lactylation is one type of PTM in which a lactyl group derived from lactate is bound via stable covalent linkage to lysine sites in proteins [27]. Lactylation was initially described for histone proteins, leading to the regulation of gene transcription [28]. Lactylation provides a direct connection between cellular metabolism, specifically glycolysis, and the epigenetic and functional regulation of proteins [29]. Elevated lactate levels, which are often observed in the tumor microenvironment (TME) because of aerobic glycolysis, known as the Warburg effect, can increase protein lactylation [30-32]. Lactylation has been reported to alter protein activity, stability, localization, and interactions [33, 34]. In addition to histones, the lactylation of nonhistone proteins contributes to multiple biological processes, such as proliferation, differentiation, apoptosis, autophagy, invasion and metastasis [35-37]. Given its close relationship with the metabolic state and cancer, including gynecological cancers, protein lactylation could be critical for tumorigenesis. Therefore, this review provides an overview of protein lactylation, particularly the enzymatic machinery responsible for writing and erasing lactyl marks (**Figure 1**). Moreover, we highlight the role of lactylation in gynecological cancers and discuss whether protein lactylation might emerge as a potential intervention point in the treatment of gynecological cancers.

Protein lactylation

Lactyltransferases

The lactyltransferases that catalyze protein lactylation have been investigated in recent

years. Some evidence suggests that p300/CBP, which is a well-known histone acetyltransferase, may also mediate histone lactylation by using lactyl-CoA as a donor molecule [38]. The mechanism by which p300 catalyzes protein lactylation remains an active area of research. Recent studies have identified alanyl-tRNA synthetases 1 and 2 (AARS1 and AARS2) as novel lactyltransferases responsible for catalyzing lysine lactylation on proteins [39]. In general, AARS1 and AARS2 function as alanyl-tRNA synthetases and charge tRNA molecules with alanine during protein translation. AARS1 and AARS2 predominantly regulate cytoplasmic and mitochondrial protein lactylation, respectively, indicating that they have spatial specificity in the regulation of lactylation. For example, one study revealed that AARS1 uses lactate and ATP to modify the YAP protein in gastric cancer [40]. AARS2 promotes ferroptosis during intestinal ischemia-reperfusion injury by driving histone lactylation [41]. In addition, hypoxia induces AARS2 accumulation to increase PDHA1 and CPT2 lactylation, leading to the suppression of oxidative phosphorylation (OXPHOS) [42].

Delactylases

Recent studies have identified certain histone deacetylases (HDACs) and sirtuins as potential delactylases. For example, one study from the Zhao group revealed that HDAC1-3 and SIRT1-3 function as delactylases to control protein lactylation [43]. Liu et al. reported that Xklp2 (TPX2) is lactylated at K249, a modification mediated by the lactylase CBP and reversed by the delactylase HDAC1, which promotes AURKA activation, cell cycle progression, and tumor growth in hepatocellular carcinoma (HCC) [44]. He et al. showed that HDAC2 promotes cisplatin resistance in triple negative breast cancer (TNBC) by delactylating METTL3, leading to enhanced m6A-mediated DNA repair, whereas HDAC2 inhibition by tucidinostat sensitizes tumor cells to cisplatin treatment [45]. Zhao et al. uncovered that lactate-induced RBM15 lactylation at lysine 850 stabilizes RBM15, enhances its interaction with METTL3, and promotes m6A methylation and tumor progression in lung adenocarcinoma, whereas HDAC3 acts as its delactylase to reduce RBM15 lactylation [46]. HDAC6 has been identified as a lactyltransferase that catalyzes α-tubulin lactylation at lysine 40 in a lactate-dependent and reversible manner, thereby enhancing microtubule dynamics and promoting neurite outgrowth [47]. SIRT1 and SIRT3 are NAD^+-dependent deacetylases (class III HDACs) that exhibit lysine delactylase activity. For instance, one study identified SIRT1 and SIRT3 as key delactylases that selectively regulate histone and nonhistone lysine lactylation, including that of the PKM2 protein [48]. However, the full repertoire of delactylation enzymes, especially those that modify nonhistone proteins, is still being investigated.

Lactyl-CoA synthetase

Lactyl-CoA synthetases catalyze the enzymatic conversion of lactate and CoA into lactyl-CoA, which makes it suitable for use as a donor molecule in protein lactylation. The nuclear enzyme GTPSCS catalyzes the conversion of L-lactate into lactyl-CoA, which enables histone lactylation through its interaction with p300 [49]. The GTPSCS/p300 axis enhances H3K18la modification and GDF15 expression, thereby promoting glioma proliferation and radiotherapy resistance [49]. Zhu et al. reported that ACSS2 can function as a lactyl-CoA synthetase whose phosphorylation and nuclear translocation upon EGFR-ERK activation enable the conversion of lactate into lactyl-CoA, which interacts with KAT2A to mediate histone H3 lactylation [50]. Moreover, ACSS2 and KAT2A promote oncogenic signaling and immune evasion in brain tumors. Furthermore, blocking the association of ACSS2 with KAT2A enhances the efficacy of anti-PD-1 therapy [50].

Lactylation functions in tumorigenesis and progression

Numerous studies have established that lactylation is an important regulator of tumorigenesis and cancer progression. One study revealed that DNA damage induces CBP-mediated MRE11 lactylation at lysine 673, which increases its DNA binding ability and promotes homologous recombination repair [51]. Another study identified that AARS1 is a lactate sensor that transfers lactate to p53 at K120 and K139, thereby impairing the phase separation and transcriptional activity of p53 [52]. Chen et al. reported that lactate-driven lactylation of NBS1 at K388, which is catalyzed by TIP60 and removed by HDAC3, enhances homologous recombination-mediated DNA repair and contrib-

Table 1. The role of lactylation in gynecologic cancer progression

Tumor type	Targets	Lactylation site	Mechanisms	Functions	Ref
Cervical cancer	PPP1R14B	K140	Increases the infiltration of CD8+ T cells	Suppresses proliferation and migration	[62]
Cervical cancer	DPF2	H3K14	Acts as an H3K14la effector, couples histone lactylation	Drives transcription and tumorigenesis	[64]
Cervical cancer	GPD2	H3K18	Lactate upregulates H3K18la-modified GPD2; promotes M2 polarization	Promote malignant transformation	[66]
Cervical cancer	DCBLD1	K172	Increases DCBLD1 stability, enhances PPP activity via stabilization of G6PD	Lactate promotes proliferation and metastasis	[70]
Cervical cancer	G6PD	K45	Suppresses PPP activation; inhibits GSH, NADPH; increases ROS	Inhibits cell proliferation	[80]
Ovarian cancer	MRE11, NBS1	Not detect	Acetylated ME2 drives glutamine-derived lactate production	Causes DNA repair and chemoresistance	[85]
Ovarian cancer	ALDH1A1, S100A4	Not detect	Elevates oxidative phosphorylation and glycolysis activity	Promotes cisplatin resistance	[86]
Ovarian cancer	Histone	H3K18	Increases migration	Associates with poor prognosis	[87]
Ovarian cancer	CCL18	H3K18	Lactate activates CCL18 expression	Promotes ovarian tumorigenesis	[88]
Ovarian cancer	PD-L1	H3K18	LDHB mediates histone lactylation to activate PD-L1	Promotes ovarian cancer immune escape	[89]
Ovarian cancer	RAD23A	H4K12	Activates RAD23A via Myc; enhances DNA damage repair ability	Promotes niraparib resistance	[90]
Ovarian cancer	PFKP	K392	Enhances glycolysis, decreases PTEN	Promotes tumor progression	[95]
Ovarian cancer	Histone	H3K9	H3K9la activates RAD51 and BRCA2 expression, facilitates HR repair	Promotes cisplatin resistance and poor prognosis	[101]
Ovarian cancer	RAD51	K73	Enhances HR repair	Enhances cisplatin resistance	[101]
Endometrial cancer	USP39	H3K18	Stimulates USP39 expression, activates PI3K/AKT/HIF-1α, stabilizes PGK1	Stimulates glycolysis, promotes tumor progression	[108]
Endometrial cancer	P53	H3K18	CAP activates the p53 transcription by H3K18 lactylation	Drives cell ferroptosis	[111]
Endometrial cancer	PFKM	K678	Involves immune infiltration	Promotes proliferation, invasion, tumor progression	[116]

utes to drug resistance [53]. AARS1 and AARS2 act as intracellular sensors of L-lactate, directly catalyzing cGAS lactylation, which dampens innate immune responses [54]. Without doubt, lactylation is strongly implicated in gynecological cancer development. The subsequent paragraphs explore its functions in tumor initiation and advancement.

Role of lactylation in gynecological cancers

Cervical cancer

As one of the most common gynecological cancers, cervical cancer continues to pose a major health challenge worldwide [55]. It has been known that chronic infection with high-risk HPVs is recognized as the primary cause leading to malignant transformation [56]. Despite advances in screening, vaccination, and therapy, challenges such as recurrence, metastasis, and therapeutic resistance continue to limit survival in patients with cervical cancer [57, 58]. Recent evidence suggests that lactylation contributes to cervical tumorigenesis and progression [59]. Protein phosphatase 1 regulatory subunit 14B (PPP1R14B) is an inhibitory regulator of protein phosphatase 1 that modulates cellular contraction, signaling, and cytoskeletal dynamics through phosphorylation-dependent pathways [60]. PPP1R14B is upregulated in cervical and endometrial cancers, predicts poor prognosis, and promotes tumor cell proliferation and survival by activating the Akt pathway [61]. One study performed a comprehensive proteomic and multiomics analysis of lysine lactylation (Kla) in cervical cancer and identified Kla-related subtypes. Moreover, PPP1R14B-K140 lactylation suppressed tumor progression in cervical cancer [62]. Here, we address the impact of lactylation on both the initiation and advancement of cervical cancer (**Table 1**).

Histone lactylation: Double PHD fingers 2 (DPF2) is a chromatin-associated protein that regulates gene transcription and cell fate decisions. For example, high DPF2 expression is associated with poor prognosis, immune evasion, and dysregulation of key pathways such as the cell cycle and Wnt signaling in hepatocellular carcinoma [63]. Zhai et al. identified that DPF2 is a reader of the histone lactylation marker H3K14la in cervical cancer, which facilitates lactate-driven histone lactylation to promote oncogene transcription and cell survival [64]. GPD2 is a mitochondrial enzyme and is involved in lipid metabolism and redox balance [65]. Huang et al. reported that the secretion of lactate from cervical cancer cells stimulates M2 macrophage polarization, a process dependent on H3K18 lactylation-driven induction of GPD2, which supports a histone lactylation-mediated mechanism to drive immune modulation and cancer progression [66]. Both DPF2 and GPD2 participate in lactate-driven epigenetic regulation and immune modulation in cervical cancer. DPF2 acts as a histone lactylation reader that promotes oncogene transcription [64], whereas GPD2, through lactate-induced histone lactylation, facilitates M2 macrophage polarization and tumor progression [66]. Overall, both factors play key roles in the lactate-lactylation-tumor development axis in cervical cancer.

DCBLD1 lactylation: The DCBLD1 gene has been implicated in the regulation of cell signaling, cell proliferation, and tumor progression [67]. For example, Shen et al. reported that DCBLD1 expression is elevated in cervical cancer tissues and promotes tumor progression by increasing cell proliferation, invasion, and survival, whereas its knockdown induces apoptosis and G1 cell cycle arrest. Mechanistically, TBP was identified as a transcriptional activator of DCBLD1 [68]. Similarly, another group illustrated that DCBLD1 expression is elevated in various cancer types, including cervical cancer, and is linked to unfavorable clinical outcomes and immune infiltration. Furthermore, silencing DCBLD1 expression suppressed tumor cell growth, motility and invasive behaviors in cervical cancer [69]. Lactate promotes cervical cancer progression by increasing DCBLD1 expression through HIF-1α-mediated transcriptional activation and stabilizing it via K172 lactylation, thereby enhancing pentose phosphate pathway (PPP) activity through the upregulation and stabilization of glucose-6-phosphate dehydrogenase (G6PD) [70]. Moreover, targeting G6PD with 6-AN effectively suppresses tumor growth by inhibiting PPP activation in mice [70]. These studies highlight the therapeutic potential of targeting the lactate-DCBLD1-PPP axis in cervical cancer.

G6PD lactylation: G6PD is a rate-limiting enzyme of the pentose phosphate pathway that regulates cellular redox homeostasis by producing NADPH [71]. G6PD has been identified to regulate tumorigenesis and tumor progression, including in cervical cancer [72, 73]. For instance, G6PD is upregulated in cervical cancer cells harboring high-risk HPV infection and promotes cell proliferation and survival, with its inhibition leading to reduced growth and increased apoptosis, particularly in HPV18+ cells [74]. Fang et al. proposed that G6PD deficiency restrains cell migratory behavior and proliferation by increasing ROS-induced apoptosis and disrupting cytoskeletal organization and biomechanical properties in cervical cancer [75]. Additionally, miRNA-1 and miRNA-206 suppress tumor progression by directly downregulating G6PD expression, resulting in decreased proliferation and elevated apoptotic activity in cervical cancer [76, 77]. Notably, one study identified HPV16 E6 as a transcriptional activator of G6PD, which promotes progression by enhancing cell growth and migratory behavior in cervical cancer via the upregulation of G6PD expression [78]. Another study revealed that HPV E6 promotes tumor progression by upregulating G6PD in cervical cancer, which upregulates STAT3 and PLOD2 expression to enhance the biological functions of tumor cells [79]. Recently, one group reported that the suppression of G6PD K45 lactylation by HPV16 E6 leads to PPP activation and increased cell proliferation, which enhances G6PD dimer formation and enzyme activity in cervical cancer [80]. In line with this point, lactylation-mimicking mutations or G6PD inhibition suppresses tumor growth in patients with cervical cancer [80]. Together, these findings underscore lactylation-dependent G6PD regulation as a critical driver of cervical cancer progression.

Ovarian cancer

Ovarian cancer is the deadliest gynecological malignancy, primarily because of its silent

onset and the absence of reliable early screening tools [81]. A large proportion of patients with ovarian cancer are diagnosed late, when peritoneal dissemination has already occurred. Cytoreductive surgery and platinum-based chemotherapy remain the mainstay treatments [82]. However, chemoresistance and recurrence remain major clinical challenges and lead to poor survival outcomes [83]. Lactylation has been reported to be involved in prognosis and drug resistance in ovarian cancer (**Table 1**). Yu et al. identified that 14 LRGs are linked to patient prognosis, patterns of immune infiltration, and responsiveness to therapy in ovarian cancer. Moreover, an eight-gene lactylation-based prognostic model demonstrated strong predictive value in ovarian cancer [84]. Zheng et al. revealed that acetylated malate enzyme 2 (ME2) drives the production of glutamine-derived lactate under glucose-limited conditions, causing DNA repair and chemoresistance through protein lactylation in ovarian cancer cells [85]. An integrative analysis of scRNA-seq and bulk RNA-seq profiles suggested that the expression of ALDH1A1 and S100A4, which are genes associated with lactylation, could drive resistance to chemotherapy in ovarian cancer [86]. In the next paragraphs, we dissect the role of lactylation in ovarian tumorigenesis and progression.

Histone lactylation: Chao et al. reported that elevated histone H3K18 lactylation is linked to poor prognosis, resistance to platinum-based therapy, and increased metastatic capacity in epithelial ovarian cancer [87]. Lactate facilitates ovarian cancer progression by inducing the expression of CCL18 through H3K18 lactylation in macrophages, which results in M2 polarization and enhanced tumor growth and metastasis via the Gpr132-CCL18 axis [88]. Hu and colleagues reported that LDHB facilitates immune escape by increasing PD-L1 levels through H3K18 lactylation at its promoter in ovarian cancer [89]. Moreover, LDHB knockdown reduced lactate production, inhibited tumor growth, and restored T-cell-mediated immune activation [89]. Furthermore, lactate-induced H4K12 lactylation upregulated RAD23A expression via superenhancer activation in ovarian cancer cells with resistance to niraparib, which resulted in enhanced DNA repair and increased drug resistance [90]. In ovarian cancer, lactate-driven histone lactylation modifications, including H3K18la and H4K12la, promotes tumor progression, metastasis, immune escape, and therapeutic resistance, highlighting histone lactylation as a key epigenetic driver of ovarian malignancy.

PFKP lactylation: Phosphofructokinase platelet type (PFKP), a central rate-determining enzyme in glycolysis, controls cell proliferation, migration, metastasis and stemness via glycolysis [91]. PFKP has been identified as a potential diagnostic marker and a drug target for various cancer types, including ovarian cancer [92, 93]. PFKP expression is strongly positively correlated with activated NK cells and follicular helper T cells but negatively correlated with naïve B cells [93]. The antiparasitic drug ivermectin has been shown to strongly suppress proliferation in epithelial ovarian cancer cells, primarily by targeting PFKP in glycolytic pathways [94]. One study revealed that the lactylation of PFKP at K392 enhances glycolysis and promotes tumor progression by downregulating PTEN expression in ovarian cancer [95]. Therefore, PFKP not only shapes the immune microenvironment but also enhances glycolysis, thereby driving ovarian cancer progression and revealing lactylation-dependent metabolic vulnerabilities.

RAD51 lactylation: RAD51 is a highly conserved protein that regulates the homologous recombinant DNA repair pathway [96]. Research has demonstrated that RAD51 governs the initiation and progression of cervical cancer [97]. For example, metformin antagonizes cisplatin efficacy in ovarian cancer by suppressing the ATM/CHK2 pathway and upregulating RAD51 expression, thereby leading to decreased apoptosis, impaired DNA damage, and chemoresistance [98]. High RAD51 expression predicts poor survival after PARPi treatment, and its upregulation is associated with acquired PARPi resistance [99]. Lysine-specific demethylase 1 (LSD1) suppression reduces the expression of BRCA1/2 and RAD51, triggers impaired HR repair, and increases the sensitivity of HR-proficient tumors to the therapeutic effects of PARP inhibitors in ovarian cancer [100]. One group demonstrated that elevated histone H3K9 and RAD51 lactylation in ovarian cancer, which are regulated by GCN5, promotes HR repair and contributes to platinum resistance [101]. Hence, RAD51 not only drives the initia-

tion and progression of ovarian cancers but also, when overexpressed or lactylated, promotes resistance to platinum and PARP inhibitors, highlighting that the RAD51-centered HR repair machinery and the regulation of its lactylation are promising therapeutic targets for overcoming treatment resistance in ovarian cancer.

Endometrial cancer

Endometrial cancer incidence is steadily increasing because of increasing obesity and aging populations [102]. Molecular alterations, including defects in DNA mismatch repair, PI3K/AKT pathway activation, and hormone receptor signaling, are involved in the pathogenesis of endometrial cancer [103]. Lactylation has been validated to play a critical role in the development of endometrial cancer (**Table 1**). For example, one group analyzed transcriptomic data from the TCGA for UCEC patients and constructed a lactylation-related risk model based on IGSF1, ZFHX4, and SCGB2A1 that predicts patient prognosis, immune infiltration, and therapeutic response in endometrial cancer [104]. IGSF1 is associated with poor prognosis, immune response, and metabolic changes in UCEC [104]. Another group also discovered 16 lactylation-related genes that provide effective prognostic, immunological, and therapeutic response prediction in endometrial carcinoma [105]. Gu et al. uncovered that six lactylation-related genes form a prognostic risk model for endometrial cancer, which links lactylation to tumor progression, immune microenvironment alterations, and drug response [106]. In the following section, we describe the function of lactylation in endometrial cancer development.

Histone lactylation: USP39, a deubiquitinase belonging to the USP family, drives tumor progression and promotes resistance to therapeutic interventions in multiple cancers [107]. One study revealed that high levels of histone lactylation promotes the tumor progression through USP39 upregulation, leading to PGK1 stabilization and subsequent activation of the PI3K/AKT/HIF-1α pathway in endometrial cancer [108]. In addition, p53 is involved in modulating biological processes such as aging, cellular senescence and tumorigenesis [109]. Abnormal p53 expression is associated with poor survival outcomes in patients with endometrioid endometrial cancer [110]. Liu et al. revealed that cold atmospheric plasma (CAP) suppresses endometrial cancer by inducing ferroptosis through the USP49-HDAC3-H3K18la-p53 axis [111]. This study highlights lactylation-regulated deubiquitinases and p53 signaling as promising therapeutic options [111].

PFKM lactylation: PFKM, a muscle-type isoform of phosphofructokinase-1, is a pivotal glycolytic enzyme whose overexpression drives metabolic reprogramming, tumor growth, and metastasis [112]. PFKM undergoes S-nitrosylation at Cys351 by NOS1, which enhances tetramer stabilization, bypasses feedback inhibition, and promotes ovarian cancer cell proliferation, tumor growth, and metastasis [113]. ZEB1 directly upregulates PFKM transcription, thereby enhancing glycolysis, proliferation, and invasion in hepatocellular carcinoma [114]. Increased ASIC1 expression promotes liver cancer cell survival under acidic conditions through increased PFKM expression, whereas ASIC1 knockdown or PFKM silencing impairs cell viability and enhances apoptosis [115]. Moreover, lactate-driven protein lactylation, particularly of PFKM, promotes endometrial cancer progression, and a lactylation score model correlated with clinical features and immune infiltration was constructed [116]. This work further links PFKM to immune-related clinical features and highlights it as a promising metabolic-epigenetic therapeutic target [116].

Lactylation and cancer therapy

In recent years, numerous compounds have been reported to regulate protein lactylation [117, 118]. Tanshinone I is a bioactive compound from *Salvia miltiorrhiza* (commonly known as danshen) that exhibits broad anticancer effects in humans via the modulation of several pathways, including the ROS, PI3K/AKT/mTOR, STAT3, NF-κB, and MAPK/ERK pathways [119, 120]. Tanshinone I inhibits cervical cancer cell proliferation and reverses cisplatin resistance by suppressing the ELK1-mediated transcription of KRAS and downregulating the KRAS-AKT signaling axis [121]. Tanshinone I facilitates the antitumor effects of paclitaxel by suppressing cell proliferation and migratory behavior through the targeting of Bax, Bcl-2, p21 and p16 in ovarian cancer

[122]. It also attenuates cell growth by suppressing glycolysis and inhibiting H3K18 lactylation in ovarian cancer, leading to downregulation of oncogenic gene expression and alleviation of the immunosuppressive TME [123]. In addition, β-alanine interferes with the ability of lactate to interact with AARS1, which reduces p53 lactylation and mitigates tumorigenesis [52]. Evodiamine in *Evodia rutaecarpa* has been shown to have antitumor effects on multiple cancer types [124, 125]. Evodiamine suppresses tumor growth by upregulating Sema3A expression, inducing ferroptosis via GPX4 inhibition, and blocking lactate-driven histone lactylation and HIF-1α activity [126]. The natural compound demethylzeylasteral (DML) downregulates the expression of the histone lactylation marker H3K18la, thereby suppressing MESP1 expression and inhibiting the malignant progression of pancreatic cancer [127]. Determining the compounds that can target protein lactylation in gynecological cancers is necessary.

Lactate enhances Treg cell stability and immunosuppressive function by inducing MOESIN Lys72 lactylation, thereby promoting TGF-β/SMAD3 signaling. Moreover, lactate degradation alone or in combination with anti-PD-1 therapy reduces Treg induction and tumor growth [128]. Lactate released from tumors downregulates macrophage RARγ expression by inducing H3K18 lactylation, leading to enhanced IL-6 production and STAT3-driven tumor promotion in colorectal cancer [129]. SRSF10 drives a self-reinforcing loop with glycolysis and H3K18la by stabilizing MYB mRNA and promoting GLUT1, HK1, and LDHA expression, thereby enhancing M2 polarization of macrophages, which dampens $CD8^+$ T-cell function and fosters an immunosuppressive TME. The small molecule 1C8, which inhibits SRSF10, restores PD-1 immunotherapy efficacy [130]. In pancreatic ductal adenocarcinoma (PDAC), tumor-derived lactate drives ENSA K63 lactylation, which activates the STAT3/CCL2 axis to recruit protumor macrophages and suppress $CD8^+$ T-cell immunity, thereby also fostering an immunosuppressive TME. ENSA-K63la causes resistance to immune checkpoint blockade, while targeting ENSA-K63la/CCL2 restores immunotherapy sensitivity [131]. How protein lactylation affects the immune response and immunotherapy in gynecological cancers remains unclear and warrants further investigation.

Conclusion and future perspectives

In summary, protein lactylation critically contributes to tumor metabolism, epigenetic regulation, and therapeutic resistance, highlighting its potential as a promising clinical biomarker and an avenue for therapeutic intervention for cervical, ovarian, and endometrial cancers. Although increasing evidence supports its emerging role in cancer biology, protein lactylation research in gynecological malignancies remains relatively limited. For example, although several enzymes have been proposed as lactylation "writers", "erasers", and "readers", their roles in gynecological cancers remain only partially defined. The lack of a comprehensive enzyme-substrate network in tumor tissues limits mechanistic interpretation and rational drug design. Moreover, several lactylated proteins such as histones, PFKM, G6PD, and RAD51 have been identified in cervical, ovarian, and endometrial cancers; however, the global lactylome in gynecologic tumors remains poorly characterized. Furthermore, current "lactylation-targeted" strategies mainly involve the modulation of upstream metabolism, such as LDH or broad epigenetic regulators, rather than specifically targeting lactylation writers, erasers, or readers.

Future perspectives should focus on the following points: First, current studies have primarily concentrated on cervical, ovarian, and endometrial cancers, with significantly less focus on vulvar and vaginal cancers. Exploring the role of lactylation in these underexplored tumor types is necessary. Second, integrating lactylation with metabolism and the TME is critical for determining how lactate production (PPP, LDHA/LDHB, G6PD, PFKM), hypoxia (HIF-1α), and stromal/immune cells (TAMs, T cells, CAFs) converge on protein lactylation to shape immune evasion and metastasis in gynecologic tumors using spatial multiomics and single-cell approaches. Third, most published works have focused on histone lactylation and its epigenetic regulation of gene expression. However, recent discoveries indicate that the lactylation of nonhistone proteins, such as p53 [52], RAD51 [101], and MRE11 [51], drives tumor proliferation, invasion, and immune evasion.

Future studies should dissect how the lactylation of specific signaling proteins rewires oncogenic pathways and contributes to gynecological cancers. Fourth, the therapeutic potential of targeting lactylation remains an exciting but underdeveloped area. Few compounds are known to modulate lactylation, such as inhibitors of lactate production (LDHA inhibitors and metabolic modulators) or small molecules that disrupt lactate-enzyme interactions (β-alanine) [132, 133]. The development of selective lactyltransferase and delactylase inhibitors to control lactylation is necessary for the treatment of gynecological cancers. Fifth, it is pivotal to develop robust, standardized assays, including IHC panels, mass-spectrometry signatures, and lactylation scores, to evaluate histone and nonhistone lactylation in cancer patient samples and validate their value for prognosis, therapy response prediction, and molecular subtyping in large, prospective cohorts of patients with gynecological cancer. Sixth, proteolysis-targeting chimeras (PROTACs) are bifunctional small molecules that recruit a target protein to an E3 ubiquitin ligase, triggering its ubiquitination and selective degradation by the proteasome [134]. PROTACs have been shown to target critical proteins in gynecologic cancers [135, 136]. One group developed a stapled peptide PROTAC targeting ZDHHC3 to degrade PD-L1 in cervical cancer cells, enhancing T-cell cytokine release [137]. Hence, PROTACs may provide innovative approaches to treat gynecological tumors by targeting lactylation-associated enzymes.

Acknowledgements

The research was supported by the Zhejiang Provincial TCM Science and Technology Plan Project (No. 2025ZR179) and Hangzhou Health Science and Technology Projects (NO. ZD20210029).

Disclosure of conflict of interest

None.

Abbreviations

AARS1, alanyl-tRNA synthetases 1; 6-An, 6-aminonicotinamide; CPT2, carnitine palmitoyltransferase 2; DCBLD1, Discoidin, CUB, and LCCL domain-containing type I; DML, Demethylzeylasteral; G6PD, glucose-6-phosphate dehydrogenase; GPD2, glycerol-3-phosphate dehydrogenase 2; GTPSCS, Guanosine triphosphate (GTP)-specific SCS; HCC, hepatocellular carcinoma; HDACs, histone deacetylases; HIF-1α, Hypoxia-Inducible Factor 1-alpha; HPV, Human papillomavirus; LSD1, Lysine-specific demethylase 1; OXPHOS, oxidative phosphorylation; PARPi, Poly (ADP-ribose) polymerase inhibitor; PPP, Pentose phosphate pathway; PPP1R14B, Protein phosphatase 1 regulatory subunit 14B; PTM, Post-translational modifications; PROTAC, proteolysis targeting chimera; TBP, TATA-box binding protein; TCGA, The Cancer Genome Atlas; TME, Tumor microenvironment; TwHF, Tripterygium wilfordii Hook F; UCEC, Uterine corpus endometrial carcinoma.

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