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REVIEW

Burning lactic acid: a road to revitalizing antitumor immunity

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Abstract **Lactic acid (LA) accumulation in tumor microenvironments (TME) has been implicated in immune suppression and tumor progress. Diverse roles of LA have been elucidated, including microenvironmental pH regulation, signal transduction, post-translational modification, and metabolic remodeling. This review summarizes LA functions within TME, focusing on the effects on tumor cells, immune cells, and stromal cells. Reducing LA levels is a potential strategy to attack cancer, which inevitably affects the physiological functions of normal tissues. Alternatively, transporting LA into the mitochondria as an energy source for immune cells is intriguing. We underscore the significance of LA in both tumor biology and immunology, proposing the burning of LA as a potential therapeutic approach to enhance antitumor immune responses.**

Keywords lactic acid; metabolism; tumor immunotherapy

Introduction

Lactic acid (LA) is an organic acid consisting of carboxyl (COOH) and hydroxyl (OH) groups in the chemical formula ($C_3H_6O_3$) and can dissociate into lactate anions and protons (H^+). It has a well-documented history of discovery, marking significant milestones in biochemical research (Fig. 1). LA was initially isolated from sour milk by Carl Wilhelm Scheele in 1780 [1]. In 1808, Jöns Jakob Berzelius identified LA in fluid extracted from meat, establishing its presence in animal tissues [2]. In 1847, Justus von Liebig found that LA existed in muscle tissues [3] and its level can significantly increase following intense exercise [4–6]. Johann Joseph Scherer and Carl Folwarczny further identified LA in human blood under pathological conditions [7–9]. In the human body, LA predominantly exists as L-lactate [10–13]. In 1859, Emil Heinrich du Bois-Reymond observed that LA accumulation could influence muscle contraction [14–16]. In 1891, Araki and Zillessen showed that LA concentration increased with oxygen demand in the muscles of mammals and birds [17–19]. In 1907, Walter Morley Fletcher and Frederick Gowland Hopkins proved lactate was a by-product of anaerobic glycolysis, particularly in skeletal muscles [20–22]. Besides, lactate production was also attributed to glutaminolysis in tumor cells [23]. Over the years, research on lactate metabolism has seen groundbreaking progress, with the introduction of the "Warburg effect" in 1923 [24,25] and Brooks' "lactate shuttle theory" in 1986 [26]. These discoveries highlighted that lactate is a key metabolic substrate for most tissue cells [27]. In 2019, Zhao *et al.* reported lactylation as a post-translational modification [28], highlighting the crucial role of lactate in promoting histone lysine residue modifications and participating in biological processes such as tumor proliferation, neuronal excitation, inflammation, embryogenesis, and pulmonary fibrosis [29–36]. These studies challenged the view of LA as a metabolic by-product [37] and gradually recognized its involvement in various physiologic or pathological processes [38–40] (Fig. 1). In this review, we explore the diverse functions of LA within TME, including its regulatory effects on tumor cells, immune cells, and stromal cells. Additionally, we discuss the antitumor therapies that target LA, addressing the challenges in clinical application and potential future research directions.

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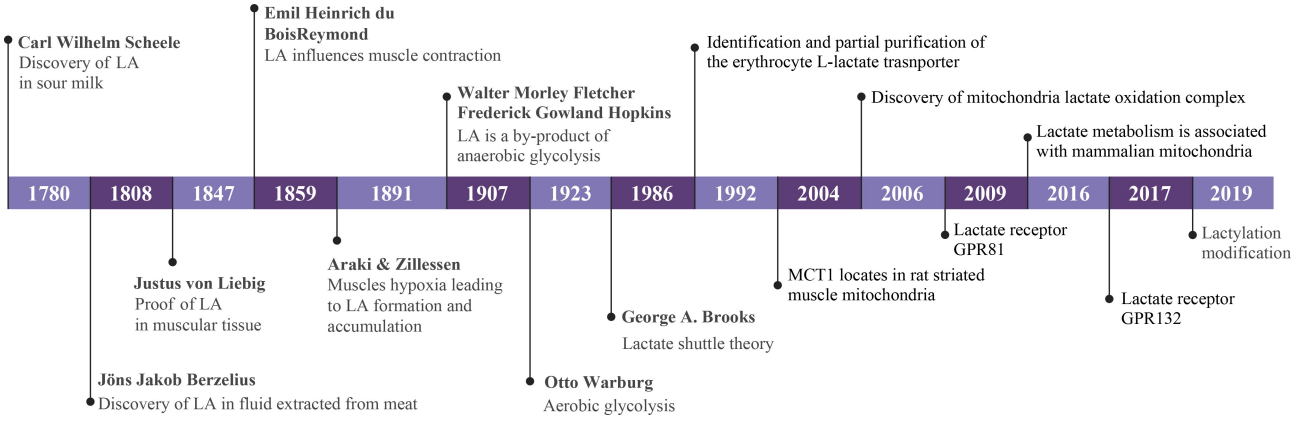

Fig. 1 Timeline of the discovery and key milestones of LA. Key milestones are indicated that have contributed to defining the discovery and functions of LA.

Functions of lactic acid

LA plays essential roles in various physiologic and pathological processes, including (1) microenvironmental pH regulation, (2) signal transduction regulation, (3) post-translational modification, and (4) metabolic remodeling (Fig. 2).

LA-mediated microenvironmental pH regulation

LA can dissociate into lactate anions and protons (H^+), thereby regulating the microenvironmental pH value, particularly in inflammatory and tumor settings [41–43]. Tumor cells with high glycolytic activity produce a large amount of lactate anions and H^+, which are co-transported via the monocarboxylate transport system and excreted into the extracellular space. This contributes to microenvironmental acidification and profoundly affects cell metabolism, phenotypes, and functions [44].

Regulation of signal transduction

Lactate plays an important role in molecular signal regulation, exerting its effects through autocrine, paracrine, and endocrine-like mechanisms, commonly called "lactormone" signaling. G-protein-coupled receptor 81 (GPR81), also known as "lactate receptor" or hydroxycarboxylic acid receptor 1 (HCAR-1), is the primary receptor responsible for sensing and transmitting lactate signals [45]. GPR81 is highly expressed in the adipose tissues, kidneys, skeletal muscle, and central nervous system [46]. Studies have demonstrated that GPR81 mediated exogenous LA signaling and involved in lipid metabolism [47,48], neuronal excitability changes [49], inflammatory regulation [50,51], tumor progression [46], and various physiologic processes [52–54]. Other G-protein-coupled receptors, such as G-protein-coupled receptor 132 (GPR132), are also implicated in sensing lactate and facilitating signal transduction in tumors [55].

Post-translational modifications

Post-translational modifications (PTMs) are essential for regulating protein function, cellular signaling, and maintaining homeostasis, and their dysregulation often contributes to various diseases. Beyond well-characterized PTMs such as acetylation, methylation, glycosylation, ubiquitination, and phosphorylation, emerging modifications like lysine lactylation (Kla), propionylation (Kpr), and 2-hydroxy isobutyrylation (Khib) have recently been identified. Most proteins contain at least one type of PTM, and interactions among these modifications facilitate significant crosstalk [56]. Lactylation, observed on histone and non-histone proteins, can alter protein expression, activity, localization, turnover, and interactions with other biomolecules like nucleic acids and lipids [57,58]. Recent research demonstrated that intracellular lactate modulated cellular function by inhibiting histone deacetylase activity or entering the tricarboxylic acid (TCA) cycle to produce acetyl-CoA, a key factor in histone acetylation [59–61]. In 2019, Zhao *et al.* discovered that lactate derived from glycolysis in inflammatory macrophages induced the lactylation of histone lysine to regulate the expression of the anti-inflammatory gene *ARG1* [28]. Subsequent studies have further established lactylation as critical in regulating cell metabolism, inflammation, and immune evasion in cancer, underscoring its role in the epigenetic regulation of cellular responses and disease progression [62,63].

LA-mediated metabolic remodeling

In resting adults, peripheral blood contains approximately 0.6 to 1.5 mM LA, rising to about 15 mM after intense exercise [64]. As the second most abundant metabolite after glucose, circulating LA can be utilized by most tissues [27,65–67]. LA is also a critical precursor in gluconeogenesis, which supports glycogen synthesis for energy

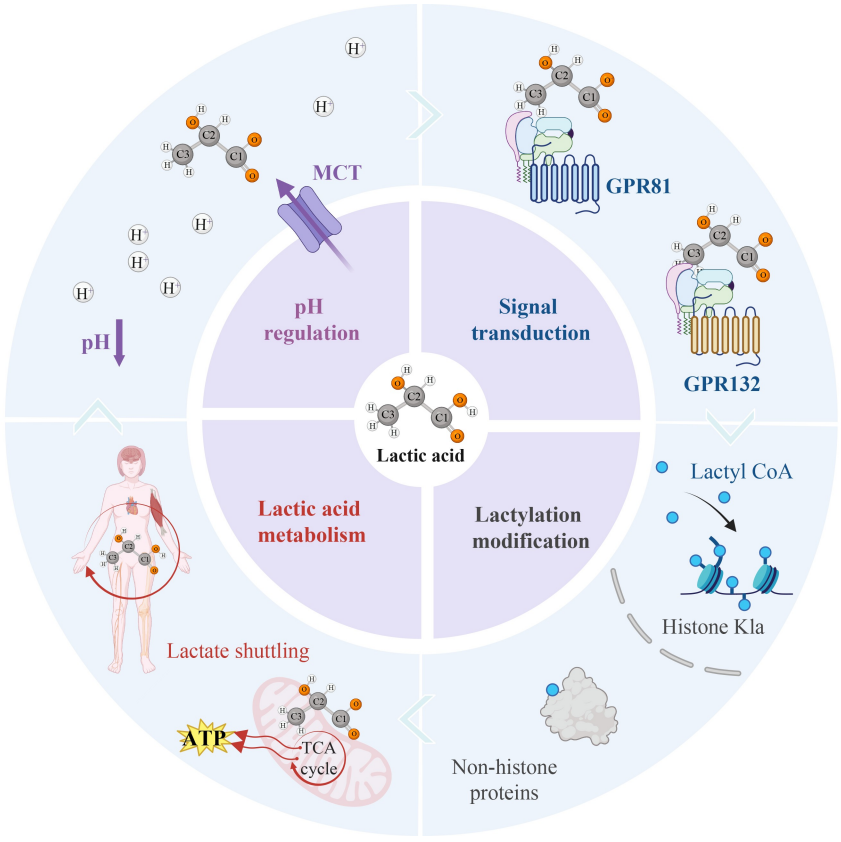

Fig. 2 Functions of LA. (1) Microenvironmental pH regulation. LA can dissociate into lactate anions and protons (H^+), thereby regulating the pH of the microenvironment. (2) Signal transduction regulation. Lactate is often referred to as "lactormone" signaling. G-protein-coupled receptor 81/132 as lactate receptor mediates lactate sensing and signal transduction, which involves various processes including inflammation, metabolism, tumor progression, and neuronal excitability. (3) Post-translational modification. Histone protein and non-histone protein lactylation impact protein expression, activity, localization, and turnover. (4) Metabolic remodeling. LA plays a vital role in metabolism as an essential fuel molecule. Lactate shuttling can occur between tissues and organs, between cells, inside cells, and between cytoplasm and mitochondria.

storage, particularly in hepatocytes [68–71]. LA metabolism is driven by cell-to-cell and intracellular LA shuttles.

Cell-cell LA shuttling

Cell-cell LA shuttling is generated through aerobic glycolysis in LA-producing cells and then released into interstitial fluid or blood circulation to reach LA-consuming cells, where it is metabolized [72] (Fig. 3). This shuttling process is especially active in cardiac and skeletal muscle, brain, and other organs [67,73–75]. For example, in skeletal muscle, glycolytic white fibers produce lactate, which is then taken up by red fibers for mitochondrial oxidative metabolism within the muscle bed [76]. Although circulating LA cannot cross the blood-brain barrier directly, astrocyte-derived LA in the brain is utilized by neurons, completing the cell-to-cell shuttle [77]. Additionally, liver and kidney cells can absorb circulating LA for gluconeogenesis, contributing to glucose and glycogen synthesis for storage and later energy use [69,78].

Intracellular LA shuttle

Lactate metabolism begins with its conversion to pyruvate, initially thought to occur in the cytoplasm (Fig. 4). However, research in active skeletal and cardiac muscle, as well as in proliferating immune cells, has shown that the cytoplasmic lactate/pyruvate ratio can rise up to 50 times higher than at rest, reaching levels of 500 or more during exercise [65]. This suggests that cells preferentially utilize glycolysis to produce lactate in activated states. Additionally, nicotinamide adenine dinucleotide (NAD^+) produced during pyruvate-to-lactate conversion is a crucial molecular signal for regulating cell proliferation [41], indicating that oxidative lactate metabolism may not occur extensively in the cytosol. The identification of mitochondrial lactate dehydrogenase (mLDH), and lactate transporters suggests that lactate metabolism is closely linked to mitochondria [79,80], enabling lactate to be transported to the mitochondria for metabolism through intracellular cytoplasmic-mitochondrial shuttling [81].

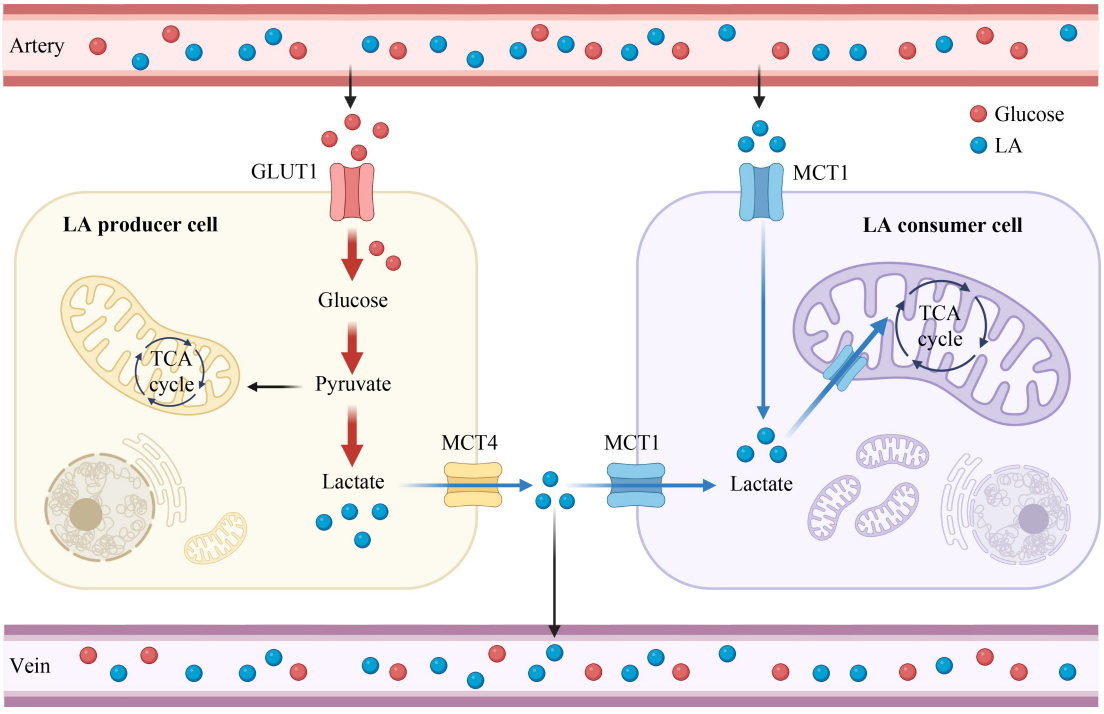

Fig. 3 Cell-cell lactic acid shuttling. Depiction of LA exchanges between blood, LA producer, and consumer cells. LA producer cells mainly uptake glucose through the glucose transporter GLUT1, produce lactate through glycolysis metabolism in the cytoplasm, and then efflux LA to the extracellular space through MCT4. LA consumer cells uptake and transport LA into mitochondria through the membrane and mitochondrial MCT1 and then oxidize LA for energy supply.

Cytoplasmic-mitochondrial LA shuttle

Mitochondrial oxidative metabolism of LA relies on specific transporters and enzymes within mitochondria. The mitochondrial LA oxidation complex (mLOC) consists of monocarboxylate transporter 1 (MCT1), the chaperone protein CD147, mLDH, and electron transport chain complex IV (COX IV) [81], which collectively mediate the intracellular LA's entry and oxidation in mitochondria [80]. While the exact localization of MCT1 and mLDH within the inner mitochondrial membrane remains unclear, two primary pathways for mitochondrial LA metabolism have been proposed: direct LA transport into mitochondria for oxidative metabolism and an indirect pathway where LA is first oxidized to pyruvate in the cytoplasm before entering mitochondria for further oxidation (Fig. 5). Recent studies using advanced LA probes have revealed elevated LA concentrations within mitochondria, suggesting a specialized mechanism for LA import. However, the specifics of this entry process require further investigation.

Role of lactic acid in tumors

Tumor cells rapidly take up glucose through glycolysis, generating significant LA levels that are exported to the extracellular space via MCT4 [82,83], thereby acidifying TME and promoting extracellular matrix degradation, immune evasion, and suppression of antitumor immune cell activity [44,84,85]. LA also serves as an energy source for gluconeogenesis, fatty acid synthesis, and the TCA cycle in tumor cells [26,27,81,86,87]. Overall, this section discusses the effects of LA on different cell types in tumors (Table 1).

Effects of LA on tumor cells

In TME, LA could directly act on tumor cells, promoting the expression of programmed death ligand 1 (PD-L1) through GPR81-cAMP-PKA-TAZ/TEAD pathway [52] and promoting glycolysis by upregulating STAT5 in cancerous leukocytes, which facilitates immune evasion. The LA generated during this process could accumulate in cells, promoting the nuclear translocation of E3BP and histone lactylation modification, thereby inducing the upregulation of PD-L1 expression [88]. It also supports breast tumor cells antioxidant capacity by increasing NADPH production through isocitrate dehydrogenase 1 (IDH1), aiding in survival under nutrient-deficient conditions [89]. Furthermore, LA efflux is accompanied by hydrogen ion release, acidifying the TME, which can reduce tumor cell uptake of chemotherapeutic agents due to protonation in acidic conditions [85]. At the metabolic level, tumor tissues comprise both glycolytic and

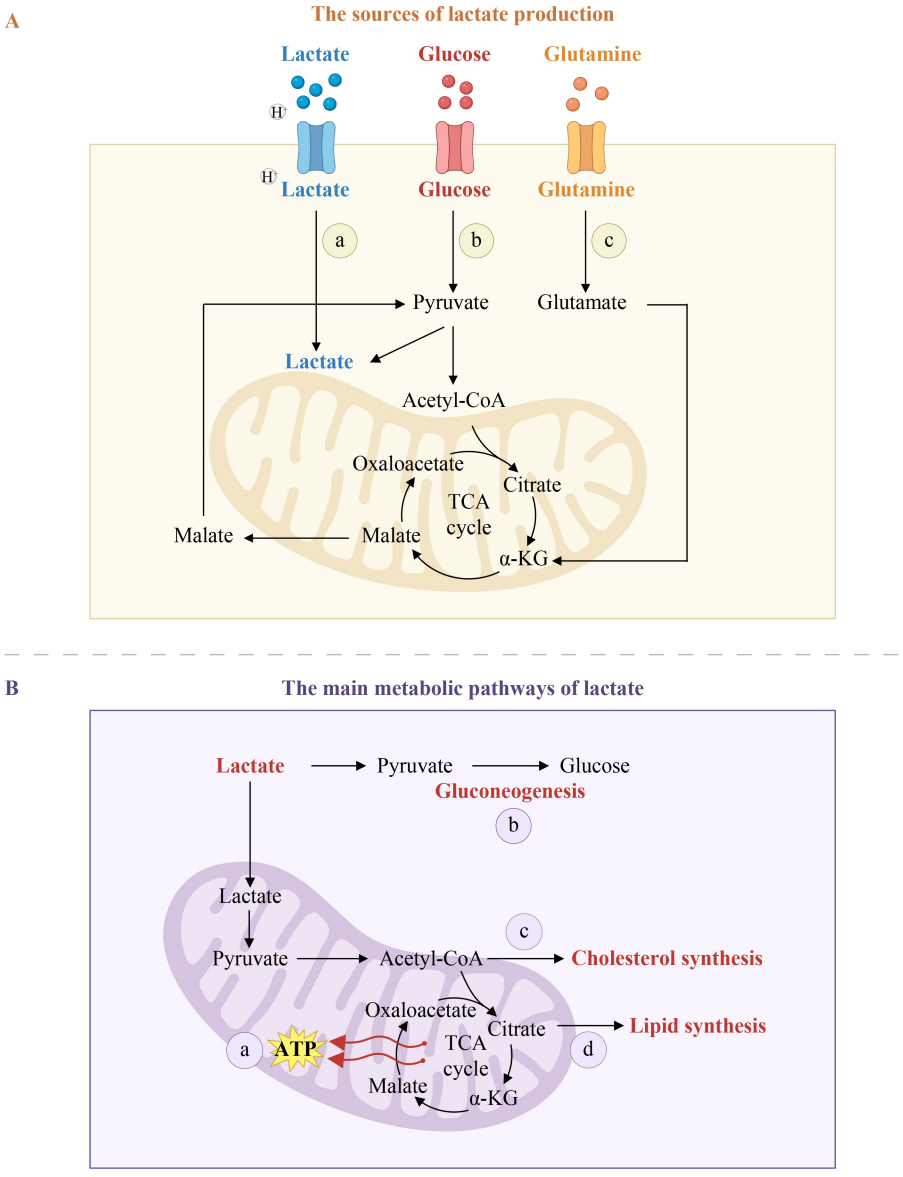

Fig. 4 Sources and metabolic pathways of lactate. (A) The sources of lactate production are (a) the uptake of extracellular lactate, (b) glycolysis metabolism, and (c) glutamine decomposition. (B) The main metabolic pathways of lactate are (a) mitochondrial oxidative metabolism, (b) gluconeogenesis, (c) cholesterol synthesis, and (d) lipid synthesis.

lactate-oxidizing tumor cells, with specific tumor cells capable of using lactate for energy production. Although the majority of tumor tissues are predominantly composed of glycolytic tumor cells, LA-oxidized tumor cells are present in a mixed composition [90]. High MCT1 expression in tumor cells facilitates fast absorption of extracellular LA, subsequently metabolizes via the TCA cycle to promote tumor cell proliferation [91]. This energy supply surpasses that of glucose [92]. This metabolic flexibility enhances tumor growth and resistance to therapies. Additionally, LA-induced lactylation of genome stability proteins, such as Nijmegen breakage syndrome 1 (NBS1) and meiotic recombination 11 (MRE11), promotes homologous recombination and chemoresistance [93,94]. Finally, LA fosters adhesion, invasion, and metastasis in breast tumor cells through the GPR132 signaling pathway [55]. Thus, as a key by-product in TME, LA contributes to tumor progression, metastasis, and chemoresistance.

Effects of LA on immune cells in TME

Tumor-associated macrophages

In TME, macrophages are inhibited by various tumor-derived factors, consequently becoming tumor-associated macrophages (TAMs) that promote tumor development [95,96]. LA acts as a critical metabolic regulator in TME,

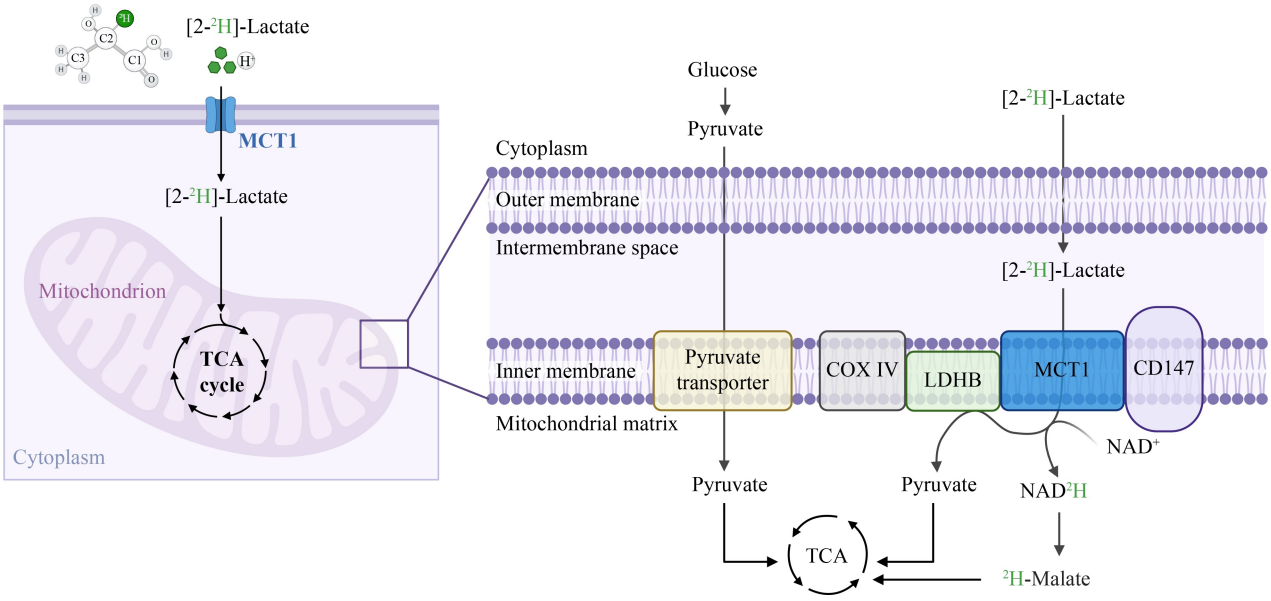

Fig. 5 Mitochondrial lactate oxidation complex. A schematic showing the cytoplasmic-mitochondrial shuttling of LA (left) and putative mitochondrial lactate oxidation complex (right). MCT1 (lactate transporter) is inserted into the mitochondrial inner membrane, strongly interacting with its chaperone protein CD147, and is also associated with COX IV and mitochondrial lactate dehydrogenase B (LDHB). TCA, tricarboxylic acid cycle.

polarizing tumor-infiltrating macrophages to a tumor-promoting (protumor) phenotype, which suppresses inflammatory responses [97]. Exogenous LA can inactivate YAP through the GPR81-AMPK/LATS pathway, reducing the binding of NF-κB to YAP and inhibiting macrophage inflammatory activation [98]. LA binds to GPR132 on macrophages to reinforce the protumor phenotype [55]. Additionally, LA induces TAM polarization in pituitary adenomas via mTORC2 and ERK pathways, resulting in CCL17 secretion and tumor metastasis [99]. The polarization of TAMs generated by LA is linked to the activation of the ERK-STAT3 signaling pathway, the stability of hypoxia-inducible factor (HIF)-1α, and the increased production of vascular endothelial growth factor (VEGF) and Arg-1 [100,101]. Furthermore, the acidic tumor microenvironment generated by lactate efflux suppresses the anticancer macrophage phenotype while fostering the protumor macrophage phenotype [102]. Thus, LA in TME drives TAM polarization by influencing transcription, signaling pathways, and epigenetic modifications, thereby accelerating tumor progression.

Dendritic cells

Dendritic cells (DCs), known as sentinels in tumor immunity, are negatively impacted by LA within TME. Reportedly, LA directly inhibits the toll-like receptor 3 (TLR3) and stimulator of interferon genes (STING) signaling, reducing the expression of type 1 interferon and SNARE vesicle-associated membrane protein 3 (VAMP3), a key regulator of antigen presentation in DCs [103]. This inhibition reduces the processing of antigenic proteins by DCs, consequently weakening the immune response in lung cancer [103]. LA also suppresses TNF-α secretion and glycolysis in monocytes, blocking DC differentiation and maturation [104,105]. Exposure to exogenous LA induces tumor-associated DC phenotypes, reduces cytokine (e.g., M-CSF, IL-6) production [105,106], and increases IL-10 in response to TLR ligands [103,107]. Acidic TME accelerates antigen degradation in DCs, impairs their chemotaxis, and thus hinders the immune system's ability to recognize tumors [107,108]. In summary, LA in TME disrupts DC maturation, antigen presentation, and cytokine production, and undermines immune surveillance, thus making it a potential target for enhancing tumor immunity and vaccine development.

Natural killer cells

Natural killer cells (NKs), vital for innate immunity [109], have their antitumor efficacy reduced by LA in TME, which inhibits IFN-γ secretion by inhibiting the cellular calcium signaling-NFAT pathway, diminishing cytotoxicity [110]. Exogenous LA rapidly acidifies NK cytoplasm through MCT1, acidifying the cytoplasm, suppressing glycolysis, and activating apoptotic pathways [110,111]. In pancreatic cancer, the highly expressed sine oculis homeobox homolog 1 (SIX1) molecule can induce the dysfunction of NKs by regulating the expression of lactate dehydrogenase A (LDHA), producing excessive

Table 1 Effects of LA on tumor cells, immune cells, and stromal cells in TME

Cell type	Mechanism	Effect
Tumor cell	Promote PD-L1 expression and mediate immune escape of lung tumor cells through the GPR81-cAMP-PKA-TAZ/TEAD pathway.	Immune escape ↑
	Promote E3BP nuclear translocation and histone lactylation and induce PD-L1 expression.	Immune escape ↑
	Catalyzed NADPH production by IDH1 supports the antioxidant capacity under nutrient-deficient conditions.	Antioxidant capacity↑
	Protonate and reduce the uptake of chemotherapeutic drugs.	Chemoresistance↑
	Uptake extracellular LA by MCT1 and metabolize LA through the TCA cycle.	Tumor growth↑
	NBS1 and MRE11 lactylation mediate DNA repair by homologous recombination	Chemoresistance, genome stability↑
Tumor-associated macrophage	Polarize macrophage to protumor phenotype through Arg-1 histone region lactylation.	Arg-1 ↑
	Suppress macrophage pro-inflammatory by inhibition of YAP through the GPR81-AMPK/LATS pathway.	IL-6, TNF-á↓
	GPR132 senses lactate signals and alters macrophages, which stimulates cancer metastasis.	Cell adhesion, metastasis, and invasion↑
	Polarize TAM by activating mTORC2 and ERK signaling pathways and release CCL17.	CCL17 ↑
	Inhibit the anti-tumor macrophage phenotype and promote the pro-tumor macrophage phenotype	iNOS, CCL2, IL-6↑
Dendritic cell	Inhibit TLR3 and STING signaling pathways and reduce antigen presentation.	Diminishing immune response
	Inhibit TNF-á secretion and the level of glycolysis in monocytes and block DC maturation.	TNF-á↓; DCs maturation↓
	Differentiate toward tumor-associated phenotype.	Tumor-associated dendritic cells↑
	Accelerate antigen degradation and inhibit the chemotaxis of circulating peripheral DC infiltration	DCs infiltration↓
NK cell	Downregulate IFN-ã secretion through the Ca^{2+}-NFAT pathway.	IFN-ã↓
	Impair cellular effector functions and activate apoptosis.	NKs apoptosis↑
	SIX1 induces NK dysfunction by regulating LDHA expression.	IFN-ã↓
	Reduce cytotoxicity.	Cytotoxicity↑
	Increase the number of myeloid-derived suppressor cells which restrain NK cells	Myeloid-derived suppressor cells↑
iNKT	Downregulate PPARã to inhibit tumor-infiltrating iNKT antitumor activity and lipid biosynthesis	Energy support↓
Treg cell	Promote Foxp3 expression by activating the NF-êB signaling pathway.	Foxp3↑
	MOESIN lactylation and enhance TGF-â signaling.	TGF-â signaling↑
	Modulate RNA splicing to promote CTLA-4 expression.	CTLA-4↑
	Metabolize LA through the mitochondrial TCA cycle via the MCT1 transportation system.	Energy support↑
	The immunosuppressive phenotype of Tregs inhibits the anti-tumor function of T cells	IL-10↑
$CD4^+$ T cell	Modify $CD4^+$ T cell polarization and lower the anti-tumoral Th 1 proportion	Th1 proportion↓
$CD8^+$ T cell	Impair $CD8^+$ T cell function and lower $CD8^+$ T cell infiltration	IFN-ã, IL-2↓
Cancer-associated fibroblasts (CAF)	Active CAF induces IL-8 secretion and mediate macrophage recruitment.	IL-8↑
	Inhibit the recruitment, maturation, proliferation, and effector functions of $CD8^+$ T cells while promoting the differentiation and maturation of Tregs.	Th1↓; Tregs↑
	Enhance CAF activity	DESMIN↑ IL-8↑
	CAF lactate uptake stimulates HGF overexpression, driving adaptive resistance	Tumor drug resistance↑
Endothelial cell	Lactate Influx, through the endothelial cell, maintains the redox state of cells	Antioxidant capacity ↑

Abbreviations: PD-L1: programmed death-ligand 1; GPR81: G-protein-coupled receptor 81; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; TAZ: transcriptional coactivator with PDZ binding motif; TEAD: TEA domain family member; E3BP: E3 binding protein; NADPH: nicotinamide adenine dinucleotide phosphate; IDH1: isocitrate dehydrogenase 1; LA: lactic acid; MCT1: monocarboxylate transporter 1; NBS1: Nijmegen breakage syndrome 1; MRE11: meiotic recombination 11; YAP: yes-associated protein; AMPK: AMP-activated protein kinase; LATS: large tumor suppressor; GPR132: G-protein-coupled receptor 132; TLR3: toll-like receptor 3; STING: stimulator of interferon genes; TNF-α: tumor necrosis factor-alpha; DC: dendritic cell; IFN-γ: interferon-gamma; NFAT: nuclear factor of activated T cells; SIX1: Sine Oculis homeobox homolog 1; NK: natural killer cell; PPARγ: peroxisome proliferator-activated receptor gamma; iNKT: invariant natural killer T cell; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B Cells; TGF-β: transforming growth factor-beta; CTLA-4: cytotoxic T-lymphocyte associated protein 4; TCA cycle: tricarboxylic acid cycle; CAF: cancer-associated fibroblasts; HGF: hepatocyte growth factor; LDHA: lactate dehydrogenase A; Arg-1: arginase-1; IL-6: interleukin-6; TAM: tumor-associated macrophage; mTORC2: mechanistic target of rapamycin complex 2; ERK: extracellular signal-regulated kinase; CCL17: chemokine (C-C motif) Ligand 17; iNOS: inducible nitric oxide synthase; CCL2: chemokine (C-C motif) ligand 2; IL-10: interleukin-10; Foxp3: forkhead box P3; IL-2: interleukin-2; IL-8: interleukin-8; Treg: regulatory T cell.

LA. However, the function and activity of NKs can be restored following inhibition of LDHA [112]. Acidic TME further reduces NK effector molecules, such as granzyme B and perforin, at low pH levels and indirectly suppresses NK cells by increasing myeloid-derived suppressor cells (MDSCs) [113,114]. LA also inhibits tumor-infiltrating invariant NK T cells via peroxisome proliferator-activated receptor γ (PPARγ) downregulation, impairing their lipid biosynthesis and antitumor effects [115,116]. Consequently, LA-mediated cytoplasmic acidification and signaling in NK cells compromise their cytotoxic function in TME.

LA and Treg cells

The regulatory T cells (Tregs) are essential to tumor immunosuppression. LA in TME directly promotes the nuclear localization of Foxp3 by activating NF-κB signaling [117]. This activation promotes the immunosuppressive phenotype of Tregs, subsequently inhibiting the effector function of antitumor T cells and promoting tumorigenesis [86,118]. When exogenous LA enters Tregs, it modifies the lysine at position 72 of the MOESIN molecule through protein lactylation, facilitating the expression of Foxp3 [119]. In addition, LA in TME can increase the expression of spliceosome USP39. This process enhances the cleavage and maturation of the mRNA for the immune checkpoint molecule cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), further amplifying the immunosuppressive functions of Tregs [120]. Elevated concentrations of LA in tumors with high glycolysis levels can enter Tregs via MCT1 expressed on the surface, which promotes the entry of the nuclear localization of activated T cells (NFAT) through PEP-Ca^{2+} signaling. It enhances the PD-1 expression, thereby reducing the efficacy of anti-PD-1 immune checkpoint therapy. Furthermore, LA serves as an energy source for Tregs, and its uptake provides functional and metabolic intermediates through the mitochondrial TCA cycle [86]. Overall, LA in TME can be used as an energy and signaling molecule as well as a regulator of cellular transgenesis and post-transcriptional modification to promote the survival, proliferation, and immunosuppressive function of Tregs.

LA and $CD8^+$ T cells

$CD8^+$ T cells are key mediators of tumor destruction. According to clinical studies, exogenous LA can inhibit $CD8^+$ T cell function (clonal proliferation, effector secretion, and cell killing) by 95% [121]. In glycolysis, LDHA catalyzes the reduction of pyruvate to lactate, consuming one molecule of NADH to regenerate NAD^+. This cycle is crucial for maintaining cytoplasmic NAD^+/NADH balance. However, the buildup of LA can negatively regulate glycolysis. Consequently, the conversion of pyruvate to lactate is blocked, disrupting the NAD^+/NADH balance. Since NAD^+ is crucial for maintaining cell proliferation, a decrease in the NAD^+/NADH ratio inhibits the proliferation of $CD8^+$ T cells [122–124]. In addition, LA can suppress GLUT10 activity, thereby hindering glucose uptake by $CD8^+$ T cells. This inhibition compromises the antitumor efficacy of $CD8^+$ T cells by impairing their metabolic capacities [125]. LA in TME increases the concentration of hydrogen ions [126], which bind to the substrate binding sites of vital glycolytic enzymes by protonation. This competition disrupts the enzyme-substrate interactions, inhibiting critical glycolytic enzymes such as hexokinase, phosphofructokinase, and pyruvate dehydrogenase. Hence, cellular metabolism is diminished, and the proliferation and functional capabilities of antitumor $CD8^+$ T cells are suppressed [85,110,127]. Furthermore, TME acidification significantly impairs T cell motility by inhibiting the formation of podosomes [128]. Neutralizing acidic TME and proton pump inhibitors can reverse the suppression of antitumor immunity and improve immunotherapy [129,130]. In addition, it has been reported that high concentrations of exogenous LA can inhibit the expression of the anti-tumor $CD8^+$ T cell transcription factor *NFAT*, thereby inhibiting the expression and secretion of its activation marker CD25 and effector interferon-gamma (IFN-γ) in tumors with high LDHA expression background. Thus, LA in TME mediates tumor immunosuppression by inhibiting the function of the anti-tumor $CD8^+$ T cell effector directly and indirectly, lowering $CD8^+$ T cell infiltration [131–133]. However, some studies have reported that LA can upregulate antitumor T cell function. Specifically, exogenous LA has been shown to increase the expression of T cell factor 1 (TCF1) through the modulation of one-carbon metabolism and histone acetylation. TCF1 is a crucial upstream signaling molecule that governs and preserves T cell stemness. Intratumoral administration of sodium lactate has demonstrated $CD8^+$ T cell-dependent antitumor effects [61,134]. These findings suggest that lactate may have a dual role in regulating $CD8^+$ T cell function. Further investigation is needed to fully understand the inhibitory effects of LA on antitumor $CD8^+$ T cells and to explore potential strategies for leveraging these effects in anti-tumor therapies.

Effects of LA on stromal cells

Numerous stromal cells, such as fibroblasts, are present in tumors and play a crucial role in maintaining the physicochemical characteristics of the TME. In addition to tumor cells, cancer-associated fibroblasts (CAFs) are another vital source of LA in TME [135]. LA activated CAFs, which secreted interleukin-8 (IL-8), thus

mediating macrophage recruitment and promoting lung cancer progression [136]. These CAFs can inhibit the recruitment, maturation, proliferation, and effector functions of $CD8^+$ T cells while promoting the differentiation and maturation of Tregs. The production of LA by CAFs leads to the maintenance of these inhibitory functions [118]. Furthermore, LA can also block the ADP-ribosylation of nuclear transcription factors AP-1, c-FOS, and c-JUN by reducing the cellular NAD^+/NADH ratio and breaking the activity of ADP-ribosylase (PARP-1), which is a critical step leading to the degradation of p62. The decrease in p62 ultimately leads to the enhancement of CAFs activity. Supplementation with NAD^+ can significantly reduce CAF activity [137]. In addition to being a source of LA, studies have found another type of LA-oxidizing CAFs in tumors that expresses MCT1, which activates the intracellular NF-κB signaling pathway, upregulates the expression of hepatocyte growth factor (HGF), and mediates tumor drug resistance through the uptake of LA [138]. In tumors, there is a communication pathway between LA and endothelial cells. Tumor-derived LA enters the cell through the uptake of MCT1 expressed by endothelial cells and produces NADH from the reduction of pyruvate to remove intracellular reactive oxygen species, thereby maintaining the redox state of cells [139]. Additionally, LA stabilizes the expression of HIF-1α, which supports the secretion of VEGF, thereby facilitating the development of the tumor vascular microenvironment [100].

Lactic acid-targeting anti-tumor therapies

Inhibiting the production or export of LA

The inhibitory role of LA in TME has led to the hypothesis that eliminating LA from this environment might be a practical therapeutic approach (Table 2). Direct removal of LA from the TME is challenging. Therefore, current strategies mainly focus on indirectly reducing LA levels by inhibiting its production or export. A synthetic glucose analog, 2-deoxyglucose (2-DG), inhibits glycolysis and reduces LA production in tumor cells, thereby inhibiting rapid tumor growth [140]. Besides its standalone use, 2-DG has been combined with metformin to synergistically inhibit the growth of breast tumor cells *in vitro* [141]. Additionally, 2-DG can enhance the formation and antitumor function of long-lived $CD8^+$ memory cells by inhibiting glycolytic flux [142]. Given that LDHA is upregulated in cancer and is responsible for the primary LA generation, it represents a potential therapeutic target. Current LDHA inhibitors include oxamate, a pyruvate analog that binds to LDHA and prevents the conversion of pyruvate to lactate, leading to pyruvate accumulation [143–145]. Diclofenac can reduce lactate generation in malignant gliomas and markedly suppress the expression of LDHA [146]. Stiripentol, an LDHA inhibitor clinically used for anti-epileptic treatment, can inhibit NBS1 lactylation. This inhibition disrupts DNA repair processes within tumor cells during chemotherapy, thereby reducing tumor chemoresistance [93]. Moreover, it can inhibit glioma cell growth and induce cell cycle arrest at the G2/M checkpoint [146]. Competitive inhibitors of LDHA, such as FX11 and gossypol, have also demonstrated anti-tumor activity. Gossypol has progressed to phase II clinical trials for the treatment of adrenocortical carcinoma; however, due to its toxicity, it showed limited efficacy as a standalone treatment [147,148]. Determining the minimal toxic dose of gossypol and its toxicity profile across different tumors remains an essential focus for future research [149]. Moreover, combining gossypol with docetaxel and cisplatin might be more effective [150]. Regarding LA transport, syrosingopine is an effective dual inhibitor of MCT1/MCT4. Studies have shown that combining syrosingopine with metformin leads to ATP depletion and cell death, presenting a potential anti-tumor therapy [151]. AZD3965, another dual inhibitor of MCT1/MCT2, is indirectly cytotoxic to breast-related malignant and non-malignant cell lines, suggesting its potential utility in anti-tumor treatment [152]. AZD3965 has completed phase I/II clinical trials for solid tumors, diffuse large B cell lymphoma, or Burkitt lymphoma (clinical trials, NCT01791595), demonstrating promise as a cancer therapy. Furthermore, the synergistic effect of lactate/GPR81 blocker (3-hydroxybutyrate, 3-OBA) and metformin *in vitro* inhibits cancer cell growth. This combination suppresses glycolysis and OXPHOS metabolism, inhibits tumor growth, and reduces serum LA levels in tumor-bearing mice [153]. Inhibiting the lactylation modification of lactate is also a potential therapeutic strategy. In gastric cancer, an increase has been observed in the concentrations of lactate and copper [154]. The atypical methyltransferase methyltransferase-like 16 (METTL16), through m^6A modification of FDX1 mRNA, acts as a critical mediator promoting copper-induced cell death (cuproptosis). Under copper stress conditions, the METTL16 lactylation at K229 is increased; however, this process is suppressed by SIRT2. Notably, the increased lactylation level induced by METTL16 enhances the therapeutic efficacy of the copper ionophore dexlansoprazole [155]. Combined with SIRT2 inhibitor AGK2, dexlansoprazole promotes copper-induced tumor cell death [155].

Blockade of lactate metabolism combined with immune checkpoint therapy

Abnormal LA concentrations within tumors have been

Table 2 Lactic acid-targeting anti-tumor therapies

		Mechanism	Type of cancer	Phase	Limitation
Inhibiting the production or export of LA					
Inhibitor	2-deoxyglucose (2-DG)	A synthetic glucose analog that inhibits glycolysis, reducing LA production in tumor cell	Melanoma	Pre-clinical	Lack of specificity of the target
	Oxamate	A pyruvate analog that binds to LDHA and prevents the conversion of pyruvate to lactate, leading to pyruvate accumulation	Breast cancer (MCF-7, T47D)	Pre-clinical	Lack of specificity of the target
	Diclofenac	Suppress LDHA expression	Malignant gliomas	Pre-clinical	Lack of specificity of the target
	Stiripentol	Inhibit NBS1 lactylation and disrupt DNA repair processes within tumor cells during chemotherapy	Glioma	Clinical	Combination of chemoradiotherapy is required
	FX11 gossypol	Competitive inhibitors of NADPH	Adrenocortical carcinoma	phase II clinical trials	Due to its toxicity, it showed limited efficacy as a standalone treatment
	AZD3965	Selective inhibitor of human MCT1 with additional activity against MCT2. Hinder lactate transport, increasing intracellular levels followed by glycolytic feedback and increased flux into the TCA cycle	Human diffuse large B cell lymphomas, Human B cell lymphoma lymphoblast, B cell non-Hodgkin lymphoma, Raji Burkitt's lymphoma cells	Completed phase I/II clinical trials for solid tumors	Lack of specificity of the target
	3-hydroxybutyrate (3-OBA) metformin	Block the synergistic effect of lactate/GPR81, suppress glycolysis and OXPHOS metabolism	Prostate cancer	Pre-clinical	Further clinical efficacy validation is lacking
	Dexlansoprazole AGK2	Promote copper-induced tumor cell apoptosis	Gastric cancer	Pre-clinical	Further clinical efficacy validation is lacking
Burning lactic acid as an energy source					
Molecule	LA oxidase (LOx) and CRISPR-mediated signal regulatory protein alpha (SIRPá) gene	This system is released and activated by acidic pyruvate produced by the LOx-catalyzed lactate oxidation	Breast cancer	Pre-clinical	Further clinical efficacy validation is lacking
	Lithium carbonate	Transporting LA into the mitochondria for oxidation	Melanoma/breast/colon cancer	Pre-clinical	Lithium-ion toxicity

Abbreviations: 2-DG: 2-deoxyglucose; LA: lactic acid; LDHA: lactate dehydrogenase A; MCT1: monocarboxylate transporter 1; MCT2: monocarboxylate transporter 2; MCF-7: Michigan cancer foundation-7; NBS1: Nijmegen breakage syndrome 1; NADPH: nicotinamide adenine dinucleotide phosphate; 3-OBA: 3-hydroxybutyrate; OXPHOS metabolism: oxidative phosphorylation metabolism; TCA cycle: tricarboxylic acid cycle; LA oxidase (LOx): lactic acid oxidase; SIRPα: signal regulatory protein alpha; GPR81: G-protein-coupled receptor 81.

shown to impact tumor-infiltrating immune cells' metabolism, differentiation, proliferation, and functions [86,110,118,121,123,156–170]. When combined with immune checkpoint inhibitors, regulating glucose metabolism to enhance cancer therapy is an encouraging new strategy. The clinical success of PD-1 inhibition is determined by the balance between $CD8^+$ T cells expressing this protein and Tregs in TME through their competitive reactivation [166]. Reportedly, Tregs utilize free fatty acids and LA to maintain their immunosuppressive function in highly glycolytic TME [166,170,171]. Tregs actively take up LA through MCT1, promoting NFAT1 translocation to the nucleus, thereby enhancing PD-1 expression [166]. The synergistic effect of PD-1 blockades and lactate enhances Tregs suppression and hinders antitumor immunity. Therefore, inhibiting lactate metabolism in Tregs enhances the sensitivity of resistant tumors to PD-1 blockade. Reportedly, the m^6A demethylase AlkB Homolog 5 (ALKBH5) inhibition or depletion enhanced sensitivity to anti-PD-1 immunotherapy in animal colorectal cancer and melanoma models. Moreover, there was a decrease in the amount of LA in the TME and the number of myeloid-derived suppressor cells and Tregs [172,173]. These results imply that ALKBH5 inhibitors may help reduce tumor immunotherapy resistance. Another study showed that immune checkpoint inhibitor treatment was sensitized, and T cell activity was enhanced when dichloroacetic acid was used to prevent LA entry into the TME, and dichloroacetate salts were used to limit tumor LA metabolism [174,175]. Daneshmandi *et al*. discovered that anti-PD-1 drugs dramatically boosted the efficacy

against melanoma by inhibiting LDHA. An increase followed this improvement in T and NK cell infiltration. The mechanism involved reduced LA levels, which raised reactive oxygen species concentrations and improved mitochondrial function [176]. LA is the main metabolic product of aerobic glycolysis in tumor cells and is one of the main reasons for the acidity of the TME, which can affect the activity of $CD8^+$ T cells, NKs, and DCs, thereby inhibiting immune function [37,44,170]. Therefore, neutralizing the TME's acidity can enhance immunotherapy's effectiveness. For example, combining oral bicarbonate buffer solution with anti-PD-1 immunotherapy can inhibit melanoma growth [47]. Recently, LA-regulated nanomedicine has emerged as an attractive and effective anticancer strategy, which is crucial for optimizing the delivery of LA regulators to achieve more precise and effective regulation and treatment. Integrating specific LA regulatory functions into various nanomedicines can overcome the inherent limitations of different treatment modalities by reshaping the pathological microenvironment, thereby enhancing anti-tumor therapy [177–179].

Burning LA as an energy source

Inhibition of LA production and transport also inhibits glycolysis-dependent antitumor immune cells, which may be one of the reasons for its poor therapeutic effects. Research has proposed an LA-catalyzed chemical kinetic approach to reprogram TAMs and improve anti-tumor immunotherapy [180]. This system is generated by encapsulating LA oxidase (LOx) and CRISPR-mediated signal regulatory protein alpha (*SIRPα*) gene editing plasmid in a metal-organic framework. This system is released and activated by acidic pyruvate produced by the LOx-catalyzed lactate oxidation. Studies have confirmed the synergistic effect of LA depletion and SIRPα signal blockade, which enhances the phagocytotic ability and repolarization of TAMs toward anti-tumor phenotypes and effectively reverses the immunosuppressive TME [180]. Research by *Huang*'s group discovered that lithium carbonate (LC, a mood stabilizer) can revitalize tumor-reactive $CD8^+$ T cells by transporting LA into the mitochondria [181]. Therefore, using LC to target LA metabolism can support anti-tumor immunotherapy. The specific mechanism involves the reversal of the immunosuppressive effects of LA on $CD8^+$ T cells by LC. The increased cytosolic LA enhances proton pumping into the lysosomes. Lithium ions interfere with V-ATPase (as a proton pump that maintains lysosomal pH), preventing lysosomal acidification and rescuing the lysosomal diacylglycerol-PKCθ signaling pathway, promoting the localization of the MCT1 to the mitochondrial membrane, thereby transporting LA into the mitochondria as an energy source for $CD8^+$ T cells. Targeting LA metabolism is becoming a potential anti-tumor therapeutic strategy, and targeting MCT1 reduces LA uptake or targets LDHA to prevent lactate generation. However, these approaches inevitably affect the physiologic functions of normal tissues. The alternative approach proposed in this study, using LC to reduce LA levels directly, is a promising strategy to activate T cell-based anti-tumor immunity.

Conclusion

LA has evolved from a metabolic by-product into a current research hotspot. While early studies primarily focused on its metabolic roles over the past century, researchers have increasingly recognized the significant implications of LA, from the Warburg effect to Brook's lactate shuttle theory. Circulating LA in the body participates in diverse metabolic pathways, shuttling between lactate-producing and lactate-consuming cells as a crucial energy molecule. Moreover, within cells, LA undergoes cytoplasmic-mitochondrial shuttling facilitated by mLDH and mitochondrial lactate transporters. LA also serves as a pH regulator and signaling molecule in physiologic and pathological processes. Additionally, it acts as a critical substrate involved in PTMs such as lactylation of histones and various proteins.

Accumulating abundantly in TME, LA affects tumor, immune, and stromal cells. LA in tumors has been considered as "metabolic waste" from cancer cell glycolysis, serving solely as a biomarker for malignant tumors. However, it is now believed to be a critical regulatory factor in tumor development, maintenance, and metastasis. Targeting the inhibition of LA and its production has emerged as a promising therapeutic strategy for cancer. Various inhibitors targeting glycolysis, LDHA, MCT, lactate-GPR81 pathway, and lactate clearance agents are currently employed clinically in oncology. Targeting tumor lactate in conjunction with immune checkpoint inhibitors enhances immune responses. Lithium carbonate targeting T cell lactate metabolism in the TME promotes the localization of MCT1 to the mitochondrial membrane, facilitating the transport of LA into mitochondria as an energy source for $CD8^+$ T cells. Tumor-derived LA can serve as an "energy supply fuel" and act as a signaling molecule, actively promoting tumor progression, angiogenesis, immune suppression, and therapy resistance, providing a promising opportunity for cancer treatment. Future research should further elucidate the multifaceted roles of LA across various physiologic and pathological processes and beyond.

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Compliance with ethics guidelines

Conflict of interest Jingwei Ma, Liang Tang, Jingxuan Xiao, Ke Tang, Huafeng Zhang, and Bo Huang declare that they have no conflict of interest.

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