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Lactate at the crossroads of tumor metabolism and immune escape: a new frontier in cancer therapy

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Abstract
Lactate, initially considered a mere metabolic byproduct, has emerged as a pivotal metabolite in the tumor microenvironment (TME), playing critical roles across a range of pathological conditions. In tumors in particular, lactate contributes to disease progression through its multifaceted biological functions. Recent studies have further identified lactate as a central mediator in the regulation of tumor immune evasion. Tumor cells, via aerobic glycolysis, secrete large amounts of lactate, leading to acidification of the TME and suppression of antitumor immunity through various mechanisms, including immune cell inhibition, epigenetic reprogramming, and metabolic competition. These findings have fueled growing interest in targeting lactate as a therapeutic strategy against cancer, encompassing approaches such as LDHA inhibitors, MCT inhibitors, and novel nanomedicine-based therapies. In this review, we summarize lactate metabolism in the body, explore its impact on various immune cell populations, elucidate its functional roles in tumor biology, and highlight recent advances in antitumor strategies that target lactate.

Keywords Lactate, Lactylation, Tumor, Immune, Therapy

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Introduction

Lactate was first discovered in yogurt by the Swedish chemist Carl Wilhelm Scheele. Subsequently, Jöns Jakob Berzelius identified the accumulation of lactate in the muscles of living animals during exercise. In the following decades, Engelhardt further distinguished between two stereoisomers of lactate found in muscle tissue and beef, namely L-lactate and D-lactate [1]. Of these, L-lactate is the predominant enantiomer present in biological systems, whereas D-lactate is mainly produced as a metabolic byproduct by the gut microbiota. Historically, lactate was predominantly considered a metabolic byproduct with limited physiological significance. This conventional perspective underwent a paradigm shift in the early 20th century when Otto Warburg first characterized the phenomenon of hyperactive glycolysis in tumor cells, concurrently observing aberrant lactate

accumulation [2]. This seminal discovery catalyzed an exponential growth in lactate research, leading to the progressive identification of its pleiotropic functions. Contemporary evidence now establishes lactate as a crucial metabolic regulator with systemic impacts on energy homeostasis, intracellular signaling cascades, and immunomodulation. The multifaceted nature of this once-misunderstood molecule continues to be elucidated through ongoing scientific investigation.

Lactate exerts multifaceted pro-tumorigenic effects through diverse mechanisms, including modulation of signaling pathways, metabolic fueling, and immune regulation. With the rising prominence of immunotherapy, considerable research efforts have been directed toward elucidating lactate's immunomodulatory effects on various immune cell populations. The most groundbreaking advancement in lactate research in recent years has been the discovery of lactylation-a novel post-translational modification representing the intersection between metabolism and epigenetics [3]. This modification has been implicated in numerous pathological conditions, where it facilitates tumor progression by enhancing malignant proliferation, invasion, and therapy resistance [4]. Understanding and targeting this lactylation modification is crucial for developing effective therapeutics against cancer progression and novel combination treatment strategies [5, 6].

Given the extensive and profound biological impacts of lactate, a systematic synthesis of its immunoregulatory mechanisms is warranted. This review comprehensively examines: (1) the metabolic fate and pleiotropic functions of lactate in physiological and pathological contexts; (2) its differential effects on distinct immune cell subsets; and (3) current therapeutic strategies targeting lactate metabolism in oncology, including pharmacological interventions under investigation. Furthermore, we provide critical perspectives on future research in this rapidly evolving field.

Lactate production, metabolism, and transport

Lactate is one of the most important metabolic byproducts in the human body. In the early 20th century, it was widely believed that under sufficient oxygen conditions, intracellular glucose undergoes glycolysis-a series of enzyme-catalyzed reactions-to produce pyruvate. This pyruvate then enters aerobic respiration pathways, generating ATP and CO_2. In contrast, under hypoxic conditions, pyruvate is converted to lactate through the action of NADH and lactate dehydrogenase A (LDHA), serving as a compensatory mechanism for ATP production in the absence of adequate oxygen, a process known as anaerobic respiration [7]. In 1927, Otto Warburg proposed that cancer cells preferentially convert glucose to lactate even under normoxic conditions—a phenomenon later termed the Warburg effect [2]. Subsequent studies have shown that the Warburg effect also plays a significant role in various non-cancerous diseases [8]. In addition to lactate production via glycolysis, alternative metabolic pathways can also contribute to lactate generation. For example, glutaminolysis provides α-ketoglutarate, which can be converted into malate and subsequently into pyruvate, ultimately leading to lactate production [9] (Fig.1).

Lactate, by its nature, is an acidic compound. Excessive accumulation of lactate can lead to serious consequences, such as lactic acidosis [10]. Therefore, the body must rapidly clear lactate through metabolic processes to prevent disruption of intracellular homeostasis. Lactate is primarily metabolized by being oxidized to pyruvate via lactate dehydrogenase B (LDHB). Subsequently, pyruvate irreversibly enters the tricarboxylic acid (TCA) cycle through the action of pyruvate dehydrogenase, ultimately resulting in the production of carbon dioxide, water, and energy [11]. Additionally, in skeletal muscle tissue, lactate produced from glucose metabolism diffuses into the bloodstream and is subsequently transported to the liver, where it is converted back into glucose via gluconeogenesis. The newly synthesized glucose then re-enters the bloodstream and is taken up again by skeletal muscle for energy utilization. This metabolic process is known as the Cori cycle [12]. Additionally, a small amount of lactate is excreted from the body through the kidneys.

Contrary to its initial characterization as a mere metabolic waste product, lactate is now recognized to play important roles in energy homeostasis and signal transduction [13]. Lactate transport between cells primarily relies on monocarboxylate transporters (MCTs). MCTs belong to the solute carrier family 16 (SLC16), among which MCT1 and MCT4 are closely associated with lactate transport [14]. MCT1 mediates the proton-coupled transmembrane transport of short-chain monocarboxylates, facilitating lactate uptake into cells [15]. In contrast, MCT4 is a high-capacity transporter that enables lactate efflux under conditions of elevated lactate concentration [16]. Under normal physiological conditions, multiple MCT isoforms cooperate to ensure efficient lactate shuttling between glycolytic and oxidative cells, thereby maintaining lactate homeostasis across different cell types.

Elucidating the mechanisms of lactate production, metabolism, and transport is fundamental to understanding how lactate exerts its effects and how it can be targeted therapeutically. In tumor cells, particularly, the heterogeneity of the tumor leads to spatial variation in lactate production. Generally, regions closer to the tumor core exhibit higher lactate concentrations, thereby exerting more profound effects on tumor progression. Lactate transport enables its shuttling between cells, allowing even those with low lactate production to maintain

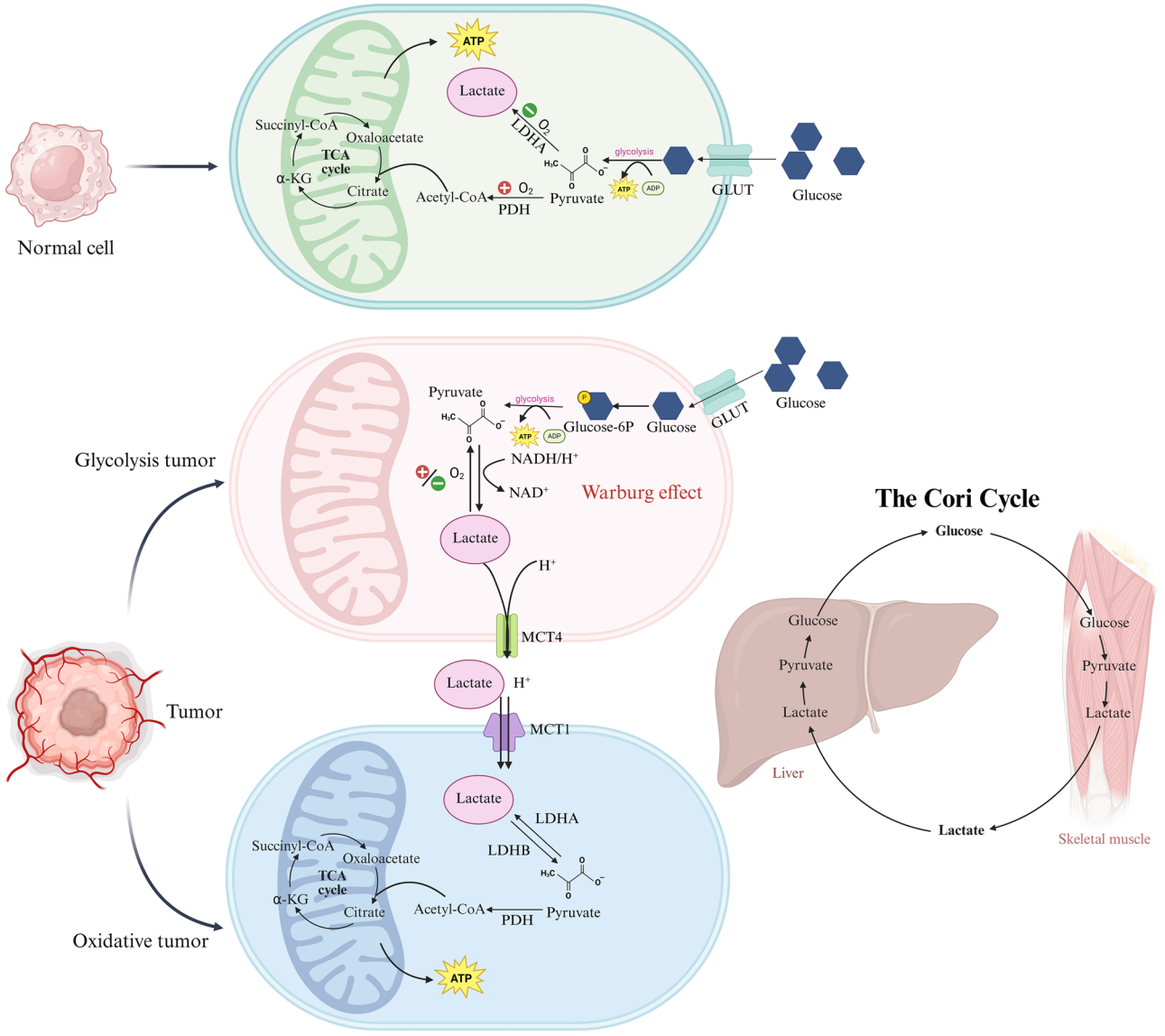

Fig. 1 Lactate production, metabolism, and transport. Glucose metabolism involves glycolysis in the cytoplasm and the TCA cycle in the mitochondria. Under normoxic conditions, normal cells primarily generate energy via the TCA cycle. Under hypoxic conditions, however, a substantial amount of lactate is produced in cytoplasm. Tumor cells, which often exhibit enhanced glycolysis, produce large quantities of lactate that are exported into the TME via MCT4. This lactate can then be taken up by oxidative tumor cells through MC, where it serves as an alternative energy substrate and enters the TCA cycle to sustain energy production. Cori cycle: During intense exercise, muscles produce lactic acid through glycolysis. Lactic acid enters the bloodstream, is taken up by the liver, and converted into glucose, which then enters the bloodstream for muscle use

elevated intracellular lactate levels. This metabolic sharing enhances energy utilization efficiency, which is crucial for sustaining the growth and development of cancer cells. Moreover, this intercellular lactate transfer resembles a mode of signal transmission—distinct from conventional signaling molecules, lactate functions more like a metabolic signal, influencing downstream cellular activities through energy-mediated pathways.

Biological functions of lactate

Energy carrier and metabolic hub

Cells primarily obtain energy through two pathways: oxidative phosphorylation and glycolysis. However, under hypoxic conditions, electron transfer within mitochondria is impaired, leaving glycolysis as the sole pathway for ATP production [17]. Traditionally, lactate was regarded as a metabolic waste product generated during rapid glucose metabolism to meet immediate energy demands [7]. With advances in research, lactate is now recognized as an active participant in energy metabolism and has even been identified as a major carbon source fueling the TCA

cycle in mammals [18–20]. For example, pharmacological inhibition of lactate shuttle between hypothalamic ependymal and glial cells disrupts energy homeostasis in pro-opiomelanocortin (POMC) neurons, indicating that these neurons preferentially utilize lactate rather than glucose as an energy substrate [20]. Cai et al. found that extracellular lactate accumulation stimulates mitochondrial electron transport chain activity, resulting in increased ATP synthesis, which subsequently suppresses glycolysis and enhances the utilization of respiratory substrates such as pyruvate [19]. Under glucose-deprived conditions, lactate supports NADPH production via isocitrate dehydrogenase 1, thereby enhancing metabolic flexibility [21]. Additionally, lactate significantly upregulates mitochondrial LDHA levels in $CD4^+$ T cells, leading to an increased intracellular 2-hydroxyglutarate (2HG)/α-ketoglutarate (α-KG) ratio [22]. Collectively, these findings highlight lactate as a crucial regulator of energy metabolism in the body.

Regulation of acid-base balance

As an acidic metabolite, lactate plays a crucial role in maintaining the body's acid-base balance. Under normal conditions, the physiological pH is approximately 7.4; however, when oxygen uptake or utilization is impaired, serum lactate concentrations can exceed 4 mmol/L, often accompanied by a blood pH below 7.35 and a reduction in bicarbonate levels, a condition known as lactic acidosis [23, 24]. Lactic acidosis can trigger a series of adverse physiological responses. For instance, Eliza et al. reported a significant correlation between lactate fluctuations and changes in insulin resistance [25]. In severe cases, lactic acidosis may lead to multiple organ failure and even death [24]. Moreover, in tumor cells, cancer cells can activate and upregulate proton and lactate transporters as well as exchangers to evade acid stress and even reverse the pH gradient, thereby promoting tumor progression [26].

Immunoregulatory molecule

Lactate acts as a double-edged sword in immune regulation. On one hand, activated immune cells require lactate to support their functions; on the other hand, lactate accumulation in the microenvironment can suppress immune cell activity [27]. For example, lactate inhibits the differentiation and maturation of dendritic cells (DCs), impairing their antigen-presenting capabilities [28]. It also induces M2 polarization of macrophages, which diminishes the production of pro-inflammatory cytokines [29, 30]. Moreover, lactate modulates the functions of basophils, neutrophils, and other immune cells [31, 32]. Consequently, lactate plays a critical role in immune regulation across various diseases, with its effects being particularly significant in tumor biology.

Epigenetic modifications

In 2019, Zhang et al. first identified lactylation, a novel post-translational modification mediated by lactate, which dynamically links cellular metabolic states to gene expression programs [3]. Specifically, similar to other post-translational modification (PTM) processes, lactylation is regulated by writers and erasers, and functions in coordination with readers. However, reports on lactylation-associated writers, erasers, and readers remain relatively scarce. For instance, Varner et al. identified lactyl-CoA as the substrate donor for lactylation in mammalian cells and tissues using liquid chromatography-mass spectrometry (LC-MS) [33]. Currently, only a limited number of writers—such as p300, GCN5, and HBO1—have been reported to catalyze lactylation [34–36]. Notably, these lactylation writers are not exclusive to lactylation but also catalyze other acylations. This functional versatility suggests that known epigenetic modifiers may similarly participate in lactylation, opening new avenues for mechanistic exploration and target discovery. Since the discovery of lactylation, an increasing number of studies have demonstrated its involvement in various diseases. For instance, Rho et al. found that the induction of hexokinase 2 expression in activated hepatic stellate cells (HSCs) is dependent on histone lactylation-mediated gene activation [37]. Wang et al. reported that histone lactylation promotes early distal activation of the reparative transcriptional response in monocytes, which is critical for establishing immune homeostasis and timely cardiac repair following myocardial infarction [36]. In cancer therapy, lactylation of NBS1, a key gene for genomic stability, has been implicated in chemotherapy resistance [38]. The discovery of lactylation pioneers a new paradigm in which metabolites directly regulate epigenetic modifications, yet its underlying mechanisms and biological significance warrant further investigation. Research on lactylation still faces many challenges. For instance, due to the structural similarity between lactylation and acetylation, traditional enzyme screening methods still encounter significant technical difficulties in achieving specific identification of lactylation. Moreover, the structural domains responsible for lactylation recognition have yet to be clearly defined. Further exploration is also needed regarding the writers, erasers, and readers of lactylation.

Signal molecule

Lactate functions as a signaling molecule by acting as an agonist of the G protein-coupled receptor GPR81, thereby mediating various biological functions [39, 40]. For example, lactate can inhibit the activation of YAP and NF-κB through GPR81-mediated signaling, suppressing the pro-inflammatory response of macrophages to LPS stimulation [30]. Laroche et al. demonstrated that lactate

and GPR81 play critical roles in the development of the visual nervous system [41]. Additionally, lactate can reprogram energy metabolism via GPR81 to regulate the malignant phenotype of breast cancer [42], and it drives breast cancer growth and invasiveness by modulating extracellular matrix (ECM) properties and Notch ligand signaling [43]. These findings highlight GPR81 as a key target for lactate-mediated signaling, significantly influencing cellular biological functions.

Moreover, lactate can participate in other metabolic pathways. For example, it can activate c-Myc to upregulate GLS1 expression, thereby enhancing glutamine uptake and metabolism in oxidative cancer cells [44]. Furthermore, lactate acts as a regulator of fatty acid oxidation. The accumulation of lactate can increase intracellular fatty acid synthesis while suppressing β-oxidation [45]. Although the precise mechanism by which lactate regulates fatty acid oxidation remains unclear, there is a clear association between lactate accumulation and impaired fatty acid oxidation [46]. Therefore, further studies are needed to investigate the role of lactate in other metabolic pathways.

Lactate exerts a wide range of functions, spanning from metabolic regulation to acting as a signaling molecule, underscoring its broad modulatory roles in physiological and pathological processes (Fig. 2). These functions are often interwoven and mutually influential. For instance, lactate alters the pH of the tumor microenvironment (TME), and the resulting acidity can further modulate the immune milieu by affecting the secretion and activity of immune-related factors. Notably, the recently identified process of lactylation has garnered considerable attention. To date, lactylation sites have been uncovered in various disease contexts, offering novel insights into potential therapeutic interventions. By inserting, removing, or modifying lactylation marks, it may be possible to

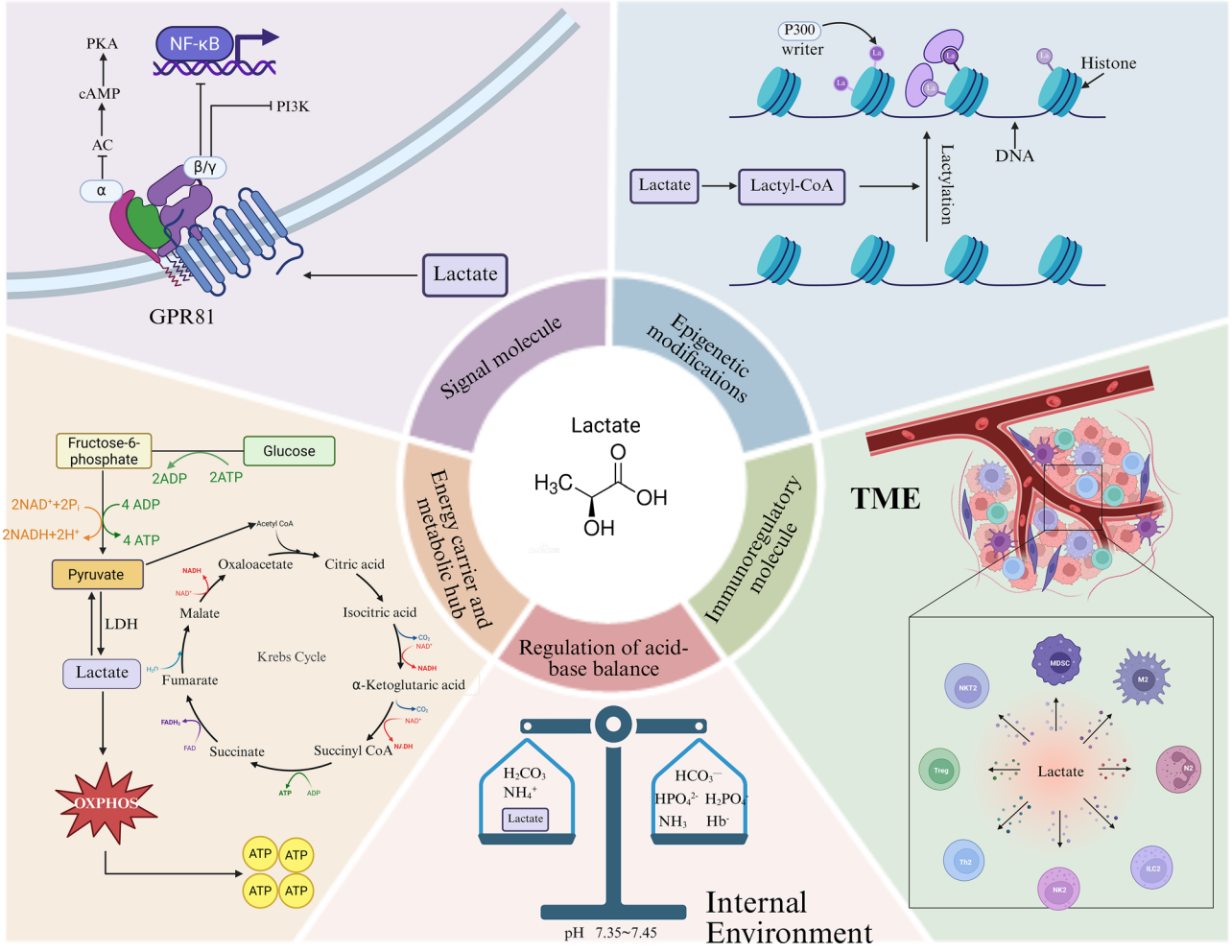

Fig. 2 Lactate function. Lactate serves a wide range of functions beyond its role as a key intermediate in energy metabolism. It not only contributes to ATP production through gluconeogenesis and the TCA cycle but also acts as a crucial regulator of immune responses. By modulating various immune cells within the TME, lactate helps establish an immunosuppressive milieu. In addition, lactate plays important roles in maintaining acid–base balance, mediating signal transduction, and regulating epigenetic modifications

alter epigenetic modifications of specific genes, thereby suppressing or even reversing disease progression. In this review, we focus specifically on the role of lactate in tumor immunity, aiming to elucidate how lactate shapes the immune landscape of tumors and to identify potential therapeutic targets based on these mechanisms.

Roles of lactate in cancer immunity

As mentioned earlier in the Warburg effect, cancer cells preferentially metabolize glucose into lactate [2]. Consequently, lactate concentrations in tumors are significantly higher than in normal tissues. Elevated lactate levels can influence tumor growth and the TME through various mechanisms. Among these, the interplay between lactate and tumor immunity is particularly noteworthy (Fig. 3).

In cancer, lactate affects immune cell functions in diverse ways, with its impact varying depending on the specific immune cell type. These effects can be either tumor-promoting or tumor-suppressing. Here, we discuss how lactate influences different immune cells according to their categories. We also summarize recent studies from the past five years on lactate's interactions with various immune cells, highlighting the underlying mechanisms and functional outcomes (Table 1).

T cell

Lactate can directly influence T cell-mediated immune responses and also mediate redox stress to limit T cell proliferation [62]. The effects of lactate vary significantly among different T cell subsets.

For $CD8^+$ T cells, lactate predominantly suppresses several key functions. Studies have shown that in non-small cell lung adenocarcinoma, lactate induces histone H3 lysine 18 lactylation (H3K18la), which activates the transcription of nuclear pore membrane protein 121 (POM121). This promotes MYC nuclear translocation and directly binds to the CD274 promoter, thereby upregulating PD-L1 expression, reducing the cytotoxicity of $CD8^+$ T cells, and facilitating tumor immune evasion [49]. In head and neck squamous cell carcinoma

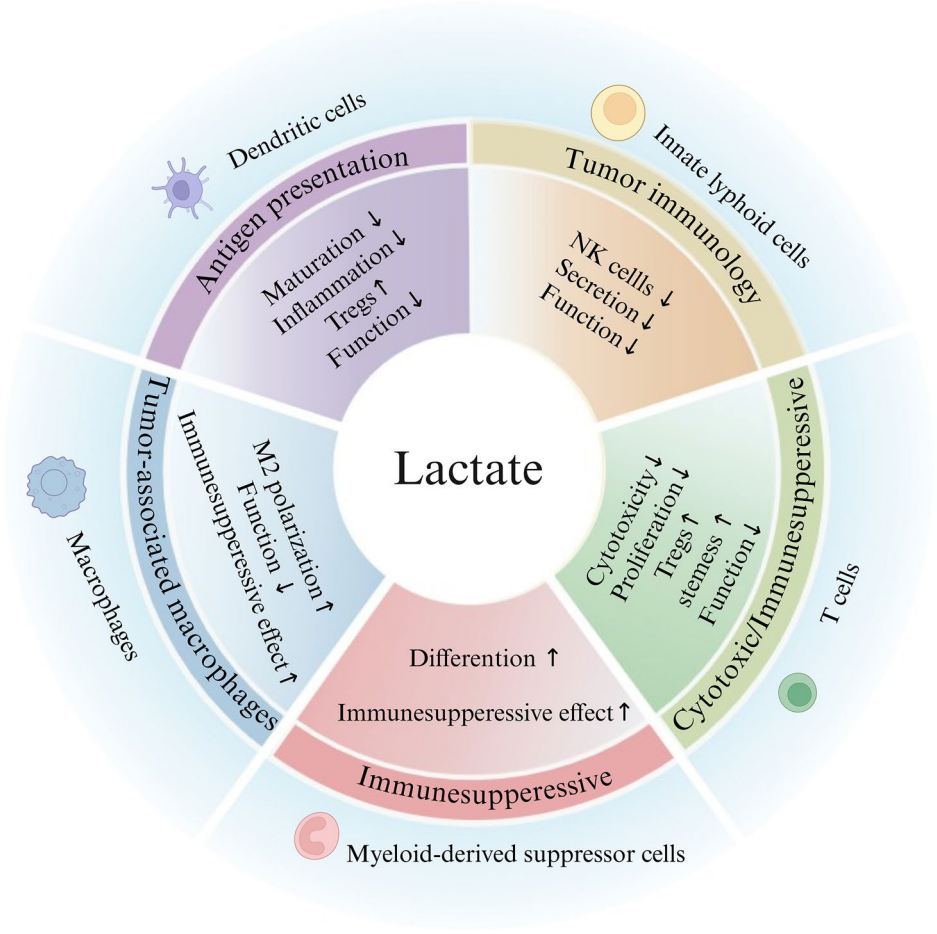

Fig. 3 Roles of lactate in cancer immunity. Within TME, lactate exerts diverse effects on various immune cell populations. It modulates both innate and adaptive immune responses by inhibiting the function of $CD8^+$ T cells, innate lymphoid cells, dendritic cells, and macrophages, thereby contributing to the establishment of an immunosuppressive milieu. Moreover, lactate promotes the differentiation and functional activity of Treg cells and MDSCs, enhancing their immunosuppressive capacity and further sustaining the immune evasion of tumor cells

Table 1 The impact of lactate in tumors on immune cells

Immune cell	Mechanism	Effect	Types of tumors	Reference
$CD8^+$ T	H3K18 and H3K9 lactylation	Activates $CD8^+$ T cells	Pan cancer	[47]
	Inhibits histone deacetylases	Increases stemness of $CD8^+$ T cells	Pan cancer	[48]
	H3K18 lactylation	Potentiates immune escape	NSCLC	[49]
	H3K9 lactylation activates the expression of IL11 in tumor cells	Promotes $CD8^+$ T cell dysfunction	HNSCC	[50]
	Activates transcription of circATXN7	Fosters tumor immunoescape	CRC	[51]
	Suppresses T cell activation by upregulating PD-L1 expression	Drives immunosuppression	AML	[52]
	Affects $CD8^+$ T cells' migration and infiltration ratio	Contributes to an immunosuppressive microenvironment	Glioblastoma	[53]
	Induces PD-L1 expression on neutrophils via MCT1/NF-κB/COX-2 pathway.	Decreases T cell cytotoxicity	HCC	[54]
	Drives the ESM1–SCD1 axis to inhibit the antitumor $CD8^+$ T-cell response by activating the Wnt/β-catenin pathway	Induce cisplatin resistance	Ovarian cancer	[55]
	Hampers the cytotoxic $CD8^+$ T cell's killing effect	Potentiates tumor immune escape	Cervical cancer	[56]
	Impairs the $CD8^+$ T cells antitumor immunity	Accelerate tumor immune evasion	GC	[57]
	Increases B7–H3 expression in tumor cells by H3K18 lactylation	Inhibits the antitumor immunity	HCC	[58]
	Promotes $CD8^+$ T cell exhaustion	Promotes immunosuppression	LUAD	[59]
	Upregulates TOX expression, leading to exhaustion of $CD8^+$ T	Promotes immunosuppression	AML	[60]
	Promotes T cell PD-1 expression	Promotes immunotherapy	NSCLC	[61]
T	Induce NAD^+ to NADH	Limits T cell proliferation	Pan cancer	[62]
	Suppresses T cell proliferation and cytokine production	Dampen T cells function	Pan cancer	[63]
Treg	Enhance MOESIN in Lys72 lactylation	Promotes the production and function of Treg cells	Pan cancer	[64]
	Promotes USP39-mediated RNA splicing to facilitate CTLA-4 expression in a Foxp3-dependent manner	Maintains the phenotype and functional status of Treg cells	CRC	[65]
	Increases TNFR2 expression	Enhances the immunosuppressive function of Treg cells	MPE	[66]
	Promotes PD-1 Tregs accumulation	Induce resistance of immune therapy	AML	[67]
	Promotes Treg cell proliferation	Aids immune evasion	NSCLC	[68]
	Modulates the PD1 expression of Treg cells	Enhances the immunosuppressive activities	GC	[69]
DC	Activates SREBP2 in tumor DCs and drives conventional DC transformation into mregDCs	Suppresses $CD8^+$ T cell responses and promotes Treg differentiation	Melanoma	[70]
	Inhibits DC maturation	Immunotherapy resistance	LUAD	[71]
	Impairs the Viability and Function of DC	Promotes immunotherapy	Melanoma	[72]
M	Promotes M2 polarization	Suppresses antitumor immunity	Lung adenocarcinoma	[73]
	Promotes M2 polarization	Suppresses antitumor immunity	HCC	[74]
	Promotes M2 polarization	Suppresses antitumor immunity	CRC	[75]
	Promotes M2 polarization	Inhibits $CD8^+$ T cell	Ovarian cancer	[76]
	Promotes M2 polarization	Leads to inhibition of T cell proliferation and cytotoxicity	CRC	[77]
	Redistribute M2-TAM subsets and upregulate PD-L1	Assists tumor immune escape	Pan cancer	[78]
	Upregulates NUPR1 expression via histone lactylation	Promotes immunosuppression	HCC	[79]
	Promotes M2 polarization	Promotes progression and metastasis	CRC	[80]
	Promotes histone lactylation within TAM,	Inhibited phagocytic capacity of activated TAM	Prostate Cancer	[81]
	Recruits TAMs or promotes M2 polarization of macrophages	Facilitates lung cancer progression	Lung cancer	[82]
	Reprograms TAM via histone lactylation, and polarizes them towards an immunosuppressive phenotype	Promotes immunosuppression	Prostate Cancer	[83]
	Promotes M2 polarization	Promotes the invasion	Pituitary adenoma	[84]
	Promotes M2 polarization	Promotes proliferation, migration, invasion, and mesenchymal transition	Glioma	[85]
	Histone lactylation inhibits RARγ expression in macrophages	Promotes colorectal tumorigenesis	CRC	[86]

Table 1 (continued)

Immune cell	Mechanism	Effect	Types of tumors	Reference
	Promotes M2 polarization	Promotes proliferation, migration, and chemoresistance	Breast cancer	[87]
	Promotes M2 polarization	Stimulates migration	Prostate cancer	[88]
	Induces M2 to macrophages secreted CCL8	Facilitates proliferation and metastasis	CRC	[89]
	Activates CCL18 expression via H3K18 lactylation in macrophages	Promotes tumorigenesis	Ovarian cancer	[90]
	Stimulates M2 polarization and HMGB1 secretion	Promotes CRC progression	CRC	[91]
	Induces macrophage polarization towards an M2-like phenotype and orchestrates GPNMB secretion	Facilitates tumor cell migration and invasion	Oral squamous cell carcinoma	[92]
	Promotes M2 polarization	Accelerates EC cell migration and proliferation	EC	[93]
	Inhibits the polarization process of inflammatory macrophages	Inhibits immune	Breast cancer	[94]
	Histone lactylation-driven GPD2 mediates M2 macrophage polarization	Promotes malignant transformation	Cervical Cancer	[95]
	Promotes protein lactylation	Promotes immunosuppressive microenvironment	Pancreatic ductal adenocarcinoma	[96]
	Inhibits M1 polarization and angiogenesis	Promotes Glioblastoma sensitivity to bevacizumab	Glioblastoma	[97]
	Induces nonhistone ENSA-K63 lactylation	Induces immunotherapy resistance	Pancreatic ductal adenocarcinoma	[98]
	Facilitates polarization of M2 macrophages	Leads to modifications in melanoma phenotypes	Melanoma	[99]
MDM	Intracellular lactate-driven histone lactylation promotes IL-10 expression	Promotes MDM immunosuppressive activity	Glioblastoma	[100]
γδT	Suppresses AMPK activation	Inhibits antitumor activity in γδT cells	Pan cancer	[101]
ILC	Enhances PD-1 expression on TbetNK1.1 ILCs within the TME	Dampened the mammalian target of mTOR signaling	Melanoma	[102]
MDSC	Enhances immunosuppressive phenotype of MDSCs after radiotherapy	Modulates Immunosuppression	Pancreatic cancer	[103]

Note: NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; CRC, colorectal cancer; AML, acute myeloid leukemia; HCC, hepatocellular carcinoma; GC, gastric cancer; LUAD, lung adenocarcinoma; MPE, malignant pleural effusion; EC, esophageal cancer; NAD, nicotinamide adenine dinucleotide; TNFR2, tumor necrosis factor receptor 2; PD-L1, programmed death-ligand 1; CCL, CC chemokine ligand; HMGB1, high mobility group box 1; AMPK, AMP-activated protein kinase

(HNSCC), lactate promotes H3K9 lactylation, which enhances IL-11 expression and activates the JAK2/STAT3 signaling pathway, leading to $CD8^+$ T cell dysfunction [50]. Interestingly, Raychaudhuri et al. reported that histone lactylation can also positively regulate $CD8^+$ T cell metabolism and function. Specifically, targeting the metabolic and epigenetic pathways that regulate H3K18 and H3K9 lactylation impacts the effector functions of $CD8^+$ T cells, thereby activating antitumor immunity [47]. Feng et al. further demonstrated that lactate enhances $CD8^+$ T cell stemness and improves antitumor immunity [48]. Additionally, Quinn et al. reported that lactate inhibits T cell proliferation by modulating the NAD(H) redox state, thereby suppressing the immune environment [62]. These seemingly contradictory observations may be due to the complex interplay between histone lactylation and other post-translational modifications in shaping the transcriptional landscape of $CD8^+$ T cells, as well as confounding effects of acid protons generated by glycolysis. Further studies revealed that lactate-mediated suppression of $CD8^+$ T cells primarily results from proton-induced acidification of the TME. Compared to equimolar lactate, free lactic acid significantly reduces cytokine production in $CD8^+$ T cells—an effect reversible upon alkaline buffer supplementation [104]. Intriguingly, subsequent work demonstrated that when lactate's acidifying effect is neutralized, it can serve as a physiological carbon source to enhance stem-like properties in $CD8^+$ T cells [48]. These findings collectively indicate that lactate dually modulates $CD8^+$ T cell function through both pH-dependent and metabolic mechanisms, suggesting these pathways should be investigated independently in physiological contexts. Notably, endogenous and exogenous lactate exert differential effects on T cells.

Although lactate generally impairs immune cell function, regulatory T cells (Tregs) represent a notable exception. Tregs play a critical role in maintaining the immunosuppressive TME, which in turn promotes their differentiation, proliferation, and functional enhancement [105]. Gu et al. found that lactate promotes Treg

generation and function by enhancing the lactylation of MOESIN, thereby facilitating tumor progression [64]. Ding et al. demonstrated that lactate regulates RNA splicing to promote CTLA-4 expression in tumor-infiltrating Tregs, sustaining their immunosuppressive activity [65]. Xue et al. further showed that lactate increases TNFR2 expression, enhancing Treg-mediated immunosuppression [66]. Collectively, Tregs exhibit superior adaptability to high-lactate environments, suggesting they may be key contributors to tumor immune evasion. However, the molecular mechanisms underlying lactate's regulation of Tregs remain underexplored, representing a promising avenue for future tumor immunotherapy research.

As innate T cells, γδ T cells are also crucial in tumor immune surveillance [106]. Mu et al. discovered that high glucose induces lactate accumulation within γδ T cells, which inhibits AMPK activation and subsequently impairs their antitumor activity [101].

Dendritic cell

Dendritic cells (DCs) are the most important antigen-presenting cells and key players in antitumor immune responses. They efficiently capture, process, and present antigenic information to $CD8^+$ T cells [107]. It has been reported that lactate can induce the differentiation of DCs into tolerogenic DCs. Specifically, tumor-derived lactate drives the activation and nuclear translocation of SREBP2, transforming DCs into $CD63^+$ mregDCs, which subsequently suppress $CD8^+$ T cell activity and promote Treg differentiation, ultimately facilitating tumor progression [70]. Moreover, Qiu et al. found that dysregulated lactate metabolism inhibits DC maturation, leading to tumor resistance to immunotherapy [71]. Additionally, Sangsuwan et al. identified a lactate-regulated signaling network in DCs and discovered that lactate exposure disrupts the STAT3, ERK, and p38 MAPK signaling cascades in DCs [108], which is critical for developing more effective antitumor therapies. On the other hand, lactate has been reported to reduce IL-12 p40 expression in DCs, an anti-inflammatory effect that may contribute to the conversion of immunologically "hot" tumors into "cold" tumors [109].

Macrophage

Macrophages switch their phenotypes according to their local microenvironment. It has been reported that tumor-derived lactate promotes M2 polarization of macrophages, thereby facilitating tumor growth [110]. For instance, lactate secreted by lung adenocarcinoma cells enhances M2 macrophage polarization and suppresses T cell function, leading to inhibition of antitumor immunity [73]. The tumor-produced lactate induces lactylation at histone H3K18 in macrophages upon lactate uptake, which activates transcription and enhances the pro-tumoral activity of macrophages [74]. Additionally, studies have shown that glucose-driven histone lactylation promotes the immunosuppressive function of monocyte-derived macrophages in glioblastoma [100]. Beyond direct effects, lactate can also influence macrophages indirectly. For example, Gu et al. reported that lactate first induces cancer-associated fibroblasts (CAFs) within the TME to secrete IL-8, which subsequently mediates tumor-associated macrophage (TAM) recruitment and M2 polarization, further driving TME remodeling and lung cancer progression [82].

Lactate modulates macrophage metabolism and immune regulatory functions, thereby negatively impacting tumor-associated immune responses. Therefore, targeting lactate-related metabolic pathways in macrophages to reverse these adverse effects represents a promising strategy to remodel the TME.

Innate lymphoid cells

Innate lymphoid cells (ILCs) constitute the first line of defense and are classified into five subsets, including natural killer (NK) cells and group 2 innate lymphoid cells (ILC2s), among others. NK cells exert antitumor effects by directly secreting cytokines and granzymes, making them important targets in cancer immunotherapy [111]. It has been reported that lactate enhances PD-1 expression on ILCs within the TME, leading to reduced secretion of IFN-γ and granzymes, thereby promoting tumor growth [102], and lactate could inhibit the function of invariant natural killer T (iNKT) cells, suppressing their antitumor responses, potentially through a phosphodiesterase-5 dependent pathway [112].

Notably, since ILCs are preferentially enriched in barrier tissues such as the skin [113], they may have heightened relevance in skin cancers. Over the past five years, studies investigating the interaction between lactate and ILCs have been scarce. Critical questions remain unanswered, including which molecular mechanisms underlie lactate's regulation of ILC phenotypes, how lactate induces metabolic reprogramming in ILCs, and whether targeting lactate-mediated modulation of ILCs could serve as a novel strategy for cancer therapy. These issues warrant further in-depth investigation.

Myeloid-derived suppressor cells (MDSC)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immunosuppressive cells that expand during cancer progression and exhibit potent ability to inhibit T cell responses [114]. It has been reported that malignant tumors produce high concentrations of lactate, which promotes the development of MDSCs and subsequently suppresses the functions of NK cells and T cells [115]. In the context of cancer therapy, lactate cumulated within MDSCs modulates

immunosuppression contributed to radiotherapy resistance in pancreatic cancer [103]. As critical regulators of tumor immunity, MDSCs play pivotal roles in immune evasion and other processes. Therefore, targeting MDSCs to reduce their immunosuppressive effects represents an effective therapeutic strategy against tumors.

Furthermore, although this review primarily focuses on the role of L-lactate, D-lactate also influences immune cells. For example, D-lactate could remodel the TME in hepatocellular carcinoma by converting M2 TAMs into the M1 phenotype [116]. Additionally, D-lactate has been reported to enhance DNA repair and modulate chemoresistance in cervical cancer cells via histone deacetylase inhibition and activation of hydroxycarboxylic acid receptor 1 [117].

Lactate is a defining feature of the TME and has long been considered a hallmark of malignant tumors. This close association has driven extensive research into how lactate contributes to tumor biology. Accumulating evidence has shown that lactate plays indispensable roles in tumor growth, invasion, and therapeutic resistance. As immunotherapy gains increasing prominence in cancer treatment, growing attention has been directed toward understanding the impact of lactate on tumor immunity, with the aim of enhancing the efficacy of immunotherapeutic strategies.

Collectively, current findings highlight the pivotal roles of lactate and lactylation in shaping immune cell function and the broader TME. Notably, the effects of lactate often extend beyond single immune cell types, simultaneously influencing multiple immune populations through its diverse functional mechanisms. This suggests that targeting lactate could exert multifaceted immunomodulatory effects within the tumor ecosystem. However, given the heterogeneity of TMEs across different tumor types, including variation in immune cell composition, the role of lactate may differ significantly between contexts. Furthermore, under certain conditions, lactate may even activate anti-tumor immune responses. This functional duality presents both challenges and opportunities for therapeutic intervention. A key question remains: how can we steer lactate's effects toward promoting antitumor immunity?

To address this, future studies must delve deeper into the intricate mechanisms underlying lactate's influence on tumors, including its impact on the composition of the extracellular matrix and other components of the TME. A more comprehensive understanding of the interplay between lactate and the immune landscape will be essential to fully elucidate its role in tumor progression and to harness its potential for cancer therapy.

Therapy targeting lactate in tumors

As one of the most abundant metabolites in the TME, lactate has been identified as a key mediator of immunosuppression and can promote tumor immune evasion through multiple mechanisms. Therefore, targeting lactate metabolism and lactylation modifications has become a critical strategy in cancer immunotherapy. For example, approaches such as inhibiting lactate production, blocking lactate transport, and modulating epigenetic modifications are employed to treat tumors or enhance their sensitivity to therapies. Here, we summarize current antitumor studies targeting lactate and lactylation, categorizing them based on their therapeutic mechanisms (Table 2 , Fig. 4)

Targeting lactate production

Considering the critical role of lactate itself in tumor immunity, inhibiting lactate production can effectively reduce lactate levels and consequently diminish its associated effects. LDHA is a key enzyme involved in lactate generation, catalyzing the conversion of pyruvate to lactate. Tumor cells rely on LDHA to bypass oxidative phosphorylation, thereby promoting cancer cell proliferation [174]. Therefore, targeting LDHA may represent a promising therapeutic strategy for cancer treatment. However, due to its non-selective toxicity, the clinical application of LDHA inhibitors may face limitations. Moreover, given tumor heterogeneity, further evaluation of LDHA's effects across different tissues and pathological tumor types is warranted.

Targeting lactate transport

Tumor cells primarily rely on MCT1 for lactate efflux and MCT4 for lactate influx [175], and the expression of MCTs is often upregulated in cancer cells [176]. Therefore, targeting MCT-mediated lactate shuttling presents a potential therapeutic approach for cancer. Compared to LDHA inhibitors, MCT inhibition may offer improved safety. For example, inhibiting MCT4 can prevent lactate export, leading to intracellular lactate accumulation, which may cause intracellular acidosis and cell death. Importantly, such MCT inhibition appears not to harm human T cells [177]. It should be noted that early MCT inhibitors lacked subtype selectivity, which could result in nonspecific adverse effects. Newer MCT inhibitors exhibit higher selectivity for individual MCT isoforms, thereby enhancing therapeutic efficacy while reducing side effects.

Furthermore, MCT transporters require chaperone proteins from the immunoglobulin superfamily for proper localization to the cell membrane. Specifically, MCT1 and MCT4 need to bind to CD147 to be correctly expressed on the cell surface [178]. CD147 expression is also regulated by MCT proteins, and this mutual

Table 2 Targeting lactate for tumor therapy

Targets	Drug	Type of tumors	Phase	ID	Reference
LDHA	FX11	Lymphoma, pancreatic cancer	-	-	[118, 119]
	Gossypol	Proneural subtype glioblastoma multiforme	II	NCT00540722	[120]
	Oxamate	Glioblastoma, neuroblastoma, NSCLC	-	-	[121–123]
	Galloflavin	Burkitt lymphoma	-	-	[124]
	N-hydroxyindole base	Pancreatic cancer	-	-	[125]
	stiripentol	Glioblastoma	-	-	[126]
	Sulforaphane	NSCLC prostate cancer	II	NCT03232138 NCT03517995	[127, 128]
	Coptis chinensis and dried ginger herb combination	GC	-	-	[129]
	Aspirin	CRC	III	NCT00002527	[130]
	Sodium butyrate	CRC	-	-	[131]
	Organic arsenical PDT-BIPA	-	-	-	[132]
	Nanodrugs incorporating LDHA siRNA	CRC	-	-	[133]
	JQ1	Ovarian cancer	-	-	[134]
	Jolkinolide B	Melanoma	-	-	[135]
	Momordicine-I	HNSCC	-	-	[136]
	Tanshinone	Ovarian cancer	-	-	[137, 138]
	Myristica fragrans	Lung cancer	-	-	[139]
	GSK2837808A	-	-	-	[140]
	Ginsenoside F2	Cervical cancer	-	-	[141]
	MS6105	Pancreatic cancer	-	-	[142]
	Diclofenac	-	II	NCT05641246	[143]
	Jiedu Sangen decoction	CRC	-	-	[144]
	1-(Phenylseleno)-4-(Trifluoromethyl) Benzene	CRC	-	-	[145]
	Carfilzomib	Esophageal squamous cell carcinoma	IV	NCT03934684	[146]
	Dimethyl itaconate	Thymic carcinoma	-	-	[147]
MCT1/4	Quercetin	Breast cancer	I	NCT04267874	[148]
	Syrosingopine	Breast cancer, pharyngeal squamous cell carcinoma	-	-	[149]
	Synthesis	-	-	-	[150]
	CHC	Breast cancer	-	-	[151]
	7-aminocarboxycoumarins	Cervical tumors, CRC	-	-	[152]
	DIDS	Lung cancer	-	-	[153]
	Lonidamine	Melanoma	-	-	[154]
CD147	AC-73	AML	-	-	[155]
	Metuzumab	Lung cancer	-	-	[156]
	CD147-Targeted Nanoparticles Carrying Phenformin	Lung cancer	-	-	[157]
MCT1	AR-C155858, AZD3965	Breast cancer, B-cell malignancies	I	NCT01791595	[151, 158–161]
	BAY8002	-	-	-	[162, 163]
	SR13800	Ovarian cancer	-	-	[164]
MCT4	VB124	HCC	-	-	[165]
	Acriflavine	Glioblastoma	-	-	[166]
	Wogonin	GC, melanoma	-	-	[167, 168]
Lactylation	Fargesin	NSCLC	-	-	[169]
	Oxamate	Glioblastoma	-	-	[121]
	Tanshinone I	Ovarian cancer	-	-	[137]
	Dexmedetomidine	Glioblastoma	-	-	[170]
	Mannose	Bladder cancer	-	-	[171]
	Demethylzeylasteral	HCC	-	-	[172]
	Royal jelly acid	HCC	-	-	[173]

Note: NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; CRC, colorectal cancer; AML, acute myeloid leukemia; HCC, hepatocellular carcinoma; GC, gastric cancer

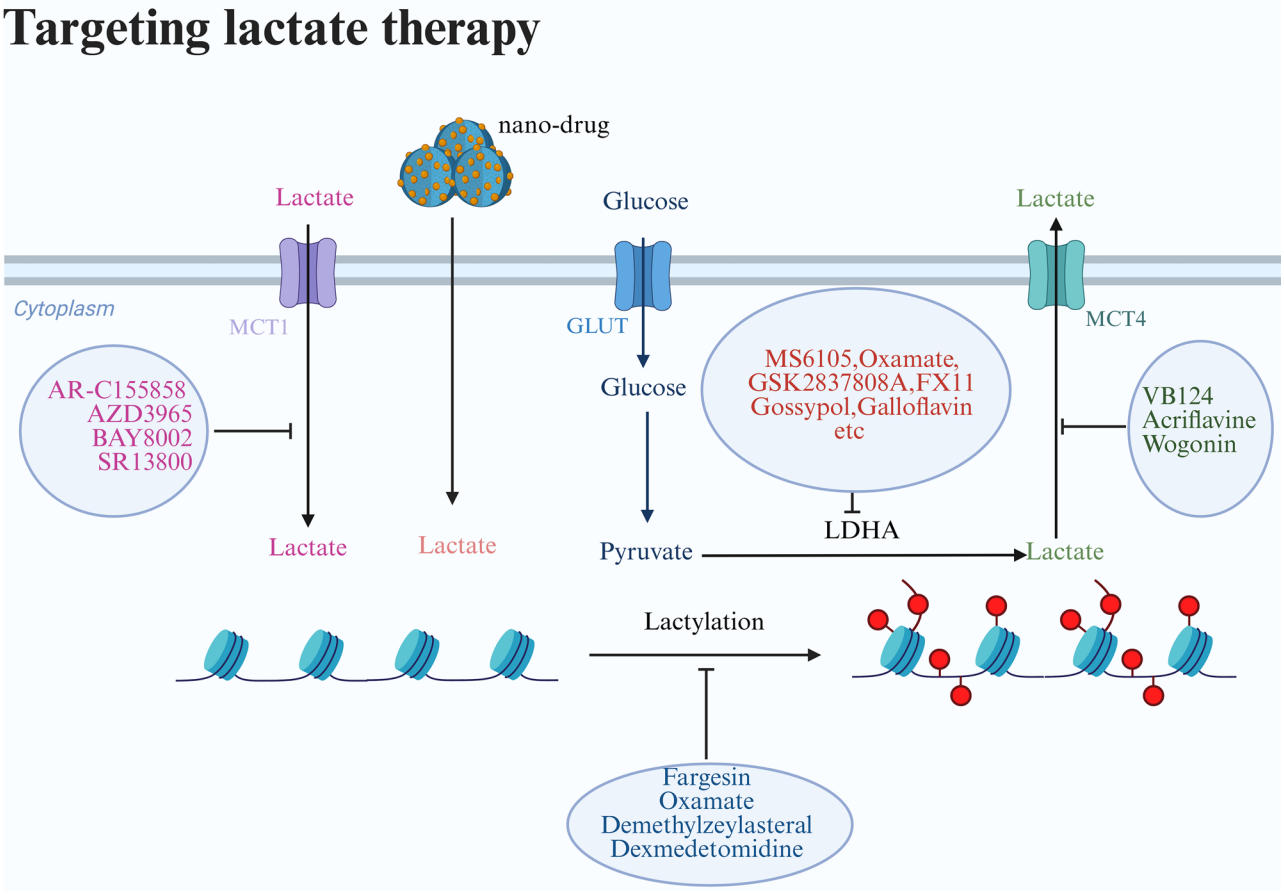

Fig. 4 Therapy targeting lactate in tumors. Therapeutic strategies targeting lactate production, metabolism, transport, and protein lactylation are emerging as promising approaches in cancer treatment

interaction stabilizes both molecules [179]. Hence, targeting CD147 is another promising anti-tumor strategy. However, CD147 also interacts with other proteins such as matrix metalloproteinases and integrins [180]. Therefore, for more precise targeting of lactate transport, specifically disrupting the MCT–CD147 interaction may be necessary to achieve effective anti-cancer therapy.

Targeting lactylation

Targeting lactate production and transport is a crucial approach for cancer treatment and improving prognosis, while the discovery of lactylation offers a new avenue in the field of anti-tumor therapy. It has been reported that AARS1 and AARS2 act as intracellular lactate sensors and function as lactyltransferases playing important roles [181]. Blocking AARS with β-alanine can reduce lactylation of P53, thereby inhibiting tumorigenesis [182]. Additionally, Pan et al. found that Demethylzeylasteral suppresses the tumorigenicity of liver cancer stem cells by inhibiting histone lactylation [172]. These findings suggest that targeting lactylation is a promising cancer treatment strategy. Its advantage lies in the ability to target specific molecules or particular modification sites, resulting in less impact on normal cells. However, as a bridge between metabolism and epigenetics, research on lactylation is still in its infancy, and further studies are needed to elucidate its role in cancer.

Although lactylation holds significant potential as a therapeutic target, it still faces considerable limitations. For instance, broad-spectrum modification inhibitors may lead to off-target effects. Consequently, the precise targeting of lactylation sites—without interfering with other post-translational modifications (e.g., methylation, acetylation)—poses a major challenge for drug development. Moreover, the precise detection of lactylation remains a major limitation. To ensure accurate measurements, potential false-positive results caused by other modifications must be minimized. Additionally, since lactylation levels are highly sensitive to rapid fluctuations in intracellular lactate concentration, cellular metabolic shifts may further complicate its detection. Furthermore, lactylation occurs on both histone and non-histone proteins, meaning that systemic inhibition of lactylation could disrupt normal metabolic and epigenetic regulation, potentially leading to adverse effects such as immune dysregulation. Therefore, future research

should prioritize the development of lactylation-specific probes and more reliable detection methods to address these challenges.

Other durgs

Although research on LDH and MCT inhibitors is gradually advancing, there is growing concern that these inhibitors may disrupt normal cellular metabolism and cause severe nonspecific side effects due to the presence of related physiological processes in normal cells. For example, FX-11 has been shown to inhibit human pancreatic cancer xenografts but also exhibits nonspecific cytotoxicity [118]. Considering this, besides the direct targeting of lactate-related pathways, researchers are increasingly focusing on altering other indirect effects caused by lactate to treat tumors.

For instance, Chen et al. developed novel poly(acrylic acid) (PAA)-coated, doxorubicin (DOX)-loaded layered double hydroxide (LDH) nanosheets (NSs), which can neutralize the acidic TME caused by lactate, repolarize TAMs towards the M1 phenotype, and activate $CD8^+$ T cells, showing potential for chemotherapy and immunotherapy [183]. Similarly, Ruan et al. designed a calcium peroxide (CaO_2)-loaded nanostructure that not only depletes lactate but also generates oxygen, remodeling the acidic and hypoxic TME and reducing lactate production at its source [184].

It is important to note that these treatment strategies often involve combination therapies rather than single-agent treatments. For example, LDHA inhibitors can be combined with MCT1 inhibitors or PDK1 inhibitors, potentially producing synergistic effects greater than the sum of their parts [185, 186]. Additionally, nanoformulations incorporating LDHA siRNA combined with oxaliplatin have been used for colorectal cancer therapy [133].

Despite the promising potential of lactate-targeted therapies, this field is still developing. Most current approaches focus on lactate production and transport, with relatively few reports targeting lactylation modifications. Targeting either lactate or lactylation for clinical therapeutic applications still faces substantial challenges. For instance, since lactate metabolic pathways are ubiquitously present in normal tissues, systemic targeting of these pathways may induce significant off-target effects, including ocular retinopathy, pulmonary complications, and metabolic acidosis [159]. Moreover, systemic suppression of lactate may disrupt organismal energy and homeostatic balance, potentially leading to lactic acidosis or organ dysfunction. Therefore, alternative strategies must be developed to target lactate without compromising normal metabolic functions, such as the use of reversible inhibitors that allow temporal modulation of lactate activity. Clinically, tumor heterogeneity and phenotypic variability limit the applicability of specific drugs. For example, poorly perfused tumor regions tend to rely on glucose metabolism and secrete large amounts of lactate, while well-perfused areas may more efficiently utilize lactate. Different tissues also vary in their dependence on glycolysis, which could lead to diverse lactylation profiles. Furthermore, given the metabolic plasticity of cancer cells, tumor populations may activate alternative metabolic pathways to compensate for inhibited lactate metabolism. This adaptive resistance mechanism suggests that combinatorial targeting of multiple metabolic pathways could represent a viable therapeutic strategy for cancer treatment. Moreover, due to lactate's multifunctional roles, modulating lactate levels may have widespread systemic effects. The complexity of the TME further complicates potential outcomes. Overcoming these challenges remains a major hurdle for the advancement of lactate-targeted cancer therapies.

Future perspectives and conclusion

Lactate is an important cellular metabolite that provides fuel for the TCA cycle and supplies energy to tumor cells. Its multifunctionality means that metabolic changes in lactate affect tumor progression in various ways. Beyond the direct molecular effects of lactate itself, it also influences the TMEs pH, redox state, signaling pathways, and more, thereby promoting tumor progression and invasion. All these aspects highlight the critical role of lactate in tumors. Given the accumulating evidence of lactate's pivotal role in tumor progression and immune modulation, monitoring lactate levels within the TME may offer a valuable approach for evaluating tumor status. Thus, lactate holds promise not only as a metabolic marker of disease progression but also as a prognostic indicator in cancer. Emerging evidence supports the clinical relevance of lactate in cancer management. For instance, multiple studies have established lactate-based prognostic models for nasopharyngeal carcinoma [187]. Additionally, novel lactylation-related signatures have been developed to predict overall survival (OS), immune status, and therapeutic response in pancreatic cancer patients [188]. Several registered clinical trials (NCT01138813, NCT01881386) further validate the clinical utility of lactate-related biomarkers. These findings collectively position lactate as a promising biomarker that could inform new strategies for cancer immunotherapy. Concurrently, lactate detection technologies have evolved significantly- progressing from conventional biochemical assays to advanced modalities including Magnetic Resonance Spectroscopy (MRS) and nanotechnology-based approaches. These technological advancements provide crucial tools to facilitate clinical translation. In tumor immunity, lactate exerts a significant impact, especially on the functions of T cells and macrophages. Deeper investigations into the mechanisms of lactate and lactylation, as well as their effects on tumor

immunity, can provide broader perspectives on immune evasion and cancer therapy. This review primarily focuses on the immunosuppressive role of lactate and lactylation in tumor immune regulation. However, it is important to note that under certain conditions, lactate and its associated modifications can also activate immune cells and enhance antitumor immunity. This duality complicates the development of therapeutic strategies that aim to harness the beneficial effects of lactate while minimizing its detrimental impacts. In addition, the spatial and temporal dynamics of lactate within the TME must be carefully considered, as its effects may vary depending on the tumor region and stage. Given the current advancements in artificial intelligence (AI), an intriguing future direction would be to employ AI algorithms to construct predictive models of lactate-mediated effects. By integrating large-scale multi-omics and clinical datasets, such approaches could facilitate the identification of optimal therapeutic strategies targeting lactate, offering a novel avenue for precision oncology. Furthermore, investigating combination therapies targeting lactate metabolism with PD-1/PD-L1 checkpoint inhibitors may offer a novel strategy to overcome immunotherapy resistance in cancer treatment [189].

Given lactate's role in tumor metabolism and its profound effects on immune cells, targeting lactate and lactylation has emerged as a promising cancer treatment strategy. By reducing lactate production in tumors and blocking lactate efflux, the interaction between lactate and tumors can be disrupted, preventing the TME from developing into an immunosuppressive state. Despite its great therapeutic potential, most related treatments are still in the preclinical stage and require further clinical trials to evaluate their efficacy. Moreover, rational drug combinations targeting multiple pathways should be considered to avoid tumor resistance and improve overall therapeutic outcomes. It is important to recognize that targeting lactate and lactylation presents several additional challenges. For instance, due to the systemic nature of lactate metabolism and transport, therapeutic interventions aimed at disrupting lactate signaling may lead to non-specific toxicities. This underscores the need to carefully evaluate the long-term adverse effects of such therapies to ensure minimal damage to normal tissues. To address this issue, recent studies have explored the use of nanotechnology to develop nanoparticle-based delivery systems encapsulating lactate-targeting agents. These systems enable precise delivery of therapeutics to tumor tissues, thereby reducing systemic side effects.

Moreover, current research on lactylation has primarily focused on histone modifications, while investigations into non-histone lactylation remain limited. Expanding our understanding of non-histone lactylation may uncover novel insights into lactate-mediated tumor immune regulation. A key objective in elucidating the mechanism of lactylation is the identification of specific modification sites. However, existing mass spectrometry-based approaches for detecting protein modifications are often complex and inefficient. Thus, developing more convenient and accurate methods for predicting lactylation sites represents a critical area of research. Furthermore, it remains unclear whether lactylation, as a post-translational protein modification, can also occur at the levels of DNA replication or transcription to directly influence gene expression. A deeper understanding of lactylation may ultimately reveal novel therapeutic strategies for enhancing antitumor immunity.

In summary, although lactate represents a vast potential "goldmine" for tumor treatment, the field is still in its early stages and requires significant effort to explore. A comprehensive understanding of lactate metabolism, functions, and its impact on immune cells is crucial for developing more effective and precise drugs and for designing more comprehensive clinical treatment strategies.

key open questions and future research priorities regarding lactate in cancer immunity

1. Comprehensive investigation into the dual immunomodulatory roles of lactate and protein lactylation across diverse immune cell populations
2. Development of lactylation-specific modulators (agonists/inhibitors) with high target selectivity to minimize off-target effects
3. The strategic integration of lactate metabolism modulation with immunotherapy represents a promising frontier in combinatorial cancer treatment.
4. The inherent complexity of the TME coupled with substantial tumor heterogeneity presents significant challenges for the clinical application of metabolism-targeting therapeutics.

Abbreviations

TME Tumor microenvironment
LDH Lactate dehydrogenase
MCT Monocarboxylate transporters
ATP Adenosine triphosphate
NADH Nicotinamide adenine dinucleotide
NADPH Nicotinamide adenine dinucleotide phosphate
TCA Tricarboxylic acid
TAM Tumor-associated macrophage
MDSCs Myeloid-derived suppressor cells

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