Journal of Zhejiang University-SCIENCE B 2026 27(11):1190-1215
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2500177

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Emerging perspectives and promising solutions: lactylation modification in chemo- and radiotherapy of cancer

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Abstract: Protein lactylation modification represents an emerging post-translational protein modification that regulates protein function through the covalent attachment of lactate to protein lysine residues, thereby linking epigenetic regulatory mechanisms to cellular metabolic activities. Tumors pose severe threats to human health, with numerous studies and hypotheses attempting to elucidate their mechanisms of progression. Significant advances have been achieved in tumor biology research, both for the proteins within the tumors and for their genetic alterations, especially in the field of epigenetics. Histone lactylation provides an epigenetic perspective to explain the underlying mechanisms of the malignant progression of tumors. Crucially, lactylation occurs not only on histones but also across diverse proteins, collectively influencing tumorigenesis and progression through transcriptional, translational, and post-translational regulation, while participating in broader physiological and pathological processes. In this review, we focus on lactylation's multifaceted associations with malignant progression in breast cancer, colorectal cancer, non-small cell lung cancer, and other malignancies, such as the promotion of glycolytic activity in tumor cells and a polarization tendency toward alternatively activated (M2-like) features in macrophages in the tumor microenvironment (TME). We also explore how current clinical practitioners can further expand therapeutic paradigms or pave the way for other therapeutic approaches to address oncological challenges of radiation and chemotherapy tolerance.

Key words: Cancer; Lactylation modification; Lactic acid; Chemotherapy; Radiotherapy

1 Introduction

Cancer is the leading cause of mortality on a global scale, affecting both developed and developing countries (Soerjomataram and Bray, 2021). A salient issue in the contemporary management of cancer pertains to the intricate heterogeneity inherent in neoplastic diseases, particularly in their etiology. This heterogeneity gives rise to a plethora of divergent perspectives, which can be articulated through a broad spectrum of viewpoints (Gilbertson, 2011). Current treatment modalities for tumors encompass surgery, radiotherapy, and chemotherapy. However, these therapeutic interventions are encumbered by the challenges of tolerance and post-treatment recurrence. Moreover, radiotherapy and chemotherapy induce toxic effects on the body. The potential for developing secondary malignancies as a consequence of radiotherapy is a salient concern (Ohno et al., 2022; Onishi et al., 2022). The potential for platinum drugs to induce nephrotoxicity, hepatotoxicity, and myelosuppression is a significant concern (Wong and Giandomenico, 1999). These factors impose limitations on treatment plans for tumors and patients' prognoses, albeit to differing extents.

The hallmarks of cancer have been summarized as activation of invasive metastasis, genomic instability, and metabolic reprogramming (Hanahan and Weinberg, 2011). A distinctive feature of tumor metabolism is the reliance of tumor cells on glycolysis, even in the presence of oxygen, to produce adenosine triphosphate (ATP). This phenomenon is known as the Warburg effect (Warburg et al., 1927). However, it is unclear why tumor cells would abandon efficient mitochondrial oxidative phosphorylation (OXPHOS), instead relying on the relatively low-yield efficiency of the glycolytic

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Received Apr. 10, 2025; Revision accepted Aug. 18, 2025;
Crosschecked July 24, 2026; Published online Sept. 7, 2026

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pathway. Lactate, the end product of the glycolytic pathway, was once considered a by-product of metabolic activity. Although increased lactate levels were found to be strongly associated with many malignant behaviors in tumors at an early stage, the exact mechanism remains poorly understood (Gottfried et al., 2006; Fischer et al., 2007). Zhang et al. (2019) reported that lactate can be involved in a novel epigenetic regulatory mechanism: lactylation. Recent investigations have shown that lactate is not only a product of glycolysis, but also a novel histone-modifying substrate. Their report elucidates the significance of the Warburg phenomenon in the metabolic pattern of tumors. This metabolic pattern is characterized by the use of lactate as a substrate by tumor cells, thereby promoting their growth and progression. The study provides a novel approach to addressing the clinical challenge of tolerance from the perspective of energy metabolism, a problem that has persisted in clinical settings for a long time.

The phenomenon of lactylation modification has been observed to be distributed widely in both the nucleus and the cytoplasm. This modification is not only an epigenetic modification of histones, but has also been shown to occur in non-histone proteins as a post-translational modification (PTM), regulating their function (Wan et al., 2022). Defects in APP-K612la of the amyloid precursor protein (APP) have been found to be closely associated with amyloid pathology and memory loss in Alzheimer's disease patients, and up-regulation of APP-K612la levels by lactic acid can help to rescue the pathology (Tian et al., 2025). Lactylation is active in a variety of physiological and pathological processes, not limited to oncological diseases, such as sepsis-related lung and kidney injury, embryonic development, and sperm meiosis (Merkuri et al., 2024; Qiao et al., 2024; Wu et al., 2024; Zhang et al., 2025). Lactylation modification is an emerging PTM, and there have been few detailed studies. Recent studies have focused mainly on metrics such as lactate levels and lactate dehydrogenase A (LDHA) (Qiao et al., 2021; Colbert et al., 2023). We hypothesize that the concept of a "lactic acid production system" can be established to refer to a number of links that can affect lactic acid production, i.e., metabolic systems related to lactic acid production or uptake, such as LDHA, pyruvate kinase M2 (PKM2), monocarboxylate transporters 1/4 (MCT1/4), and glucose transporter 1/3 (GLUT1/3). This will not only facilitate communication when targeting some of the current studies that have not yet explored the depths of lactylation modification, but may also serve as a perspective for regulating the level of lactylation modification along with lactylation modification writers, erasers, and readers.

In this review, we summarize the current body of knowledge and important advances in lactylation modification in the field of oncology/radiotherapy, with a particular focus on the various attempts to address the phenomenon of radiotherapy tolerance, and discuss the entry point and clinical progress of lactylation as a new therapeutic and adjuvant treatment approach.

2 Lactylation

2.1 Discovery of lactylation

The hypothesis that lactylation could serve as a novel histone modification was originally proposed by Zhang et al. (2019). In their study, endogenously produced lactate induced lactylation of histones. Histone H3 lysine 18 lactylation (H3K18la) acted as a "lactate clock" during classical activated (M1) polarization of macrophage, which was initiated by aerobic glycolysis during M1 polarization and by epigenetic mechanisms late in the inflammatory process, and induced alternatively activated (M2-like) features in macrophages. M2-type macrophages differentiate in response to interleukin-4 (IL-4) and IL-13 and participate in T helper 2 (Th2)-type responses. They are widely recognized to be closely associated with humoral immunity and tissue repair (Gordon, 2003) and have a significant promotional effect on tumor development (Qian and Pollard, 2010). The study by Zhang et al. (2019) linked lactate, which for a long time has been regarded almost as a by-product of metabolism, to epigenetic regulation. This not only brings new perspectives on glycolytic activity beyond energy metabolism, but also, based on the extensive links between glycolytic phenomena, lactate, and the M2-like features of macrophages and tumors, brings new connections between the fields of oncology and cellular energy metabolism.

Zhang et al. (2019) discovered histone lactylation using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). Conventional

methods used for the elementary estimation of lactic acid include colorimetric techniques (Barker and Summerson, 1941), enzyme spectrophotometry (Martí et al., 1997), proton nuclear magnetic resonance (Nishijima et al., 1997), and voltammetric methods (Schmitt et al., 2012). In recent years, significant progress has been made in lactate detection methods. Huang and Liu (2023) discovered that human serum DNA aptamers can simultaneously detect L-lactate and D-lactate. This work expanded the application scope of aptamers to simple metabolites and provided useful probes for continuous and multiplexed monitoring. Shao et al. (2022) developed a novel nanocomposite material for lactate detection. Owing to its high selectivity, excellent reproducibility, and stability, this material shows considerable potential for rapid lactate detection applications. With regard to the clinical implications of lactylation, Zheng et al. (2024) identified two lactylation-related genetic subtypes and established a risk scoring system to evaluate the prognosis of pancreatic ductal adenocarcinoma (PDAC) patients as well as their responses to immunotherapy and chemotherapy. Their work highlighted centromere protein A (CENPA) as a promising therapeutic target for PDAC. Lin et al. (2024) used XGBoost to identify lactylation-related long non-coding RNA (lncRNA) signatures, revealing potential connections between lysine lactylation (Kla)-associated lncRNAs and breast cancer, thereby providing innovative therapeutic guidelines for breast cancer management. In clinical practice, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and magnetic resonance imaging (MRI) have become routine imaging techniques, with well-established associations with cellular glycolytic activity (Brindle, 2008; Melkus et al., 2008; Plathow and Weber, 2008). With the growing understanding of lactylation and its physiological and pathological significance, the close relationship between lactylation and glycolytic activity warrants renewed examination and consideration. Melkus et al. (2008) proposed a short-echo spectroscopic imaging technique for lactate characterization. Furthermore, Sattler et al. (2010) demonstrated the connection between non-invasive lactate imaging technology and radioresistance, highlighting its critical clinical value in predicting radiotherapy outcomes and monitoring patient radiation responses.

2.2 Mechanisms of lactylation modification

2.2.1 Readers

Since lactylation was reported as a form of histone modification in 2019, the reader of lactylation modification remained unidentified for a considerable period (Fig. 1a). Hu et al. (2024) showed that brahma-related gene 1 (BRG1) is involved in the reprogramming mechanism of induced pluripotent stem cells (iPSCs) in response to H3K18la, demonstrating its role as a histone reader. Zhai et al. (2024) showed that in cervical cancer cells, double plant homeodomain (PHD) fingers 2 (DPF2) assumes the role of H3K14la reader and co-localizes with it in oncogene promoters. The disruption of DPF2–H3K14la interactions attenuates cell survival and the expression of cancer-associated genes (Zhai et al., 2024).

2.2.2 Writers

Among the enzymes that assume the role of writer during lactylation modification are alanyl-transfer RNA (tRNA) synthetases 1 and 2 (AARS1/2), which normally mediate alanine and tRNA ligation (Fig. 1b). Mao et al. (2024) reported that AARS2 plays a writer's role in mouse muscle cells under hypoxic conditions, inducing lactylation of pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1) and carnitine palmitoyltransferase 2 (CPT2) and limiting the OXPHOS process in cells. AARS1 has been identified as a catalyst for the lactylation of Yes-associated protein (YAP)-transcriptional enhanced associate domain (TEAD) and p53 in tumor cells, thereby playing a pivotal role in the regulation of cell proliferation signaling (Ju et al., 2024; Zong et al., 2024). The mechanism by which AARS1/2 exert their lactylation transferase action is divided into two main steps: first, AARS1/2 activate L-lactate to form lactate-adenosine monophosphate (Lac-AMP) and release pyrophosphate; then AARS1/2 transfer L-lactate to the lysine residue of the substrate and release AMP. Furthermore, AARS1/2 function as integral lysine lactyltransferases, thereby regulating cyclic GMP-AMP synthase (cGAS) and affecting the innate immune response (Li HY et al., 2024).

Another critical lactyl writer is p300, which was predicted by Zhang et al. (2019) to be a potential histone Kla-writing protein. p300 was reported to catalyze Yin Yang 1 (YY1) lactylation and H3K18la in PDAC cells, confirming that it can act as a lactate

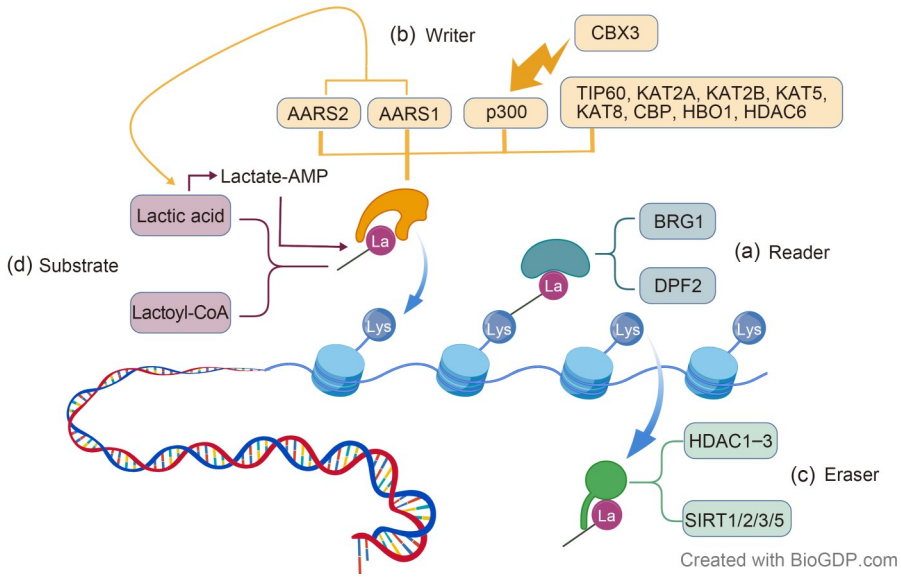

Fig. 1 Regulation of lactylation: reader (a), writer (b), eraser (c), and substrate (d). The lactyl group can be supplied by lactoyl-CoA or directly derived from lactate (La). In the writer process, which is catalyzed by AARS1/2, lactate first forms lactate-AMP as a direct substrate, which subsequently transfers the lactyl group to lysine (Lys) residues of target proteins. In contrast, p300 uses lactoyl-CoA as its substrate. Although CBX3 lacks intrinsic catalytic activity for the lactyl group incorporation, it enhances the substrate specificity of p300 toward lactoyl-CoA, thereby facilitating lactylation. The identification of lactylation readers remained elusive for a long time. This review identifies two recently characterized readers, BRG1 and DPF2, which mediate the lactyl group recognition and functional execution of lactylation modifications. The schematic diagram was created with BioGDP.com (Jiang et al., 2025). CoA: coenzyme A; AARS1/2: alanyl-transfer RNA (tRNA) synthetases 1 and 2; AMP: adenosine monophosphate; CBX3: chromobox protein homolog 3; TIP60: Tat-interactive protein 60; KAT: lysine acetyltransferase; CBP: cyclic AMP (cAMP)-response element-binding protein; HBO: histone acetyltransferase-binding to ORC; HDAC: histone deacetylase; BRG1: brahma-related gene 1; DPF2: double plant homeodomain (PHD) fingers 2; SIRT: sirtuin.

writer (Huang JX et al., 2024; Li F et al., 2024a). In addition, although chromobox protein homolog 3 (CBX3), a heterochromatin component, does not inherently exhibit direct lactyltransferase activity, it binds p300 and enhances its specificity for the substrate lactoyl-coenzyme A (lactoyl-CoA) (Wang S et al., 2024). In addition, Tat-interactive protein 60 (TIP60), lysine acetyltransferase 2A (KAT2A), KAT2B, KAT5, KAT8, cyclic AMP (cAMP)-response element-binding protein (CBP), histone acetyltransferase-binding to ORC1 (HBO1), and histone deacetylase 6 (HDAC6) have also been reported to be lactyl writers (Sun WX et al., 2023; Sun SS et al., 2024; Chen HX et al., 2024; Chen YP et al., 2024; Niu et al., 2024; Xie et al., 2024; Lu et al., 2025; Zhu et al., 2025).

2.2.3 Erasers

Lysine deacetylase (KDAL) is composed mainly of HDAC (Li HD et al., 2024) and sirtuin (SIRT) (Jin et al., 2023) (Fig. 1c). HDAC1–3 have lactyl group eraser activity (Moreno-Yruela et al., 2022b). During the development of atherosclerosis, HDAC3 downregulation due to lactate accumulation in vascular smooth muscle cells promotes H4K12la expression, which in turn exacerbates vascular smooth muscle cell (VSMC) senescence (Li XS et al., 2024). Moreover, HDACs were noted to vary in catalytic efficiencies when targeting D-lactic acid and L-lactic acid, a pair of mirror-image stereoisomers (Moreno-Yruela et al., 2022a). Recent findings have shown that the elevated extracellular lactate concentration leads to suppression of the deacetylase activity of HDACs (Latham et al., 2012; Wagner et al., 2015). Therefore, it is pertinent to inquire whether HDACs would play a comparable role in mediating lactyl group removal and potentially establish a novel positive feedback transduction pathway. This question deserves further investigation. With regard to SIRTs, SIRT1/2/3/5 all have delactylation activity, with SIRT2 being the most active and reported to be an effective eraser of multiple histone lactylation sites (Zu et al., 2022). In addition to delactylases, a study on *Escherichia coli* noted

that CobB could function as a lysine delactylase (Dong et al., 2022).

2.2.4 Substrates

There are two main substrates for the lactylation process: the use of synthetic lactoyl-CoA or the direct use of lactic acid (Fig. 1d). When lactylation was first discovered, because of its similarity to histone acetylation, Zhang et al. (2019) suggested that lactoyl-CoA would be the main lactoyl donor. In 2025, acyl-CoA synthetase short-chain family 2 (ACSS2) and guanosine triphosphate-specific succinyl-CoA synthetase (GTPSCS) were found to function sequentially as lactoyl-CoA synthetases, using lactic acid to synthesize lactoyl-CoA as a direct lactyl donor for lactyltransferases (Liu et al., 2025; Zhu et al., 2025). However, observations have shown extremely low levels of lactoyl-CoA in tumor cells, which may interfere with the action of several lactyltransferases in vivo (Li HY et al., 2024). In addition to their role as important and highly efficient lactyltransferases, another characteristic of AARS1/2 is that they use lactate as a direct lactyl donor without undergoing the synthesis of lactoyl-CoA (Li HY et al., 2024).

2.3 Histone and non-histone lactylations: multi-level regulation in physiological and pathological contexts

Lactylation constitutes a PTM of both histone and non-histone proteins. From the perspective of the effect on the functional level of proteins, lactylation modification orchestrates protein regulation across three levels: transcriptional (pre-translational), translational, and post-translational. Critically, the outcomes of lactylation simultaneously encompass physiological homeostasis and pathological progression.

2.3.1 Three-dimensional mechanism for regulating protein function via histone and non-histone lactylations

Histone lactylation is found mainly on lysines in H2A, H2B, H3, and H4, and lysine lactylation has been demonstrated at many sites, including H2BK6, H3K9, H3K14, H3K18, H3K23, H3K56, H4K5, H4K80, and H4K12, with H3K18, in particular, being the most extensively studied (Zhao et al., 2025). H3K18la can be enriched in the promoter regions of target genes and thus regulate gene expression—that is the content and function of proteins at the transcriptional level (Fig. 2a). In lung alveolar epithelial cells (AECs), H3K18la promotes the transcription of YT521-B homology (YTH) domain family protein 1 (YTHDF1) and ultimately leads to the progression of lung fibrosis (Wang PW et al., 2024). The activation of fibroblast growth factor receptor 4 (FGFR4) by H3K18la is closely related to the process of calcium oxalate crystal formation and kidney injury (Ye et al., 2025).

In contrast, while histone lactylation regulates the functional state of target proteins at the transcriptional level, non-histone lactylation focuses on regulating the biological function of proteins at the post-translational level (Fig. 2c). For instance, the lactylation of α-myosin heavy chain (α-MHC) at lysine 1897 promotes the interaction of α-MHC with titin, thereby maintaining the structural and functional integrity of the heart and contributing to the retardation of the progression of heart failure (Zhang et al., 2023). Conversely, the lactylation of Serpina3k proteins facilitates maintenance of protein stability, which is imperative for the mitigation of myocardial reperfusion injury following hypoxia (Wang et al., 2025). Interestingly, lactylation can also occur on guanosine triphosphate hydrolases (GTPases) such as eukaryotic translation elongation factor 1 alpha 2 (eEF1A2) (Fig. 2b). In this case, PTM promotes protein function, thereby affecting the subsequent activity of downstream proteins at the translational level in an early manner (Xie et al., 2024).

2.3.2 Lactylation in numerous diseases

Lactylation plays a pivotal role in a variety of disease processes, irrespective of whether they are classified as neoplasia. A notable biomarker of sepsis prognosis is the serum lactate level, and elevated lactate levels are frequently associated with a more unfavorable prognosis (Broder and Weil, 1964). At the level of lactylation modification, the enrichment of H3K18la in the promoter region of N^6-methyladenosine (m^6A) methyltransferase-like 3 (METTL3) promotes m^6A modification of acyl-CoA synthetase long-chain family member 4 (ACSL4), which in turn promotes ferroptosis of alveolar epithelial cells involved in the formation of septic lung injury (Wu et al., 2024) (Fig. 2d). Furthermore, the enrichment of H3K18la at the promoter of Ras homolog family member A (RhoA) activates its transcription and promotes sepsis-associated acute kidney injury (SA-AKI) through a series of downstream pathways (Qiao et al., 2024) (Fig. 2e). High-mobility group

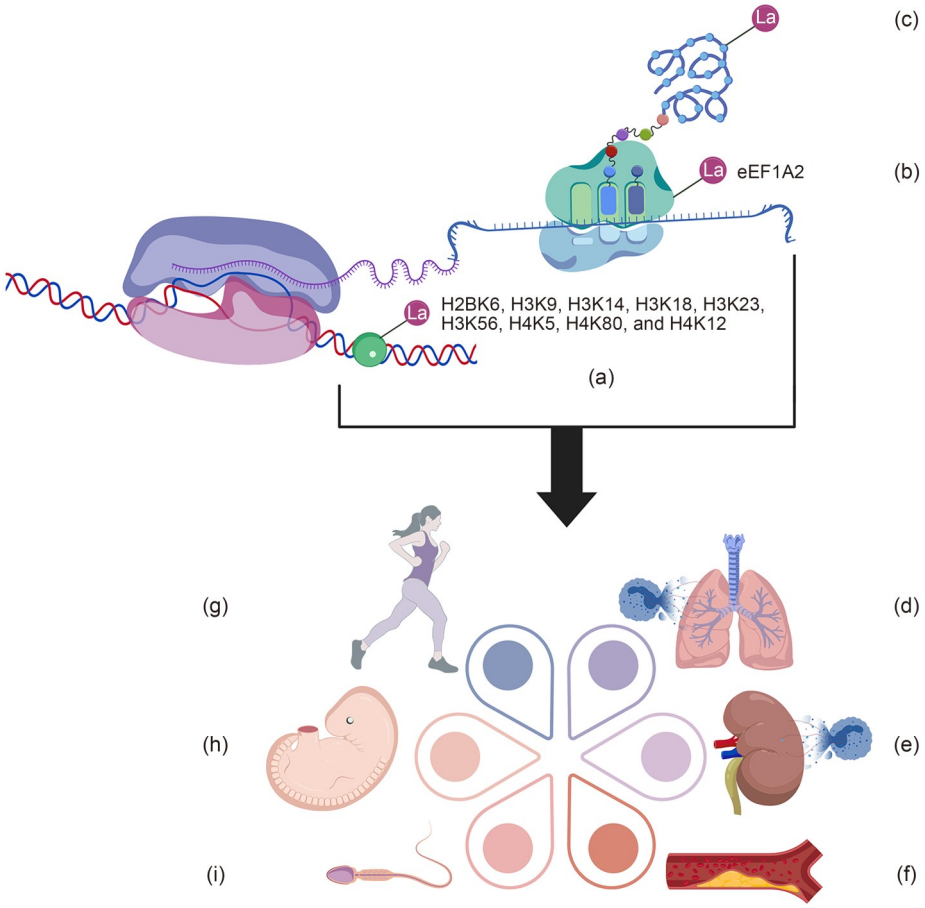

Fig. 2 Lactylation regulation of proteins across three levels and its involvement in various processes. (a–c) Lactylation modifications occur on histone proteins (such as H3K18 in various promoters) (a), non-histone proteins (GTPases) (b), and other proteins (c). (d–f) From an organismal perspective, lactylation-mediated protein regulation is ubiquitously involved in both physiological and pathological processes. Examples include sepsis-induced lung injury, renal injury, and atherosclerosis. (g–i) Lactylation also has critical regulatory roles in endurance exercise, embryonic development, and spermatogenic meiosis. The schematic diagram was created with BioGDP.com (Jiang et al., 2025). H3K18: histone H3 lysine 18 lactylation; GTPases: guanosine triphosphate hydrolases; eEF1A2: eukaryotic translation elongation factor 1 alpha 2; La: lactate.

box 1 (HMGB1), which is secreted by macrophages, is involved in inflammation regulation and positively correlates with poor patient prognosis (Sundén-Cullberg et al., 2005; Karlsson et al., 2008; Andersson and Tracey, 2011; Deng et al., 2018; Yang et al., 2020). Lactylation of HMGB1 stimulates its release from macrophages in the form of exosomes (Yang et al., 2022).

The pathological senescence of vascular endothelial cells and smooth muscle cells has been widely recognized as an important factor contributing to the development of atherosclerosis (Bi et al., 2021; Xu et al., 2021; Li XS et al., 2023). In vascular endothelial cells, H3K18la is up-regulated by lipid peroxidation and contributes to endothelial-to-mesenchymal transition (EndMT)-induced atherosclerosis (Dong et al., 2024). In vascular smooth muscle cells, elevated levels of H4K12la activate the transcriptional expression of the senescence-associated secretory phenotype (SASP) to promote senescence, which is involved in atherosclerosis development (Li XS et al., 2024). In addition, nuclear receptor subfamily 4, group A, member 3 (NR4A3), a pivotal regulator of apoA-IV-induced atherosclerosis progression, has been reported to promote calcium deposition in vascular smooth muscle cells by activating phosphatase orphan 1 (PHOSPHO1) transcription and expression through enhanced glycolysis, thereby promoting lactylation modification of histones, which has been shown to correlate positively with vascular calcification (Ma et al., 2024) (Fig. 2f).

2.3.3 Lactylation physiology

Lactate is not a substance exclusive to disease environments; rather it is predominantly a by-product of normal cellular metabolism in the body (Figs. 2g–2i). For instance, the contraction of skeletal muscle results in the production of substantial amounts of lactate. Additionally, lactate plays a crucial role in downstream mitochondrial respiration by serving as an essential link between glycolysis and aerobic pathways. According to the lactate shuttle theory, this linkage could occur between cells of different tissues in an aerobic environment across compartmentalized barriers (Brooks, 2018). Consequently, lactylation modifications, which are closely related to lactate, should also play an essential role in normal physiology.

In their original report on lactylation, Zhang et al. (2019) described lactylation as a "lactate clock" that regulates the resolution of the inflammatory process. That is, the lactate secreted by M1-type macrophages as a result of their proinflammatory function facilitates the expression of their M2-like features, thereby shifting from proinflammatory to anti-inflammatory and thus participating in the resolution of inflammation instead of persisting indefinitely (Zhang et al., 2019).

During the process of embryonic development, lactylation modification has been reported in glycolytic cells, such as the neural crest (NC) and germ layer precursors. The lactylation phenomenon in these locations would promote the accessibility of active enhancers and the deployment of the NC gene regulatory network (GRN), whereas the reduction of marker deposition by targeting LDHA/B would lead to NC gene down-regulation and impaired cell migration. The presence of lactylation links cellular metabolism to the GRN, which orchestrates embryonic development (Merkuri et al., 2024) (Fig. 2h). A study in 2025 described the dynamics of lactylation of H4K5/8/12 in mouse spermatozoa during prophase I of meiosis. H4K8la was reported to induce up-regulation of key meiotic genes and have a strong association with recombination hotspots (Zhang et al., 2025) (Fig. 2i). Under hypoxic conditions, such as during muscle endurance exercise, lactylations of PDHA1 at lysine 336 and CPT2 at lysine 457/458 inactivate both enzymes and inhibit OXPHOS by limiting the influx of pyruvate and fatty acid-oxidizing acetyl-CoA. The physiological significance of this process is that it limits the capacity for OXPHOS during muscle exercise, thereby reducing myocyte damage due to overexertion (Mao et al., 2024) (Fig. 2g).

In summary, since the initial report in 2019, lactylation has been shown to have significant potential, warranting in-depth research. From the four key regulatory aspects—reader, writer, eraser, and substrate—we have systematically summarized the known lactyl modification systems. From a functional perspective, lactylation can be understood as a PTM that influences protein functional states at transcriptional, translational, and post-translational levels, ultimately playing crucial roles in various pathological phenomena and normal physiological processes.

Building upon this foundation, we propose two key considerations. (1) Given that lactylation is already known to regulate protein function at transcriptional, translational, and post-translational levels, does it also exert regulatory functions during DNA replication? Considering the critical role of histones in DNA replication, this question warrants further investigation. (2) Research into the precise regulatory mechanisms of lactylation—and its specific roles in normal physiological functions and processes—remains relatively limited. Further investigations targeting these two aspects are warranted.

3 Lactylation in neoplasm biology

A complex interaction exists between tumors and lactylation modification activities. Lactate levels are significantly up-regulated in tumors due to the Warburg effect, which facilitates intracellular lactylation modification activities. Extensive histone and non-histone lactylations in tumor cells would also exert significant impacts on tumorigenesis and other biological activities. The current research on lactylation in tumors can be broadly summarized into three aspects: (1) the direct promotion of tumor proliferation or malignancy; (2) the reprogramming of other metabolic activities; and (3) the role of the tumor immune microenvironment. Lactylation is not solely a consequence of the Warburg phenomenon in tumor cells; to some extent, it can also facilitate a more profound understanding of the behavioral characteristics of malignant tumors.

3.1 Breast cancer

According to the International Agency for Research on Cancer (IARC), breast cancer accounted for 11.6% of all cancers and 6.9% of all cancer deaths globally in 2022 (Bray et al., 2024) and has been widely recognized as the leading cause of cancer incidence among women. Potassium two-pore domain channel subfamily K member 1 (KCNK1) has previously been reported to be a biomarker associated with cellular proliferation, migration, and hypersensitivity to paclitaxel in breast cancer (Sun XY et al., 2023). In breast cancer cells, highly expressed KCNK1 binds to and activates LDHA to promote increased lactate production and pan-histone lactylation; while numerous downstream H3K18la modifications have been found to be associated with the malignant behavior of breast cancer. Note that LDHA itself acts as one of the downstream targets activated by H3K18la, thus forming a vicious cycle of "LDHA-H3K18la-LDHA," which further aggravates the malignant progression of breast cancer (Hou et al., 2024). HBO1, also known as KAT7 or MYST2, is a highly conserved member of the MYST family of KATs and functions as a multifunctional histone acyltransferase that catalyzes acetylation, crotonylation, propionylation, and butyrylation (Xiao et al., 2021). Niu et al. (2024) discovered that HBO1 catalyzes H3K9la at the aquaporin-1 (*AQP1*) gene locus and induces up-regulation of its expression, which in turn establishes a strong link to the malignant behavior of breast cancer. Triple-negative breast cancer (TNBC) is a distinct immunohistochemical subtype of breast cancer that accounts for about 15%–20% of all breast cancer cases (Hossain et al., 2021). In TNBC, the expression level of H4K12la is generally elevated, and H4K12la promotes the malignant progression of TNBC through the down-regulation of schlafen 5 (SLFN5). Consequently, H4K12la has been evaluated by some researchers as a promising biomarker for TNBC (Cui et al., 2024; Li JY et al., 2024). Based on Cox regression and eXtreme Gradient Boosting (XGBoost) methods, Lin et al. (2024) identified and screened eight Kla-associated lncRNAs to construct a prognostic risk model. Notably, the model-derived risk scores exhibited a substantial correlation with immune function, as evidenced by increased tumor mutational burden (TMB) and decreased tumor immune dysfunction and exclusion (TIDE).

3.2 Colorectal cancer

Globally, colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related death (Bray et al., 2024). Lactate levels are significantly elevated in CRC cells, with substantial up-regulation of extranuclear lactylation in the nucleus. Both lactate levels and lactylation levels are independent prognostic factors affecting CRC (Huang HX et al., 2024). In CRC, KAT8 functions as a lactoyltransferase, and facilitates eEF1A2 K408 lactylation and its GTPase activity in response to aminoacyl (aa)-tRNA stimulation. It then induces translational elongation and enhances protein synthesis, rendering CRC translational activity to adapt to the heightened demands of malignancy (Xie et al., 2024) (Fig. 3b). In addition to CRC cells themselves, in their tumor microenvironment (TME), macrophage H3K18la down-regulates retinoic acid receptor gamma (RARγ), thereby deregulating the inhibitory effect on nuclear factor-κB (NF-κB) signaling, leading to the production of IL-6 and activation of signal transducer and activator of transcription 3 (STAT3) signaling, which ultimately correlates closely with poor prognosis in CRC patients (Li XM et al., 2024) (Fig. 3a).

The main cause of mortality in patients with CRC is the presence of colorectal liver metastases (CRLMs). The current etiological and pathophysiological characteristics of CRLM can be summarized as follows: anatomical-physiological characteristics of the liver; epithelial-mesenchymal transition (EMT); the presence of circulating tumor cells (CTCs) in the patient's bloodstream; the interaction between CRC cells metastasized to the liver and cells in situ and thus the formation of special ecological niches, and the roles of liver sinusoidal endothelial cells (LSECs), Kupffer cells, natural killer (NK) cells, macrophages, hepatic stellate cells, cluster of differentiation 4-positive ($CD4^+$)/$CD8^+$ T cells, and B cells (Jin ZH et al., 2025). In terms of lactylation, up-regulation of ubiquitin-specific peptidase 3-antisense RNA 1 (USP3-AS1) expression in CRC significantly enriches glycolysis and the myelocytomatosis oncogene (MYC) signaling pathway, which in turn regulates cell division cycle 27 (CDC27) expression via H3K18la modification in CRC cells, ultimately "initiating" CRLMs (Zhou JM et al., 2025). In addition, high expression of G protein-coupled receptor 37 (GPR37) in CRC activates the Hippo pathway to promote glycolysis and LDHA expression,

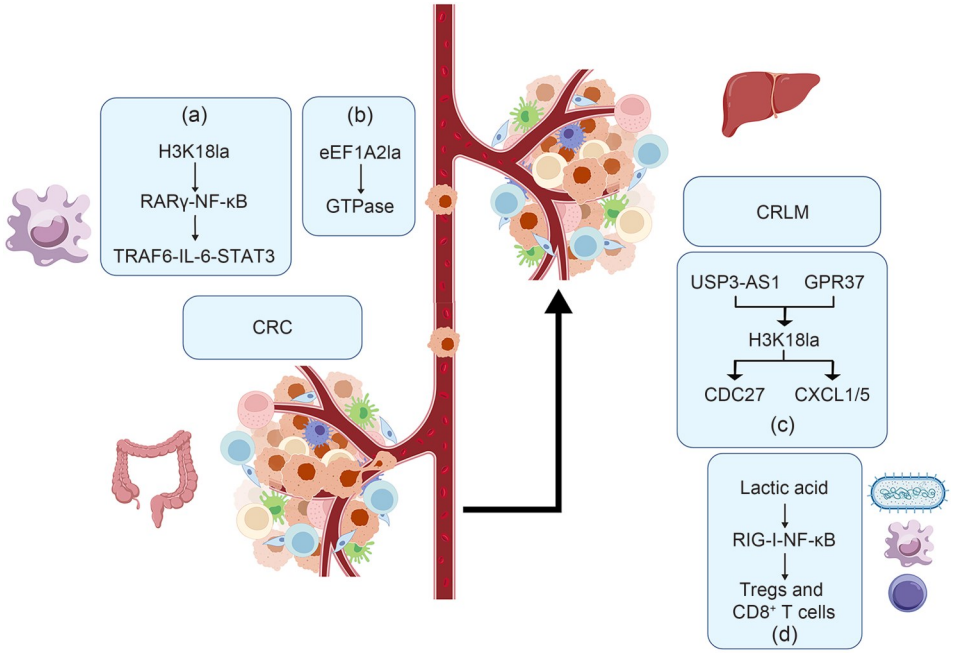

Fig. 3 Mechanisms underlying CRC malignancy (a, b) and CRLM (c, d). The lactate–lactylation axis in cancer cells and TME promotes malignant behaviors and hepatic metastasis processes. The schematic diagram was created with BioGDP.com (Jiang et al., 2025). CRC: colorectal cancer; CRLM: colorectal liver metastasis; TME: tumor microenvironment; NF-κB: nuclear factor-κB; IL: interleukin; eEF1A2: eukaryotic translation elongation factor 1 alpha 2; GTPase: guanosine triphosphate hydrolase; H3K18: histone H3 lysine 18 lactylation; RARγ: retinoic acid receptor gamma; TRAF6: TNF receptor-associated factor 6; STAT3: signal transducer and activator of transcription 3; USP: ubiquitin-specific peptidase; GPR: G protein-coupled receptor; CDC: cell division cycle; RIG: retinoic acid-inducible gene; Tregs: regulatory T cells; $CD8^+$ T cells: cluster of differentiation 8-positive T cells.

which in turn up-regulates the expression of C-X-C motif chemokine ligand 1/5 (CXCL1/5) through the up-regulation of H3K18la, and ultimately contributes to CRLM (Zhou et al., 2023) (Fig. 3c). Most notably, Gu J et al. (2024) revealed that the microbiota residing in the tumor also play a pivotal role in the development of CRLM. Lactic acid produced by intratumoral-resident *E. coli* inhibits NF-κB signaling via lactylation of retinoic acid-inducible gene I (RIG-I), and then inhibits nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing 3 (NLRP3) transcription. This mediates M2 macrophage polarization and impairs the immunosuppressive function of regulatory T cells (Tregs) while diminishing the anti-tumor activity of $CD8^+$ T cells (Fig. 3d). In this new research area, a review by Richter et al. (2025) outlines in vivo, ex vivo, and in vitro methods that can be used to mimic early-onset CRC (EO-CRC) and to assess the effects of intestinal microbes on tumor development and growth. This might provide a more systematic and comprehensive methodological guidance for researchers who plan to conduct further research targeting this axis.

3.3 Non-small cell lung cancer

Lung cancer consistently exhibits the highest incidence and mortality rates among malignancies worldwide (Bray et al., 2024). The World Health Organization (WHO) classifies lung cancers into four major histological subtypes: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma. These neoplasms are typically categorized into two groups based on biological behavior and therapeutic response: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of cases according to epidemiological data (Suster and Mino-Kenudson, 2020). Both histone and non-histone lactylation modifications hold significant pathophysiological relevance in NSCLC. Elevated H3K18la levels observed in NSCLC directly activate transcription of pore membrane protein 121 (POM121), thereby facilitating MYC nuclear translocation and its subsequent binding to the CD274 promoter to induce programmed cell death-ligand 1 (PD-L1) expression—ultimately

enhancing tumor immune evasion (Zhang C et al., 2024). Concurrently, Treg-derived H3K18la modulates NF-κB p65 transcription, up-regulating tumor necrosis factor receptor 2 (TNFR2) expression and accelerating malignant pleural effusion (MPE) progression (Xue et al., 2024). Attempts to address the many malignant consequences of H3 histone lactylation can be made by directly targeting the lactylation modification process or by targeting the glycolysis pathway, lactic acid transport system, or glucose transport and metabolism system. A natural product, fargesin (FGS), has been reported to inhibit the expression of a range of oncogenes including LDHA, LDHB, PKM2, and solute carrier family 2 member 1 (SLC2A1). PKM2 has been validated as a target for the antitumor effects of FGS; by inhibiting glycolysis, FGS indirectly inhibits global H3 histone lactylation (Guo et al., 2024). In addition, the direct targeting of the lactylation-modification process can be attempted with the lactylation reader, writer, eraser, and substrate, as previously described. Other anti-lactylation therapeutics targeting lactate production/transport, glucose metabolism, and transport are also worthy of further investigation. Regarding non-histone lactylation, SRY-box transcription factor 9 (SOX9)—a developmental regulator involved in embryogenesis and sex determination—undergoes lactylation modifications correlated with stemness maintenance, enhanced migration, and invasive capacity in NSCLC (Gruber et al., 2005; Yan et al., 2024).

3.4 Prevalence of lactylation in numerous kinds of cancers

Beyond the three most prevalent and lethal malignancies discussed above, lactylation modifications exert extensive and profound effects on other tumor types (Table 1). In glioblastoma (GBM) with high aldehyde dehydrogenase 1 family member A3 (ALDH1A3) expression, the interaction between ALDH1A3 and PKM2 induces lactylation of X-ray repair cross-complementing 1 (XRCC1) at lysine 247. This modification alters its affinity for importin α, facilitating enhanced nuclear translocation of XRCC1 and subsequent augmentation of DNA repair (Li GZ et al., 2024). In advanced-stage tumors, monocyte-derived macrophages (MDMs) overexpressing GLUT1 promote histone lactylation, thereby up-regulating IL-10 to suppress T cell activity (de Leo et al., 2024). In glioma stem cells (GSCs), polypyrimidine tract-binding protein 1 (PTBP1) K436 lactylation attenuates the interaction with tripartite motif-containing 21 (TRIM21), inhibiting PTBP1 proteasomal degradation. Concurrently, lactylated PTBP1 enhances RNA-binding capacity and stabilizes 6-phosphofructo-2-kinase/fructose-2,

Table 1 Lactylation in the cancers

Tissue/cell	Protein	Site	References
Breast cancer	H3	K18	Hou et al., 2024
		K9	Niu et al., 2024
	H4	K12	Cui et al., 2024; Li JY et al., 2024
CRC/CRLM	eEF1A2	K408	Xie et al., 2024
	H3	K18	Zhou JM et al., 2023, 2025; Li XM et al., 2024
	RIG-I	K852	Gu J et al., 2024
NSCLC	H3	K18	Xue et al., 2024; Zhang C et al., 2024
	SOX9		Gruber et al., 2005; Yan et al., 2024
GBM	XRCC1	K247	Li GZ et al., 2024
GSC	PTBP1	K436	Zhou ZJ et al., 2025
PDAC	H3	K18	Li F et al., 2024a
AML	H4	K5	Huang ZW et al., 2023
Cervical cancer	DCBLD1		Meng et al., 2024
HCC	ABCF1	K430	Hong et al., 2025
ICC	NCL	K477	Yang et al., 2024
Bladder cancer	H3	K18	Xie et al., 2023

CRC: colorectal cancer; CRLM: colorectal liver metastasis; NSCLC: non-small cell lung cancer; GBM: glioblastoma; GSC: glioma stem cell; PDAC: pancreatic ductal adenocarcinoma; AML: acute myeloid leukemia; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; eEF1A2: eukaryotic translation elongation factor 1 alpha 2; RIG: retinoic acid-inducible gene; SOX9: SRY-box transcription factor 9; XRCC1: X-ray repair cross complementing 1; PTBP: polypyrimidine tract binding protein; DCBLD1: LCCL domain-containing type I; ABCF1: ATP-binding cassette sub-family F member 1; NCL: nucleolin.

6-bisphosphatase 4 (*PFKFB4*) messenger RNA (mRNA), further amplifying glycolysis (Zhou ZJ et al., 2025). PDAC exhibits H3K18la enrichment at promoters that activate the transcription of mitotic checkpoint regulators TTK protein kinase (TTK) and BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B). Notably, TTK and BUB1B reciprocally up-regulate p300 expression, establishing a positive feedback loop that reinforces glycolytic flux (Li F et al., 2024a). In acute myeloid leukemia (AML), STAT5 overexpression promotes glycolysis and pan-histone lactylation. This activity facilitates E3-binding protein (E3BP) nuclear translocation, enhances H4K5la levels, and drives PD-L1 transcription to reinforce immunosuppression in AML (Huang ZW et al., 2023). Cervical cancer cells show lactate-induced up-regulation of discoidin, CUB, and LCCL domain-containing type I (DCBLD1) expression and lactylation. The lactylated DCBLD1 activates the pentose phosphate pathway (PPP) to accelerate tumor progression (Meng et al., 2024). Hepatocellular carcinoma (HCC) exhibits up-regulated ATP-binding cassette sub-family F member 1 (ABCF1) K430 lactylation (ABCF1-K430la). Post-lactylation, ABCF1 retains E2 ubiquitin-conjugating enzyme activity and translocates to the nucleus to bind to the lysine demethylase 3A (KDM3A) promoter, up-regulating its expression and activating the KDM3A–H3K9me2–HIF1A axis. This challenges the conventional understanding of ABCF1 as solely functioning in cytoplasmic protein translation (Hong et al., 2025). In HCC, elevated METTL5 stabilizes c-Myc via USP5 regulation, activating glycolytic genes—including *LDHA*, enolase 1 (*ENO1*), triosephosphate isomerase 1 (*TPI1*), *SLC2A1*, and *PKM2*—to increase glycolysis (Xia et al., 2023). In intrahepatic cholangiocarcinoma (ICC) under active glycolysis, p300-mediated lactylation of nucleolin (NCL) at K477 enables binding to primary mitogen-activated protein kinase activating death domain (MADD) transcripts. This interaction bypasses alternative splicing that generates premature termination codons, facilitating productive MADD translation (Yang et al., 2024). Bladder cancer shows Hippo pathway-mediated suppression of H3K18la via 5'–3' exoribonuclease 2 circular RNA (circRNA) (circXRN2). Down-regulation of this regulatory axis correlates with malignant behavior (Xie et al., 2023). In ocular melanoma, elevated histone lactylation specifically up-regulates alpha-ketoglutarate-dependent dioxygenase homolog 3 (ALKBH3) in high-risk tumors. This enzyme removes m^1A methylation from SP100A, weakening promyelocytic leukemia (PML) tumor-suppressive condensate formation and promoting malignant transformation (Gu X et al., 2024).

Collectively, lactylation modifications show a protumorigenic propensity during tumorigenesis and progression across multiple malignancies. While our analysis has systematically investigated three high-incidence malignancies with substantial mortality burden (breast cancer, CRC, and NSCLC), emerging evidence reveals that elevated lactylation levels in other oncological contexts, including bladder cancer, HCC, and leukemia, exhibit consistent associations with adverse prognostic implications. Notably, lactylation manifests a "paradoxical dual capacity" in tumor radio/chemotherapy: it concurrently increases therapeutic resistance through multiple mechanisms while providing actionable molecular targets for overcoming such resistance. This critical dichotomy will be analyzed comprehensively in the next section.

4 Lactylation in chemo- or radio-resistance: copious solutions

4.1 Resistance to chemotherapy

Current research strategies to combat chemoresistance through targeting lactylation modifications focus mainly on two approaches: (1) modulating the immunosuppressive TME; and (2) intervening in inhibition-induced DNA repair mechanisms. Additionally, numerous studies that cannot be categorized under these two paradigms are discussed in Section 4.1.3 of this review, where we highlight several noteworthy advancements. However, examining lactylation-associated anti-resistance strategies through the lens of cancer type-specific therapeutic modalities reveals intriguing mechanistic diversity. To enhance accessibility and practical utility, we have compiled our review's contents in Table 2, which systematically organizes key findings according to tumor classifications and corresponding intervention approaches.

4.1.1 Tumor microenvironment

The immunosuppressive nature of the TME remains a major obstacle in cancer immunotherapy. Lactylation research focuses mainly on two cellular

Table 2 Lactylation in the tumor chemotherapy resistance

Neoplasm	Tolerance	Lactylation site	Solution	References
CRC	Immunotherapy	H3K18; METTL3	Targeting circATXN7 in CTLs, or genetic ablation of circATXN7 in $CD8^+$ T cells	Xiong et al., 2022; Zhou et al., 2024
	Irinotecan	H3K12	Coordinate loss of SMC4 and PGAM1	Sun XD et al., 2023
	Bevacizumab	H3K18	2-DG or oxalates	Li WH et al., 2024
HCC	Immunotherapy	H3K18	Targeting H3K18la	Cai et al., 2024
	FOLFOX	H3K14	Targeting NEDD4	Zeng et al., 2025
	Lenvatinib	IGF2BP3	2-DG or liposomal delivery of IGF2BP3-targeting siRNA	Lu et al., 2024
NSCLC	PD-1/PD-L1 inhibitor	APOC2-K70	Anti-APOC2-K70la antibodies	Chen J et al., 2024
GBM	TMZ	H3K9la	Stiripentol	Yue et al., 2024
GSC		XRCC1 K247	D34-919	Li GZ et al., 2024
Bladder cancer	Cisplatin	H3K18	H3K18la	Li F et al., 2024b
MM	PI	IGF-1R		Wang XB et al., 2024
Gastric cancer	Doxorubicin	NSUN2 K508	Targeting NSUN2 K508la	Niu et al., 2025

CRC: colorectal cancer; METTL3: m^6A methyltransferase like 3; CTLs: cytotoxic T lymphocytes; 2-DG: 2-deoxy-D-glucose; HCC: hepatocellular carcinoma; FOLFOX: folinic acid+fluorouracil+oxaliplatin; NEDD4: neuronal precursor cell-expressed developmentally down-regulated 4; PD-1: programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; APOC2: apolipoprotein C2; TMZ: temozolomide; XRCC1: X-ray repair cross complementing 1; NSCLC: non-small cell lung cancer; GBM: glioblastoma; GSC: glioma stem cell; MM: multiple myeloma; PI: proteasome inhibitor; IGF-1R: insulin-like growth factor 1 receptor; H3K18: histone H3 lysine 18; $CD8^+$ T cells: cluster of differentiation 8-positive T cells; SMC4: structural maintenance of chromosomes 4; NSUN2: NOP2/Sun RNA methyltransferase 2; circATXN7: circRNA ataxin 7; PGAM1: phosphoglycerate mutase 1; IGF2BP3: insulin-like growth factor 2 (*IGF2*) mRNA-binding protein 3; siRNA: small interfering RNA.

components within the TME, macrophages and T cells, aiming to provide novel mechanistic insights and enhance the therapeutic efficacy of mainstream treatments like immune checkpoint inhibitors (ICIs).

Tumor-infiltrating myeloid cells (TIMs) represent a crucial cellular population involved in tumor immune evasion. METTL3 inhibitors have been reported as adjuvant immunotherapeutics targeting TIM-mediated immunosuppression in CRC. In CRC, up-regulated lactylation of both H3K18 and METTL3 within TIMs activates the Janus kinase 1 (JAK1)–STAT3 signaling pathway, thereby potentiating their immunosuppressive functions (Xiong et al., 2022). Immunotherapy also constitutes a vital therapeutic approach for HCC. The serine- and arginine-rich splicing factor 10 (SRSF10) inhibitor 1C8 shows potential for overcoming immunosuppressive therapy resistance caused by M2 macrophage polarization in HCC patients. Mechanistically, SRSF10 promotes glycolytic activity and subsequent H3K18la up-regulation, which reciprocally enhances SRSF10 expression via a positive feedback loop. This lactate-driven process reinforces M2 polarization and establishes an immunosuppressive TME (Cai et al., 2024).

In prostate cancer, phosphatase and tensin homolog (PTEN)/tumor protein p53 (TP53)-mutant tumors show increased aerobic glycolysis, inducing M2 macrophage polarization and conferring immunotherapy resistance. A therapeutic regimen combining androgen deprivation therapy (ADT), phosphoinositide 3-kinase pathway inhibitor (PI3Ki), anti-programmed death-1 (anti-PD-1), and porcupine inhibitors has shown efficacy in counteracting immunotherapy resistance in metastatic castration-resistant prostate cancer (mCRPC) (Chaudagar et al., 2023). Apolipoprotein C2 (APOC2) K70la lactylation (APOC2-K70la) modification has been identified as critically associated with PD-1/PD-L1 inhibitor resistance in NSCLC. Combinatorial therapy using anti-APOC2-K70la antibodies suppresses free fatty acid (FFA) release and Treg accumulation, effectively controlling immune resistance and metastasis in NSCLC (Chen J et al., 2024).

T cell-mediated cytotoxicity forms the basis of cellular immunotherapies. Histone lactylation activates circRNA ataxin 7 (circATXN7) transcription in tumor-specific cytotoxic T lymphocytes (CTLs), leading to NF-κB inactivation and increased susceptibility to activation-induced cell death (AICD), thereby promoting immunotherapy resistance. Engineered CTLs with circATXN7 knockdown have been shown to enhance tumor suppression in NOD-SCID mice bearing CRC patient-derived xenografts through improved

CTL persistence, offering novel strategies for cellular immunotherapy (Zhou et al., 2024).

4.1.2 DNA repair

Substantial evidence shows that DNA repair processes, particularly homologous recombination (HR), play pivotal roles in mediating chemoresistance across various cancers (Ray Chaudhuri et al., 2016; Chen et al., 2018; Russo et al., 2019). Platinum-based agents, which are clinically established as first-line chemotherapy for numerous malignancies, face persistent challenges due to resistance (Zhang et al., 2022). Formation of the MRE11-RAD50-NBS1 (MRN) complex and subsequent recruitment of HR repair proteins to DNA double-strand break sites significantly enhance DNA repair fidelity, a mechanism closely associated with platinum resistance. Notably, lactylation modifications of both Nijmegen breakage syndrome protein 1 (NBS1) and MRE11 within the MRN complex potentiate DNA repair activity. This mechanistic insight has prompted therapeutic strategies combining platinum agents with the LDHA inhibitor stiripentol and the MRE11-targeting cell-penetrating peptide K673-PE to counteract chemoresistance (Chen HX et al., 2024; Chen YP et al., 2024).

Temozolomide (TMZ), a blood–brain barrier (BBB)-penetrant alkylating agent, exerts cytotoxicity through methylation of guanine and adenine in central nervous system (CNS) tumors (Thomas et al., 2017). In GBM, H3K9la-mediated activation of LUC7-like 2 (LUC7L2) induces retention of mutL homolog 1 (MLH1) intron 7, down-regulating MLH1 expression and impairing mismatch repair (MMR), thereby driving TMZ resistance. Intriguingly, stiripentol-mediated lactylation inhibition has also been validated as a viable approach to overcome this resistance mechanism (Yue et al., 2024).

GSCs exhibit ALDH1A3-driven PKM2 activation, which enhances glycolysis and promotes XRCC1 K247 lactylation to facilitate DNA repair. The ALDH1A3/PKM2 inhibitor D34-919 effectively reverses XRCC1 lactylation by suppressing glycolytic flux, offering a promising strategy to mitigate chemoresistance (Li GZ et al., 2024).

4.1.3 Surge of studies addressing lactylation modification

Beyond its roles in TME modulation and DNA repair, histone and non-histone lactylation critically contribute to diverse chemoresistance mechanisms. In CRC, H3K12la shows tripartite associations with tumor diapause-like phenotypes and structural maintenance of chromosomes 4 (SMC4) protein down-regulation, mediating irinotecan resistance through ATP-binding cassette transporter activation (Sun XD et al., 2023). H3K18la facilitates autophagosome maturation, enhancing hypoxia tolerance in CRC cells and conferring bevacizumab resistance. Pharmacological inhibition of lactylation (via oxamate) and autophagy (via chloroquine, CQ) synergistically reverses this resistance, with enhanced efficacy in combination therapy (Li WH et al., 2024). In bladder cancer, H3K18la-driven transcriptional activation of Y-box-binding protein 1 (YBX1) and YY1 underpins cisplatin resistance, establishing H3K18la as a promising therapeutic target for overcoming platinum resistance (Li F et al., 2024b). HCC exhibits glycolysis-elevated H3K14la that up-regulates ubiquitin E3 ligase expression, promoting resistance to folinic acid+fluorouracil+oxaliplatin (FOLFOX) regimens. Thus, ubiquitin E3 ligase neuronal precursor cell-expressed developmentally down-regulated 4 (NEDD4) emerges as a potential target for counteracting FOLFOX chemoresistance (Zeng et al., 2025). Multiple myeloma (MM) studies have revealed MUC20-mediated suppression of insulin-like growth factor 1 receptor (IGF-1R) lactylation, which inhibits MET activation and alleviates proteasome inhibitor (PI) resistance through cellular cuproptosis induction (Wang XB et al., 2024). In gastric cancer, lactate-induced NOP2/Sun RNA methyltransferase 2 (NSUN2) K508la lactylation (catalyzed by NAA10) confers resistance to doxorubicin-induced ferroptosis, positioning NSUN2 as a prognostic biomarker and therapeutic target (Niu et al., 2025). Non-histone insulin-like growth factor 2 (*IGF2*) mRNA-binding protein 3 (IGF2BP3) lactylation drives lenvatinib resistance in HCC via the IGF2BP3–phosphoenolpyruvate carboxykinase 2 (PCK2)–*S*-adenosylmethionine (SAM)–m^6A axis. Liposomal delivery of IGF2BP3-targeting small interfering RNA (siRNA) or glycolytic inhibitor 2-deoxy-D-glucose (2-DG) restores lenvatinib sensitivity in preclinical models (Lu et al., 2024).

Collectively, histone and non-histone lactylation modifications provide novel molecular perspectives for understanding chemoresistance across diverse malignancies, establishing critical connections between therapeutically recalcitrant phenotypes and tumor-specific

aerobic glycolysis at the mechanistic level. In this review, we comprehensively summarize multiple therapeutic strategies targeting lactylation modifications or key nodes in associated pathways. Approaches targeting key nodes of glucose metabolism and transport, glycolytic regulation, and lactate production and transport, exemplified by the LDHA inhibitor stiripentol and glycolytic inhibitor 2-DG, demonstrate pan-lactylation suppression across various tumor types. Conversely, context-specific solutions are required for distinct resistance mechanisms within the same malignancy, as illustrated by targeting SRSF10 to overcome immunotherapy resistance versus modulating NEDD4 to counteract FOLFOX chemoresistance in HCC.

4.2 Resistance to radiotherapy

Radiotherapy remains a cornerstone in the management of malignant tumors. However, its clinical utility is constrained by two fundamental challenges: (1) ionizing radiation-induced toxicities in normal tissues; and (2) the development of radioresistance in malignant lesions. In this section, we elucidate the bidirectional regulatory interplay between lactylation and ionizing radiation through two complementary perspectives: the impact of lactylation on radiation biological effects, and radiation-induced modulation of lactylation dynamics. Furthermore, we summarize emerging lactylation-related biomarkers discovered within the past year that hold potential for optimizing radiation oncology practice, aiming to facilitate clinically translatable research.

4.2.1 Lactylation-induced alterations in radiotherapy

Both histone and non-histone lactylation modifications influence radiotherapy efficacy. Current evidence indicates that elevated H3K18la levels correlate with radioresistance (Liu et al., 2025) (Fig. 4a), and NBS1 lactylation plays an essential role in MRN complex assembly and HR repair protein recruitment at DNA double-strand break sites—a critical mechanism of cellular defense against ionizing radiation damage (Chen HX et al., 2024) (Fig. 4b). Nevertheless, current research focuses mainly on lactate and glycolytic flux in radiation response, with limited exploration of lactylation-mediated regulatory networks.

PKM2, a key glycolytic enzyme, also participates in repairing radiation-induced DNA damage (Sizemore et al., 2018). Heat shock protein 90 (HSP90) inhibitors,

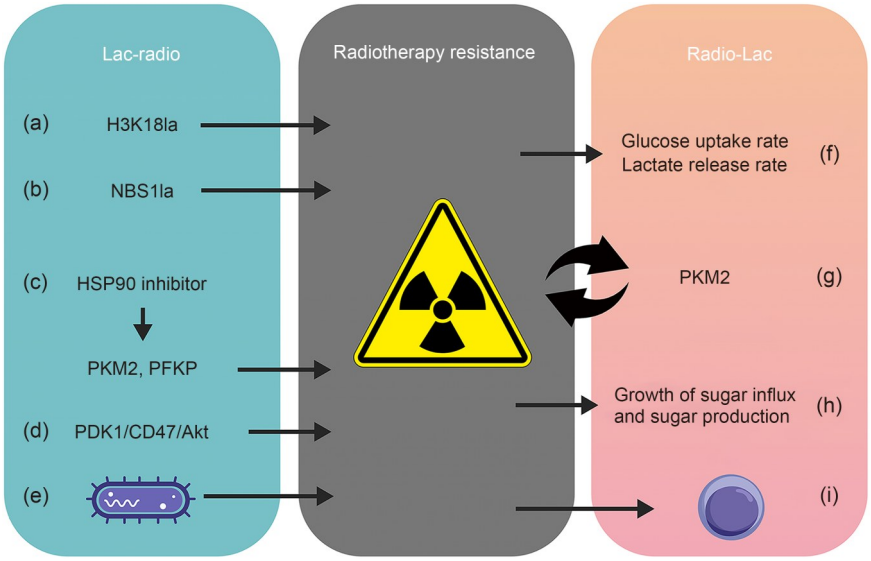

Fig. 4 Complex causal relationship between ionizing radiation and the lactate–lactylation axis. Intracellular lactylation and bacteria-derived lactate in the TME significantly influence the biological effects of ionizing radiation, such as H3K18la and NBS1la modifications. Conversely, ionizing radiation profoundly modulates cellular lactate production systems, such as increasing glycolytic uptake rate and lactate efflux rate under radiation exposure. Notably, up-regulated PKM2 functionality following radiation exposure has been observed, thereby reciprocally increasing cellular radioresistance, forming a positive feedback loop. The schematic diagram was created with BioGDP.com (Jiang et al., 2025). TME: tumor microenvironment; H3K18la: histone H3 lysine 18 lactylation; NBS1la: Nijmegen breakage syndrome 1 lactylation; HSP90: heat-shock protein 90; PKM2: pyruvate kinase M2; PFKP: platelet phosphofructokinase; PDK1: pyruvate dehydrogenase kinase 1; CD47: cluster of differentiation 47; Akt: protein kinase B.

encompassing DNA alkylators, DNA replication inhibitors, and poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP) inhibitors represent promising anticancer modalities (Stecklein et al., 2012). The HSP90 inhibitor ganetespib confers radioresistance by suppressing PKM2 and platelet-type phosphofructokinase (PFKP) activity (Chen FH et al., 2024) (Fig. 4c). The mechanism through which radioresistance is alleviated by pyruvate dehydrogenase kinase 1 (PDK1) inhibition has also been reported to be related to PDK1/CD47/protein kinase B (Akt)-mediated glycolytic axis down-regulation (Pai et al., 2021) (Fig. 4d).

Beyond intracellular glycolysis, extracellular lactate may originate from acidogenic bacteria. Certain bacterial species, exemplified by *Helicobacter pylori* in gastric carcinogenesis, exhibit oncogenic potential. In cervical, colorectal, lung, head-neck, and skin cancers, intratumoral *Lactobacillus iners*-derived L-lactate activates multiple oncogenic signaling pathways and metabolic reprogramming, ultimately promoting radiotherapy tolerance (Colbert et al., 2023) (Fig. 4e).

In conclusion, glycolysis—or more specifically, lactylation and lactate—shows profound connections with radiotherapy tolerance. From one perspective, a substantial body of research investigating glycolytic pathways has yet to establish direct associations with lactylation modifications, representing a critical gap requiring urgent attention. From another angle, lactylation provides novel epigenetic insights that elucidate the well-established glycolysis–lactate–radioresistance axis, not only deepening our understanding of tumor metabolic reprogramming but also providing complementary validation for prevailing theoretical frameworks.

4.2.2 Impact of ionizing radiation on lactylation

Under conditions that simulate a hypoxic environment, cobalt chloride is reported to promote glycolysis in breast cancer cells during radiation therapy (Zhao et al., 2017) (Fig. 4f). PKM2 isoforms have been reported to rewire glucose metabolism and promote radioresistance in GBM during radiation therapy (Bailleul et al., 2023) (Fig. 4g). Moreover, an increase in glucose influx and glycogen synthesis was observed in lung cancer cells that survived irradiation (Tsolou et al., 2023) (Fig. 4h). These studies suggest that the lactic acid production system is altered to a certain extent by the effects of ionizing radiation during radiotherapy and that the aforementioned radiation-induced changes are associated with tumor radioresistance.

Furthermore, the findings indicate that ionizing radiation leads to decreased glycolysis in T cells, while tumor cells exhibit an increase in lactic acid production and the acidification of the TME under radiotherapy (Liu SB et al., 2023). These findings suggest that ionizing radiation may also contribute to the development of tolerance to immunotherapy following radiotherapy (Fig. 4i).

4.2.3 Emerging biomarkers in radiotherapy

In radiotherapy, the bidirectional interplay between lactate/lactylation levels and ionizing radiation establishes lactate production systems and lactylation status as potential biomarkers for predicting therapeutic efficacy, treatment response, and clinical outcomes in radiation oncology patients.

From one perspective, prognostic assessment and therapeutic monitoring in radiotherapy are in the spotlight. Radiotherapy remains the first-line treatment for nasopharyngeal carcinoma according to clinical guidelines (Bossi et al., 2023). Serum LDH levels show significant prognostic value in primary nasopharyngeal carcinoma when measured at one-week and three-month post-radiotherapy intervals (Liu YY et al., 2024). Elevated LDH levels also correlate with poor prognosis in IDH-wildtype GBM (IDH-wt GBM) patients (Tini et al., 2025). Beyond LDH quantification, ^{18}F-FDG-PET/CT serves as a clinical standard for assessing tumor glycolytic activity. The apparent diffusion coefficient (ADC), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) exhibit substantial prognostic significance in head-neck malignancies, NSCLC, and rectal cancer (Avallone et al., 2019; Grambozov et al., 2023; Trada et al., 2023). From another perspective, radiation-induced toxicity also needs adequate attention. Deficiency in liver X receptor (LXR) nuclear receptors exacerbates macrophage radiation damage and mortality while amplifying proinflammatory mediators under radiotherapy, positioning LXR as a biomarker for radiation-induced inflammatory responses (Tabraue et al., 2019).

In summary, a reciprocal causal relationship exists between lactylation and tumor radiotherapy. Elevated lactate production and lactylation modifications are associated with diminished radiotherapeutic response and increased radioresistance, while ionizing radiation

itself modulates lactate metabolism and induces immunosuppressive reprogramming within the TME, suggesting non-negligible mechanistic links between radiotherapy resistance and immunotherapy tolerance. Lactate/lactylation-related biomarkers, such as serum LDH levels and ^{18}F-FDG-PET/CT-based glycolytic activity assessment, hold significant value for prognosis and therapeutic monitoring. However, critical knowledge gaps persist regarding radiation-induced lactylation dynamics: (1) spatiotemporal modulation of lactylation levels during radiotherapy; (2) molecular mechanisms and site-specific effects of radiation on lactylation; (3) whether there are distinct characteristics or patterns in the effects of different types, doses, or dose rates of ionizing radiation on lactylation modifications (low-dose/low-dose-rate radiation is worth more serious consideration in view of its characteristic biological effect); and (4) whether there are potential associations between radiation-driven lactylation alterations and tissue damage, repair cascades, or secondary carcinogenesis in radiotherapy processes or abnormal exposure. These four points are worth further exploration. In addition, identifying lactylation-associated biomarkers predictive of radiotherapy-induced normal tissue complications remains an underexplored research frontier with high potential.

5 Promising solutions aiming at lactylation

5.1 Current strategies to antagonize lactylation modification

5.1.1 Tumor microenvironment

The Warburg effect establishes LDH as a critical metabolic node for energy acquisition in tumor cells (Fig. 5a). Up-regulated LDHA expression represents a hallmark of multiple malignancies, with elevated LDH levels serving as a robust prognostic indicator of poor clinical outcomes (Augoff et al., 2015). As reviewed previously, pharmacological inhibition of lactate production has been achieved mainly through stiripentol (an LDHA inhibitor) and 2-DG. Oxamate, another validated LDH inhibitor (Zhao et al., 2015; Liu et al., 2016), shows dual antitumor effects in NSCLC patient-derived xenograft models by suppressing LDHA

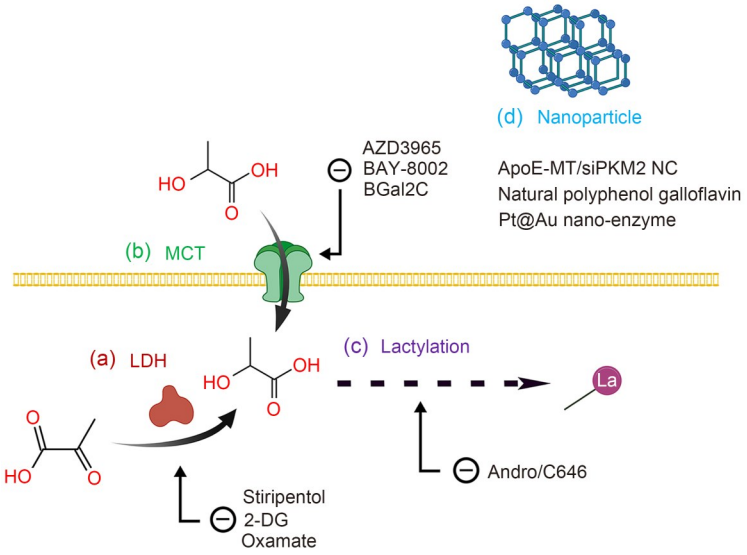

Fig. 5 Key therapeutic strategies targeting lactylation. Lactate can be synthesized intracellularly via LDH (endogenous lactate) or imported into cells via MCT-mediated transport (exogenous lactate). (a) Targeting LDH with stiripentol, 2-DG, or oxamate inhibits the up-regulation of endogenous lactate. (b) Targeting MCTs using AZD3965, BAY-8002, or BGal2C suppresses the up-regulation of exogenous lactate. The MCT1 inhibitor AZD3965 has completed phase I/II clinical trials and shows promise as a novel adjuvant therapy for tumors. (c) Beyond targeting lactate-producing systems, directly targeting the lactylation modification process, for example by using Andro/C646 to inhibit p300 or tanshinone I to down-regulate H3K18la, represents another strategy. (d) The precision of targeted drug delivery can be enhanced by developing nanoscale cascade drug delivery systems, thereby reducing the systemic adverse effects associated with targeting lactylation, and even mitigating therapy resistance and enhancing immune responses. The schematic diagram was created with BioGDP.com (Jiang et al., 2025). MCT: monocarboxylate transporter; LDH: lactate dehydrogenase; 2-DG: 2-deoxy-D-glucose; BGal2C: β-galactose 2C; H3K18la: histone H3 lysine 18 lactylation; Andro: andrographolide; NC: nanocapsule.

activity and synergistically enhancing anti-PD-1 immunotherapy efficacy (Qiao et al., 2021).

Beyond LDHA, LDHD emerges as a promising metabolic target. In esophageal squamous cell carcinoma (ESCC), cyclin-dependent kinase 7 (CDK7)–YAP–LDHD axis-mediated D-lactate depletion is essential for oncogenic initiation. LDHD-driven metabolic reprogramming, characterized by D-lactate consumption and pyruvate accumulation, reinforces ferroptosis resistance in ESCC. Targeting LDHD-associated metabolic pathways may thus potentiate chemotherapeutic efficacy in ESCC management (Lv et al., 2023).

5.1.2 Monocarboxylate transporters

MCTs mediate transmembrane lactate shuttling (Fig. 5b). MCT1, MCT2, and MCT4 isoforms have been identified across various malignancies, including breast, bladder, and cervical cancers. MCT4 facilitates lactate efflux, whereas MCT1 mediates exogenous lactate uptake. Their concerted action establishes intercellular lactate exchange networks in tumors. Classical MCT inhibitors include non-selective agents such as phloretin, quercetin, and 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS), and selective compounds like AR-C155858 (Payen et al., 2020).

BAY-8002, a novel MCT inhibitor, suppresses cisplatin- and doxorubicin-induced migratory enhancement in breast cancer cells via lactate transport blockade (Vera et al., 2024). In tumor immunology, MCT1 inhibition reprograms dendritic cell (DC) metabolism by counteracting tumor-derived glycan-, sialyl-Tn antigen-, and fucose-mediated skewing of cDC1 and cDC2 subsets, thereby restoring antitumor T cell adaptability (Niveau et al., 2025).

In addition, β-galactosidase 2C (BGal2C) disrupts physical and functional interactions between carbonic anhydrase IX (CAIX) and MCT1/4 in *Xenopus laevis* oocytes, reducing proton-coupled lactate flux rates (Combs et al., 2024).

5.1.3 Direct modification of lactylation

Current therapeutic strategies directly targeting lactylation modifications focus mainly on lactyltransferases (Fig. 5c). Andrographolide (Andro), a natural diterpenoid, suppresses breast cancer progression through dual mechanisms: (1) inactivation of p300 signaling and vascular endothelial growth factor (VEGF) pathways; and (2) inhibition of cyclooxygenase-2 (COX-2) expression and angiogenesis (Peng et al., 2018). Furthermore, the selective p300 inhibitor C646 potentiates gemcitabine-induced apoptosis in pancreatic cancer (Ono et al., 2016).

5.2 Nanoparticle-mediated lactylation antagonism with spatiotemporal specificity

Conventional anticancer drugs usually face the limitations of high systemic toxicity and low targeting specificity. The widespread intracellular glycolysis phenomenon and its generation of lactic acid form the base of lactylation modification. Concurrently, lactylation modification is involved in the functional regulation of various histones and non-histone proteins, as well as various physiological and pathological processes. Consequently, it is imperative to improve therapeutic targeting. Nanomedicine delivery systems have been engineered to enhance drug performance, improve target specificity, facilitate multi-drug co-delivery, and extend drug circulation time in vivo, thereby achieving therapeutic efficacy while minimizing systemic toxicity (Liu SL et al., 2023). Furthermore, nanomedicine has shown efficacy in overcoming drug resistance and enhancing the immune response (Fig. 5d) (Li JX et al., 2023).

A novel TMZ nanocapsule (ApoE-MT/siPKM2 NC) was prepared, in which PKM2 siRNA (siPKM2) was used to inhibit glycolysis, and TMZ crossed the BBB for the treatment of CNS tumors, as previously described. The combination of TMZ as the shell, siPKM2 as the core, and a glutathione (GSH)-containing disulfide-bonded responsive linker ensures "targeted burst" cleavage of the nanocapsules to release TMZ and siPKM2 in the high-GSH environment of glioma cells for more precise therapeutic effects (Zhang YK et al., 2024).

The use of a nanocomplex loaded with the natural polyphenol galloflavin based on metal-phenolic coordination networks has been shown to inhibit LDHA activity and thus improve the immunosuppressive conditions in the TME and enhance cancer therapeutic efficacy (Zhang Z et al., 2024). A self-cascading catalytic Pt@Au nanoenzyme interferes with intratumoral glucose metabolism. It could function as a radiosensitizing agent that consumes glucose using glucose oxidase (GOx), catalase (CAT), and peroxidase (POD)-like activities, and induces a cascade of hydrogen peroxide (H_2O_2) reactions, as well as ameliorating intratumoral hypoxia and increasing reactive oxygen species (ROS) accumulation (Zhang YX et al., 2024).

5.3 Clinical status

The MCT1 inhibitor AZD3965 has completed phase I/II clinical trials (Fig. 5b) and is expected to function as an adjuvant antitumor therapy. As previously outlined, the inhibition of MCT1 impedes lactate transport, thereby establishing a robust correlation with tumor treatment efficacy. A phase I dose-escalation study conducted by the Cancer Research UK's Centre for Drug Development and collaborators reported that the most common adverse events were grade 1 and/or 2, with the most prevalent being electroretinographic changes (indicative of retinopathy), fatigue, anorexia, and constipation. Seven patients receiving a dosage of ⩾20 mg/d experienced dose-limiting toxicity (DLT): grade 3 cardiac troponin elevation (n=1), asymptomatic ocular DLT (n=5), and grade 3 metabolic acidosis (n=1). Plasma pharmacokinetics showed the achievement of target concentrations, while pharmacodynamic measurements indicated on target activity (Halford et al., 2023).

In clinical settings, restricting specific nutrients or providing targeted supplementation is a prevalent practice. This strategy aims to foster healthier physiological conditions in patients, thereby promoting recovery from various diseases. However, it has been observed that nutrient restriction can also have an impact on tumor immunity in certain contexts. A clinical trial showed that a serine/glycine-free diet enhances antitumor immunity and that a PD-1/PD-L1 inhibitor hinders cytotoxic T cells from facilitating immune escape—partly via suppression of PD-1 lactylation. The synergistic effect of the two in combination could greatly enhance the prognosis of patients (Tong et al., 2024). Our review indicates that the efficacy of this therapy was limited by treatment tolerance. However, perhaps combination with an anti-APOC2$^{K70\text{-}lac}$ antibody may reduce treatment-related intolerance and thereby further improve patient outcomes (Chen J et al., 2024).

5.4 Challenges and prospects: complications of neoplasms and neoplasm radiotherapy

Neoplasm-related complications and radiotherapy-induced complications should be incorporated into treatment decision-making processes. Below, we summarize two complications that may be significantly associated with lactate levels. Research on targeted interventions for cancer cachexia and tumor lysis syndrome (TLS) remains limited, warranting further exploration in this field. Based on the preceding review, targeting key nodes directly linked to lactate production or lactylation modification may represent a promising therapeutic strategy for these conditions.

The etiology of death in patients with malignant neoplasms is frequently not attributable to direct compression by the tumor itself, but rather to a variety of complications arising from malignancy. For instance, malignancy itself is a significant cause of death in such patients. Liu XD et al. (2024) reported that lactate activates the lactate-specific G protein-coupled receptor 81 (GPR81), which mediates the development of malignant stroma by sequential activation of the inhibitory G protein (G_i)–G protein βγ subunits (Gβγ)–Ras homolog family member A (RhoA)/Rho-associated coiled-coil containing protein kinase 1 (ROCK1)–p38 mitogen-activated protein kinase (MAPK) signaling cascade.

TLS is a post-treatment complication of malignancy, commonly observed in hematologic malignancies such as Burkitt's lymphoma and acute lymphoblastic leukemia. A recent pathology report documented a patient with prostate cancer who exhibited a substantial increase in lactate dehydrogenase levels and severe muscle weakness following treatment, ultimately leading to death after the second course of therapy (Sahafi et al., 2024).

6 Conclusions

Lactylation, a prevalent PTM of both histone and non-histone proteins, has multifaceted regulatory roles spanning physiological processes and pathological alterations. The discovery of lactylation not only innovatively bridges metabolic activity with epigenetic regulation but also reveals intricate interconnections between pathological mechanisms and normal physiological functions. This review systematically consolidates the fundamental framework of protein lactylation. Starting from its initial characterization in 2019, we summarize current knowledge on lactylation mechanisms, histone and non-histone lactylation phenomena, and their pathophysiological significance. Regarding lactylation's contributions to disease pathogenesis, which are predominantly pro-tumorigenic, this review focuses mainly on tumor-related aspects. In the three

globally most prevalent cancers (breast cancer, CRC, and NSCLC) according to IARC data, lactylation promotes tumorigenesis and malignant progression. Similarly, lactylation also shows detrimental pro-tumor effects in HCC, glioblastoma, and cervical cancer. Furthermore, it is implicated in resistance to various ratio- and chemotherapeutic regimens, including cisplatin and TMZ treatments. To address these challenges, current strategies involve: (1) targeting lactate production/transport systems (e.g., LDHA and MCT inhibition); and (2) directly intervening in lactylation modifications through inactivation of lactyltransferases or activation of delactylases. Clinically, lactylation-related therapeutic approaches for managing cancer and radiotherapy complications have achieved remarkable progress.

Three main conclusions emerge from this review:

(1) Lactylation represents a protein PTM occurring across diverse proteins, not limited to epigenetic regulation. Through modifications of histones, various non-histone proteins, and even GTPase activity, lactylation comprehensively regulates protein functions at transcriptional, translational, and post-translational levels, participating extensively in physiological and pathological processes. These processes frequently exhibit significant metabolic correlations, suggesting substantial unexplored potential in lactylation research.

(2) Lactylation exacerbates disease progression, directly promoting tumor initiation/development and contributing to tumor resistance against radio/chemotherapies. Lactylation is significantly increased in tumors due to the Warburg effect, and meanwhile, numerous lactylation modification phenomena reciprocally fuel tumorigenesis and malignant progression. Moreover, lactylation and its associated glycolytic system interact bidirectionally with ionizing radiation–lactylation to influence radiotherapy efficacy while radiation modulates lactylation-related metabolic networks.

(3) Targeting lactate production systems and lactylation modifications represents a promising therapeutic/adjuvant strategy. While lactylation modulation shows potential for overcoming treatment resistance, its involvement in normal physiological processes necessitates stringent targeting specificity. Nanomedicine and targeted drug delivery systems may provide optimal solutions for clinical translation.

In conclusion, lactylation research holds tremendous potential, though it remains in its nascent stage. Improved detection technologies and refined mechanistic understanding remain critical needs. Regarding radiotherapy, radiation–lactylation metabolic interactions require focused investigation. By targeting lactylation-related modification mechanisms and metabolic systems, more novel agents with therapeutic or adjuvant therapeutic effects are expected to be discovered. Therapeutic development should prioritize pathological lactylation targeting while preserving physiological functions, potentially opening new avenues for cancer management and broadening treatment paradigms.

Acknowledgments

This work was supported by the National Natural Science of Foundation of China (No. 82102096) and the Science and Technology Development Plan of Jilin (Nos. 20240101275JC and YDZJ202401200ZYTS), China.

We express our sincere gratitude to Miss Jin WANG (Jilin University) for her support during the formative phase of this manuscript endeavor.

Author contributions

Jiaqi LIANG conducted primary literature collection, drafted the manuscript, and designed the figures. Rongrong LIU assisted in manuscript writing and revision. Shuo LIANG performed the writing – review and editing. Zhicheng WANG and Hongguang ZHAO contributed to the conceptualization, methodology, project administration, supervision, and writing – review and editing. All authors have read and agreed to the final manuscript.

Compliance with ethics guidelines

Jiaqi LIANG, Rongrong LIU, Shuo LIANG, Zhicheng WANG, and Hongguang ZHAO declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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