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Impact of lactate on immune cell function in the tumor microenvironment: mechanisms and therapeutic perspectives

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Lactate has emerged as a key regulator in the tumor microenvironment (TME), influencing both tumor progression and immune dynamics. As a byproduct of aerobic glycolysis, lactate satisfies the metabolic needs of proliferating tumor cells while reshaping the TME to facilitate immune evasion. Elevated lactate levels inhibit effector immune cells such as CD8⁺ T and natural killer cells, while supporting immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, thus fostering an immunosuppressive environment. Lactate promotes epigenetic reprogramming, stabilizes hypoxia-inducible factor-1 α , and activates nuclear factor kappa B, leading to further immunological dysfunction. In this review, we examined the role of lactate in metabolic reprogramming, immune suppression, and treatment resistance. We also discuss promising therapeutic strategies targeting lactate metabolism, including lactate dehydrogenase inhibitors, monocarboxylate transporter inhibitors, and TME neutralization methods, all of which can restore immune function and enhance immunotherapy outcomes. By highlighting recent advances, this review provides a theoretical foundation for integrating lactate-targeted therapies into clinical practice. We also highlight the potential synergy between these therapies and current immunotherapeutic strategies, providing new avenues for addressing TME-related challenges and improving outcomes for patients with cancer.

KEYWORDS

lactate metabolism, tumor microenvironment, immunosuppression, targeted therapy, immunotherapy

1 Introduction

Lactate, a byproduct of glycolysis, plays a critical role in shaping the tumor microenvironment (TME). Under normal conditions, pyruvate from glycolysis enters the mitochondria to undergo oxidative phosphorylation (OXPHOS), generating 36 adenosine triphosphates (ATP) per glucose molecule. However, in the context of tumorigenesis, tumor cells shift to aerobic glycolysis, known as the Warburg effect, in which pyruvate is converted to lactate by lactate dehydrogenase A (LDHA) even in the presence of oxygen (1). This metabolic adaptation allows tumors to sustain rapid proliferation by maintaining glycolytic flux despite a lower ATP yield (2 ATP per glucose molecule). In addition to glucose metabolism, glutamine metabolism provides an alternative source of lactate, which further fuels tumor growth.

Lactate accumulation in tumors is regulated by hypoxia-inducible factor-1 α (HIF-1 α) and c-Myc. These factors enhance the expression of glycolytic enzymes such as hexokinase 2 (HK2) and glucose transporter 1 (GLUT1) while inhibiting pyruvate dehydrogenase (PDH), which normally channels pyruvate into the mitochondrial tricarboxylic acid (TCA) cycle (2). As a result, lactate accumulates within tumor cells, indicating the need for efficient export mechanisms to prevent intracellular acidification and maintain metabolic homeostasis.

Monocarboxylate transporters (MCTs) mediate lactate transport in the TME. MCT4, which is highly expressed in glycolytic tumor cells, facilitates lactate and proton (H⁺) export, leading to extracellular acidification. The acidic environment promotes tumor invasion, angiogenesis, and immune suppression (3). In contrast, MCT1 supports bidirectional lactate transport, enabling oxidative tumor cells and cancer-associated fibroblasts (CAFs) to absorb lactate as energy sources (4). This metabolic cooperation sustains tumor progression by allowing different cell populations to adapt to changing nutrient and oxygen conditions.

The acidification of the TME has profound effects on immune function. A low extracellular pH directly impairs cytotoxic T-cell and natural killer (NK) cell activity, reducing their ability to kill tumor cells (5). At the same time, lactate stabilizes HIF-1 α and activates NF- κ B, promoting an immunosuppressive phenotype (6). This change in the acidic environment enhances the function of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) while inducing tumor-associated macrophages (TAMs) to adopt an M2-like phenotype, further dampening antitumor immunity (7). These metabolic and immune adaptations not only drive tumor progression but also contribute to resistance to immune checkpoint inhibitors (ICIs).

Lactylation is a recently discovered post-translational modification (PTM) that was originally described by Zhao et al. in 2019 (8). Increased lactate concentrations enhance lactylation via multiple pathways, subsequently affecting cellular functions and disease progression (9). In this process, lactate coenzyme A (L-lactyl-CoA) covalently modifies lysine residues (10). “Writer” enzymes such as p300/CBP mediate lactylation, whereas “eraser” enzymes such as HDAC1-3 and SIRT1-3 regulate its reversibility (11). Lactylation occurs in both histone and non-histone proteins

and is closely linked to cellular metabolic activity. Lactylation significantly affects chromatin remodeling, gene expression, and cellular function in the TME (12).

Given its central role in tumor metabolism and immune suppression, lactate metabolism and transport, as well as lactylation, are promising targets for cancer therapy. Strategies such as blocking MCTs, inhibiting lactate production, or modulating TME acidity could enhance immune cell function and improve the efficacy of existing cancer therapies. Understanding the interplay between lactate metabolism, lactylation, and immune evasion is essential for developing new interventions that restore antitumor immunity and improve patient outcomes. In this review, we explore the complex role of lactate in tumor progression, its impact on immune regulation, and potential therapeutic strategies to counteract lactate-driven immunosuppression.

2 Role of lactate in the TME and immunotherapeutic strategies

2.1 Immunoregulatory role of lactate in the TME: intersection of immunosuppression and metabolic reprogramming

As outlined in the previous section, lactate metabolism and transport lead to its accumulation in the TME, where its concentration can reach 20–40 mM, compared to 1.5–3 mM in normal tissues (13). This accumulation significantly lowers the extracellular pH to 6.0–6.5, well below the normal range of 7.3–7.4. Such an acidic environment impairs immune cell function and metabolism, promoting tumor immune evasion—a hallmark of cancer development (14, 15). The acidic pH reduces the metabolic flexibility of CD8⁺ T cells and NK cells while enhancing the immunosuppressive properties of Tregs and MDSCs. The role of lactate in the TME is illustrated in Figure 1.

Different cancer types exhibit varying degrees of lactate accumulation (Table 1). For example, lactate concentrations are significantly higher in tumors with metastatic spread (12.3 ± 3.3 μ mol/g) than in those without metastasis (4.7 ± 1.5 μ mol/g) (16). In contrast, cervical cancer samples show a more modest increase in lactate, with concentrations of 10.0 ± 2.9 μ mol/g in tumors with metastasis and 6.3 ± 2.8 μ mol/g in those without (13). In breast cancer, lactate concentrations vary widely, with values of 0.6–8.0 μ mol/g in late-stage tumors (17). The variations in lactate concentration indicate that distinct tumor types exhibit differences in lactate accumulation, potentially influencing their vulnerability to metabolically targeted therapies. Lactate promotes immunosuppression and tumor progression, but its role in the TME of different tumor types is unclear. Therefore, an in-depth study of the function of lactate in the TME will help to understand its role in tumor metabolism and provide ideas for future targeted therapies.

Metabolic reprogramming is the adjustment of cellular metabolic pathways and product distribution in response to physiological or pathological conditions, enabling cells to adapt to growth, differentiation, and environmental changes. In the tumor

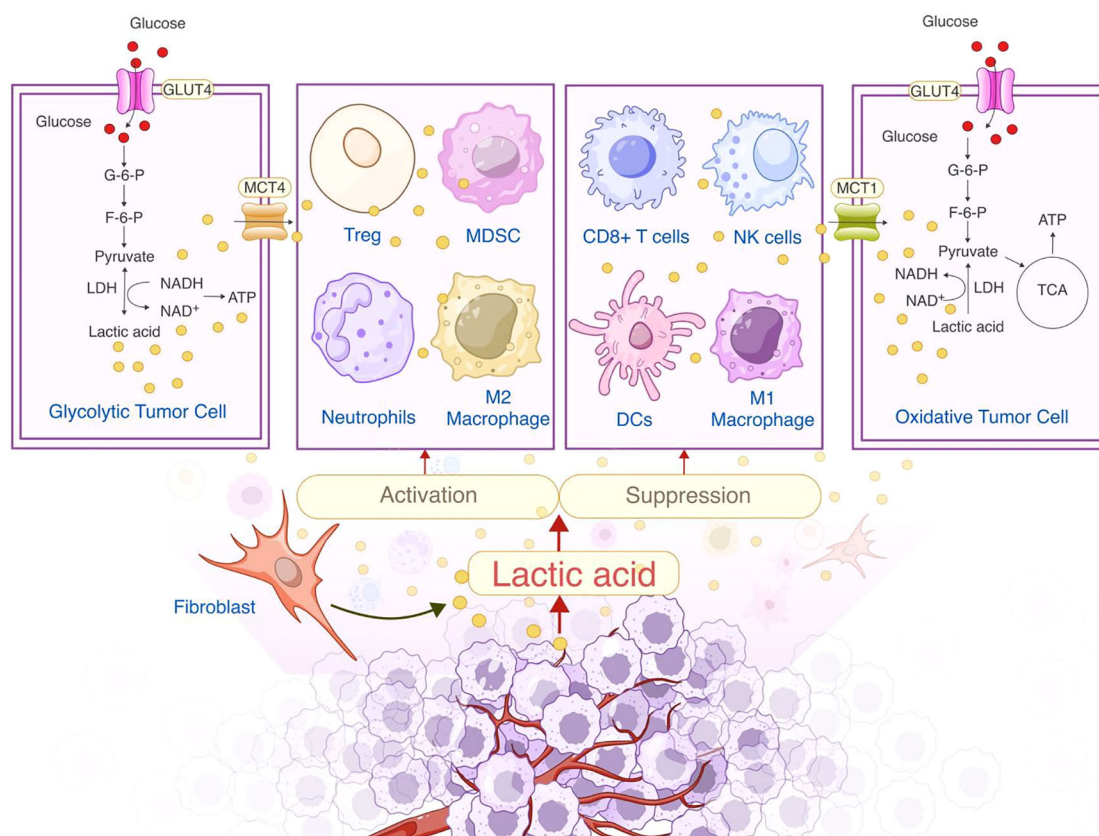


FIGURE 1 Dual role of lactate in the tumor microenvironment: Metabolic regulation and immunosuppression.

microenvironment, this process alters immune cell function by modifying metabolic substrates and signaling pathways (18). These connections between lactate metabolism and immune suppression highlight the pivotal role of metabolic reprogramming in shaping tumor immune environments. In the subsequent sections, we explore the varied effects of lactate accumulation on different immune cell types and the implications of lactate accumulation for therapeutic strategies aimed at countering immune evasion.

TABLE 1 Lactate concentration and metastatic spread in cancer types.

Cancer Type	Lactate Concentration	References
Head and Neck Cancer	12.3 ± 3.3 μmol/g (with spread) 4.7 ± 1.5 μmol/g (without spread)	(16)
Colorectal Cancer	13.4 ± 3.8 μmol/g (with spread) 6.9 μmol/g (without spread)	(154)
Breast Cancer	0.6–8.0 μmol/g (median concentration range)	(17)
Cervical Cancer	10.0 ± 2.9 μmol/g (with spread) 6.3 ± 2.8 μmol/g (without spread)	(13)
Lung Cancer (Metastatic)	1.8 ± 2.2 mmol/L (maximal levels)	(155)
Astrocytomas	12.35 mmol/L (with spread) 8.28 mmol/L (without spread)	(156)

2.1.1 Inhibitory effects of lactate on effector immune cells

2.1.1.1 T lymphocytes

Lactate is a key regulator that inhibits T-cell antitumor activity at multiple levels, including by suppressing T-cell receptor signaling by decreasing p38 and JNK phosphorylation, which lowers the production of interferon-γ (IFN-γ) and tumor necrosis factor-α (19–21), thereby inhibiting T-cell proliferation and cytotoxicity. Lactate also affects the NAD⁺/NADH redox balance, inhibiting glycolysis, decreasing ATP production, and contributing to T-cell exhaustion (19, 22). In high-lactate environments, such as those found in melanoma and other tumor models, NAD⁺ depletion leads to T-cell apoptosis and a significant reduction in antitumor responses (23, 24).

Interestingly, recent studies have identified lactate as a TCA fuel for certain tumor cells and untransformed tissues *in vivo* (25–27). It is an important carbon source for CD8⁺ T cells, and at its physiological concentration, lactate promotes mitochondrial oxidation and supports OXPHOS, thereby enhancing energy production and cellular biosynthesis, especially during functional T cell responses *in vivo* (28). Similarly, lactate produced by innate immune cells or tumor cells may provide energy for effector T cells in inflammatory tissues (29, 30). Lactate serves a dual function in T-cell immunity, seemingly contingent upon varying lactate concentrations. Lactate enhances T-cell metabolism and activity

at lower doses (0.5–3 mmol). However, at concentrations exceeding 5 mmol, lactate impedes T cell functionality and results in T cell dysfunction.

Furthermore, lactate plays a direct role in driving T-cell exhaustion through its influence on immune checkpoint pathways. Lactic acid enhances the expression of programmed death ligand 1 (PD-L1) on tumor cells through its receptor GPR81, which inhibits CD8⁺ T cell-mediated cytotoxicity and fosters immune tolerance in the TME (31, 32). Additionally, lactate-driven SIRT1 activation results in deacetylation and degradation of T-bet, a transcription factor essential for maintaining CD8⁺ T cell effector function, thereby shifting T cells toward a more exhausted phenotype with higher PD-1 expression and diminished cytokine production (33).

Lactate also modulates CTLA-4 signaling, further reinforcing T cell dysfunction. Increased extracellular lactate enhances FOXP3 expression in Tregs, promoting an immunosuppressive microenvironment that inhibits the activation of effector T cells via CTLA-4-mediated suppression (34). Moreover, lactate influences T cell dysfunction by modulating chemokine production and receptor signaling, thereby restricting T cell infiltration into tumor tissues (35, 36). This phenomenon not only prevents effective immune surveillance but also intensifies the PD-1/CTLA-4-driven dysfunction state by further inhibiting T cell function in proinflammatory circuits that could otherwise restore function.

These inhibitory effects significantly impair immune cell function in the TME, facilitating tumor immune evasion. Given the profound role of lactate in sustaining T-cell exhaustion via the PD-1/CTLA-4 axis, therapeutic strategies targeting lactate metabolism, such as MCT inhibitors, LDHA blockade, or buffering agents, may enhance the efficacy of ICIs by reprogramming dysfunctional T cells and restoring their antitumor activity. Future studies should further investigate how lactate-targeting approaches could synergize with ICIs to reverse exhaustion and reinvigorate T-cell function within the TME.

2.1.1.2 NK cells

Lactate diminishes the antitumor efficacy of NK cells in the TME via various pathways, including direct metabolic effects, immune modulation, and acidic environments. Elevated lactate concentrations (> 15 mM) suppress the NFAT signaling pathway in NK cells, reducing IFN- γ production and impairing antitumor signaling (21, 37). Lactate-induced intracellular acidification disrupts lipid biosynthesis, impairs mitochondrial function, and increases oxidative stress, ultimately resulting in NK cell apoptosis (38). These metabolic disturbances significantly reduce NK cell cytotoxicity and overall antitumor capacity. Lactate also suppresses critical cytokine synthesis in NK cells by inhibiting the mTOR signaling pathway, which is essential for their activation and function (38, 39).

Furthermore, lactate inhibits NK cell activity, primarily by acidifying the TME, which impairs NK cell degranulation and reduces key cytotoxic markers such as perforin and CD107a in various cancer models, including pancreatic and breast cancers

(40–42). Therapeutic strategies that neutralize acidity and target lactate metabolism show promise in reversing these immunosuppressive effects.

2.1.1.3 Dysfunction of Dendritic Cells (DCs)

Lactate inhibits DC activity in the TME through multiple mechanisms, significantly impairing their antitumor immune functions. This suppression is primarily due to the interference of lactate with DC development and maturation, which prevents DCs from effectively presenting antigens and activating effector T cells. Lactate inhibits the expression of MHC-II and co-stimulatory molecules such as CD80 and CD86, leading to DC dysfunction (43, 44). Lactate also stimulates IL-10 secretion while inhibiting IL-12 synthesis, further diminishing the ability of DCs to activate cytotoxic T lymphocytes (CTLs) (45, 46). In melanoma models, inhibiting lactate production enhances DC function and antitumor efficacy, highlighting the fundamental role that lactate plays in DC dysfunction (47).

Glycolysis is a key metabolic process in DCs for antigen presentation and adaptive immune responses. However, lactate disrupts DC energy supply by inhibiting glycolysis and the calcium signaling pathway by activating GPR81, thereby worsening intracellular acidification and ultimately impairing DC function (48, 49). It has also been demonstrated that DC motility and migration are largely dependent on glycolysis (50), and thus, lactate-induced glycolysis impairs the ability of DCs to mount antitumor immunity. Lactate also activates SREBP2 in tumor DCs, driving the conversion of conventional DCs into mature regulatory DCs, which are then directed to tumor-draining lymph nodes, thereby inhibiting DC-mediated antigen cross-presentation (51).

2.1.2 Enhancing effect of lactate on immunosuppressive cells

2.1.2.1 Regulatory T cells

Lactate in the TME significantly affects the metabolic balance, signaling pathways, and epigenetic regulation of Tregs, enhancing their immunosuppressive capabilities and contributing to tumor immune evasion (52). Studies have shown that elevated MCT1 expression enables Tregs to absorb and utilize lactate more efficiently, enhancing their survival and functionality (53). In mouse melanoma models, Tregs lacking MCT1 exhibit decreased lactate uptake, reduced immunosuppressive abilities, and diminished tumor-promoting actions, highlighting the pivotal role of lactate in Treg regulation (27, 54, 55).

In addition to metabolic adaptation, lactate influences Tregs through signaling pathways and epigenetic modifications that enhance their stability and suppressive function. Lactate activates the PI3K/Akt/mTOR pathway, increasing FOXP3 expression and enhancing Treg-mediated suppression of effector T cells (56). Lactate also promotes Treg recruitment and infiltration into the TME by upregulating chemokines such as CXCL12 and CX3CL1, further contributing to an immunosuppressive environment (55, 57).

Lactate also enhances Treg immunosuppression by boosting the release of cytokines such as IL-10 and TGF- β (58, 59), which

intensify the inhibitory effects of Tregs on effector immune cells, facilitating immune evasion. Comparative studies have shown that lactate-rich environments foster greater Treg suppressive activity than glucose-rich environments, highlighting the crucial role of lactate in Treg-mediated immunosuppression (52).

2.1.2.2 Myeloid-derived suppressor cells

In addition to enhancing Treg-mediated immunosuppression, lactate drives the activity and recruitment of MDSCs, a key component of the immunosuppressive network in the TME. Lactate directly promotes the metabolic adaptation and immunosuppressive function of MDSCs through complex control involving epigenetic modifications and signaling networks. Lactate affects MDSC metabolism by modulating HIF-1 α activity, promoting the upregulation of ARG1 and iNOS expression (60, 61). This depletes arginine, which is essential for T-cell activation, while producing reactive oxygen species and nitric oxide, which directly impair the functions of effector T and NK cells (62–64). Furthermore, lactate improves the immunosuppressive potential of MDSCs by upregulating PD-L1 expression (60, 65). In breast cancer models, lactate-induced HIF-1 α activation enables MDSCs to suppress effector T cells and accelerate tumor growth (66).

Beyond metabolic control, lactate boosts MDSC recruitment and accumulation in the TME by acting as a chemoattractant and activating the mTOR and GPR81 signaling pathways (67, 68). A pancreatic cancer study showed that lactate-mediated GPR81 activation significantly promoted MDSC growth and immunosuppressive activity (7, 60, 69). Furthermore, lactate indirectly inhibits NK cell activity by promoting the growth and activation of MDSCs (7, 70).

2.1.2.3 Tumor-associated macrophages

TAMs undergo significant metabolic and gene expression changes during lactate-driven reprogramming, typically polarizing toward the immunosuppressive M2 phenotype (71). Lactate enhances the immunosuppressive function of TAMs by activating the ERK/STAT3 and GPR132 signaling pathways, in part through its regulation of HIF-1 α (72, 73). Activation of these pathways boosts the production of vascular endothelial growth factor (VEGF) and ARG1, promoting angiogenesis and immune evasion (74). Lactate also encourages M2-polarized TAMs to release immunosuppressive molecules (IL-10 and TGF- β), which impair the activity of CTLs and NK cells while recruiting Tregs (71, 75–77). Furthermore, lactate-driven metabolic reprogramming shifts the energy supply of TAMs from glycolysis to OXPHOS, making them more adaptable to the hypoxic, high-lactate TME (78, 79). This metabolic transition, in which lactic acid is efficiently converted to pyruvate, is mainly due to the preferential dependence of M2 macrophages on mitochondrial metabolism (80–82). Pyruvate then enters the mitochondria via the MPC1 transporter and enters the TCA cycle, further supporting OXPHOS (83). This process ensures that M2 macrophages are able to receive continuous energy production. This adaptation increases the release of matrix-degrading enzymes, such as matrix metalloproteinases, which promote extracellular matrix remodeling, tumor invasion, and metastasis (79, 84).

These lactate-induced changes in TAM function have been observed in various cancer models, including breast and gastric cancer and melanoma, highlighting their crucial role in tumor development, immune evasion, and resistance to treatment (85). These findings highlight the importance of TAMs in the TME and indicate that targeting lactate metabolism and TAM polarization may offer promising strategies for antitumor therapies.

2.1.3 Effects of lactylation on TME immunoregulation

2.1.3.1 Lactylation: an emerging PTM and its biological functions

Lactylation has been newly discovered and plays a crucial role in immune regulation through transcriptional activation. For example, H3K18la lactylation on histone 3 enhances chromatin accessibility and activates the transcription of tumor-promoting genes (86). This modification upregulates arginase-1 (ARG1) and interleukin (IL)-10 in TAMs, driving them toward an immunosuppressive M2 phenotype and facilitating tumor immune escape (73). In addition to histones, lactylation affects non-histone proteins, leading to various physiological effects. For example, lactylation of Aldolase A inhibits glycolysis, and modification of RIG-I suppresses the NF- κ B signaling pathway, maintaining an immunosuppressive TME (87).

In addition to immune cells, lactylation may regulate key stromal components of the TME, including cancer-associated fibroblasts (CAFs) and endothelial cells. CAFs play a critical role in extracellular matrix remodeling, metabolic crosstalk, and immune modulation, and accumulating evidence suggests that lactate metabolism may influence their activation (88). Recent studies have indicated that lactylation of histone marks may enhance the transcription of pro-tumorigenic genes, such as fibroblast activation protein (FAP) and α -SMA (ACTA2), promoting fibroblast-mediated extracellular matrix remodeling and tumor progression (89). This effect is likely mediated through TGF- β and Notch signaling pathways, both of which have been implicated in lactylation-induced fibroblast activation (90, 91).

Similarly, endothelial cells exposed to high lactate levels exhibit increased angiogenic potential, and lactylation may contribute to the expression of angiogenesis-related genes, such as VEGFA and ANGPT2, thereby facilitating neovascularization within tumors. Mechanistically, HIF-1 α lactylation enhances VEGF signaling, driving tumor vascularization even under normoxic conditions (92). However, whether lactylation directly modifies VEGF-related transcription factors or acts through broader chromatin remodeling remains unclear.

Collectively, lactylation serves as a critical link between metabolic shifts and epigenetic regulation, contributing to an immunosuppressive and tumor-supportive microenvironment. In addition to immune regulation, its emerging roles in fibroblast activation and angiogenesis suggest that lactylation-dependent pathways may serve as promising therapeutic targets. However, further research is needed to delineate the precise molecular mechanisms by which lactylation shapes tumor-stroma interactions, providing new opportunities for metabolism-based cancer therapies.

2.1.3.2 Lactylation as a key epigenetic regulator of immune cell activity in the TME

Lactate induces lactylation of both histone and non-histone proteins, significantly altering the functional states of CD8⁺ T cells, Tregs, TAMs, MDSCs, and other immune cells (Figure 2). Studies have shown that lactate stimulates histone lactylation (e.g., H3K18la), which regulates the expression of MCT1 and MCT4 (93). One of the key effects of lactylation is its role in immune checkpoint regulation. This effect is partly mediated by lactate-induced histone lactylation, which upregulates PD-1 transcription and reinforces the exhausted phenotype (94). In addition, lactylation significantly affects effector immune cells such as NK and CD8⁺ T cells. In acute myeloid leukemia, lactate-induced H4K5la changes enhance PD-L1 expression, which directly inhibits CD8⁺ T cell activation (95).

The aforementioned text indicates that lactate can influence Treg function via lactylation. Lactate modulates TGF- β signaling in Tregs by lactylating MOESIN, thus stabilizing FOXP3 expression and promoting a metabolic shift from glycolysis to OXPHOS (96).

Lactate-induced histone lactylation drives the transcription of genes associated with Treg activity and stabilizes FOXP3 expression through epigenetic mechanisms (96, 97). In multiple tumor models, including human colorectal cancer tissues, histone lactylation at FOXP3 regulatory regions correlates with heightened Treg activation and tumor progression (12, 98). This metabolic reprogramming enhances Treg survival in the TME and amplifies their immunosuppressive function. Lactate also regulates the expression of the chemokine receptor CCR8, facilitating Treg migration to tumors (99).

Lactylation also critically influences macrophage and MDSC activity. Lactate induces H3K18la histone modifications in the TME, driving the polarization of proinflammatory M1 macrophages toward the immunosuppressive M2 phenotype (100). Similarly, in MDSCs, lactate-induced histone lactylation increases the expression of key immunosuppressive genes. For example, in melanoma and lung cancer models, histone lactylation upregulates IL-10 production, further supporting MDSC expansion and suppressive activity (7). These synergistic

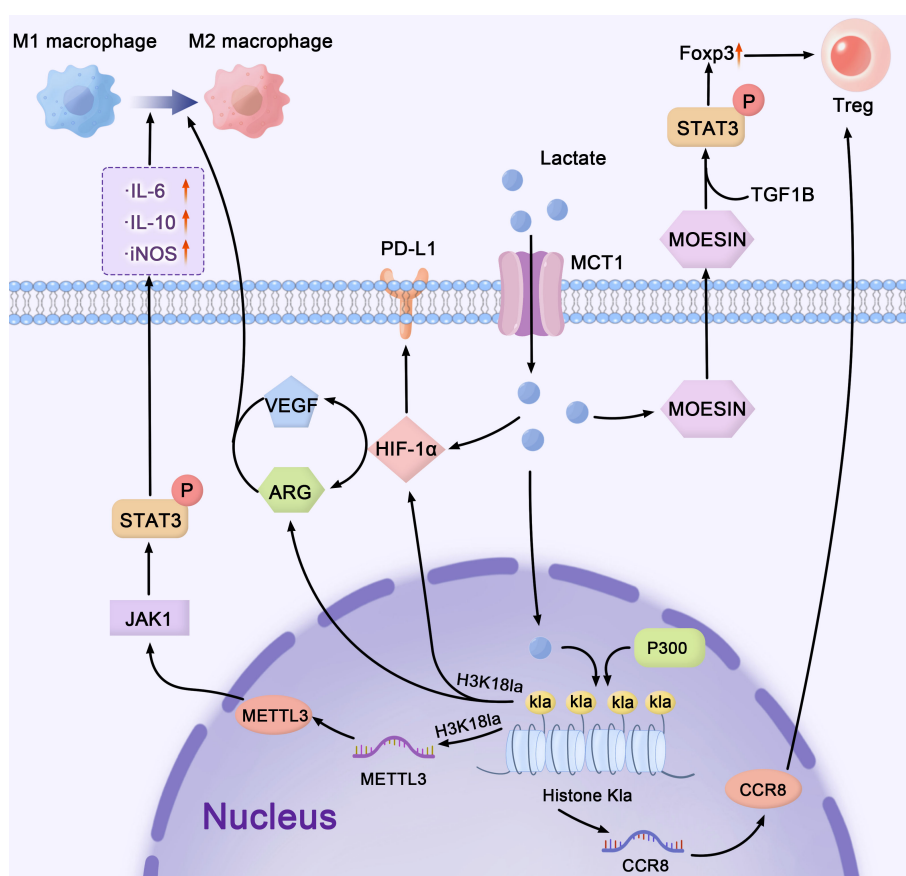


FIGURE 2

Lactate-mediated crosstalk: bridging metabolism, epigenetics, and immune regulation in the tumor microenvironment. Lactate, as a major mediator, connects cellular metabolism, transcriptional control, and immunological signaling networks in the TME. Lactate enters cells through MCT1 and upregulates MOESIN, stimulating the TGF- β /STAT3 pathway to enhance Treg cell development and immunological suppression. Lactate regulates HIF-1 α stability, VEGF, and PD-L1 expression, facilitating immune evasion. In the epigenetic landscape, METTL3 promotes gene transcription through m6A RNA alterations, whereas p300 acetylates histones (Kla), hence increasing transcriptional activity. These interrelated pathways govern the TME by balancing M1 and M2 macrophage polarization, as well as directing immunological homeostasis and tumor growth. The pathways shown represent select examples of lactate's downstream effects on immune modulation. TME, tumor microenvironment; MCT, monocarboxylate transporters; VEGF, vascular endothelial growth factor; PD-L1, programmed death ligand 1.

processes highlight the crucial role of lactate in the promotion of MDSC-mediated immunosuppression. Lactate-induced lactylation of METTL3 regulates m6A RNA modifications, which increase STAT3 phosphorylation and promote the release of IL-6 and IL-10, further supporting immunosuppressive signaling (101).

Overall, lactylation is a key regulator of immune cell activity within the TME and plays a crucial role in tumor immune evasion through its dual influence on metabolism and epigenetics. From histone lactylation upregulating PD-1 and FOXP3 expression to METTL3 lactylation enhancing m6A RNA modifications and IL-10 production, lactate-induced epigenetic modifications orchestrate an intricate immunosuppressive network. These interconnected pathways form a critical regulatory system that drives tumor progression. The complex role of lactate in the regulation of immune cell function highlights its potential as a therapeutic target. Indeed, novel strategies could restore immune cell function and boost antitumor immunity by disrupting lactate-driven immunosuppressive networks, blocking histone lactylation, or neutralizing TME acidity.

2.2 Lactate metabolism and tumor immunotherapy: targeting strategies and future directions

2.2.1 Neutralizing acidity in the TME: an innovative strategy for restoring immune cell function

The acidic TME resulting from lactate accumulation significantly impairs the function of CTLs and NK cells, promoting immune evasion and tumor growth. To address this issue, several novel strategies have been developed to neutralize the acidity of the TME and restore immune cell function. **Table 2** outlines potential extracellular pH (pHe) modulation techniques, including buffering agents such as sodium bicarbonate and carbonic anhydrase IX (CAIX) inhibitors.

Lactate-induced immunosuppression in NK cells can be mitigated by neutralizing the acidic TME. Buffering agents, such as NaHCO_3 , can raise the pHe in tumor tissues, reducing TME acidity (102). Bicarbonate buffers, which elevate pH, have demonstrated the ability to restore NK cell functions, including $\text{IFN-}\gamma$ production and cytotoxicity (103, 104). In lymphoma models, these buffering strategies significantly enhance tumor control, emphasizing the therapeutic potential of lactate-targeted interventions (103, 104). Preclinical breast cancer models have shown that NaHCO_3 enhances T-cell infiltration and activation, considerably increasing the levels of cytokines such as $\text{IFN-}\gamma$, IL-2, and IL-12p40 (105). Alkalinizing the TME with NaHCO_3 also reduces PD-L1 expression, enhances T cell activity, and improves ICI efficacy. This combined approach has demonstrated notable tumor regression in preclinical studies, highlighting the therapeutic potential of buffering therapy (105). However, systemic pH modulation lacks specificity, and off-target effects on normal tissues remain a concern, limiting its broader clinical application.

Another pH-modulating strategy involves proton pump inhibitors (PPIs). For instance, esomeprazole improves CTL activity and slows tumor progression by modulating the local tumor pH (106). A phase III study (NCT01069081) found that intermittent high-dose esomeprazole enhanced chemotherapy effectiveness (docetaxel and cisplatin) in patients with metastatic breast cancer while reducing toxicity (107). Furthermore, PPIs such as omeprazole exhibit radiosensitizing effects by inducing G1 phase cell-cycle arrest through p21 overexpression, impairing DNA repair and enhancing radiation efficacy (108, 109). While promising, the main benefit of PPIs may be in combination with radiation and chemotherapy. In a clinical trial combining PPIs with atezolizumab, researchers found that PPI use was a negative prognostic indicator for patients with non-small cell lung cancer (110). Similarly, another meta-analysis showed that PPIs reduced the effectiveness of ICIs (111).

In contrast to buffering agents and PPIs, CAIX inhibitors provide a tumor-specific approach to regulating pH. Overexpressed in hypoxic tumor regions, CAIX catalyzes the conversion of CO_2 to bicarbonate (HCO_3^-) and protons (H^+), maintaining an acidic environment that supports tumor cell survival and resistance to treatments (112–116). Inhibiting CAIX with drugs such as SLC-0111 disrupts the pH balance, increasing the susceptibility of cancer cells to chemotherapy and radiation (117). This selective targeting reduces off-target effects and is a promising approach for integration with existing therapies. However, CAIX inhibitors have significant drug delivery limitations at physiologic pH (7.4). Studies have shown that although CAIX inhibitors such as U-104 can enhance tumor cell penetration of drugs (e.g., adriamycin) in an acidic environment, they do not significantly improve drug delivery efficiency at physiological pH (118). Therefore, combination therapy may be an effective strategy to improve therapeutic efficacy.

In summary, each of these approaches offers distinct advantages and challenges. Although buffering agents effectively raise the pH of the TME, their systemic effects limit their targeted application. Moreover, PPIs, although useful in modulating tumor acidity, primarily benefit chemotherapy and radiation response rather than directly restoring immune function. CAIX inhibitors present a more precise strategy but require improved tumor-specific delivery mechanisms to overcome resistance and maximize efficacy (119). Considering these differences, combining pH modulation with other immunotherapies may provide an optimal strategy for overcoming TME-induced immune suppression. For instance, buffering therapy could enhance the ICI response by restoring immune cell activity, whereas CAIX inhibitors could be paired with chemotherapy or radiation to improve treatment outcomes. Additionally, integrating pH modulation with lactate transport inhibitors (e.g., MCT inhibitors) could simultaneously target both TME acidity and metabolic dependencies, offering a comprehensive approach to disrupting tumor-driven immune evasion (103, 120).

Addressing these limitations and enhancing the understanding of the molecular mechanisms involved in pH regulation are essential for promoting the efficacy of TME-targeted therapies

and improving cancer treatment outcomes. This includes examining the impact of pH variations on molecular pathways, including immune cell activation, cytokine production, and immune checkpoint regulation. The role of pH regulation in tumor angiogenesis, extracellular matrix remodeling, and drug resistance in treatment modalities, including chemotherapy and immunotherapy, requires further investigation. Investigating these unresolved molecular interactions is crucial for advancing pH-targeted therapies and improving their clinical efficacy.

2.2.2 Targeted lactate transport intervention: therapeutic potential of MCT inhibitors

Lactate transport plays a pivotal role in tumor metabolic reprogramming, primarily mediated by MCT1 and MCT4. These transporters help sustain glycolysis, regenerate NAD⁺, and maintain an acidic TME, all of which promote tumor growth and immune suppression. Given their crucial role, MCTs represent promising therapeutic targets for altering tumor metabolism and alleviating immune suppression. The MCT inhibitors are listed in [Table 3](#).

MCT1 inhibition has shown significant preclinical potential. AZD3965, a specific MCT1 inhibitor, increases intracellular lactate levels, disrupts glycolysis, and induces tumor cell death ([121](#), [122](#)). In lymphoma and small-cell lung cancer models, AZD3965 substantially reduced tumor growth and is currently being evaluated in a phase I clinical study (NCT01791595) ([123](#)). However, the compensatory effect of MCT4 can reduce the effectiveness of MCT1-targeted therapies. To address this issue, dual MCT1/MCT4 inhibition strategies were explored. For instance, syrosingopine inhibits lactate transport through multiple pathways, and when combined with metabolic modulators such as metformin, it enhances antitumor activity in solid tumor models ([124](#)).

In addition to direct tumor cytotoxicity, MCT inhibitors have significant immunomodulatory effects. MCT1 promotes lactate

uptake in Tregs and TAMs, thereby maintaining their immunosuppressive phenotype. Inhibiting MCT1 reduces Treg accumulation in lactate-rich TMEs, enhancing CD8⁺ T cell activity and restoring antitumor immunity. In preclinical models, MCT4 inhibition was shown to enhance NK cell function, thereby improving tumor control ([139](#), [140](#)). Similarly, it can reduce the acidification of the TME, upregulate chemokines such as CXCL9 and CXCL10, and improve the responses to ICIs in hepatocellular cancer models ([125](#)). Recently, diclofenac was demonstrated to inhibit MCT1 and MCT4, thereby reducing glycolytic activity and lactate accumulation within the tumor microenvironment. This effect showed that diclofenac not only reverses tumor acidosis but also preserves T cell effector functions, enhancing the efficacy of ICIs such as anti-PD1 treatment ([126](#)).

Selective MCT1 inhibition (e.g., AZD3965) effectively disrupts lactate efflux and tumor metabolism but can be counteracted by MCT4 compensation, limiting its standalone efficacy. Preclinical studies have shown that the combination of AZD3965 and ICIs can produce encouraging results ([127](#)). Dual inhibition (e.g., syrosingopine or diclofenac) overcomes this limitation but increases the risk of systemic toxicity, as MCTs are essential for lactate transport in normal cells, such as erythrocytes and muscle cells ([123](#), [128](#)). Combination strategies may enhance treatment efficacy while mitigating these drawbacks. For example, MCT inhibitors could be paired with ICIs to restore immune cell function by lowering lactate-driven immunosuppression, improving antitumor immunity. Additionally, combining MCT inhibition with metabolic modulators, such as metformin, may amplify metabolic stress in tumor cells, leading to more pronounced therapeutic effects ([129](#)).

Despite these advancements, resistance and toxicity remain significant barriers to clinical application. Resistance often arises from compensatory metabolic changes, whereas systemic toxicity affects lactate-dependent normal tissues. Future research should focus on enhancing the selectivity of MCT inhibitors, exploring

TABLE 2 pH modulation targets in tumor microenvironment.

Compound	Cancers	Research status
Sodium Dichloroacetate (DCA)	Breast cancer; prostate cancer; colon cancer; melanoma; glioma; acute myeloblastic leukemia; myeloma; lung cancer	Preclinical and Phase IV (147 , 157–164)
Bafilomycin A1	Lung adenocarcinoma; breast cancer; glioma	Preclinical (165 , 166)
Bromopyruvate	Glioma	Preclinical (167)
Esomeprazole	Glioma	Preclinical (168)
Omeprazole, Pantoprazole, Lansoprazole	Glioma	Preclinical (168–172)
Sodium Bicarbonate	Breast cancer	Preclinical (105)
Acetazolamide	Lymphoma;	Clinical Practice Research (173)
Sodium Bicarbonate	Pancreatic cancer	Phase I/II (174)
SLC-0111	Colorectal cancer; lung cancer; clear cell carcinoma of the kidney; and sarcoma	Phase I (117)
G250 (NCT04969354)	Renal cell carcinoma	Recruiting
Lonidamine (NCT00435448)	Prostate cancer	Phase III (175)

TABLE 3 LDH and MCT inhibitors.

Mechanism of action	Compound	Cancers	Research status
MCT1/4	AZD3965	Breast and colon cancer, lymphoma xenografts, human diffuse large B-cell lymphomas, human B-cell lymphoma, lymphoblast, B-cell non-Hodgkin lymphoma, Raji Burkitt's lymphoma cells	Phase I and Preclinical (121, 122)
	α -Cyano-4-hydroxycinnamate	Glioma, breast cancer, pancreatic ductal adenocarcinoma	Preclinical (176–178)
	Syrosingopine	Breast, colon, cervical cancer, and leukemia cells	Preclinical (124)
	BAY-8002	Diffuse large B cell lymphoma	Preclinical (179)
	7ACC2	Pancreatic adenocarcinoma	Preclinical (180)
	AR-C155858	Breast cancer tumor xenografts	Preclinical (181)
	Diclofenac	Melanoma, cervical cancer, bladder cancer, colorectal cancer	Preclinical (126, 182)
	Gossypol (NCT02697344)	Multiple myeloma	Phase I
LDHA/LDHB	Galloflavin	Colorectal, endometrial, and breast cancer	Preclinical (143–145)
	1-(Phenylseleno)-4-(Trifluoromethyl) Benzene	Large cell lung cancer, breast cancer, hepatocellular carcinoma, malignant melanoma, colorectal adenocarcinoma, murine lung cancer cells	Preclinical (183)
	Oxamate	Colorectal, pancreatic, gastric, and non-small cell lung cancer	Preclinical (136–139)
	GSK 2837808A	Nasopharyngeal carcinoma, pancreatic cancer xenografts	Preclinical (184, 185)
	AZ-33	Breast cancer	Preclinical (186)
	GNE-140	Breast, colorectal adenocarcinoma, and lung cancer, glioma xenografts	Preclinical (187–189)
	Compound 24	Pancreas carcinoma	Preclinical (190)
	Compounds 5 and 11	Osteosarcoma	Preclinical (191)

LDH, lactate dehydrogenase; MCT, monocarboxylate transporter.

combination therapies with ICIs or glycolysis modulators, and employing nanoparticle delivery systems to improve tumor-specific targeting (130, 131). By addressing these challenges, MCT-targeted therapies can substantially improve cancer treatment outcomes by modifying tumor metabolism and restoring immune function. Furthermore, combining lactate-targeted strategies with ICIs offers a promising approach to counteract TME-induced immunosuppression, as discussed below.

2.2.3 Targeting LDH: Dual potential in metabolic and immune regulation

LDHA plays a crucial role in tumor metabolism by converting pyruvate to lactate, replenishing NAD⁺ for glycolysis, and acidifying the TME, all of which promote immune evasion and tumor growth. These functions render LDHA an appealing therapeutic target for disrupting tumor metabolic pathways and reducing TME-driven immunosuppression (132–135). LDH-targeting drugs are shown in Table 2.

Studies targeting LDHA have shown promising results in preclinical models. For example, both Oxamate (a competitive inhibitor) and FX11 (an inhibitor targeting the NADH binding site) reduced lactate production, decreased TME acidity, and

inhibited tumor growth in gastric, lymphoma, and pancreatic cancers (136–142). In addition, the combination of FX11 with the NAD⁺ production inhibitor FK866 enhanced antitumor activity via a dual metabolic blockade. New inhibitors, such as Galloflavin and N-hydroxyindole (NHI) derivatives, further expand LDHA inhibition strategies. Galloflavin has shown significant lactic acid inhibition in preclinical trials, whereas NHI derivatives address resistance to single-target inhibitors by targeting both LDHA and LDHB (143–146). Combining LDHA inhibitors with other therapies, such as metformin, has also shown promise in significantly inhibiting melanoma growth by increasing metabolic stress in tumor cells. Targeting LDHB offers additional therapeutic opportunities for cancers that rely on autophagy and lysosomal pathways (147, 148).

Despite these promising findings, a more critical evaluation of LDHA-targeted therapies is needed, particularly regarding the high drug concentrations required for effective inhibition because of the strong expression of LDHA in tumors (149). These high concentrations may lead to off-target effects in glycolysis-dependent healthy tissues, such as CTLs and NK cells, which could limit the overall efficacy of tumor immune control. Moreover, the strong expression of LDHA in immune cells like CTLs and NK cells can

impede their effector functions, thus reducing the therapeutic benefit of LDHA inhibition in immunotherapy. Future research should focus on developing selective inhibitors that can specifically target tumor cells while minimizing toxicity to immune cells, as well as exploring combination strategies with ICIs to enhance the therapeutic impact of LDHA inhibitors (150). Furthermore, advanced delivery technologies, such as nanoparticles, could help improve drug specificity and reduce systemic side effects (130).

2.2.4 Lithium carbonate-mediated metabolic reprogramming to enhance immune function

As mentioned previously, lactate can function as a carbon source to enhance oxidative phosphorylation in T cells. The role of lithium carbonate (LC) in this metabolic reprogramming process has been shown to significantly improve T-cell function in the TME. LC enhances T-cell function in the tumor microenvironment by facilitating lactate entry into mitochondria for ATP production, shifting energy metabolism from glycolysis to oxidative phosphorylation. This process improves mitochondrial function, counteracts lactate-induced immunosuppression, and supports T-cell survival and anti-tumor activity. LC also facilitates long-term T-cell memory formation and persistence in tumors, thereby addressing a major limitation of current cancer immunotherapies. In preclinical models, LC treatment was found to restore the effector functions of CD8⁺ T cells, increasing their ability to kill tumor cells and improving tumor control (151).

The ability to switch between different metabolic pathways based on carbon source availability is regulated by key signaling pathways such as mTORC1 and AMPK (152). These pathways control the balance between glycolysis and oxidative phosphorylation, directly affecting T-cell differentiation and function. Lithium carbonate's ability to enhance oxidative metabolism and reduce lactate-mediated suppression of T-cell function makes it a promising tool for enhancing the efficacy of ICIs and other immunotherapies (153).

In summary, promoting the mitochondrial use of lactate, as observed with lithium carbonate treatment, is a powerful strategy to boost CD8⁺ T cell metabolism, function, and persistence within the TME. This approach provides a comprehensive method to reprogram

T cells, enhance their anti-tumor activity, and potentially overcome the metabolic barriers that hinder current immunotherapeutic strategies. By targeting the metabolic pathways that regulate T-cell function, lithium carbonate offers a novel therapeutic route for improving T-cell-based therapies in cancer treatment. Nonetheless, as noted earlier, regulatory T cells, a specific subset of T cells, can be activated in environments with elevated lactate levels. In the therapeutic approaches outlined in this section, these cells may also be stimulated. Their immunosuppressive and tumor-enhancing properties could adversely affect treatment efficacy or result in other unforeseen complex outcomes. Consequently, these therapeutic strategies warrant additional research.

In conclusion, although current pharmacological strategies targeting lactate show good potential, they also face significant challenges, largely because the effects of these drugs tend to be widespread and not limited to specific cell populations. Therefore, to provide a clearer understanding of their therapeutic perspectives, we summarized the main strengths and limitations of the four lactate-targeted therapeutics mentioned above in Table 4.

3 Conclusions

Lactate metabolism plays a crucial role in tumor development and immune evasion and acts as a link between tumor metabolic reprogramming and the immunosuppressive TME. Targeting lactate metabolism presents a promising therapeutic approach, with preclinical data showing its potential to alter tumor glycolysis, reduce TME acidity, and boost antitumor immune responses. Strategies such as LDH and MCT inhibitors, particularly when combined with ICIs, have demonstrated synergistic benefits, paving the way for clinical application.

Future research should focus on improving the specificity of lactate-targeting therapies, exploring their role in various cancer types, and combining them with emerging treatments, such as CAR-T therapy. Developing biomarkers to guide patient selection is crucial for optimizing treatment outcomes. A deeper understanding of lactate metabolism and its integration with immunotherapy has the potential to transform cancer treatment by advancing precision medicine.

TABLE 4 Advantages and disadvantages of lactate-targeted therapies.

Therapies	Advantages	Disadvantages
Neutralizing Acidity	Enhancement of immune cell function, improvement of ICI efficacy, and potential for multimodal therapy	Non-specific effects, potential toxicity, limited efficacy
MCT Inhibition	Direct targeting of tumor metabolism, immunomodulatory effects, and enhanced ICI efficacy	Compensation mechanisms, systemic toxicity, risk of drug resistance
Targeting LDH	Dual mechanism of action, combined therapeutic potential, multi-target inhibition	High concentration requirement, immune cell suppression, risk of drug resistance
Lithium Carbonate-Mediated Metabolic Reprogramming	Synergistic effect, enhances ICI efficacy, possesses long-term immune memory, well-supported by extensive preclinical validation	Risk of resistance, clinical translation challenges
Integration of Lactate-Related Pathways with Immunotherapy	Synergistic effect, improves T cell function	Risk of resistance, clinical translation challenges

Author contributions

X-YG: Conceptualization, Writing – original draft, Writing – review & editing. J-LY: Investigation, Writing – original draft, Writing – review & editing. RL: Investigation, Writing – original draft, Writing – review & editing. Z-JZ: Funding acquisition, Visualization, Writing – review & editing. DT: Funding acquisition, Writing – review & editing. LH: Investigation, Writing – review & editing. L-JZ: Supervision, Writing – review & editing.

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