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Review

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Emerging perspectives and promising solutions: lactylation modification in chemo- and radio-therapy 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 internal 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 the induction of the polarization tendency of M2-like features in macrophages in the tumor microenvironment. We also explore how current clinical practitioners can further expand therapeutic paradigms or pave the way for other therapeutic approaches to address the current oncological issues 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 medical malignancies as a consequence of radiotherapy is a salient concern (Ohno, 2022; Onishi, 2022). The potential for platinum drugs to induce nephrotoxicity, hepatotoxicity, and

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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 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, instead relying on the relatively low-capacity efficiency of the glycolytic 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, 2006; Fischer, 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, 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 in sepsis-related lung and kidney injury, embryonic development, and sperm meiosis (Wu et al., 2024; Qiao et al., 2024; Merkuri et al., 2024; Zhang et al., 2025). Lactylation modification is an emerging post-translational modification (PTM), and there have been few detailed studies. Recent studies have focused mainly on metrics such as lactate levels and lactate dehydrogenase A (LDHA) (Colbert et al., 2023; Qiao et al., 2021). 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 dehydrogenase M2, monocarboxylate transporters1/4 (MCT1/4), and glucose transport protein1/3 (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/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 lactylation (H3K18la) acted as a "lactate clock" during macrophage M1 polarization, which was initiated by aerobic glycolysis during M1 polarization and by epigenetic mechanisms, late in the inflammatory process, and induced M2-like features in macrophages. M2-type macrophages, also referred to as activated macrophages,

differentiate in response to IL-4 and IL-13 and participate in 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. 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, 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. In 2022, 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 lncRNA signatures, revealing potential connections between lysine lactylation (Kla)-associated long non-coding RNAs (lncRNAs) and breast cancer, thereby providing innovative therapeutic guidelines for BC management. In clinical practice, ^{18}F-FDG PET/CT and magnetic resonance imaging (MRI) have become routine imaging techniques, with well-established associations with cellular glycolytic activity (Plathow and Weber, 2008; Brindle, 2008; Melkus et al., 2008). With the growing understanding of lactylation and its physiological/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

2.2.1Readers

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. Gui et al. (2024) showed that in cervical cancer cells, Double 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 (PHDA1) and carnitine palmitoyltransferase 2 (CPT2)

and limiting the oxidative phosphorylation (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 (AMP) and release pyrophosphate, then they transfer L-lactate to the Lys 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 et al., 2024).

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

2.2.3 Erasers

Lysine deacetylase (KDL) (Fig. 1c) is composed mainly of HDAC (Li et al., 2024) and Sirtuin (SIRT) (Jin et al., 2023). HDAC1-3 have lactyl group eraser activity (Moreno-Yruela et al., 2022). During the development of atherosclerosis, HDAC3 downregulation due to lactate accumulation in vascular smooth muscle cells promotes H4K12la, which in turn exacerbates vascular smooth muscle cell (VSMC) senescence (Li et al., 2024a). Moreover, HDAC was noted to vary catalytic efficiencies when targeting D-lactic acid and L-lactic acid, a pair of mirror-image stereoisomers (Moreno-Yruela et al., 2022). Recent findings have shown that the extracellular lactate concentration leads to a 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 lactoyl erasure and potentially establish a novel positive feedback transduction pathway. This question deserves further investigation. With regard to SIRT, SIRT1/2/3/5 all have delactosylation 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 delactosylases, a study on Escherichia coli noted that CobB could function as a lysine delactase (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, ACSS2 and guanosine triphosphate-specific SCS (GTPSCS) were found to function sequentially as lactoyl-CoA synthetases, using lactic acid to synthesize lactoyl-CoA as a direct lactosyl donor for lactyltransferases (Zhu et al., 2025; Liu 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 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 lactosyl donor without undergoing the synthesis process of lactoyl-CoA (Li et al., 2024).

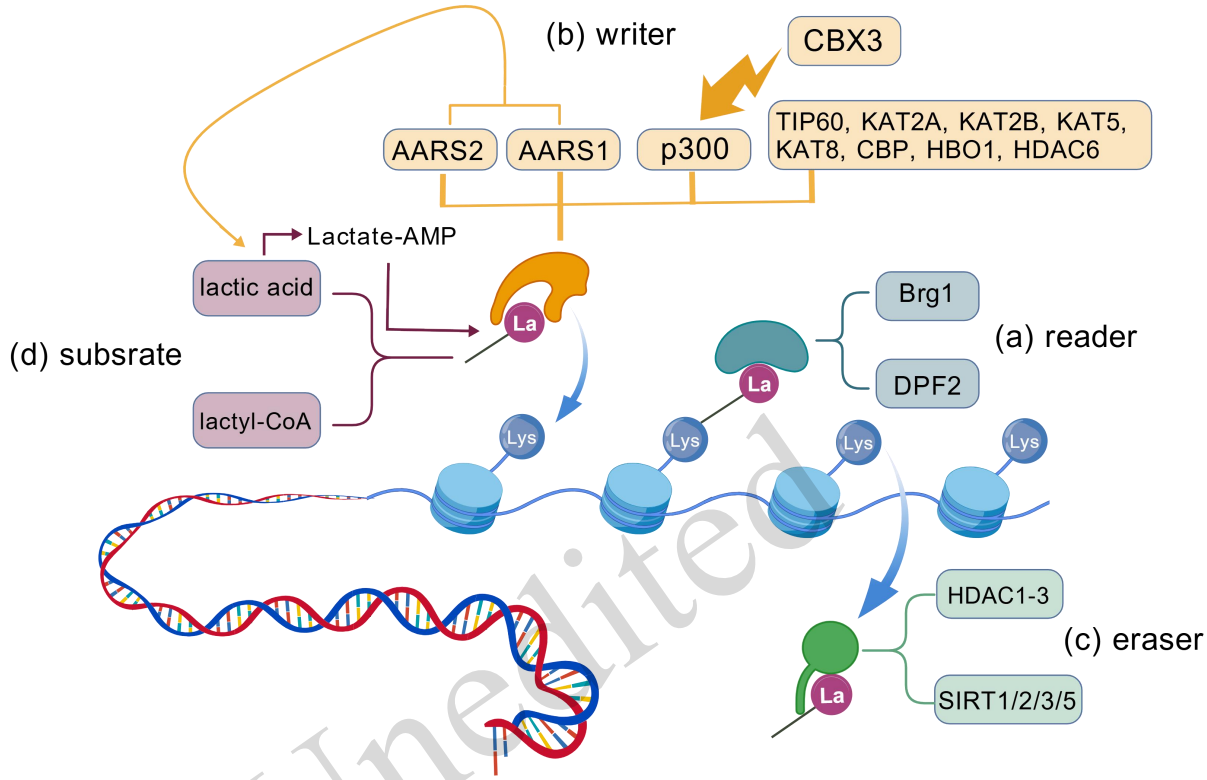

Fig. 1 Regulation of lactylation: reader (a), writer (b), eraser (c), and substrate (d). The lactoyl group can be supplied by lactoyl-CoA or directly derived from lactate. In the writer process, catalyzed by AARS1/2, lactate first forms lactoyl-AMP as a direct substrate, which subsequently transfers the lactoyl group to lysine residues of target proteins. In contrast, p300 uses lactoyl-CoA as its substrate. Although CBX3 lacks intrinsic catalytic activity for lactoyl 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 lactoyl group recognition and functional execution of lactylation modifications.
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AARS: alanyl-transfer RNA synthetases; TIP60: tat-interactive protein; KAT: lysine ascetyltransferase; CBP: cAMP-response element binding protein; HBO: histone acetyltransferase binding to ORC; HDAC: histone deacetylase; Brg: brahma-related gene 1; DPF: double PHD fingers 2; SIRT: sirtuin.

2.3 Histone and non-histone lactylation: 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-traslational), translational, and post-translational. Critically, the outcomes of lactylation simultaneously cover physiological homeostasis and pathological progress.

2.3.1 Histone and non-histone lactylation constitute a three-dimensional mechanism for regulating protein function

Histone lactylation is found mainly on lysines in H2A, H2B, H3 and H4, and lysine lactonylation has been demonstrated at many sites, including H2BK 6, 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, i.e., the content and function of proteins at the transcriptional level (Fig. 2a). In lung alveolar epithelial cells (AECs), H3K18la promotes the transcription of YTH domain family protein 1 (YTHDF1) and ultimately leads to the progression of lung fibrosis (Wang et al., 2024). The activation of fibroblast growth factor 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 GTPases such as eukaryotic translation elongation factor 1 alpha 2 (eEF1A2) (Fig. 2b). In this case, post-translational modification 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 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 homologous gene 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 box-1 (HMGB1), secreted by macrophages, is involved in inflammation regulation and positively correlates with poor patient prognosis (Yang et al., 2020; Deng et al., 2018; Andersson and Tracey, 2011; Karlsson et al., 2008; Sundén-Cullberg et al., 2005). 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 (Li et al., 2023; Xu et al., 2021; Bi et al., 2021). In vascular endothelial cells, H3K18la is upregulated by lipid peroxidation and contributes to 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 et al., 2024). In addition, nuclear receptor subfamily 4, group A, member 3 (NR4A3), a pivotal regulator of apo A-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 to promote 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 byproduct of normal cellular metabolism in the body (Fig. 2g-i). 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 abrogation of the inflammatory process. That is to say, 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 inhibitory and thus participating in the abrogation 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 downregulation 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, lactylation of pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1)-K336 in the pyruvate dehydrogenase complex with CPT2 at lysine 457/8 inactivates both enzymes and inhibits 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 oxidative phosphorylation during muscle exercise, thereby reducing myocyte damage due to overexertion (Mao et al., 2024) (Fig. 2g).

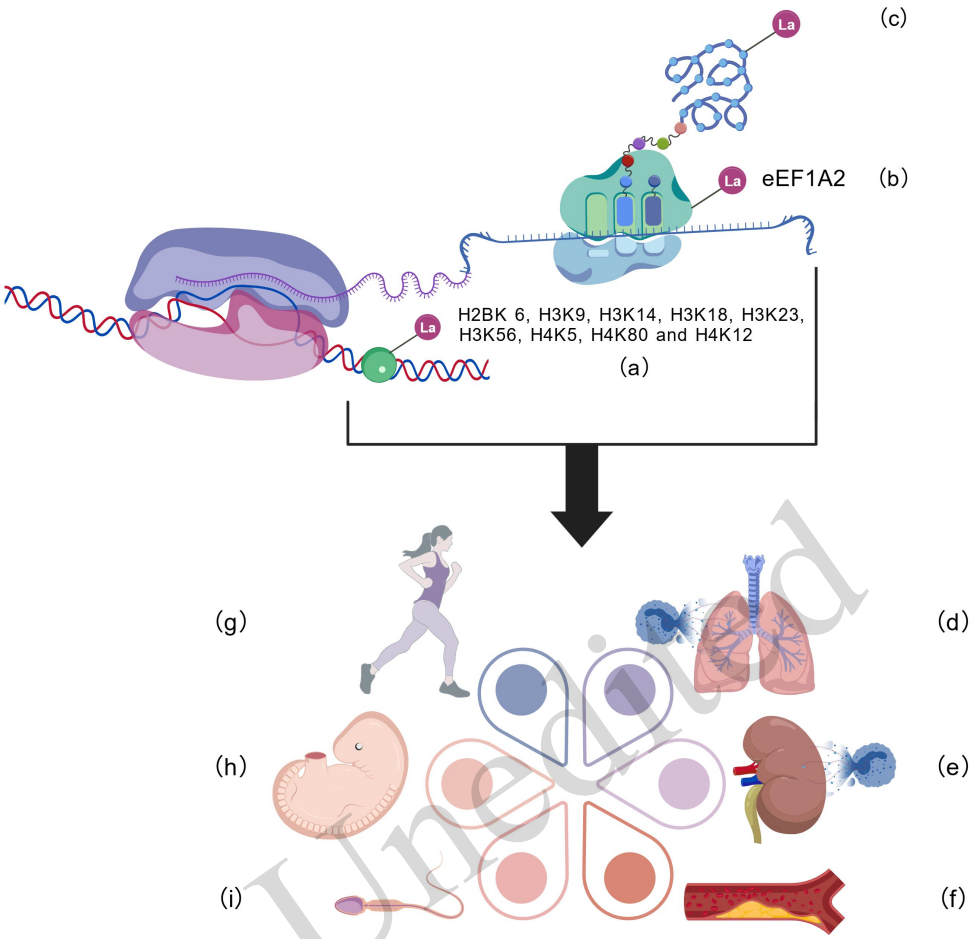

Fig. 2 Lactylation regulates protein across three levels and is involved in various processes. (a) Lactylation modifications occur on histones (such as H3K18 in various promoters), (b) non-histone proteins (GTPases), and (c) other proteins. From an organismal perspective, lactylation-mediated protein regulation is ubiquitously involved in both physiological and pathological processes; (d, e, and f). Examples include sepsis-induced lung injury, renal injury, and atherosclerosis. Lactylation also has critical regulatory roles in (g, h, and i) endurance exercise, embryonic development, and spermatogenic meiosis.
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eEF1A2: eukaryotic translation elongation factor 1 alpha 2.

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 modification systems of the lactyl group. From a functional perspective, lactylation can be understood as a modification 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 have regulatory functions during DNA replication? Considering the critical role of histones in DNA replication, this question warrants further discussion and exploration. (2) Research on the more precise regulatory mechanisms of lactylation and its specific roles in normal physiological functions or 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 upregulated in tumors due to the Warburg effect, which facilitates intracellular lactylation modification activities. Extensive histone and non-histone lactylation 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; (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 acknowledged as the leading cause of female tumor incidence. 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 et al., 2023). In breast cancer cells, high expression of KCNK1 binds and activates LDHA to promote increased lactate production and pan histone lactylation, while numerous downstream target 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 KATs and is a multifunctional histone acyltransferase that catalyzes acetylation, crotonylation, propionylation, and butyrylation (Xiao et al., 2021). Niu et al. (2024) discovered that HBO1 catalyzes the H3K9la modification process of the aquaporin-1 (AQP1) gene and induces upregulation 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 schlafen5 (SLFN5). Consequently, H4K12la has been evaluated by some researchers as a promising biomarker for TNBC (Li et al., 2024; Cui et al., 2024). Based on Cox regression and XGBox methods, Lin et al. (2024) identified and screened eight KLA-associated lncRNAs to construct a prognostic risk model. Notably, the model output risk scores exhibited a substantial correlation with immune function, as shown by increased TMB and decreased TIDE.

3.2 Colorectal cancer

Globally, colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer deaths (Bray et al., 2024). Lactate levels are significantly elevated in colorectal cancer cells, with substantial up-regulation of extranuclear lactylation in the nucleus. The levels of lactate and lactylation are independent prognostic factors affecting CRC (Huang et al., 2024). In CRC, KAT8 functions as the lactoyltransferase, and facilitates eEF1A2K408 lactylation modification and its GTPase activity in response to aa-tRNA stimulation. It then induces translational elongation and enhances protein synthesis, rendering CRC translational activities adaptable to the more intense demands of malignancy (Xie et al., 2024) (Fig. 3b). In addition to CRC cells themselves, in their tumor microenvironment (TME), macrophage H3K18la down-regulates RARγ, thereby deregulating the inhibitory effect on nuclear factor-κB-gene-binding (NF-κB,) leading to the production of IL-6 and enhancing the signaling role of STSA3, which ultimately correlates closely with a poor prognosis in CRC patients (Li et al., 2024) (Fig. 3a).

The main factor of lethality in patients with CRC is the presence of colorectal liver metastases (CRLMs) in liver metastases. 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 tumor-circulating cells (CTCs) in the bloodstream of the patient, the interaction between CRC cells metastasized to the liver and cells in situ and thus the formation of special ecological niches, and the role of liver sinusoidal endothelial cells (LSECs), Kupffer cells, NK cells, macrophages, hepatic stellate cells, $CD4^+$/$CD8^+$ T cells and B cells (Jin et al., 2025). In terms of lactylation, up-regulation of ubiquitin-specific peptidase3 antisense RNA 1 (USP3-AS1) in CRC significantly enriches glycolysis and the myelocytomatosis oncogene (MYC) signaling pathway, which in turn regulates cell division cycle 27 (CDC27) expression via H3K18la within the CRC, ultimately "initiating" CRLMs (Zhou et al., 2025). In addition, high expression of G protein-coupled receptor 37 (GPR37) in the CRC activates the Hippo pathway to promote glycolysis and LDHA expression, which in turn upregulates CXCL1/5 through the upregulation of H3K18la, and ultimately contributes to CRLM88 (Zhou et al., 2023) (Fig. 3c). Most notably, Gu 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 intratumorally-resident E. coli inhibits NF-κB signaling via lactylation of retinoic acid-inducible gene 1 (RIG-I), and then inhibits NOD-like receptor thermal protein domain associated protein 3 (NLRP3) transcription, which mediates M2 macrophage polarization and affects the immunosuppressive activity of regulatory T cells (Tregs) and the antitumor 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 angle.

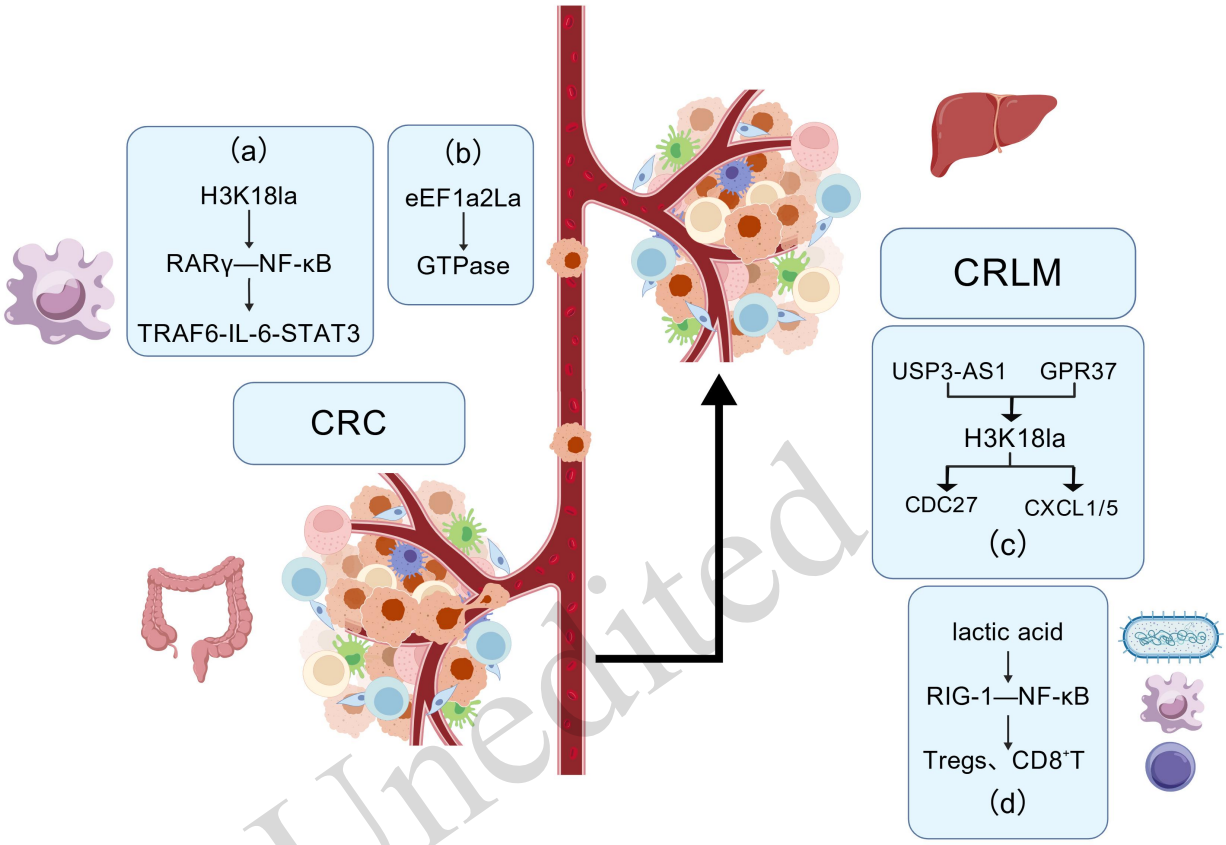

Fig. 3 Mechanisms underlying CRC malignancy (a and b) and CRLM (c and d). The lactate-lactylation axis in cancer cells and TME promotes malignant behaviors and hepatic metastasis processes.
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NF-κB: nuclear factor-κB-gene-binding; IL: interleukin; eEF1A2: eukaryotic translation elongation factor 1 alpha 2; GTPase: guanosine triphosphate hydrolases; CRC: colorectal cancer; CRLM: colorectal liver metastases; USP:ubiquitin-specific peptidase; GPR: G protein-coupled receptor; CDC: cell division cycle; RIG: retinoic acid-inducible gene; Tregs: regulatory T cells

3.3 Non-small cell lung cancer

Lung cancer consistently shows the highest incidence and mortality rates among malignancies worldwide (Bray et al., 2024). The World Health Organization (WHO) classifies lung cancer into four histological subtypes: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma. These neoplasms are typically categorized into two groups based on biological and therapeutic distinctions: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC constituting about 85% of cases as per epidemiological data (Suster and Mino-Kenudson, 2020). Both histone and non-histone lactylation modifications have significant pathophysiological relevance in NSCLC. Elevated H3K18la levels observed in NSCLC directly activate the 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 increasing tumor immune evasion (Zhang et al., 2024). Concurrently, regulatory T cell-derived H3K18la modulates NF-κB p65 transcription, upregulating 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/lactic acid transport system/glucose transport or metabolism system. A natural product, fargesin (FGS), has been reported to inhibit the expression of a range of oncogenes in LDHA/B, pyruvate kinase2 (PKM2), and solute carrier family 2 member 1 (SLC2A1). PKM2 has been validated as a target for the antitumor effects of FGS, which indirectly inhibits the lactylation of H3 histones by inhibiting the level of glycolysis (Guo et al., 2024). In addition, the direct targeting of the lactylation-modification process can be attempted with the lactylation reader, writer, eraser, and substitute, 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 – exhibits lactylation modifications correlated with stemness maintenance, enhanced migration, and invasive capacity in NSCLC (Yan et al., 2024; Gruber et al., 2005).

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 impacts 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, permitting enhanced nuclear translocation of XRCC1 and subsequent DNA repair augmentation (Li et al., 2024). In advanced-stage tumors, monocyte-derived macrophages (MDMs) overexpressing GLUT1 promote histone lactylation, thereby upregulating 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 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, 6-Biphosphatase 4 (PFKFB4) mRNA, further amplifying glycolysis (Zhou 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 upregulate p300 expression, establishing a positive feedback loop that reinforces glycolytic flux (Li et al., 2024). In acute myeloid leukemia (AML), STAT5 overexpression promotes glycolysis and pan-lactylation. This facilitates E3BP nuclear translocation, enhances H4K5la levels, and drives PD-L1 transcription to reinforce immunosuppression in AML (Huang et al., 2023). Cervical cancer cells show lactate-induced upregulation 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 upregulated ATP‐binding cassette sub‐family F member 1 (ABCF1)-K430la. Post-lactylation, ABCF1 retains E2 ubiquitin ligase activity and translocates to the nucleus to bind the lysine demethylase 3A (KDM3A) promoter, upregulating 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 2circRNA (circXRN2). Downregulation of this regulatory axis correlates with malignant behaviors (Xie et al., 2023). In ocular melanoma, elevated histone lactylation specifically upregulates alpha-ketoglutarate-dependent dioxygenase homolog 3 (ALKBH3) in high-risk tumors. This enzyme removes m1A methylation from SP100A, weakening promyelocytic leukemia

(PML) tumor-suppressive condensate formation and promoting malignant transformation (Gu et al., 2024).

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	Li et al., 2024; Cui et al., 2024
CRC/CRLM	eEF1A2	K408	Xie et al., 2024
	H3	K18	Li et al., 2024; Zhou et al., 2025; Zhou et al., 2023
	RIG-I	K852	Gu et al., 2024
NSCLC	H3	K18	Zhang et al., 2024; Xue et al., 2024
	SOX9		Yan et al., 2024; Gruber et al., 2005
GBM	XRCC1	K247	Li et al., 2024
GSC	PTBP1	K436	Zhou et al., 2025
PDAC	H3	K18	Li et al., 2024
AML	H4	K5	Huang 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 metastases; eEF1A2: eukaryotic translation elongation factor 1 alpha 2; RIG: retinoic acid-inducible gene; SOX9: SRY-box transcription factor; 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; NCL: nucleolin.

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, colorectal cancer, and non-small cell lung cancer), emerging evidence reveals that elevated lactylation levels in other oncological contexts, including bladder cancer, hepatocellular carcinoma, 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 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 (TME)

The immunosuppressive nature of the TME remains a major obstacle in cancer immunotherapy. Lactylation research focuses mainly on two cellular 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 TIMC-mediated immunosuppression in CRC. In CRC, upregulated lactylation of both H3K18 and METTL3 within TIMCs activates the 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 upregulation, 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)/TP53-mutant tumors show increased aerobic glycolysis, inducing M2 macrophage polarization and conferring immunotherapy resistance. A therapeutic regimen combining ADT/PI3Ki/anti-PD-1/Porcupine inhibitors has shown efficacy in counteracting immunotherapy resistance in metastatic castrate-resistant prostate cancer (mCRPC) (Chaudagar et al., 2023). Apolipoprotein C2 (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 regulatory T cell accumulation, effectively controlling immune resistance and metastasis in NSCLC (Chen et al., 2024).

T cell-mediated cytotoxicity forms the basis of cellular immunotherapies. Histone lactylation activates circATXN7 transcription in tumor-specific cytotoxic T lymphocytes (CTLs), leading to NF-κB inactivation and increases susceptibility to activation-induced cell death (AICD), thereby promoting immunotherapy resistance. Engineered CTLs with circATXN7 knockdown have shown enhanced 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 (Chen et al., 2018; Chaudhuri et al., 2016; Russo et al., 2019). Platinum-based agents, clinically established as first-line chemotherapy for numerous malignancies, face persistent challenges due to resistance (Zhang et al., 2022). The 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 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 et al., 2024a; Chen et al., 2024b).

Temozolomide (TMZ), a blood-brain barrier-penetrant alkylating agent, exerts cytotoxicity through guanine and adenine methylation 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, downregulating 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 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 chromosome 4 (SMC4) protein downregulation, mediating irinotecan resistance through ATP-binding cassette transporter activation (Sun 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 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 et al., 2024). HCC exhibits glycolysis-elevated H3K14la that upregulates ubiquitin E3 ligase expression, promoting resistance to folinic acid + fluorouracil + oxaliplatin (FOLFOX) regimens. Thus, ubiquitin E3 ligase neuronal precursor cell-expressed developmentally downregulated 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-1 R) lactylation, which inhibits MET activation and alleviates proteasome inhibitor (PI) resistance through cellular cuproptosis induction (Wang et al., 2024). In gastric cancer, lactate-induced NSUN2-K508la (catalyzed by NAA10) confers resistance to doxorubicin-induced ferroptosis, positioning NSUN2 as a prognostic biomarker and therapeutic target (Niu et al., 2025). Non-histone IGF2mRNA binding protein 3 (IGF2BP3) lactylation drives lenvatinib resistance in HCC via the IGF2BP3-PCK2-SAM-m^{6}A axis. Liposomal delivery of IGF2BP3-targeting 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 paper, we have comprehensively reviewed multiple therapeutic strategies targeting lactylation modifications or key nodes in associated pathways. Approaches targeting key nodes of glucose metabolism/transport, glycolytic regulation, and lactate production/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 (5-fluorouracil/oxaliplatin/leucovorin) chemoresistance in HCC.

Table 2 Lactylation in the tumor chemotherapy resistance

Neoplasms	Tolerance	Lactylation Sites	Solutions	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	The coordinate loss of SMC4 and PGAM1	Sun et al., 2023

	bevacizumab	H3K18	2-DG or oxalates	Li et al., 2024
HCC	Immunotherapy	H3K18	Targeting H3K18la	Cai et al., 2024
	FOLFOX	H3K14	Targeting NEDD4	Zeng et al., 2025
	Lenvatinib	IGF3BP3	2-DG or liposomal delivery of IGF2BP3-targeting siRNA	Lu et al., 2024
NSCLC	PD-1/PD-L1 inhibitor	APOC2K70	anti-APOC2-K70la antibodies	Chen et al., 2024
GBM	TMZ	H3K9la	Stiripentol	Yue et al., 2024
GSC		XRCC1 K247	D34-919	Li et al., 2024
Bladder cancer	Cisplatin	H3K18	H3K18la	Li et al., 2024
MM	PI	IGF-1R		Wang 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; FLOFOX: folinic acid + fluorouracil + oxaliplatin; NEDD4: neuronal precursor cell-expressed developmentally downregulated 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.

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 nijmegen breakage syndrome protein (NBS1) lactylation plays an essential role for MRN complex assembly and HR repair protein recruitment at DNA break sites–a critical mechanism of cellular defense against ionizing radiation damage (Chen 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). HSP90 inhibitors, encompassing DNA alkylators, DNA replication inhibitors, and poly (ADP-ribose) polymerase (PARP) inhibitors, represent promising anticancer modalities (Stecklein et al., 2012). The HSP90 inhibitor Ganetespib confers radioresistance by suppressing PKM2 and platelet phosphofructokinase (PFKP) activity (Chen et al., 2024) (Fig. 4c). The mechanism of radioresistance alleviated by pyruvate dehydrogenase kinase 1 (PDK1) inhibition has also been reported to be related to PDK1/CD47/Akt-mediated glycolytic axis downregulation (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

In 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 reconnect glucose metabolism and promote radioresistance in glioblastomas during radiation therapy (Bailleul et al., 2023) (Fig. 4g). Moreover, an increase in glucose influx and glycogenesis 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 above changes induced by ionizing radiation can be closely related to the phenomenon of radioresistance in tumors.

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

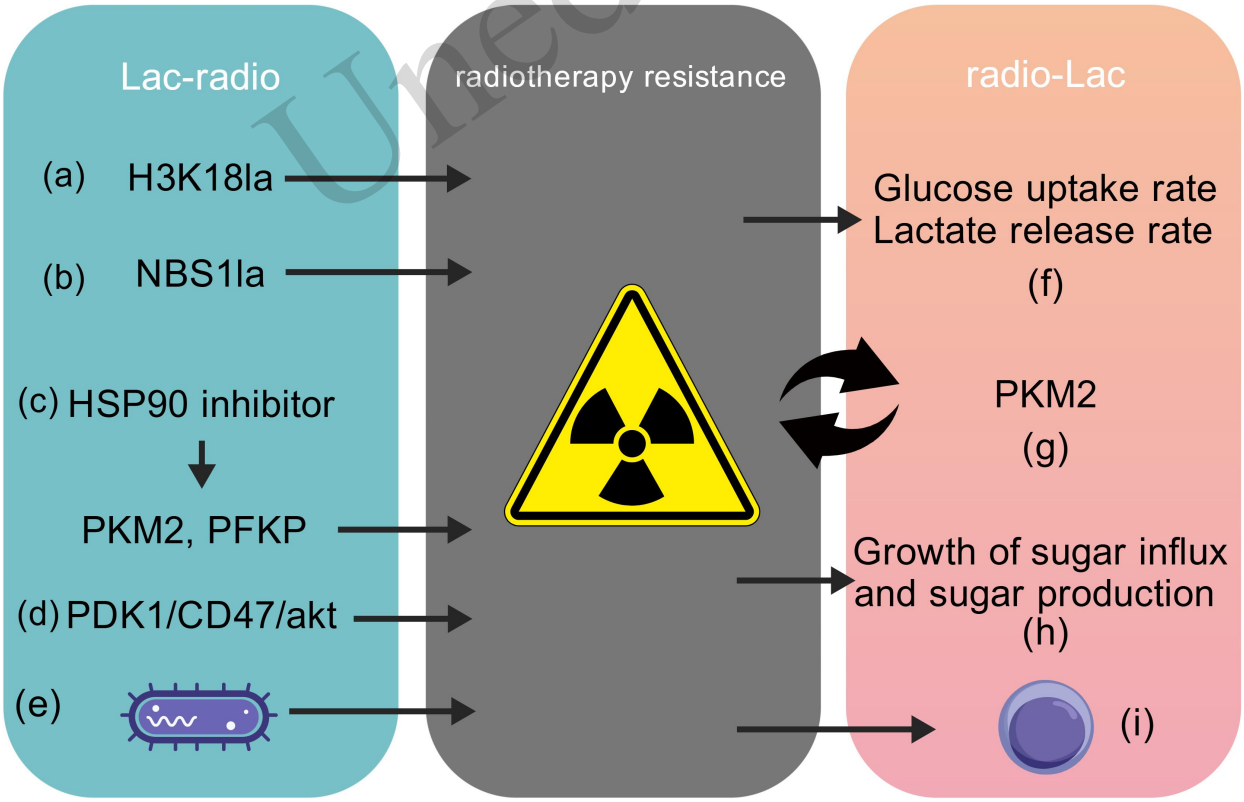

Fig. 4 A complex causal relationship exists between ionizing radiation and the lactate-lactylation axis.

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, upregulated PKM2 functionality following radiation exposure has been observed, thereby reciprocally increasing cellular radioresistance, forming a positive feedback loop.
Created with BioGDP.com (Jiang et al., 2025)
HSP90: heat-shock protein 90; OKM2:pyruvate kinase2; PFKP: platelet phosphofructokinase; PDK1: pyruvate dehydrogenase kinase 1; CD47: C]cluster of differentiation 47.

4.2.3 Acting as 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 and therapeutic monitoring in radiotherapy are in the spotlight. Radiotherapy remains the first-line treatment for nasopharyngeal carcinoma per 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 et al., 2024). Elevated LDH levels also correlate with poor prognosis in IDH-wildtype glioblastoma (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, non-small cell lung cancer, and rectal cancer (Trada et al., 2023; Grambozov et al., 2023; Avallone et al., 2019). 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.

(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 remain 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 (TME)

The Warburg effect establishes LDH as a critical metabolic node for energy acquisition in tumor cells (Fig. 5a). Upregulated LDHA expression represents a hallmark of multiple malignancies, with elevated LDH levels serving as a robust prognostic indicator for poor clinical outcomes (Augoff et al., 2015). As reviewed previously, pharmacological inhibition of lactate production has been achieved mainly through stiripentol (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 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), CDK7-YAP-LDHD axis-mediated D-lactate depletion is essential to 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). MCT1/2/4 isoforms have been identified across various malignancies, including breast, bladder, and cervical cancers. MCT4 facilitates lactate efflux, and 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 DIDS, and selective compounds like AR-C155858 (Payen et al., 2020).

BAY-8002, a novel MCT inhibitor, suppresses cisplatin/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/fucose-mediated skewing of cDC1/cDC2 subsets, thereby restoring antitumor T cell adaptability (Niveau et al., 2025).

In addition, β-galactose 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 Directly targeting the process of lactylation modification

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 VEGF pathways, and (2) inhibition of 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).

Alternative approaches to reduce lactylation levels involve modulating glycolytic lactate production. Tanshinone I, a bioactive constituent of Salvia miltiorrhiza, exhibits anti-proliferative effects in ovarian cancer by suppressing Foxk1-mediated H3K18la upregulation (Jin et al., 2025).

5.2 Nanoparticle-mediated delivery refines lactylation antagonism with spatiotemporal specificity

Conventional anticancer drugs usually face the limitation of high systemic toxicity and low targeting. 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 and various physiological and pathological processes. Consequently, it is imperative to improve therapeutic targeting. Nanomedicine delivery systems have been engineered to enhance drug performance, target drugs more effectively, facilitate multi-drug co-delivery, and extend drug circulation time in the body, thereby achieving therapeutic efficacy while maintaining low toxicity (Liu et al., 2023). Furthermore, nanomedicine has shown efficacy in overcoming drug resistance and enhancing the immune response (Fig. 5d) (Li 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 temozolomide crossed the blood-brain barrier 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 blast" cleavage of the nanocapsules to release MT and siPKM2 in the high GSH environment of glioma cells for more precise therapeutic effects (Zhang et al., 2024).

The use of a nanocomplex loaded with the natural polyphenol galloflavin based on metal-phenolic ligands has been shown to inhibit LDHA activity and thus improve the immunosuppressive conditions in the TME and enhance cancer therapeutic efficacy (Zhang et al., 2024). A self-cascading catalytic Pt@Au nano-enzyme 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 ROS accumulation (Zhang et al., 2024).

5.3 Clinical status

The MCT1 inhibitor AZD 3965 has concluded Phase I/II clinical trials (Fig. 5b) and is expected to function as a novel adjuvant tumor therapy. As previously outlined, the inhibition of MCT1 can impede lactate transport, thereby establishing a robust correlation with tumor treatment efficacy. A phase I dose-escalation study conducted by 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 (retinopathy), fatigue, anorexia, and constipation. Seven patients receiving a dosage of ⩾ 20 mg/day experienced dose-limiting toxicity (DLT): grade 3 cardiac troponin elevation (n=1), and asymptomatic ocular DLT: grade 3 cardiac troponin elevation (n=1), and asymptomatic ocular DLT: grade 3 cardiac troponin elevation (n=1). Seven patients receiving a daily dosage of ⩾20 mg experienced DLT, characterized by grade 3 cardiac troponin elevation (n=1), asymptomatic ocular DLT (n=5), and grade 3 acidosis (n=1). Plasma pharmacokinetics showed the achievement of target concentrations, while pharmacodynamic measurements indicated targeted activity (Halford et al., 2023).

In clinical settings, restricting nutrients or providing additional supplementation is a prevalent practice. This strategy aims to foster healthier physical 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 via PD-1 lactylation. The synergistic effect of the two in combination could greatly enhance the prognosis of patients (Tong et al., 2024). Our review suggested that the efficacy of this therapy was limited by treatment tolerance. However, perhaps combination with an anti-APOC2K70-lac antibody might reduce the tolerance of this therapy and thus further improve the prognosis of the patients (Chen et al., 2024).

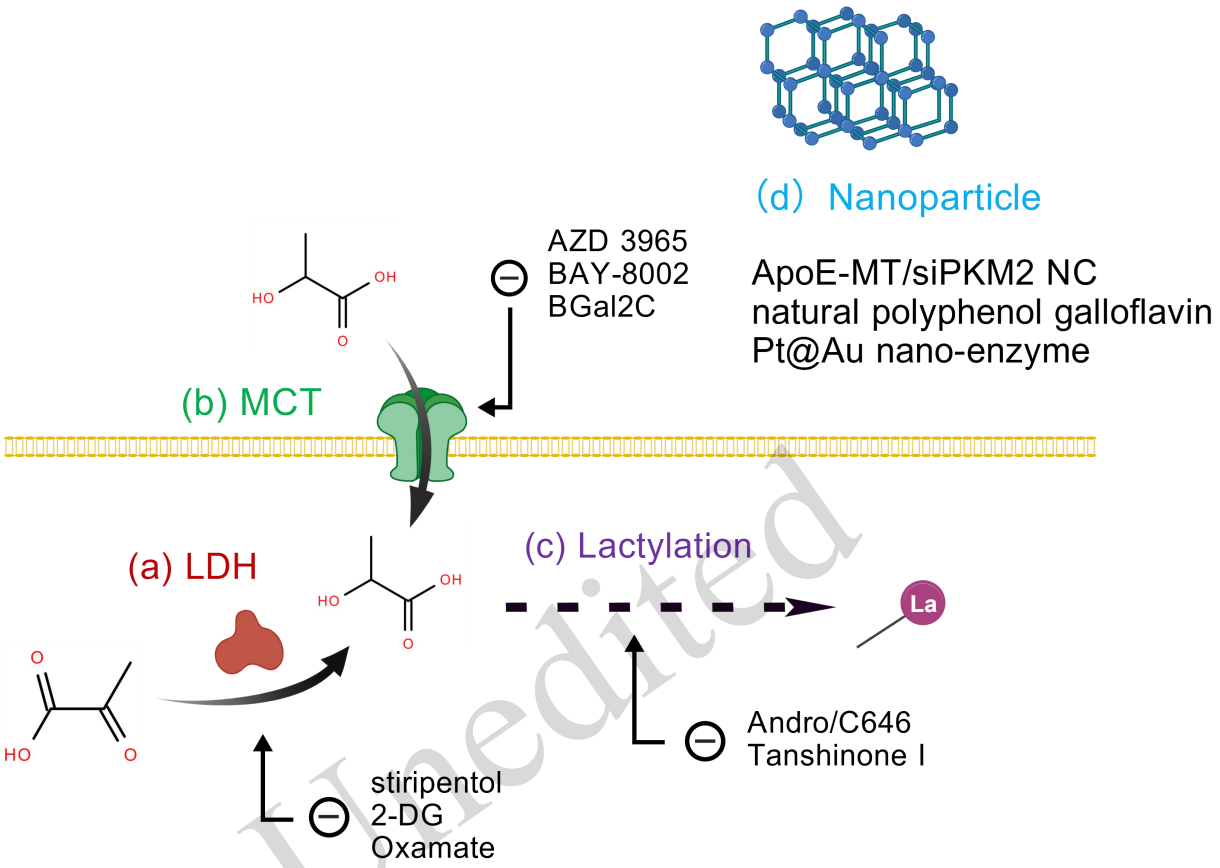

Fig. 5 Key Therapeutic Strategies Targeting Lactylation. Lactate can be synthesized intracellularly via LDH (endogenous lactate) or imported into cells via MCT-mediated transport (exogenous lactate). (a) Targeting LDH with stiripentol, 2-DG, or oxamate inhibits the upregulation of endogenous lactate. (b) Targeting MCTs using AZD 3965, BAY-8002, or BGal2C suppresses the upregulation of exogenous lactate. The MCT1 inhibitor AZD 3965 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 downregulate 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.
Created with BioGDP.com (Jiang et al., 2025)
MCT: monocarboxylate transporters; LDH: lactate dehydrogenase; BGal2C: β-galactose 2C.

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 of the neoplasm itself, but rather to a variety of complications arising from the neoplasm. For instance, malignancy itself is a significant cause of death in patients. A 2024 study reported that lactate activates the lipid-specific GPR81, which mediates the development of malignant stroma by sequential activation of the Gi-Gβγ-RhoA/ROCK1-p38 signaling cascade (Liu et al., 2024).

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 treatment (Sahafi et al., 2024).

6 Conclusions

Lactylation, a prevalent post-translational modification of both histones 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/non-histone lactylation phenomena, and their pathophysiological significance. Regarding lactylation's contributions to disease pathogenesis, which are predominantly pro-tumorigenic, this review focused mainly on tumor-related aspects. In the three globally most prevalent cancers (breast, colorectal, and non-small cell lung cancers) according to IARC data, lactylation promotes tumorigenesis and malignant progression. Similarly, lactylation also shows detrimental pro-tumor effects in hepatocellular carcinoma, glioblastoma, and cervical cancer. Furthermore, it is implicated in resistance to various radio/chemotherapeutic regimens, including cisplatin and temozolomide treatments. To address these challenges, current strategies involve: (1) targeting lactate production/transport systems (e.g., LDHA and MLT inhibition), and (2) directly intervening in lactylation modifications through inactivation of lactylation-associated enzymes. 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 post-translational modification 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 show significant metabolic correlations, suggesting substantial unexplored potential in lactylation research.

(2) Lactylation exacerbates mainly 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 need focused investigation. By targeting lactoylation-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.

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Author contributions

Jiaqi LIANG: Conducted primary literature collection, drafted the manuscript, Figure design. Rongrong LIU: Assisted in manuscript writing and revision. Shuo LIANG: Writing-review & editing. Zhicheng WANG: Conceptualization, Methodology, Project administration, Supervision, Writing-review & editing. Hongguang ZHAO: Conceptualization, Methodology, Project administration, Supervision, Writing-review & editing. All authors have read and agreed the final manuscript.

Compliance with ethics guidelines

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

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

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