Protein lactylation and immunotherapy in gliomas: A novel regulatory axis in tumor metabolism (Review)

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Abstract. Gliomas are the most common primary brain tumors, and exhibit highly heterogeneous and aggressive biological behaviors. Metabolic reprogramming is a hallmark of gliomas, and lactate accumulation serves a critical role in tumor progression. In addition to its traditional role as a metabolic byproduct, lactate has been recognized as a signaling molecule that modifies proteins through lactylation, which is a novel post-translational modification. Lactate-induced lactylation of histone and non-histone proteins is emerging as a key epigenetic and metabolic regulator that influences glioma development, immune evasion, angiogenesis and therapeutic resistance. The present review provides mechanistic insights into protein lactylation, its role in glioma progression and its potential therapeutic implications. Targeting lactate metabolism and lactylation-modifying enzymes holds promise for improving glioma treatment outcomes.

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Abbreviations: ACSS2, acyl-CoA synthetase short chain family member 2; CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; CBX3, chromobox protein homolog 3; DMG, diffuse midline glioma; FX11, 7-benzyl-2,3-dihydroxy-6-methyl-4-propylnaphthalene-1-carboxylic acid; GBM, glioblastoma multiforme; GSC, glioma stem cell; GTPSCS, guanosine triphosphate-specific succinyl-CoA synthetase; H3K9la, histone H3K9 lactylation; H3K18la, histone H3 lysine 18 lactylation; HIF-1α, hypoxia-inducible factor-1α; KAT2A, lysine acetyltransferase 2A; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PTM, post-translational modification; TCA, tricarboxylic acid; TME, tumor microenvironment; TMZ, temozolomide

Key words: lactylation, gliomas, metabolism, immunotherapy, PTM, therapy

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1. Introduction

Glioma is one of the most common types of brain tumors, accounting for ~30% of all brain tumors and 80% of all malignant brain tumors (1). There are several types of gliomas, including astrocytomas, oligodendrogliomas and ependymomas. Low-grade gliomas (LGGs) grow slowly, whereas high-grade gliomas, such as glioblastoma multiforme (GBM), are highly aggressive (2,3). LGGs generally have a more favorable prognosis, whereas GBMs have a 5-year survival rate of <7% (4,5). Common symptoms vary depending on the tumor location and may include headaches, seizures, memory loss, personality changes, nausea and disrupted vision (6). Standard treatments for gliomas include surgery, radiation therapy and chemotherapy (7). Additionally, immunotherapy and targeted therapies are emerging as approaches for glioma treatment (8-10).

Metabolic adaptations, particularly the Warburg effect, facilitate rapid tumor growth by shifting cellular energy production toward glycolysis, even in the presence of oxygen (11). This metabolic shift leads to the excessive accumulation of lactate, which has traditionally been considered to be a metabolic waste product (12,13). However, recent studies have highlighted the role of lactate as a crucial signaling molecule that is capable of modifying proteins through lactylation, which is an epigenetic and metabolic regulatory mechanism that impacts tumor behavior (14,15). Lactylation, which is a type of post-translational modification (PTM) that was first identified as a histone modification, influences gene expression and immune cell differentiation (16-19). In addition to histone lactylation, non-histone protein lactylation has been implicated in various cellular processes, including tumor cell proliferation, immune suppression, angiogenesis and therapy resistance (20-22).

Lactylation has been demonstrated to serve critical roles in glioma development and progression (23). Lactylation-related genes that were identified using single-cell RNA-sequencing data revealed two distinct molecular subtypes, forming a prognostic signature that classified patients with glioma into high-score and low-score groups (24). Notably, high-score patients exhibited greater immune infiltration, elevated expression of chemokines and immune checkpoints, and poorer overall survival but an enhanced response to immunotherapy compared with low-score patients. This classification provides a valuable tool to predict survival outcomes and optimize treatment strategies (24). A pan-cancer multi-omics analysis of lactylation-associated genes has revealed that the prognostic significance of the lactylation score differs across tumor types. The lactylation score is a protective factor in LGG, kidney renal clear cell carcinoma, adrenocortical carcinoma, rectum adenocarcinoma and uveal melanoma (25). Higher lactylation scores are associated with a cold tumor microenvironment (TME), reduced immune cell infiltration and poorer responses to immunotherapy (25). The present review investigates the mechanisms and functional significance of lactate-induced protein lactylation in gliomas, emphasizing its implications for tumor progression and potential therapeutic interventions. The functions of protein lactylation in non-glioma cancer types are also described, indicating that protein lactylation occurs not only in gliomas but also serves a role in the development and progression of other tumors.

2. Mechanisms of protein lactylation

Lactate production and accumulation in cancer cells. Under normal conditions, cells generate ATP through glycolysis and mitochondrial oxidative phosphorylation (26,27). During these processes, glycolysis converts glucose into pyruvate, which then enters the tricarboxylic acid (TCA) cycle in mitochondria for energy production. However, a number of cancer cells preferentially rely on aerobic glycolysis, which is a phenomenon known as the Warburg effect (28,29). In cancer cells, most pyruvate is converted into lactate rather than entering the TCA cycle. This metabolic shift is influenced by multiple factors, including hypoxia, hypoxia-inducible factor 1-α (HIF-1α) activation, oncogene activation and mitochondrial dysfunction (30). HIF-1α is frequently upregulated in tumor cells and enhances the expression of key glycolytic enzymes, such as hexokinase, phosphofructokinase and pyruvate kinase M2 (PKM2), and it promotes the expression of lactate dehydrogenase A (LDHA) (31,32).

LDHA catalyzes the conversion of pyruvate into lactate (33). Monocarboxylate transporter (MCT)1 and MCT4 regulate lactate flux: MCT1 facilitates the import of lactate into cells, whereas MCT4 exports lactate from highly glycolytic cells, preventing intracellular acidification (34,35). Numerous oncoproteins such as c-Myc, Akt and KRAS promote glycolysis and lactate production, reinforcing the metabolic reprogramming of cancer cells (36,37). Additionally, mitochondrial dysfunction can shift metabolism toward glycolysis, leading to increased lactate accumulation (38,39). In recent years, lactate has been recognized not only as a metabolic byproduct but also as a key signaling molecule (40). Lactate serves as a substrate for protein lactylation, which modifies gene expression and promotes tumor progression (40-42).

Biochemical basis of protein lactylation. Protein lactylation is a type of PTM that involves the covalent attachment of lactate-derived acyl groups to lysine residues on histone or other proteins (43). This process is medicated by specific enzymes that regulate the addition and removal of lactyl groups. Several key enzymes, including histone lactyltransferases [p300 and lysine acetyltransferase 2A (KAT2A)], acyl-CoA synthetase short chain family member 2 (ACSS2), LDHs and histone deacetylases (HDACs), have been demonstrated to contribute to protein lactylation (44-46). p300, which is primarily known as a histone acetyltransferase, also mediates histone lactylation by transferring the lactyl group from lactyl-CoA to lysine residues on histones (47). KAT2A, which is also known as general control non-depressible 5, has been reported to exhibit lactyltransferase activity. ACSS2 converts lactate into lactyl-CoA, which serves as a donor molecule for protein lactylation (45). KAT2A often works in conjunction with ACSS2, which produces lactyl-CoA from lactate, enabling KAT2A to perform its lactyltransferase function (45).

LDHA and LDHB catalyze the conversion of pyruvate to lactate, increasing intracellular lactate levels, which can provide the necessary substrate for lactyl-CoA synthesis (48). Sirtuin 1 (SIRT1) has been identified as a delactylase that is responsible for removing lactylation marks from histones (49). Additionally, HDAC2 and HDAC3 have been implicated in the removal of lactylation, further regulating this modification (50-52). Although chromobox protein homolog 3 (CBX3) is not a direct lactyltransferase, it binds to lactylated histones and facilitates transcriptional regulation through interactions with p300 (53). MCT1 and MCT4 regulate lactate transport into and out of the cell, which influences the availability of lactate for lactyl-CoA synthesis (54,55). Therefore, protein lactylation is a highly dynamic process that involves a complex interplay of multiple enzymes that work together to maintain a balance between lactylation and delactylation (56) (Fig. 1).

Histone and non-histone protein lactylation

Histone lactylation. Both histone and nonhistone proteins are modified, and these modifications serve important roles in gene expression, metabolism and cell signaling (57). For example, tumor-derived lactate induces bevacizumab resistance in colorectal cancer (CRC) by enhancing rubicon-like autophagy enhancer expression through histone H3 lysine 18 lactylation (H3K18la) (58). Similarly, H3K18la promotes cisplatin resistance in bladder cancer by enhancing glycolytic metabolism and activating the key transcription factors Y-box binding protein 1 (YBX1) and YY1, while targeted inhibition of H3K18la restores cisplatin sensitivity (59). Evodiamine suppresses semaphorin 3A-mediated angiogenesis and programmed death-ligand 1 (PD-L1) expression in prostate cancer by impairing HIF-1α histone lactylation and inducing ferroptosis (60). In CRC, G protein-coupled receptor 37 promotes glycolysis and histone lactylation through the Hippo pathway, promoting liver metastasis (61). Furthermore, the m5C methyltransferase NOP2/Sun RNA methyltransferase 2 (NSUN2) promotes CRC progression by reprogramming glucose metabolism through the NSUN2/YBX1/m5C-enolase

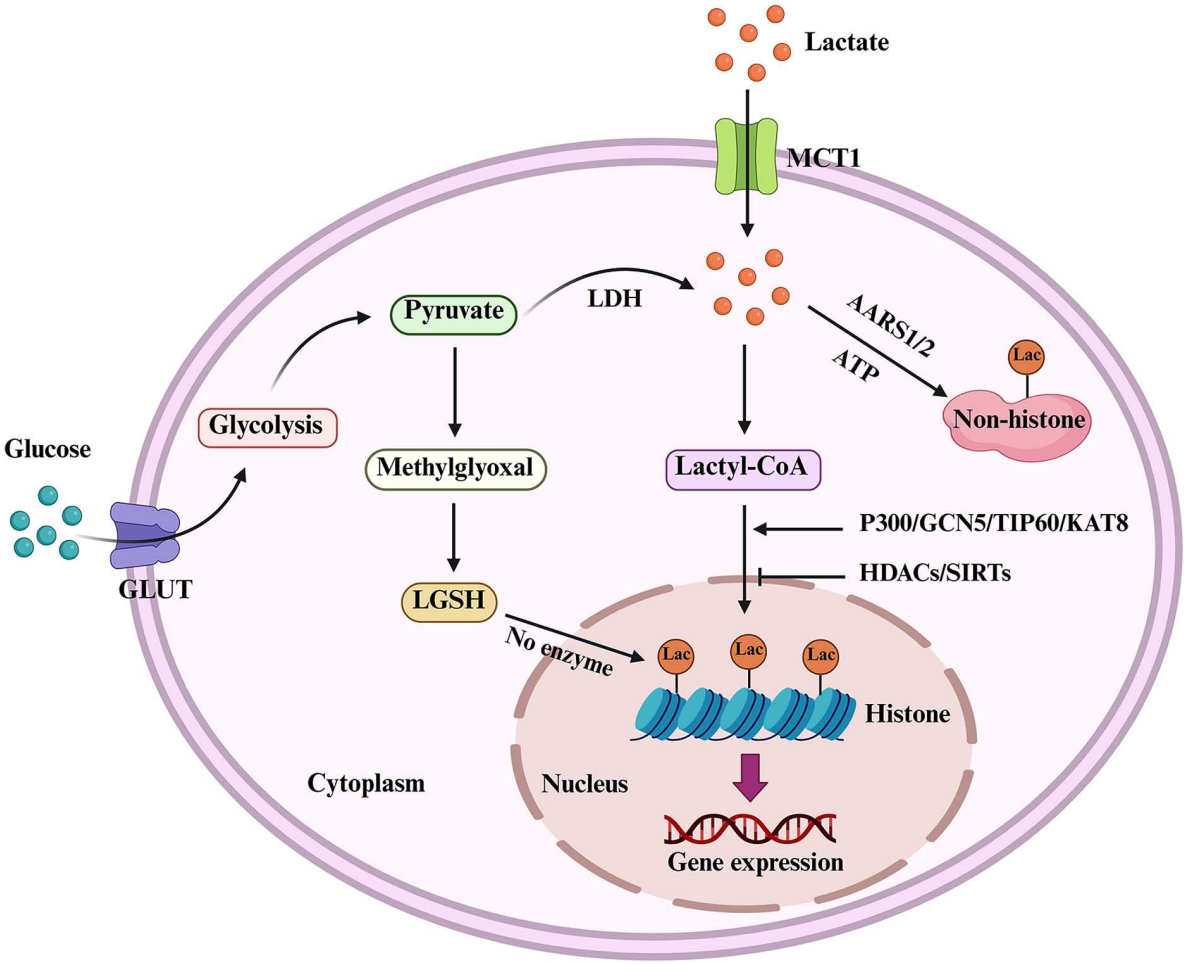


Figure 1. Process of protein lactylation. Lactate-derived acyl groups are covalently attached to lysine residues on histones or other proteins. This process is mediated by several enzymes, including AARS, p300, GCN5, TIP60, KAT8, HDACs and SIRTs, which regulate the addition and removal of lactyl groups. The figure was created using BioRender (https://www.biorender.com). AARS, alanyl-tRNA synthetase; GCN5, general control non-depressible 5; GLUT, glucose transporter; HDAC, histone deacetylase; KAT8, lysine acetyltransferase 8; Lac, lactate; LDH, lactate dehydrogenase; LGSH, L-lactyl coenzyme A (L-La-CoA) and S,D-lactoylglutathione; MCT1, monocarboxylate transporter 1; SIRT, sirtuin; TIP60, Tat-interactive protein 60.

1 axis, whereas lactate accumulation enhances NSUN2 expression and its lactylation via H3K18la (62). In pancreatic cancer, H3K18la is highly expressed in tumor tissues, and is positively associated with the serum lactate, CA19-9 and CEA levels, demonstrating its potential for use as a novel biomarker for diagnosis and prognosis (63). Elevated H3K18la levels in pancreatic ductal adenocarcinoma (PDAC) are associated with poor prognosis and promote the transcription of TTK and BUB1 mitotic checkpoint serine/threonine kinase B, which enhance p300 expression and glycolysis (64). Additionally, TTK phosphorylates LDHA, leading to increased lactate production and H3K18la levels (64).

Downregulation of aldo-keto reductase family 1 member B10 reduces cell proliferation and alters the expression of key target genes, including Bcl-2, Bax, Pan histone lysine lactylation (Kla) and H3K18la, highlighting the role of histone lactylation in the pathogenesis of hepatocellular carcinoma (HCC) (65). In HCC, protein arginine methyltransferase 3 (PRMT3) facilitates tumor immunosuppression by upregulating PD-L1 expression through the PRMT3-pyruvate dehydrogenase kinase 1-lactate-H3K18la axis (66). Targeting this pathway with JX06 or anti-PD-L1 therapy effectively suppresses tumor growth and restores $CD8^+$ T cell infiltration, suggesting a promising immunotherapeutic approach (66). In ovarian cancer, high histone H3K18la levels are associated with poor prognosis, advanced tumor stage, shorter platinum recurrence time and increased metastasis (67). Similarly, elevated H3K18la levels in gastric cancer are associated with poor prognosis (49). SIRT1, which acts as a histone delactylase, disrupts a positive feedback loop involving H19, glycolysis and H3K18la, suggesting a novel strategy for the treatment of gastric cancer (49). In breast cancer, elevated H3K18la in tumor tissues promotes peroxisome proliferator activated receptor δ expression, which increases AKT transcription and phosphorylation to support cell survival under anaerobic glycolytic conditions (52).

Nonhistone protein lactylation. Nonhistone protein lactylation has been reported in various cancer types, including PDAC, breast cancer and HCC (16). The p53 tumor suppressor protein is a key regulator of cell cycle arrest, apoptosis, DNA repair and senescence, and it functions as a critical guardian of genomic stability to prevent tumorigenesis (68). Recently, p53 has been identified to be lactylated. Specifically, alanyl-tRNA synthetase 1 acts as a lactate sensor in tumor

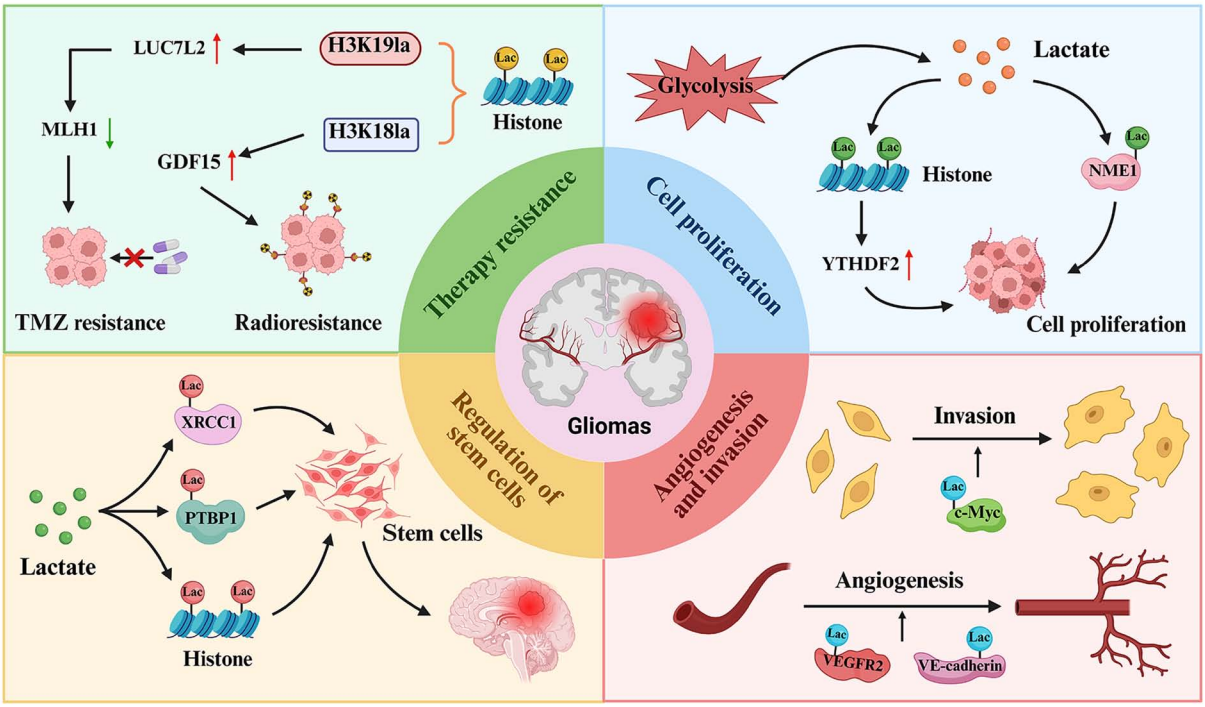


Figure 2. Role of protein lactylation in glioma. Lactate-induced protein lactylation is involved in progression, invasion, angiogenesis and therapy resistance. The figure was created using BioRender (https://www.biorender.com). GDF15, growth differentiation factor 15; H3K18la, histone H3 lysine 18 lactylation; H3K19la, histone H3 lysine 19 lactylation; Lac, lactate; MLH1, mutL homolog 1; NME1, NME/NM23 nucleoside diphosphate kinase 1; PTBP1, polypyrimidine tract binding protein 1; TMZ, temozolomide; VE-cadherin, vascular endothelial cadherin; XRCC1, X-ray repair cross complementing 1; YTHDF2, YTH N6-methyladenosine RNA binding protein F2.

cells, mediating global lysine lactylation, including the lactylation of p53, which impairs its function and promotes tumorigenesis (69). Notably, β-alanine disrupts this process and reduces cancer progression (69). In pancreatic cancer, RHOF promotes tumor progression by upregulating c-Myc, enhancing PKM2-mediated glycolysis and inducing Snail1 lactylation, which drives epithelial-mesenchymal transition and promotes tumor growth (70). Elevated lactylation in PDAC reshapes the TME and promotes immunotherapy resistance by inducing K63 lactylation of endosulfine α (ENSA) and activating STAT3-C-C motif chemokine ligand 2 (CCL2) signaling. Targeting the ENSA-K63la or CCL2 pathway enhances the efficacy of immune checkpoint blockade therapy (71).

In triple-negative breast cancer (TNBC), increased levels of the m6A modification via the HDAC2-mediated delactylation of METTL3 promote cisplatin resistance. Inhibition of HDAC2 by tucidinostat enhances cisplatin sensitivity (51). In cervical cancer, lactate-induced lactylation of DCBLD1 at K172 stabilizes its expression, promoting glucose-6-phosphate dehydrogenase activity and the subsequent pentose phosphate pathway activation, thereby facilitating cancer cell proliferation and metastasis (72). In HCC, lactylation at K28 inhibits adenylate kinase 2 function, thus promoting cell proliferation and metastasis by regulating cellular metabolism (73). Additionally, a study has identified lactylation of phosphofructokinase platelet at lysine 688 and aldolase A at lysine 147 in colon cancer cells (74). These studies highlight the metabolic impact of protein lactylation on cancer progression and treatment (70-73).

3. Functional roles of protein lactylation in gliomas

Protein lactylation has been identified to be a pivotal regulator of gene expression by promoting the transcription of genes that are involved in cell proliferation, angiogenesis, apoptosis, the cell cycle, invasion and drug resistance (20). This section discusses the functional roles of protein lactylation in gliomas (Fig. 2).

Influence on tumor cell proliferation. Numerous studies have shown that protein lactylation regulates cell proliferation in a wide range of human cancer types, including gliomas (75,76). Batsios *et al* (75) revealed a crucial role of lactate in nucleotide biosynthesis in pediatric diffuse midline gliomas (DMGs). The oncogenic H3K27M mutation (a mutation in the histone H3 gene where lysine 27 is replaced with methionine) upregulated phosphoglycerate kinase 1, leading to increased lactate production from glucose in DMGs. Lactate subsequently activated the nucleoside diphosphate kinase NME/NM23 nucleoside diphosphate kinase 1 (NME1) through lactylation, promoting the synthesis of nucleoside triphosphates, which are essential for tumor cell proliferation. Their study established a novel H3K27M-lactate-NME1 axis, suggesting potential clinical strategies for tumor monitoring and therapy evaluation (75). Dong *et al* (76) reported that lactylation of transcription factors, such as HIF-1α, augmented hypoxia-driven tumor progression. Hypoxia-induced HIF-1α upregulation enhanced glycolysis and promoted glioma progression by promoting BCL2 interacting protein 3 (BNIP3)-dependent mitophagy. Notably, H3K18la upregulated YTH N6-methyladenosine

RNA binding protein F2 (YTHDF2) to sustain mitophagy. Conversely, YTHDF2 downregulation disrupted this process and inhibited tumor progression. Therefore, HIF-1α orchestrates metabolic reprogramming through BNIP3-dependent mitophagy, which is a process that is modulated by H3K18la-induced YTHDF2 expression, ultimately contributing to glioma cell proliferation and invasion (76).

Regulation of angiogenesis and invasion. Lactylation of proteins has been implicated in the regulation of cellular invasion and angiogenesis in GBM. For example, dexamethasone (Dex) inhibits GBM cell viability, migration, invasion and glycolysis (77). The oncogene C-Myc is highly expressed in GBM cells but its expression is reduced following Dex treatment (78). Dex suppresses c-Myc lactylation by inhibiting glycolysis, leading to decreased stability of the c-Myc protein. Notably, the administration of sodium lactate reverses the inhibitory effects of Dex, restoring GBM cell proliferation and invasion (77). These findings suggest that Dex modulates GBM progression by disrupting glycolysis-dependent c-Myc stabilization via the regulation of c-Myc lactylation, highlighting potential metabolic vulnerability that can be used in the treatment of GBM (77). Additionally, MAPK6P4 promotes vasculogenic mimicry (VM) in GBM by encoding the peptide P4-135aa, which phosphorylates KLF transcription factor 15, enhancing its stability and nuclear translocation to activate LDHA. LDHA, in turn, facilitates the lactylation of VEGFR2 and vascular endothelial cadherin, leading to their increased expression. Conversely, MAPK6P4 deficiency suppresses VM development, as confirmed in xenograft mouse models (79). VEGFR2 has been shown to serve an important role in tumor metastasis and angiogenesis through the regulation of multiple signaling pathways, including the PI3K, AKT and MAPK pathways (80,81). Therefore, VEGFR2 lactylation may be linked to tumor angiogenesis in GBM.

Regulation of cancer stem cells (CSCs). CSCs exhibit stem-like properties, including self-renewal, differentiation potential and tumorigenic capacity (82). Extensive evidence suggests that glioma stem cells (GSCs) are the primary contributors to glioma progression, recurrence and drug resistance (83-85). The common biomarkers for GSCs include CD133, nextin, CD44, integrin a6, CD15, SOX2, aldehyde dehydrogenase 1 family member A3 (ALDH1A3), L1 cell adhesion molecule and A2B5 (86,87). Protein lactylation has been demonstrated to participate in the maintenance of CSCs in glioma. For example, the ALDH1A3-PKM2 interaction enhances lactate accumulation in glioblastoma stem cells, leading to X-ray repair cross complementing 1 (XRCC1) lactylation. This modification increases the affinity of XRCC1 for importin α, promoting its nuclear translocation and affecting DNA repair, thereby influencing tumor progression (88). Another study revealed that global lactylation levels were elevated in GSCs, with polypyrimidine tract binding protein 1 (PTBP1) hyperlactylation maintaining GSC self-renewal and promoting glioma progression. Specifically, lactylation of PTBP1 prevented its degradation via tripartite motif containing 21, enhanced its RNA-binding capacity, stabilized 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 mRNA and increased glycolysis. Conversely, SIRT1 counteracted this process by inducing PTBP1 delactylation, thereby suppressing tumor growth (89). Additionally, Warburg effect-induced H3 histone lactylation drives the expression of NF-κB-related LINC01127 in GBM, promoting self-renewal by regulating MAP4K4 expression and activating the JNK/NF-κB axis. Targeting the JNK/NF-κB pathway hinders tumor growth (90). Overall, these findings underscore the critical roles of protein lactylation in sustaining cancer stemness and driving glioma development and progression.

Regulation of therapy resistance. Drug resistance, which includes intrinsic resistance and acquired resistance, is a major obstacle in cancer therapy and contributes to poor prognosis (91). Intrinsic resistance refers to a pre-existing insensitivity of cancer cells to therapy, while acquired resistance develops after initial responsiveness through adaptive changes or mutations (92,93). Gliomas are resistant to standard therapies, including radiotherapy, chemotherapy and immunotherapy (94-96). Resistance to temozolomide (TMZ) remains a major challenge in glioma treatment (97). The mechanisms of drug resistance include efflux of drugs, drug inactivation, alteration of drug targets and epigenetic alterations (98,99). For example, upregulation of efflux transporters expels chemotherapeutic agents from GBM cells, reducing intracellular drug concentrations (100). Intercellular adhesion molecule-1 reduces TMZ sensitivity in gliomas with acquired resistance by promoting the membrane localization of ATP binding cassette subfamily B member 1 transporters (101). O-6-methylguanine-DNA methyltransferase (MGMT) repairs TMZ-induced O6-methylguanine DNA lesions, with its promoter hypermethylation predicting TMZ sensitivity, while MGMT genomic rearrangements drive chemotherapy resistance in gliomas (102). Mutations in tumor-derived protein tyrosine phosphatase receptor type K impair its functional activity and modify cell responsiveness to chemotherapeutic agents in glioma (103). USP6 N-terminal like (USP6NL), in coordination with the EGFR signaling pathway, modulates ubiquitin-dependent DNA repair mechanisms and contributes to TMZ resistance in GBM (104). TNF receptor associated factor 4 (TRAF4) sustains the deubiquitination of Caveolin-1, thereby enhancing glioblastoma stem cell characteristics and resistance to TMZ (105). Additionally, TMA exposure upregulates high mobility group box 1, which facilitates GSC formation through activation of the toll like receptor 2 (TLR2)/nuclear paraspeckle assembly transcript 1/Wnt signaling cascade (106). Therefore, various factors such as USP6NL, TRAF4 and TLR2 contribute to TMZ resistance in GBM (107).

Lactylation has been revealed to participate in the regulation of drug resistance in breast cancer, HCC and GBM (108-110). For instance, cancer-associated fibroblast (CAF)-derived lactate promotes doxorubicin (DOX) resistance in TNBC by enhancing histone lactylation-mediated ZFP64 expression. ZFP64 inhibits ferroptosis through the upregulation of GTP cyclohydrolase 1 and ferritin heavy chain 1, while targeting this pathway can restore DOX sensitivity (110). Similarly, USP34 promotes HCC progression and cisplatin resistance by regulating histone lactylation levels, and USP34 knockdown enhances cisplatin sensitivity (109). In GBM, the interaction between ALDH1A3 and PKM2 promotes PKM2

tetramerization and lactate accumulation. By profiling the lactylated proteome in GSCs with elevated lactate levels, lysine 247 of XRCC1 has been identified as a key lactylation site (88). This modification enhances the binding affinity between XRCC1 and importin α, thereby facilitating XRCC1 nuclear import and promoting more efficient DNA repair (88). Using high-throughput screening of a small-molecule compound library, D34-919 has been found to effectively disrupt the interaction between ALDH1A3 and PKM2, thereby inhibiting ALDH1A3-induced PKM2 tetramer formation. Treatment with D34-919 increases the susceptibility of GBM cells to apoptosis following chemoradiotherapy. Collectively, these results highlight ALDH1A3-driven PKM2 tetramerization as a promising target for enhancing chemoradiotherapy sensitivity in GBM (88).

Yue *et al* (111) reported that histone H3K9 lactylation (H3K9la) was increased in TMZ-resistant cells as well as in recurrent GBM tissues. Chronic TMZ exposure upregulated lactate and H3K9la levels in GBM cells and subcutaneous xenograft mice (111). Suppression of H3K9la using short hairpin RNAs targeting LDHA and LDHB increases TMZ sensitivity in GBM. Furthermore, stiripentol, an anti-epileptic drug, reduces H3K9la levels and leads to TMZ sensitivity in TMZ-resistant cells (111). Additionally, H3K9la promotes TMZ resistance by activating LUC7L2 transcription, which induces retention of intron 7 of mutL homolog 1 (MLH1), thereby reducing MLH1 expression and impairing mismatch repair in GBM (111). Additionally, Liu *et al* (112) analyzed the crystallographic structure of guanosine triphosphate-specific succinyl-CoA synthetase (GTPSCS) and L-lactate, and performed mutagenesis experiments. The authors revealed that GTPSCS translocated into the nucleus, interacted with p300 and specifically enhanced H3K18la. This nuclear translocation relied on a signal within the G1 subunit and acetylation at lysine 73 of the G2 subunit, which facilitated its binding to p300. GTPSCS and p300 cooperatively increased H3K18la, leading to promotion of growth differentiation factor 15 expression, thereby driving glioma cell proliferation and resistance to radiotherapy. The study identified GTPSCS as the first enzyme to catalyze lactyl-CoA synthesis for epigenetic regulation in glioma, which supports its role in therapy resistance (112).

4. Regulation of immune evasion and immunotherapy

Studies have shown that protein lactylation governs immune evasion and immunotherapy in human cancer (113-116). For example, serine and arginine rich splicing factor 10 (SRSF10) promotes immune evasion and anti-programmed cell death protein 1 (PD-1) resistance in HCC by driving a positive feedback loop that involves glycolysis, lactate production, H3K18la and M2 macrophage polarization (113). Pharmacological inhibition of SRSF10 with 1C8 enhances the efficacy of anti-PD-1 therapy, indicating that SRSF10 is a potential therapeutic target for overcoming immune resistance (113). Glycolysis-driven H3K18la upregulates B7 homolog 3 protein (B7-H3) expression via the cAMP responsive element binding protein 1/E1A binding protein P300 axis, promoting tumor immune evasion by inhibiting $CD8^+$ T cell cytotoxicity. Notably, the inhibition of glycolysis and B7-H3 enhances antitumor immunity and improves the efficacy of anti-PD-1 therapy (116). In ovarian cancer, knockdown of LDHB suppresses cancer cell proliferation, reduces lactate production, enhances T cell-mediated immune activation and inhibits PD-L1 expression by decreasing H3K18la at the PD-L1 promoter, thereby reducing immune evasion (114). In cervical cancer, lactate that is secreted by tumor cells promotes M2 macrophage polarization by upregulating glycerol-3-phosphate dehydrogenase 2 expression through H3K18la-mediated histone lactylation, contributing to tumor progression (115). In bladder cancer, single-cell analysis has identified parkin RBR E3 ubiquitin protein ligase (PRKN) as a key regulator of mitophagy in M2 macrophages, with H3K18la-enhanced PRKN expression promoting M2 polarization, immune suppression and tumor progression (117). In gastric cancer, CAFs reduce the efficacy of PD-1/PD-L1 immunotherapy by secreting lysyl oxidase, activating TGF-β signaling, promoting insulin like growth factor 1 expression, enhancing glycolysis and inducing H3K18la-mediated PD-L1 transcription, thereby reinforcing immune evasion (118).

Lactate-induced protein lactylation has been identified to regulate the tumor immune microenvironment and influence immunotherapy strategies across various cancer types, including gliomas (119,120). H3K18la and H3K9la function as transcription initiators in $CD8^+$ T cells, modulating their activity and antitumor immunity through metabolic and epigenetic modulation (121). For example, H3K18la promotes immune evasion in non-small cell lung cancer (NSCLC) by activating the POM121/MYC/PD-L1 pathway. However, metabolic reprogramming and immunotherapy can restore $CD8^+$ T-cell cytotoxicity and enhance antitumor efficacy (122). In glioma, high-score cases based on lactylation-related genes exhibit greater immune infiltration, elevated checkpoint expression and poorer survival (123). In addition, lactate production in GBM induces histone lactylation, leading to CD47-dependent immune evasion by promoting an immunosuppressive transcriptional program. Targeting lactate production or inhibiting CBX3 enhances anti-CD47 therapeutic efficacy and tumor cell phagocytosis, providing a promising strategy to overcome immune resistance in GBM (53).

Hypoxia enhances the malignancy of glioma cells by promoting glycolysis and lactic acid accumulation (124). This lactate is absorbed by macrophages to induce M2 polarization through the MCT-1/H3K18la signaling pathway, which subsequently upregulates tumor necrosis factor superfamily member 9 expression and facilitates glioma progression (124). Chimeric antigen receptor (CAR) T-cell therapy is an advanced immunotherapy that harnesses the power of the immune system in patients to fight cancer (125,126). CAR-T cells recognize specific antigens on cancer cells and destroy cancer cells with high specificity, and this approach has shown success in the treatment of certain hematologic malignancies, such as B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma, as well as some solid tumors (127,128). One group has revealed that oxamate enhanced the immune activation of tumor-infiltrating CAR-T cells in a GBM model by altering immune molecule phenotypes, increasing regulatory T cell infiltration, and reducing the histone H3K18la-mediated expression of CD39, CD73 and C-C motif chemokine receptor 8 (129). Another group has revealed that EGFR activation triggered ERK-mediated phosphorylation of ACSS2, leading to its

nuclear translocation and interaction with KAT2A, enabling histone H3 lactylation. This process activated Wnt/β-catenin, NF-κB and PD-L1 expression, promoting brain tumor growth and immune evasion (45).

5. Therapeutic implications of targeting lactylation in gliomas

Inhibition of lactate production. Evidence suggests that targeting lactate metabolism with inhibitors of LDHA [7-benzyl-2,3-dihydroxy-6-methyl-4-propylnaphthalene-1-carboxylic acid (FX11)] and MCT1 (AZD3965) reduces lactate accumulation, thereby limiting lactylation-mediated tumor progression (130,131). For example, inhibition of LDHA by FX11 has been shown to suppress tumor progression in various cancer types, including lymphoma (132), pancreatic cancer (133,134), prostate cancer (135), osteosarcoma (136), neuroblastoma (137), gallbladder carcinoma (138), papillary thyroid carcinoma (139) and breast cancer (140). One study demonstrated that inhibition of LDHA by FX11 suppressed proliferation, migration and invasion, while promoting apoptosis in prostate cancer cells by reducing the Warburg effect, glucose consumption, lactate secretion, and MMP-9, PLAU and cathepsin B expression (131). AZD3965, which is a promising MCT1 inhibitor, exerts antitumor effects by inducing metabolic reprogramming (130); this represents a novel therapeutic approach in various cancer types, including small cell lung cancer (141,142), NSCLC (143), lymphoma (144,145), breast cancer (146) and bladder cancer (147). Additionally, AR-C155858 selectively inhibits MCT1 and MCT2, which are responsible for the transport of monocarboxylates, such as lactate, pyruvate and ketone bodies, across the cell membrane (148). One study has shown that AR-C155858 inhibited the migration and invasion of pancreatic cancer cells (149). Further research is needed to explore the therapeutic potential of FX11, AZD3965 and AR-C155858 in glioma.

Modulation of protein lactylation. Given that p300 is a key regulator of lactylation, inhibitors of p300 (such as A-485) may suppress the lactylation of both histone and nonhistone proteins, thereby altering glioma epigenetics and metabolism. Several inhibitors of p300 have been observed to have anticancer effects in various malignancies (150-153). For example, in neuroblastoma, the expression of cyclooxygenase-2, which is induced by enterovirus 71, is inhibited by pretreatment with the p300 inhibitor GR343 (150). In acute myeloid leukemia, the p300 inhibitor C646 selectively enhances apoptosis and triggers cell cycle arrest (154). Similarly, C646 suppresses human papillomavirus E6-E7 transcription, leading to p53 accumulation, inhibition of cell proliferation, disruption of glucose metabolism and induction of apoptosis in cervical cancer cells (151). Additionally, C646 effectively overcomes the resistance of resistant melanoma cells to BRAF inhibitors (153). The p300 inhibitor A-485 has been demonstrated to suppress cell proliferation, growth hormone secretion and tumor growth by downregulating key oncogenes and pathways, including Pttg1, c-Myc, cAMP and PI3K/AKT/mTOR, in growth hormone pituitary adenoma (152). Furthermore, A-485 induces proteasome-mediated degradation of SOX10 in melanoma cells, effectively inhibiting tumor cell proliferation (155).

In GBM, the CREB-binding protein/p300 inhibitor CPI-1612 suppresses H3K27Ac, targets c-MYC, synergizes with TMZ and penetrates into the brain, which makes it a promising therapeutic candidate (156). Other compounds have also been implicated in modulating lactylation-driven tumor progression. Tanshinone I inhibits ovarian cancer cell proliferation by blocking glycolysis, reducing histone H3K18la, downregulating tumor-associated gene expression (such as TTK, platelet-derived growth factor receptor β, YTHDF2 and rubicon-like autophagy enhancer), and alleviating the immunosuppressive TME (157). Additionally, in lung cancer, collagen triple helix repeat containing 1 $(CTHRC1)^+$ CAFs promote EGFR-tyrosine kinase inhibitor resistance by enhancing glycolysis and creating a histone lactylation-driven positive feedback loop. Notably, gambogenic acid disrupts this loop to improve therapeutic efficacy, suggesting that $CTHRC1^+$ CAFs are a predictive biomarker and therapeutic target in lung cancer (158).

Combination approaches with radiotherapy, chemotherapy and immunotherapy. A study has demonstrated that structural maintenance of chromosomes 4 serves a crucial role in CRC cell dormancy, where its attenuation enhances glycolysis, increases lactate production and upregulates ABC transporters via histone lactylation, ultimately leading to chemotherapy resistance (159). In HCC, histone lactylation has been linked to tumor prognosis and may serve as an independent biomarker (160). The genes nuclear receptor subfamily 6 group A member 1, oxysterol binding protein 2 and unc-119 lipid binding chaperone B are associated with prognosis, immunotherapy response and chemotherapy resistance in HCC (160). Similarly, high nijmegen breakage syndrome protein 1 lactylation predicts chemotherapy resistance, whereas reduction of lactate levels via LDHA inhibition impairs DNA repair and sensitizes tumors to therapy (161). In oral squamous cell carcinoma (OSCC), Kla-specific genes serve key roles in tumor progression, with BCAM, cingulin like 1, diacylglycerol kinase γ and oxidized low density lipoprotein receptor 1 serving as prognostic markers (162). Notably, BCAM promotes invasion, angiogenesis and chemotherapy resistance in OSCC (162). In ovarian cancer, malate enzyme 2 (ME2) promotes lactate production and chemotherapy resistance by converting glutamine-derived malate to pyruvate (163). In addition, chemotherapy-induced glucose reduction triggers ME2 acetylation by acetyl-CoA acetyltransferase 1, enhancing lactate production and the lactylation of homologous recombination repair proteins, leading to increased DNA repair capacity and drug resistance (163).

Given the critical role of lactylation in therapy resistance, strategies that target lactylation pathways may sensitize gliomas to radiation and TMZ by impairing DNA repair mechanisms and drug efflux pathways. Lactylation-related gene expression has been used to classify patients with GBM into high-score and low-score groups, with high-score patients exhibiting an improved response to immunotherapy (123). Notably, the antiepileptic drug stiripentol, which crosses the blood-brain barrier and inhibits LDHA/B activity, inhibits lactylation, sensitizing GBM cells to TMZ in both *in vitro* and *in vivo* models (111). Furthermore, blocking the ACSS2-KAT2A interaction combined with anti-PD-1 therapy enhances tumor inhibition in brain tumors (45). Furthermore, a lactate

generation inhibitor has been revealed to reprogram CSC metabolism, reduce tumor immunosuppression and decrease CAR-regulatory T cell infiltration, potentially enhancing the efficacy of CAR-T-cell therapy in GBM (129).

6. Conclusion and future perspectives

Lactate-induced protein lactylation represents a novel regulatory mechanism with profound implications for glioma progression, immune suppression and therapy resistance (Fig. 2). Understanding the molecular landscape of lactylation in gliomas provides novel avenues for the development of therapeutic interventions. Several reviews have addressed lactylation in the context of glioma progression (164,165). Pienkowski *et al* (164) primarily focused on PTMs such as phosphorylation, methylation, acetylation, ubiquitination and glycosylation, but did not discuss lactylation in detail. Han *et al* (165) explored the role of protein lactylation in various brain diseases, including cerebrovascular disorders, neurodegenerative diseases, neuroinflammation, mental disorders and brain tumors; however, the role of lactylation in GBM could not be discussed in detail due to space limitations. Qiu *et al* (23) highlighted lactylation in GBM, emphasizing its role as a link between epigenetic plasticity and metabolic reprogramming. By contrast, the present review provides a comprehensive discussion on the functional roles of protein lactylation in GBM, including its involvement in proliferation, angiogenesis, invasion, therapeutic resistance, regulation of CSCs and immune evasion. Furthermore, we hypothesized that targeting lactate metabolism, lactylation-modifying enzymes and immune evasion mechanisms holds promise for improving glioma treatment outcomes. It is important to mention that several critical challenges must be addressed to fully elucidate the molecular mechanisms underlying the role of lactylation in glioma development and treatment. First, although p300 is known to catalyze lactylation, to the best of our knowledge, the enzymatic regulation of lactylation removal remains unclear. Identifying delactylases is critical for better understanding the dynamic lactylation in glioma. Characterizing lactyltransferase and delactylases will be pivotal for developing targeted pharmacological modulators of lactylation. Furthermore, the regulation of histone vs. non-histone protein lactylation in different glioma subtypes and stages requires further investigation. Second, the integration of lactylation with glioma metabolism and the TME requires comprehensive analysis. Given the hypoxic and lactate-rich nature of the TME in glioma, lactylation could act as a critical mediator of immunosuppression. Single-cell epigenomics ad spatial transcriptomics could elucidate how lactylation shapes cellular interactions in the glioma niche. Third, current inhibitors that target p300 or lactate metabolism lack specificity for lactylation, necessitating the development of small molecules that selectively inhibit protein lactylation to design more precise therapeutic strategies. Inhibitors of lactate production (LDHA inhibitors), lactylation writers (p300) or delactylase activators could synergize with chemotherapy or immune checkpoint blockade. Using patient-derived glioma models and organoids could be essential for preclinical validation of drugs targeting lactylation. Additionally, p300 has been identified as an acetyltransferase capable of catalyzing multiple types of protein modifications, including acetylation (166,167), propionylation (168), butyrylation (169,170) and lactylation (171-173) in oncogenesis. Targeting of lactylation by p300 inhibitors could also affect other PTMs in tumorigenesis. Fourth, identifying lactylation-specific biomarkers in gliomas could aid in early diagnosis, patient stratification and treatment response monitoring. In parallel, lactylation-associated gene signatures could be integrated into existing molecular classification frameworks to enhance predictive accuracy for therapy response. To the best of our knowledge, to date, no clinical trials specifically targeting lactylation have been reported. Therefore, clinical trials are essential to determine the feasibility and efficacy of targeting lactylation in patients with glioma in the future. Continued exploration of lactylation and its role in gliomas may pave the way for the development of innovative treatment strategies, ultimately improving patient outcomes and advancing the field of glioma therapy.

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Authors' contributions

TL, LL, HW and SW were involved in writing the manuscript draft. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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