Potential of lactylation as a therapeutic target in cancer treatment (Review)

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Abstract. Post-translational modifications (PTMs) of proteins influence their functionality by altering the structure of precursor proteins. These modifications are closely linked to tumor progression through the regulation of processes such as cell proliferation, apoptosis, angiogenesis and invasion. Tumors produce large amounts of lactic acid through aerobic glycolysis. Lactic acid not only serves an important role in cell metabolism, but also serves an important role in cell communication. Lactylation, a PTM involving lactate and lysine residues as substrates, serves as an epigenetic regulator that modulates intracellular signaling, gene expression and protein function, thereby serving a crucial role in tumorigenesis and progression. The identification of lactylation provides a key breakthrough in elucidating the interaction between tumor metabolic reprogramming and epigenetic modification. The present review primarily summarizes the occurrence of lactylation, its effect on tumor progression, drug resistance, the tumor microenvironment and gut microbiota, and its potential as a therapeutic target for cancer. The aim of the present review was to provide novel strategies for potential cancer therapies.

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1. Introduction

It has been demonstrated that a number of proteins in the human body undergo post-translational modifications (PTMs) (1). With the advance of mass spectrometry techniques, an increasing array of PTMs has been identified, which can be classified into phosphorylation, glycosylation, SUMOylation, ubiquitination, acetylation and methylation, based on the covalent attachment of different small molecular groups to amino acid residues (2,3). These modifications induce alterations in the structure and function of proteins, enhancing the flexibility and diversity of protein functionalities through different types of PTMs (4). By regulating protein stability, localization and conformation, PTMs are involved in various biological processes, including signal transduction and gene expression regulation (5). Aberrant levels of PTMs have been closely linked to numerous diseases, including cancer (6). As such, PTMs hold considerable potential as biomarkers for disease and therapeutic targets (7).

Under normal physiological conditions, glucose within cells undergoes glycolysis and oxidative phosphorylation to produce substantial amounts of ATP. However, in contrast to normal cells, tumor cells preferentially generate energy through glycolysis, even in the presence of oxygen, to adapt to the hypoxic, acidic and nutrient-deprived tumor microenvironment (TME); a phenomenon known as the Warburg effect (8). This aerobic glycolysis in tumor cells results in the accumulation of lactate, which exacerbates the hypoxic conditions that fuel tumor growth, further intensifying lactate production and facilitating processes such as angiogenesis, invasion, metastasis and treatment resistance (9,10). Traditionally regarded merely as an energy substrate and metabolic byproduct, lactate is now recognized as a pivotal molecule linking cellular metabolism to the regulation of cellular activities (11). Furthermore, lactate serves as a metabolic substrate that drives PTMs of proteins, with lactylation, a lactate-induced modification, previously identified in histones (12). The excessive production of lactate

sustains the hypoxic and acidic TME, promoting tumor angiogenesis, invasion, metastasis and resistance to therapies (13). On the other hand, lactate can influence tumorigenesis through epigenetic modifications, acting as a bridge between tumor metabolism and epigenetic regulation (14). This novel understanding of the role of lactate broadens potential avenues for cancer therapy.

Cancer-related diseases, as a leading global health burden, have sparked widespread interest in understanding the molecular mechanisms underlying tumorigenesis, progression and treatment (15). Epigenetic modifications have emerged as critical regulatory factors in cancer development (16). Lactylation, a novel form of epigenetic modification, serves a pivotal role in regulating various biological processes and influencing disease onset (17). For instance, Kla of Sox10 leads to macrophage-like vascular smooth muscle cell accumulation and increases vascular inflammation (18). Recent studies have identified a growing prevalence of lactylation modifications across multiple cancer types (19,20), positioning it as a key molecular mechanism in cancer progression (21-23) Furthermore, research has shown that protein lactylation is a dynamic and reversible process (24), suggesting its potential as a promising therapeutic target for cancer treatment (25).

Lactylation, as an emerging form of modification, offers a promising therapeutic target for cancer treatment. A comprehensive understanding of the role lactylation serves in tumorigenesis and progression will provide profound insights for the development of novel cancer treatment strategies. This not only enhances the understanding of lactate metabolism but also paves the way for future drug identification by offering novel perspectives and insights into molecular mechanisms. The present review summarizes the research progress on lactylation modification in tumor development, examines the underlying mechanisms linking lactylation with cancer therapy resistance and the TME, and describes the potential crosstalk between lactylation and gut microbiota. Furthermore, it explores the therapeutic potential of targeting lactylation as a novel approach for cancer treatment, offering valuable insights for the development of innovative therapeutic strategies.

2. Regulation of lactylation modifications

The formation of lactylation is closely linked to the metabolic processes of tumors. Lactylation primarily arises from lactate produced during metabolism (26), with endogenous lactate generation serving as a critical determinant of lactylation levels. Under the influence of specific enzymes, lactate molecules covalently bind to lysine residues on proteins. Lactylation can be categorized into histone lactylation and non-histone lactylation, with histone lactylation serving a role in regulating gene expression, cellular signaling and metabolism (27) (Fig. 1). Currently, lactylation modifications have been observed in various proteins located in the nucleus, cytoplasm and mitochondria (28). The identification of lactylation has broadened the understanding of tumor metabolic reprogramming and epigenetic modifications.

The levels of protein lactylation are regulated by various factors, primarily by lactoyltransferases and de-lactoyltransferases. Lactoyltransferases and de-lactoyltransferases are responsible for the addition and removal of lactoyl groups, respectively, thereby influencing lactylation modifications. For instance, under the action of the acetyltransferase p300, lactoyl groups are transferred to lysine residues on histones, leading to covalent binding of lysine residues with lactate and resulting in lactylation modifications (29). Lactate transferase p300/cAMP-response element binding protein (CREB) binding protein (CBP) includes the cysteine-histidine rich 1, CREB binding kinase-inducible domain interacting, bromodomain, histone acetyltransferase, CH3 and steroid receptor coactivator interaction domains (30). Overexpression or depletion of the acetyltransferase p300 can increase or decrease the levels of histone Kla in cells (12).

Alanyl-transfer RNA (tRNA) synthetase (AARS) retains a conserved prototype structure throughout the entire biological process, including catalytic, tRNA recognition, editing and C-Ala domains (31). AARS1 acts as a lactoyltransferase by recognizing and catalyzing the activation of lactate molecules, subsequently facilitating the binding of lactate to lysine residues on target proteins to form lactylation modifications (32). AARS1 can also translocate into the nucleus, directly utilizing lactate as a lactoyl donor and ATP as an energy source to catalyze the lactylation of histones K90 of yes-associated protein and K108 of TEA domain transcription factor 1 (33).

As research progresses, more lactoyltransferases have been identified. For example, lysine acetyltransferase 8 (KAT8) mainly contains an acetyl-CoA binding site and a C2HC zinc finger motif. Through the KAT8-dependent pathway, it can catalyze the lactylation of non-histone proteins (34). KAT8 has also been found to serve as a lactoyltransferase catalyzing the lactylation of non-histone proteins (35). Researchers have employed anti-Kla antibodies to confirm the occurrence of lysine lactylation in *Escherichia coli* and identified YiaC as a potential lactoyltransferase (36). YiaC belongs to the GCN5-related N-acetyltransferase family (37) and it possesses lysine acetyltransferase activity while also catalyzing lysine lactylation. Structurally, it has a specific N-terminal domain, a conserved acetyltransferase domain, conserved histone acetyltransferase structural domains and a C-terminal bromodomain at the C-terminus (38). Furthermore, a study has revealed alternative pathways regulating lactylation modifications, such as macrophages absorbing extracellular lactate through monocarboxylate transporters, which promote the lactylation of high mobility group box 1 via a p300/CBP-dependent mechanism (39).

In the process of lactylation formation, lactoyltransferases serve a crucial role, while de-lactoyltransferases can reverse the lactylation modifications. For instance, histone deacetylases (HDACs) 1-3 have been found to dynamically and reversibly regulate histone L-lactylation (40). HDAC1-3 contain an N-terminal catalytic domain (41). A study has indicated that sirtuin 3 (SIRT3) can de-lactylate the lactylation at the H4K16la site (42). SIRT3 has a catalytic core region with a large and structurally homologous Rossmann folding domain characteristic of NAD-binding proteins and a zinc finger structure (43). Identifying the key regulatory enzymes involved in lactylation pathways and their substrate proteins will lay the groundwork for functional studies of lactylation modifications and their associated regulatory pathways.

However, little is currently known regarding how de-lactoyltransferases exert their reversible effects and transitions. Furthermore, the precise enzymes and mechanisms

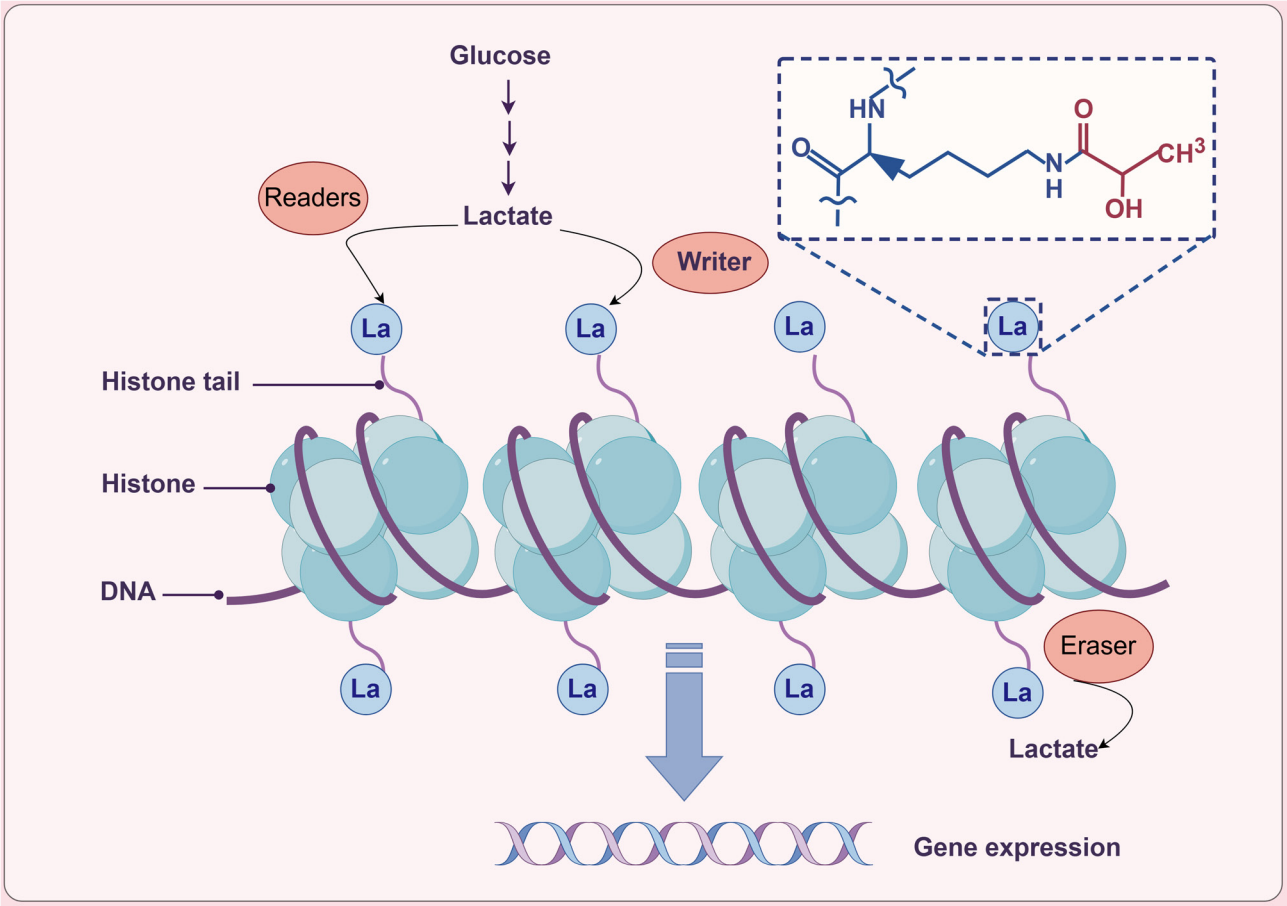

Figure 1. Regulation of lactylation. La is lactated under the action of readers, writers and erasers to regulate downstream gene targets. La, lactic acid.

involved in the regulation of lactylation within cells remain largely unknown, highlighting the need for further research in the field of de-lactoyltransferases.

It is worth noting that histone acetylation and lactylation exhibit a high degree of distribution similarity in the genome (12) and acetyltransferases p300 and HDAC1-3 may regulate the acetylation levels of histones while modifying them with lactylation. On the one hand, it is possible to simultaneously increase the modification levels of both to regulate gene expression levels (39). On the other hand, influenced by the level of lactate metabolism, lactylation modification may competitively inhibit acetylation modification (44,45). This crosstalk mechanism between lactylation and acetylation is not yet fully understood and requires further in-depth exploration. In addition to enzyme-catalyzed lactylation, lactoyl glutathione, an intermediate metabolic product of glyceraldehyde during glycolysis, can directly modify lysine residues through a non-enzymatic reaction, resulting in lactylation (46). This non-enzymatic pathway for lactylation expands the routes through which lactylation can occur, enriching the understanding of cellular metabolism and further underscoring the significance of lactylation modifications in biological processes.

3. Influence of lactylation on tumor biological behavior

The hallmark features of tumors involve the dysregulation of critical pathways that maintain the dynamic balance of normal cells. These pathways include sustaining proliferative signaling, evading growth suppression, resisting cell death, achieving replicative immortality, inducing angiogenesis, and activating invasion and metastasis (47). Lactylation modifications exhibit differential expression across various tumors and serve a pivotal role in regulating intracellular signal transduction, thereby impacting tumor initiation and progression (48).

In non-small cell lung cancer (NSCLC), the lactylation of SOX9 has been reported to promote stemness, migration and invasion of NSCLC by enhancing glycolysis (49). Furthermore, a study has demonstrated that histone H3K18la enhanced immune evasion in NSCLC cells by activating the POM121 transmembrane nucleoporin/MYC/programmed death-ligand 1 axis (50). Hypoxia-induced lactylation of the serine hydroxymethyltransferase 2 protein stimulates glycolysis and stemness in esophageal cancer cells (51). In colorectal cancer, lactylation of β-catenin facilitates cancer cell proliferation via the Wnt signaling pathway (52).

Histone lactylation has also been implicated in ocular melanoma, where it enhances the recognition of RNA N6-methyladenosine modifications by YTH N6-methyladenosine RNA binding protein F2, promoting the degradation of period circadian regulator 1 and TP53 mRNA, ultimately fostering proliferation and migration of melanoma cells (53). In pancreatic cancer, lactylation of transcription factor EB enhances autophagy and lysosomal activity (54).

Table I. Lactate modification for tumor progression.

First author/s, year	Cancer type	Target component	Biological function	(Refs.)
Yan, 2024	NSCLC	SOX9	Facilitating migration and invasion	(49)
Zhang, 2024	NSCLC	POM121	Facilitating immune escape	(50)
Qiao, 2024	Esophageal cancer	SHMT2	Facilitating glycolysis	(51)
Miao, 2023	Colorectal cancer	β-catenin	Promoting the cell proliferation and stemness of colorectal cancer	(52)
Yu, 2021	Ocular melanoma	YTHDF2	Promoting cell proliferation	(53)
Huang, 2024	Pancreatic cancer	TFEB	Elevating autophagy and lysosomal activity	(54)
Yang, 2023	HCC	AK2	Facilitating migration and invasion	(55)
Yang, 2022	ccRCC	PDGFRβ	Facilitating migration and invasion	(56)
Hou, 2024	Breast cancer	LDHA	Facilitating proliferation, migration and invasion	(57)
Sun, 2023	Gastric cancer	METTL16	Promoting cuproptosis	(58)
Xie, 2023	Bladder cancer	LCN2	Promoting tumor progression	(59)
Wang, 2023	Anaplastic thyroid cancer	H4k12la	Promoting tumor progression	(60)

ccRCC, clear cell renal cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer.

Elevated lactylation of adenylate kinase 2 (AK2) in hepatocellular carcinoma has been linked to metabolic alterations, with lactylation at K28 inhibiting AK2 function, thereby promoting hepatocellular carcinoma cell proliferation and metastasis (55).

In clear cell renal cell carcinoma, histone lactylation stimulates tumor progression by activating the transcription of platelet-derived growth factor receptor β (56). In breast cancer, lactylation of histone lysines induces lactate dehydrogenase A expression, increasing glycolysis and lactate production, which drives tumor proliferation, invasion and metastasis (57). Furthermore, non-histone lactylation of METTL16 at K229 promotes copper ion deposition in gastric cancer (58). In bladder cancer, histone H3K18 lactylation serves a pro-oncogenic role by upregulating lipocalin 2 expression (59). Additionally, the Warburg effect, mediated by metabolite-driven histone lactylation, promotes the proliferation of anaplastic thyroid cancer cells harboring the BRAFV600E mutation (60). Lactylation offers novel insights for both the diagnosis and treatment of tumors. However, it is important to note that the role of lactylation may vary across different types of cancer.

Currently, lactylation sites detected in a number of tumors are primarily located on histone H3K18 (61,62), e.g., renal clear cell carcinoma (56) and bladder cancer (59), which may be attributed to the limitations of existing lactylation detection technologies (63). To broaden the scope of lactylation research across various modification sites, it is imperative to develop more diverse lactylation antibodies or advanced detection methods. Furthermore, research on non-histone protein lactylation is still in its infancy, warranting greater attention to the identification of lactylation sites in non-histone proteins. Histone and non-histone lactylation are both closely associated with tumor initiation and progression (Table I).

As scientific advancements continue, it is expected that more lactylation modification sites will be identified, and targeting lactylation may provide novel biomarkers and therapeutic targets for clinical cancer diagnosis and treatment. Further investigation into lactylation will deepen the understanding of its role in cancer, offering a promising strategy for cancer therapy.

4. Effect of lactylation on tumor therapy resistance

Chemotherapy remains one of the primary treatments for human malignancies, yet chemotherapy resistance in cancer cells is a factor contributing to poor prognosis in a number of patients (64). Tumor metabolism, particularly the production of lactate, can influence chemotherapy efficacy and DNA repair mechanisms (65). Lactate-induced lactylation modifications intricately link tumor metabolism with epigenetic regulation. Investigating the mechanisms by which lactylation contributes to therapy resistance in tumors will provide deeper insights into treatment outcomes and prognosis, potentially offering novel strategies to overcome tumor resistance and improve therapeutic efficacy.

Lactylation serves a crucial role in tumor resistance to therapy (66,67). A study has shown that elevated levels of NBS1 K388 lactylation promoted homologous recombination-mediated DNA repair, leading to chemotherapy resistance (65). Additionally, histone H3K9 lactylation activates the transcription of LUC7L2, thereby inhibiting mismatch repair and ultimately contributing to temozolomide resistance in glioblastoma (68). H3K18la drives key transcription factors Y-box binding protein 1 and YY1, which facilitate cisplatin resistance in bladder cancer (69). In colorectal cancer, lactylation of histones, particularly H3K18la, enhances the expression of rubicon like autophagy enhancer, a protein

involved in autophagy, promoting resistance to bevacizumab treatment (70). These findings underscore the significance of lactylation in regulating tumor drug resistance and highlight novel therapeutic targets for cancer treatment. Developing combined cancer therapy strategies may help overcome drug resistance, improve treatment efficacy and enhance patient prognosis (71).

Current research has identified lactate as serving a critical role in tumor resistance; however, traditional lactate-targeting therapies have not achieved the desired clinical outcomes (72). Consequently, the development of specific inhibitors targeting histone lactylation may offer more effective therapeutic strategies. While lactylation has provided a theoretical basis for understanding tumor resistance, the knowledge regarding the modification sites, processes and related proteins remains limited. As technologies for studying lactylation, such as lactylation proteomics, continue to advance, it is probable that more lactylation-modified proteins contributing to tumor resistance will be identified.

5. Role of lactylation in remodeling the TME

The TME is a highly complex and heterogeneous ecosystem, comprising tumor cells, extracellular matrix, immune cells, stromal cells, endothelial cells and an array of signaling molecules (73). The survival and growth of tumors are intricately linked to the support provided by the TME (74). Through the Warburg effect and glutamine hydrolysis, tumors produce substantial amounts of lactate, which activates transport receptors on the surface of tumor cells, facilitating the rapid export of intracellular lactate to prevent excessive intracellular acidification (75). The accumulation of extracellular lactate and the resulting acidification of the TME are pivotal processes that drive tumor progression (76). The extensive buildup of extracellular lactate increases protein lactylation levels, which can recruit and regulate cancer-associated fibroblasts, tumor-infiltrating myeloid cells, including macrophages, dendritic cells and regulatory T cells (Treg cells), and cancer stem cells. These processes collectively remodel the TME and promote tumor proliferation and progression (77).

In the TME, lactylation of tumor cells, cancer stem cells and tumor-infiltrating immune cells can actively promote cancer progression by modulating the expression of downstream genes (78). Immune cells are critical components of the TME and their infiltration influences tumor progression. For instance, in colorectal cancer, METTL3 enhances its binding affinity to RNA m^6A modification targets through lactylation, mediating the immunosuppressive function of tumor-infiltrating myeloid cells and facilitating tumor immune evasion (79). Additionally, the relationship between T-cell lactylation and tumor progression has attracted widespread attention. It has been shown that the lactylation of MOESIN enhances TGF-β signaling, promoting tumorigenesis by inducing the efficient generation of Treg cells (80). Treg cells, in turn, impede the activity of cytotoxic T cells, further driving tumor progression (81). Additionally, the lactylation of histone H3 at the K18la site enhances the activity of pro-tumor macrophages, which suppresses the enrichment of $CD8^+$ T cells and the proportion of interferon-γ^+CD8^+ T cells within the TME, resulting in an immunosuppressive environment (82). However, inhibiting histone lactylation in tumor-associated macrophages has been found to activate macrophage phagocytosis and M2 polarization (12,83). These studies collectively suggest that lactylation may reshape the TME and immune evasion, ultimately promoting tumor progression.

Lactic acid produced by tumor metabolism remodels the TME through lactylation, thereby contributing to tumor progression (Fig. 2). This marks a new era in the study of tumor metabolism and the TME, as protein lactylation not only expands the field of PTMs but also provides novel directions for research into the role of lactate in tumor immunity and other areas. By reshaping the TME, lactylation modulates cancer progression, offering a theoretical foundation for targeting lactylation as an antitumor strategy. Understanding the interplay between lactylation and the TME will be key to developing novel cancer therapies. Furthermore, the current research on the role and mechanisms of lactylation in relation to other key cellular components within the TME remains limited and warrants further investigation.

6. Crosstalk between lactylation and gut microbiota

Epigenetic modifications and metabolic reprogramming are two fundamental biological processes closely associated with tumor progression (84). While current clinical treatments for tumors primarily include targeted therapies, immunotherapy and surgery, limited research has explored the therapeutic potential of targeting gut microbiota at the level of epigenetic and metabolic reprogramming. The gut microbiota serves a crucial role in regulating the epigenetic modifications of the host, influencing early development, homeostasis and disease progression (85). Increasing evidence suggests that the gut microbiota contributes to the initiation and progression of malignant tumors (86), influencing tumor development through various mechanisms (87).

A substantial number of microbial-derived molecules are absorbed by the host, exerting profound effects on epigenetic modifications (88). On the one hand, the gut microbiota synthesizes numerous bioactive compounds, which serve as substrates, cofactors or regulators of epigenetic enzymes (89), inducing histone modifications that result in chromatin alterations (90). On the other hand, the gut microbiota can suppress aerobic glycolysis in tumors via signaling molecules, leading to a reduction in lactate production (91), thereby lowering the levels of lactylation. Furthermore, lactylation can reciprocally affect tumor metabolic reprogramming, consequently influencing the gut microbiota composition (92).

The gut microbiota and its metabolites modulate gene expression through epigenetic regulation, affecting tumor cell metabolism and thereby affecting lactylation levels. For instance, a study has shown that lipopolysaccharide induces histone lactylation, upregulating LINC00152 expression and promoting tumor invasion, highlighting the potential connection between gut microbiota and lactylation (93). The gut microbiota is diverse and different gut microbiota and their metabolic derivatives have varying effects on lactylation levels. On one hand, gut microbes can generate lactate through metabolism (94), which will increase the lactate-dependent lactylation levels of the host. On the other hand, the gut microbiota can also reduce the production of lactate and exert HDAC

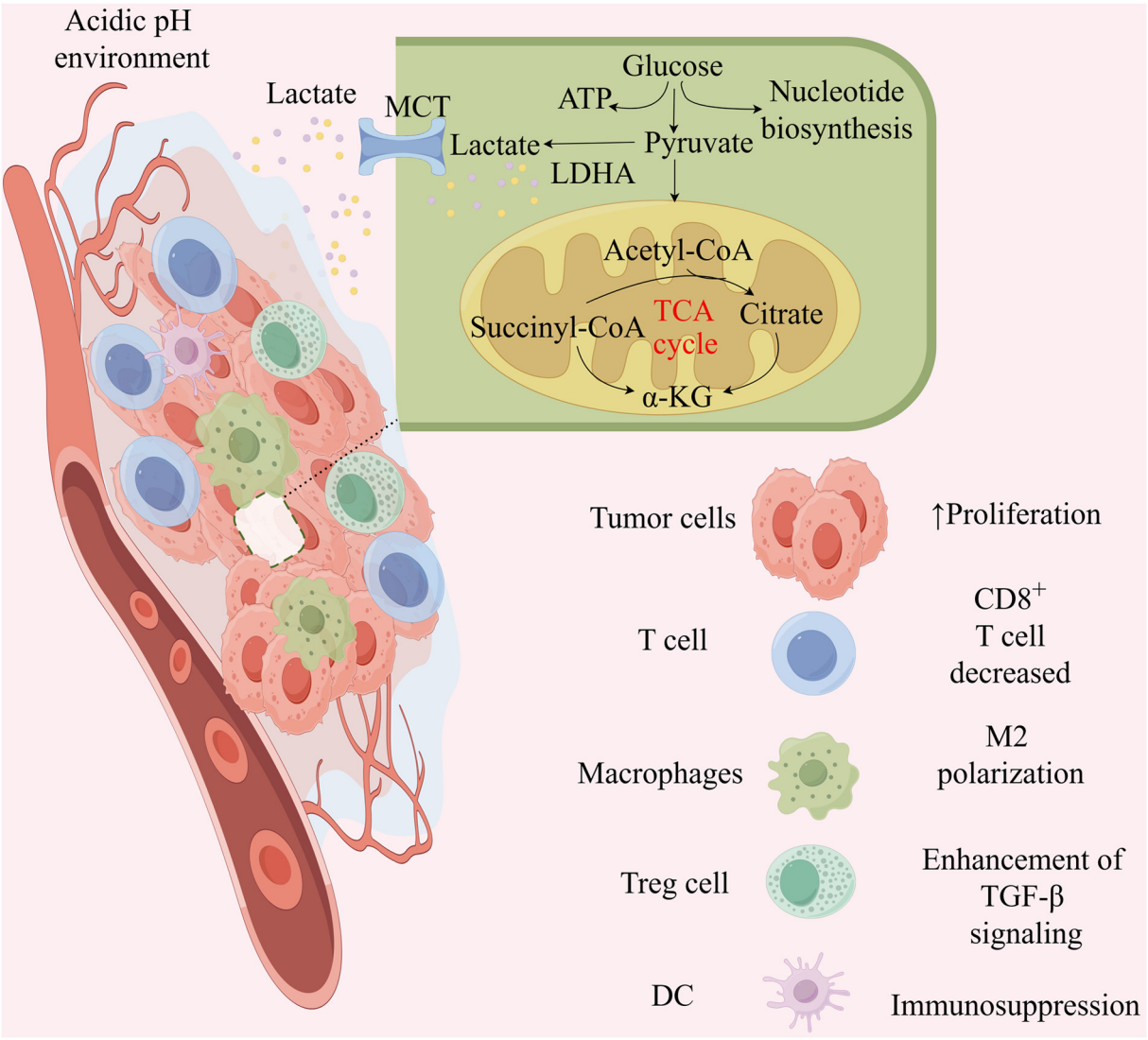

Figure 2. Remodeling of the TME by lactylation. Tumor cells produce lactic acid, which is transported from inside the cells to the TME via MCTs. The large amount of lactic acid increases the acidity of the TME and also promotes the elevation of lactate modification levels within it. An increase in lactate modification levels can promote the polarization of macrophages towards the M2 phenotype, suppress the immune functions of $CD8^+$ T cells and dendritic cells, and enhance TGF-β signaling to maintain the immunosuppressive function of Treg cells. This, in turn, hinders antitumor immunity and facilitates the immune evasion of tumor cells, leading to tumor progression. α-KG, α-ketoglutaric acid; DC, dendritic cell; LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter; TCA, tricarboxylic acid; TME, tumor microenvironment; Treg cell, regulatory T cell.

inhibitory activity by converting lactate into short-chain fatty acids (95), thereby reducing the overall lactylation modification levels in the host. Currently, there is limited research on the effect of lactylation on the gut microbiota and a study has shown that lactylation modification regulates the metabolic pathways of the microbiota (96), indirectly affecting the microbial ecology. Furthermore, lactylation of proteins can enhance the virulence mediated by pathogen toxins (97). Additionally, lactylation may co-regulate cellular activities via the crosstalk between tumor metabolic reprogramming and gut microbiota.

While bioactive metabolites produced by the microbiota promote epigenetic modifications, the specific mechanisms by which lactylation and gut microbiota crosstalk influence tumor progression require further investigation. Future research on the intricate crosstalk between lactylation and gut microbiota may pave the way for more targeted and effective combination therapies for cancer treatment.

7. Lactylation as a potential target for disease treatment

The regulation of lactate production and transport is a crucial strategy for improving tumor prognosis (98). The identification of lactylation further suggests that targeting lactylation may offer novel options to inhibit cancer progression and enhance antitumor therapies (99). Based on the mechanisms of lactylation and its carcinogenic processes, potential therapeutic approaches can target lactate metabolism, transport or lactylation generation (100).

Lactylation is primarily influenced by lactate levels (48). Inhibiting key enzymes involved in lactate production in tumor cells can effectively reduce lactylation by lowering lactate levels. For instance, reducing lactate dehydrogenase activity during glycolysis can inhibit the conversion of pyruvate to lactate, thereby lowering lactylation levels (12). Additionally, some drugs targeting lactate metabolism

and transport are currently in clinical trials and combined treatment strategies may provide improved therapeutic outcomes (101). However, it is important to note that inhibitors targeting lactate metabolism may not only affect lactylation but also disrupt normal metabolic processes in cells (102). Future research should focus on developing specific metabolic inhibitors to minimize side effects and improve efficacy. Researchers have reported that demethylated zeylastal could inhibit liver cancer stem cell tumorigenesis both *in vitro* and *in vivo* (103). Besides lactate metabolism, enzymes related to lactylation also affect lactylation levels and the identification of such enzymes may provide more therapeutic targets for cancer (104). These studies demonstrate the potential of lactylation as a therapeutic target for cancer, highlighting the importance of exploring the mechanisms and regulatory sites of lactylation to identify effective cancer treatment targets. Targeting lactylation, along with combination therapies such as chemotherapy, radiotherapy and immunotherapy, could provide additional options for cancer treatment in the future.

8. Summary and outlook

PTMs are an indispensable component in the regulation of protein functionality, occurring both prior to and subsequent to protein biosynthesis, thereby enhancing the functional diversity of the proteome (105). PTMs modulate cellular signaling, protein localization and the maintenance of cellular functions by altering protein structure and activity, serving a pivotal role in cellular development (106). Lactylation, as a novel type of PTM, is critical for elucidating the pathological processes associated with tumors.

The present review summarizes the mechanisms underlying the generation of lactylation and its biological effects on tumor progression. Additionally, it elucidates the relationship among lactylation, tumor drug resistance and the remodeling of the TME. Furthermore, it explores the intricate crosstalk between lactylation and gut microbiota, and examines the potential of targeting lactylation as a novel therapeutic strategy for cancer. By providing a comprehensive overview of the regulatory role of lactylation in tumor development, the present review aimed to clarify its scientific significance, highlight critical unresolved questions and pave the way for novel avenues in targeted cancer therapy.

It is well established that cancer is a multifactorial disease arising from a myriad of mechanisms and the precise mechanisms driving tumorigenesis remain incompletely understood. Lactylation closely links tumor metabolism with tumor development (107), providing a novel perspective on the role of lactate and presenting a promising potential therapeutic approach for cancer treatment.

However, there is currently a lack of specific inhibitors targeting lactylation modifications. Furthermore, during tumorigenesis, lactylation may be activated in tandem with other oncogenic signals, further complicating targeted therapies. Additionally, since lactylation shares common writers or erasers with other PTMs, targeting lactylation may inadvertently affect other protein modifications. This interdependence poses challenges to the development of lactylation-specific therapeutic agents (108).

Lactylation modifications can promote tumor metabolic reprogramming by regulating gene expression, particularly through their impact on enzymes involved in glucose metabolism. However, there is limited research on the role of lactylation in other fundamental metabolic pathways. Further exploration of the relationship between lactylation modifications and tumor metabolism will enhance the comprehensive understanding of tumor epigenetics and metabolism, laying the groundwork for the development of novel therapeutic targets in cancer treatment. Additionally, the potential interplay between lactylation and gut microbiota may offer novel insights for cancer therapy. Dysbiosis of the gut microbiota not only promotes tumor progression but also affects the efficacy of antitumor drugs (109). Combining treatments that target both the gut microbiota and lactylation may enhance the effectiveness of cancer therapies (110).

Lactylation, along with a spectrum of other PTMs, adds a layer of complexity to the epigenetic regulation of tumors, making the development of sensitive and specific PTM detection methods a crucial direction for research on tumor modifications. Furthermore, the interactions between different PTMs are not mutually independent; rather, their crosstalk influences disease onset and progression (111). The interplay between these modifications serves a pivotal role in tumorigenesis (112). However, the mechanisms through which lactylation interacts with other PTMs to affect tumor development require further investigation. In summary, understanding the crosstalk between lactylation and various modifications will provide valuable insights into the intricate relationship between tumor metabolism and epigenetic processes.

Future research on lactylation could prioritize the following areas: Investigating the effect of lactylation-related enzymes on tumor progression; unveiling the complex molecular mechanisms by which different lactylation modification sites influence cancer development; and developing specific lactylation inhibitors for cancer treatment.

9. Conclusion

In summary, lactylation, as a novel PTM, serves a role in the pathogenesis of tumors and holds substantial potential for novel diagnostic and therapeutic approaches in cancer. Currently, research targeting lactylation remains largely theoretical, with a number of mechanisms of non-histone lactylation yet to be elucidated. Future investigations should focus on exploring the specific mechanisms of lactylation and its intricate relationships with other PTMs. A deeper understanding of the regulatory roles of lactylation in various pathological processes may pave the way for the development of innovative therapeutic strategies, offering more options and hope in clinical settings.

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Authors' contributions

ZZ, XZ and PZ conceived and designed the review. ZZ and XZ wrote the manuscript. GX, CC and XK critically revised and polished the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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