Immune cross talk and therapeutic advances in lactate metabolism in the tumor microenvironment (Review)

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Abstract. The excessive buildup of lactic acid within the tumor microenvironment (TME) serves as a hallmark of metabolic reprogramming in cancer. New studies have revealed that lactic acid is an energy metabolic product and a core biological signal that regulates the malignant process of tumors. It plays multiple roles in metabolic reprogramming, protein lactate modification, immune escape, drug resistance generation, epigenetic regulation and metastatic spread. It also has significant negative implications for patient survival. In this review, the advances in understanding the metabolic mechanisms of lactate in the TME and its crosstalk with various of immune cells were systematically reviewed and its therapeutic potential in the following ways was explored: Targeting lactate synthesis (e.g., lactate dehydrogenase inhibitors); interfering with lactate catabolism (e.g., monocarboxylate transporter blockers); and regulating lactate shuttling (microenvironmental cell-to-cell communication). The review aimed to identify new targets and ideas for anticancer strategies by analyzing the lactate metabolic network.

Contents

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Abbreviations: TME, tumor microenvironment; MCT, monocarboxylate transporter; CAFs, cancer-associated fibroblasts; LDHA, lactate dehydrogenase A; NAD+, nicotinamide adenine dinucleotide (oxidized form); NADH, nicotinamide adenine dinucleotide (reduced form); TILs, tumor-infiltrating lymphocytes; ECM, extracellular matrix; GLUT, glucose transporter

Key words: lactate metabolism, TME, nanoparticles, immunity

1. Introduction

Tumors cover both benign and malignant types and are a serious concern. Various anticancer treatments, such as surgery, chemoradiotherapy, immunotherapy, gene therapy, phototherapy and targeted therapy, have been introduced to overcome this problem (1). However, the adaptive evolution of cancer cells and the complex construction of the tumor microenvironment (TME) still largely constrain the further enhancement of therapeutic effects (2). The TME is a complex ecosystem composed of diverse cellular constituents, including immune and stromal cells, alongside an acellular milieu of cytokines, growth factors, hormones and the extracellular matrix (ECM) (3). Through intricate interactions with tumor cells, these components collectively foster an environment that promotes cancer cell survival, proliferation and invasion (4). Additionally, the TME can create a protective ecological niche for tumor cells, allowing them to evade conventional treatment and leading to treatment failure (5,6). Therefore, a comprehensive understanding of the metabolic dynamics within the TME is of paramount importance for the advancement of cancer therapy.

The concentration of lactic acid in the TME is one of its key features and reflects the metabolic adaptive evolution of tumor cells. Far from being a simple metabolic waste product, a substantial body of research has revealed that lactic acid is a multifaceted signaling molecule within the TME (7-9). Its influence extends beyond regulating the metabolism and proliferation of cancer cells to profoundly reshaping the tumor immune microenvironment, and it is strongly associated with adverse patient outcomes (10).

Numerous researchers and scholars have made remarkable breakthroughs in tumor therapy by regulating lactate metabolism within the TME (11,12). In this article, the current research on the metabolic regulation of lactate within the TME and the emergence of new therapies in this field were reviewed. An in-depth discussion of these studies and therapies was provided to comprehensively dissect the field and provide useful guidance for the development of lactate metabolism modulation approaches for tumor therapy.

2. Sources of lactate in the TME

As early as the 1920s, Otto Warburg and his team reported that cancer cells have special metabolic characteristics; tumor cells still consume substantial quantities of glucose and generate high levels of lactate under conditions of sufficient oxygen (13), unlike normal cells, tumor cells, instead of choosing the normal metabolic pathway, tend to rely on the glycolytic transformation of glucose into lactate, a phenomenon termed the 'Warburg effect' (14), which is a major source of lactic acid production in the TME.

The TME is a multicellular system driven by intricate tumor-stroma interactions, in which cancer-associated fibroblasts (CAFs) are a major and stroma-rich cell type. Notably, in contrast to neighboring cancer cells, CAFs in the tumor stroma are more prone to activating glycolysis and autophagy, thereby triggering the reverse Warburg effect (15-17). Through the reverse Warburg effect, CAFs can deliver nutrients such as lactate to cancer cells and the TME (Fig. 1). Additionally, in tumors, high expression of the lactate dehydrogenase A (LDHA) isoform drives the efficient transformation of pyruvate into lactic acid, a reaction coupled with the regeneration of nicotinamide adenine dinucleotide (oxidized form; NAD+) from NADH (reduced form), thereby leading to substantial lactate accumulation (18,19).

In addition, cancer cells and CAFs express lactate transporters such as monocarboxylate transporter proteins (MCTs), which transport a vast amount of lactic acid produced intracellularly into the microenvironment where it accumulates within the TME (20).

Together, these sources contribute to the creation of a lactate-rich TME. The increase in lactate and acidification in the TME have significant implications for tumor development, including immune escape, tissue invasion, tumor metastasis, angiogenesis and tumor resistance (21-23) (Fig. 2).

3. Role of lactic acid in the TME

Lactate's influence extends past the tumor cells themselves to actively remodel the stromal landscape of the TME (24,25). It weakens the effector functions of key immune cells (such as CD8+ T cells), governs the metabolism of cancer-associated fibroblasts and fosters an intercellular 'metabolic symbiosis'. Notably, the role of lactate is not limited to promoting tumor development, but also appears to supply immune cells with a carbon source, thus contributing to cancer immunity to a certain extent, and this 'dual' role deserves to be explored in depth (26). Within the TME, lactate plays a dual role: It not only contributes to microenvironmental acidification through lactic acidosis but also functions as a crucial metabolic shuttle, moving between diverse cell populations such as tumor cells, cancer-associated stromal cells, tumor-associated macrophages (TAMs) and tumor-infiltrating lymphocytes, thus creating immune crosstalk between different cell populations (27) (Fig. 3). All in all, lactic acid is important in the TME.

Lactate promotes malignant growth and therapeutic resistance. When in an environment of hypoxia and a low energy supply, cancer cells rely on lactate to maintain their proliferative capacity. At different levels, lactic acid is a metabolic fuel for tumor growth and acts as a signaling molecule. Cancer cells maintain high glycolytic activity with the help of monocarboxylic acid transport proteins (MCTs) and take up large amounts of lactate from the surrounding environment (28). Adequate amounts of NADH produced by oxidation can enter the mitochondria via the malate-aspartate shuttle mechanism, which in turn fuels the respiratory chain. This mechanism is beneficial to the autophagy process in cancer cells. In humans, lactate predominantly exists as the L-isomer, which stands in contrast to the far less common D-lactate. The D-isomer originates from the metabolic activity of gut microorganisms and is specifically catabolized by the mitochondrial enzyme D-lactate dehydrogenase. The efficiency of this process is significantly more pronounced in cancerous tissues compared to their healthy counterparts, a phenomenon that consequently fuels malignant cell proliferation. Within tumor cells, the pivotal lactate receptor G protein-coupled receptor 81 (GPR81) orchestrates a state of mitochondrial hyperactivity by modulating the expression of peroxisome proliferator-activated receptor γ coactivator 1-α, CD147 and MCT, an effect that culminates in enhanced cancer cell proliferation (29).

Recent investigations have revealed that lactate accumulation is closely correlated with the insensitivity of cancers to drugs (30). Lactic acid can enhance the drug resistance of tumor cells (31). In cancer cells, the aberrant activation of Pl3K stimulates its downstream effector, PKB/AKT, which in turn drives a signaling cascade that ultimately enhances glucose uptake (32). Inhibitors that specifically target AKT, a key downstream node in the Pl3K signaling pathway, are extensively employed in both preclinical research and clinical trials (33). However, the accumulation of lactic acid in cancer cells may lead to evasion of Pl3K blockade. Lactate supplementation by itself has been reported to induce insensitivity to Akt inhibitors within colon cancer cells, which can be reversed when MCT-mediated transport is inhibited or eliminated by OXPHOS treatment (34). Another study confirmed that the expression of telomerase complex genes in breast cancer cells is promoted when the lactate concentration is high. In addition, cells that are chronically exposed to exogenous lactic acid show the activation of EGFR, which correlates with the emergence of acquired tamoxifen resistance. Additionally, the literature indicates a direct link between lactic acid acidification and tumor drug resistance. Recent investigations have revealed that in lung cancer, the upregulation of aldo-keto reductase drives the lactonization process of H4K12, which ultimately triggers chemoresistance (35). In view of the continuing challenges associated with drug resistance in tumors, the association between lactic acid and drug insensitivity of tumor cells still needs to be explored in depth.

Lactic acid activates the CAF phenotype. CAFs regulate multiple functions by secreting signaling molecules and inflammatory cytokines, altering their intrinsic bioenergetics to ensure the provision of vital metabolic substrates and factors that promote cell survival, and affecting tumor epithelial cells by remodeling the ECM. The collaborative effects of CAFs and epithelial cells drive malignant tumor progression and may also adversely affect cancer therapy by

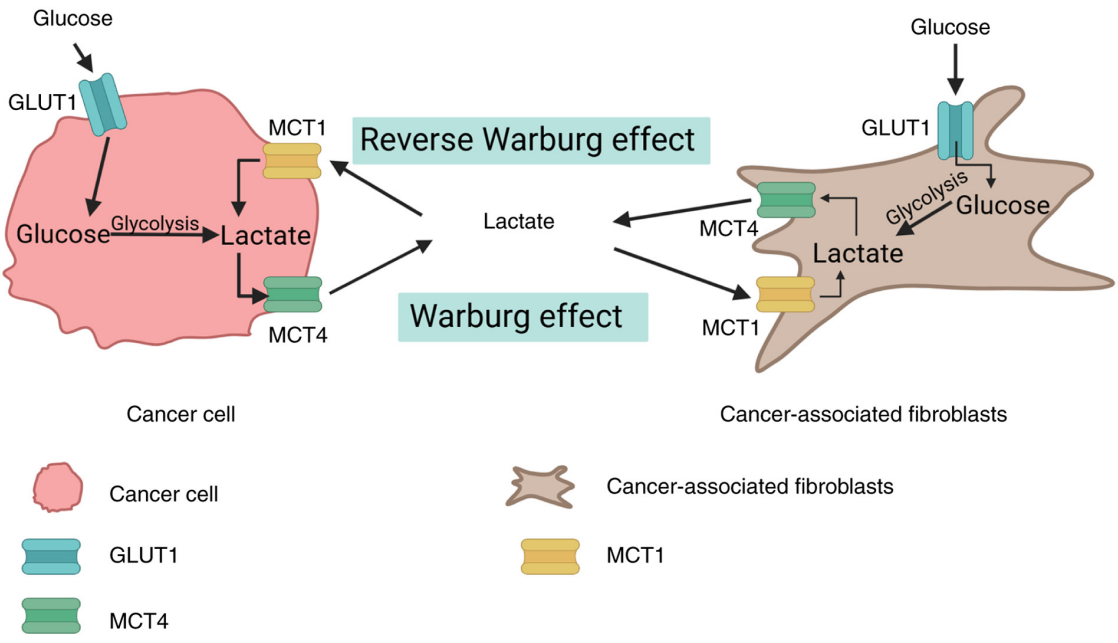

Figure 1. Warburg effect and the reverse Warburg effect. MCT, monocarboxylate transporter; GLUT, glucose transporter.

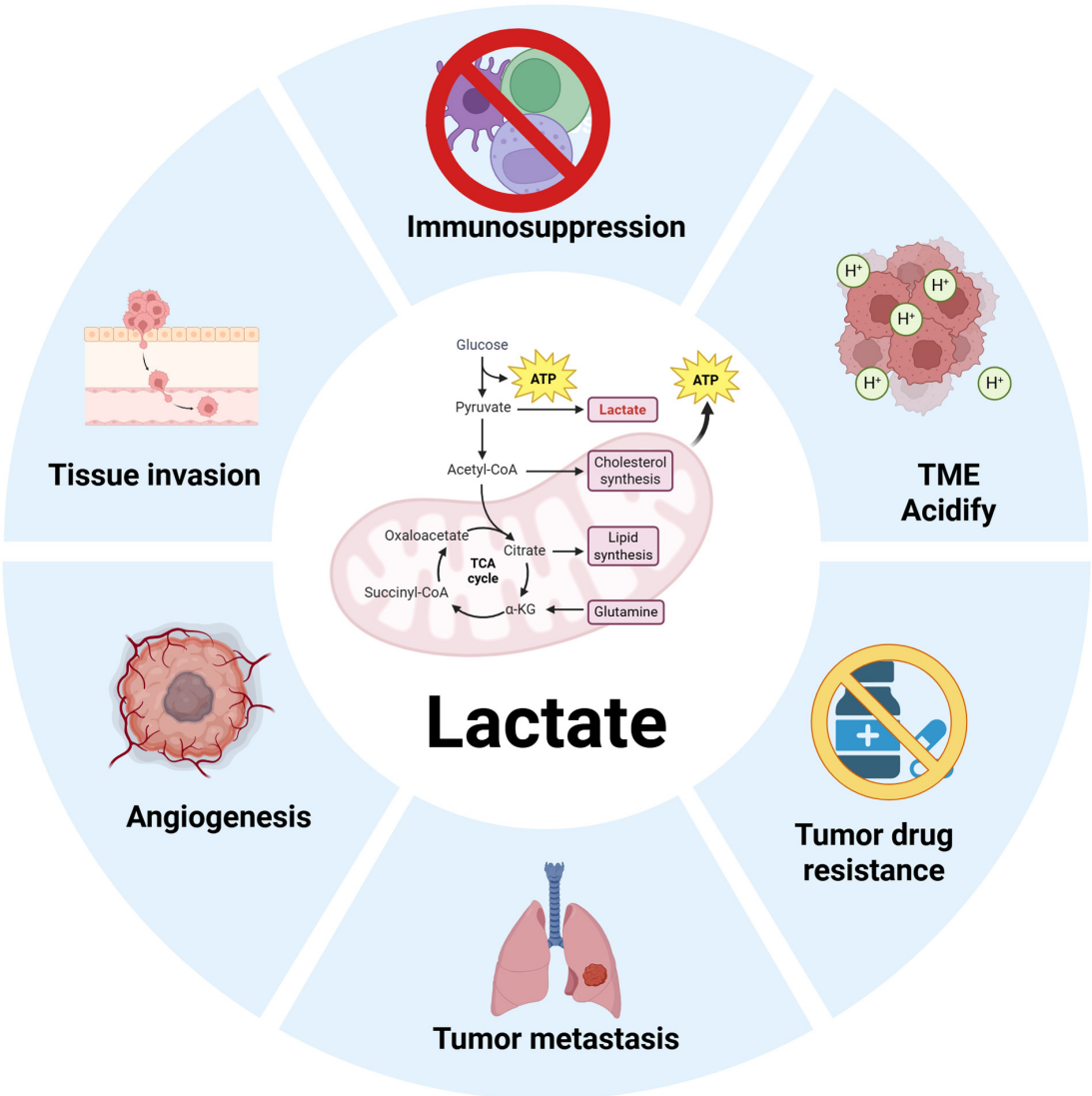

Figure 2. Role of lactic acid in the TME. TME, tumor microenvironment; TCA, tricarboxylic acid; KG, ketoglutarate.

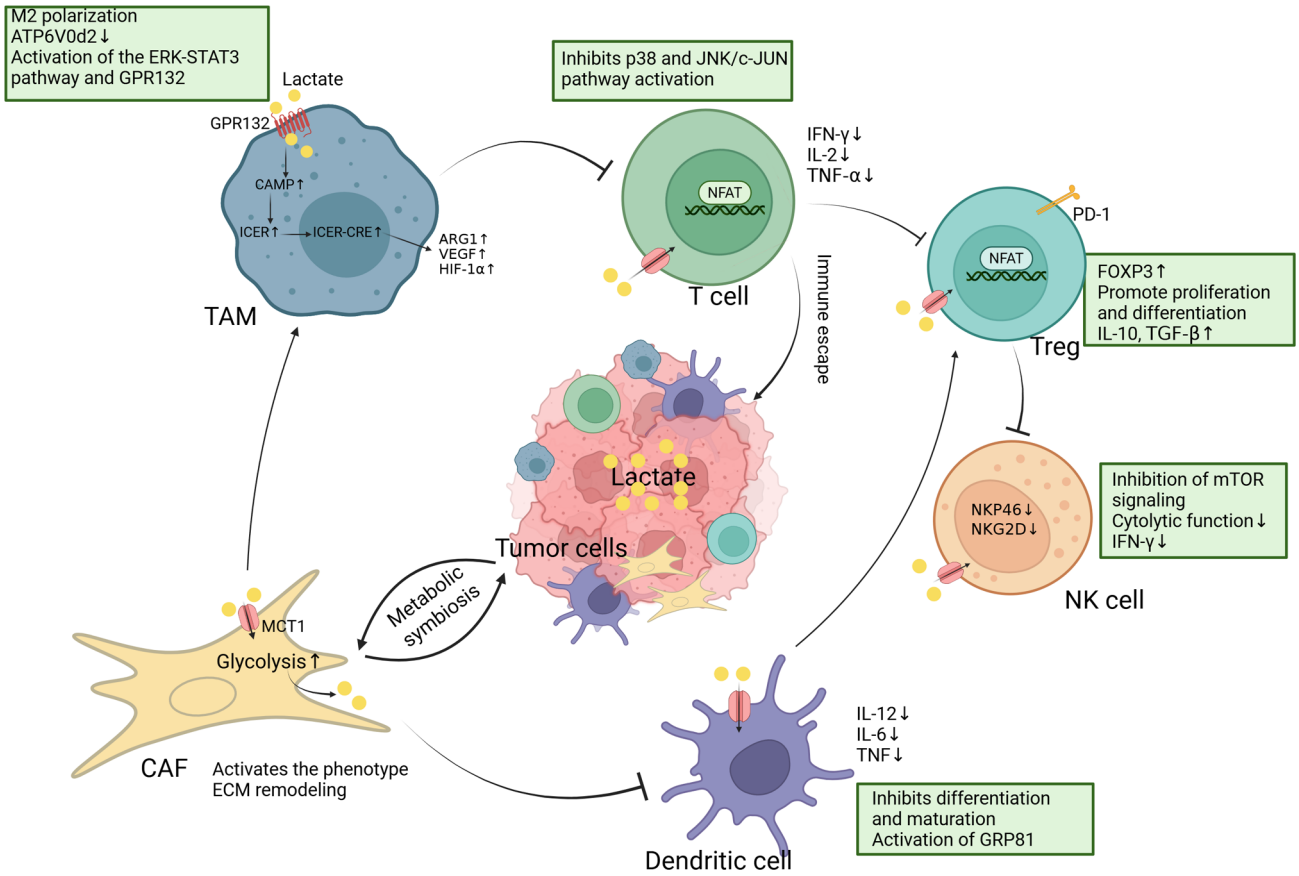

Figure 3. Crosstalk between lactic acid and various immune cells. TAM, tumor-associated macrophage; T cell, T lymphocyte; Treg, regulatory T cell; NK cell, natural killer cell; CAF, cancer-associated fibroblast; DC, dendritic cell; ERK, extracellular signal-regulated kinase; STAT, signal transducer and activator of transcription; GRP, G protein-coupled receptor; CAMP, cyclic adenosine monophosphate; ICER, inducible cAMP early repressor; ARG, arginase; VEGF, vascular endothelial growth factor; NFAT, nuclear factor of activated T cells; PD-1, programmed cell death protein 1; mTOR, mechanistic target of rapamycin; NKP46, natural cytotoxicity triggering receptor 1; NKG2D, natural killer group 2, member D; p38, p38 mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; c-Jun, Cellular Jun (proto-oncogene), component of AP-1 transcription factor; HIF, hypoxia-inducible factor.

promoting tumor cell aggregation. In conclusion, activation of the CAF phenotype facilitates tumor cell malignant growth and tissue infiltration, which in turn endangers the health of the organism. In addition, there is a metabolic symbiosis between tumor cells and tumor stromal cells. An example is the reverse Warburg effect, which refers to the ability of CAFs to undergo glycolysis under aerobic conditions and supply energy to cancer cells by secreting lactate (36). Lactic acid secreted by CAFs has been reported to increase the invasive potential of breast cancer cells through the stimulation of the TGF-β1/p38MAPK/MMP2/9 signaling axis and by bolstering mitochondrial bioenergetics (37). Besides, lactic acid enrichment in the TME can activate fibroblasts around tumors, which allows them to acquire a CAF phenotype (24). Low NAD+ levels were found to be a key factor in the inhibition of p62 and its CAF phenotypic activation in fibroblasts by lactate (38). These findings further point to a possible link among lactic acid metabolism, TME cells and epigenetic reprogramming in tumors.

Regulation of immune cells by lactic acid. Lactate can also influence other TME immune cells via specific mechanisms, which in turn modulate the immune response. These changes, in turn, contribute to a specific new homeostatic scenario for tumor progression.

TAMs. TAMs found in TME participate in cancer progression (39). Depending on the microenvironmental signals they receive, macrophages can differentiate into two main subtypes: Classically activated (M1) or alternatively activated (M2), where the M2-type plays a pro-tumor progression role. Lactic acid suppresses M1 polarization and contributes to their differentiation toward an M2-like phenotype (40). Lactic acid-induced acidosis can inhibit M1 macrophage function by decreasing the production of C-C motif chemokine ligand 2, inducible nitric oxide synthase and IL-6. In addition, lactic acid can suppress the production of ATPase H^+ transporting V0 subunit d2 in TAMs, which in turn promotes the progression of cancer. Lactate-induced polarization of M2 macrophages is associated with hypoxia-inducible factor (HIF)-1α stabilization, the signaling pathway of ERK-STAT3 and GPR132 activation (27,41). As a highly abundant receptor on the macrophage cell surface, GPR132 is a key mediator in inducing a proinflammatory phenotype in macrophages. Extracellular lactate sensing through GPR132 induces cyclic AMP production, which in turn induces inducible cAMP early repressor and ultimately upregulates the expression of numerous cytokines, contributing to the change of macrophages to a proangiogenic phenotype (42).

T cells and natural killer (NK) cells. In the TME, lactate accumulation triggers tumor lactatemia, which in turn inhibits cytotoxic T-lymphocyte function by suppressing the signaling

of p38 and JNK/c-Jun (43). It also interferes with the signaling pathway of mTOR, resulting in impaired NK T-cell function (44). Lactate-mediated intracellular acidification hampers the activation of nuclear factor of activated T cells (NFAT) in T cells and NK cells, thereby inhibiting IFN-γ secretion and their function and survival, which in turn weakens their immunosurveillance (12). The action of lactic acid on cytotoxic cells is complex and cannot be unilaterally categorized as a single effect. On one hand, the effects produced by lactic acid on cells may vary with the concentration or pH. On the other hand, lactate affects numerous aspects of the physiological functions of cells, such as cellular respiration, metabolic processes and immune functions.

Studies have shown that lactic acid is a crucial carbon source in physiological activities and plays a vital role in physiological processes such as energy metabolism. Some scholars have noted that the suppression of CD8+ immune function is related mainly to the acidic environment induced by lactic acid, but it can also serve as an energy source for T-cell metabolism, which can stimulate cellular vitality to a certain extent (45). Notably, the upregulation of LDHB enhances cellular respiration and partially reverses the suppression of T-cell function by lactate by counteracting with the inhibitory effect of lactic acid on the expression of intracellular cytokines (46). These observations suggest that enhancing the lactate metabolism of immune cells may promote immune-cell function to a certain extent.

Dendritic cells (DCs). DCs are pivotal parts in antigen presentation in antitumor immunity. In the TME, lactate is a known regulator of interfering with the effective antigen-presenting function of DCs by preventing lysosome formation via a process reliant on Chop that regulates endoplasmic reticulum stress (47). Tumor-secreted lactate is a key regulator of DC phenotype in the TME (48). According to reports related to lung cancer, lactic acid impacts DCs' role in orchestrating adaptive immune responses, accelerating antigen breakdown and interfering with cross-presentation (47). In the case of breast cancer, lactic acid influences DC activity through the activation of GPR81, which hinders the recognition of tumor antigens by other immune cells. In addition, lactic acid can restrict the process of IFN-α and IFN-γ induction in plasmacytoid DCs, thus restricting the antitumor immune response (49).

T-regulatory (Treg) cells. Tregs promote tumor immune tolerance by suppressing the growth and activation of immune cells and secreting immunosuppressive cytokines. Notably, Tregs utilize lactate to increase function and growth (50,51). In a low-glycemic and lactic acid-rich environment, Tregs have an advantage in metabolism and rely on the uptake and metabolism of lactic acid to maintain their potent inhibitory functions (52-54). At the mechanistic level, lactate may be able to regulate Treg cell activity by mediating the lactation of MOESIN and enhancing TGF-β signaling, thereby promoting Treg cell maturation and differentiation (55). In addition, in the glycolysis-dominant TME, lactate functions as a key metabolic regulator, modulating the activity of Tregs by enhancing programmed cell death (PD)-1 expression. The monocarboxylate transporter 1 is instrumental in this process, importing lactate into Tregs. This lactate influx then promotes the nuclear accumulation of NFAT1, ultimately leading to increased expression of the key immunosuppressive receptor PD-1 (21). Some investigators have suggested that the induction of Tregs in the TME may be enhanced via a lactate-dependent pathway (56,57). These findings imply that increased lactate from tumor glycolysis may impact immune tolerance in the TME via Treg checkpoint pathways.

Neutrophils. In a preclinical model of sepsis, lactic acid reportedly contributes to the upregulation of the PD-L1 immune checkpoint molecule on neutrophils via an MCT1-dependent mechanism, giving rise to a decrease in apoptosis and exacerbation of the morbidity of the disease (58). In mouse experiments, prolonged, high-intensity exercise yielded decreased levels of lactate-driven neutrophil extracellular traps (NETs). Conversely, lactate drives NET release from human neutrophils through NADPH oxidase (NOX)-mediated and NOX-independent NETotic processes (59).

Myeloid-derived suppressor cells (MDSCs). In the TME, MDSCs drive immunosuppression effects, including T-cell suppression and congenital immunomodulation. As early as 2013, it was shown that lactate from tumors boosted the count of MDSCs, which in turn inhibited NK cytotoxicity (60). Follow-up studies have confirmed that lactic acid recruits MDSCs and regulates their development, influencing the dynamic relationship between anti-tumor immunity and malignant progression (61,62). Another pancreatic cancer study indicated that lactic acid activates MDSCs via the pathway of GPR81/mTOR/HIF-1α/STAT3 and enhances their immunosuppression (63).

In conclusion, lactic acid is crucial for the TME and is no longer considered 'metabolic waste'. It regulates cellular metabolism and immunity in the TME through various signaling molecules and mechanisms, and these findings indicate a promising avenue in the targeting of lactate metabolism in tumor therapy.

4. Lactate metabolism combined with targeted therapy

A wealth of research has revealed that lactate occupies an indispensable position in the TME, and its metabolism has been increasingly studied with the aim of enhancing the therapeutic effects on tumors. The process of lactate metabolism can be divided into three parts: Lactate anabolism (Fig. 4), lactate catabolism and lactate transmembrane transport. By regulating the three phases of lactate metabolism, researchers aim to find increasingly effective ways to treat tumors.

Blocking lactate anabolism. Blocking lactate anabolism can decrease lactate enrichment in the TME from the root and break down the metabolic adaptations of tumors, thus curbing their survival and development in a hostile environment. Oncogenic lesions in tumors increase the levels and activity of enzymes involved in glycolysis, which drive the metabolic shift to aerobic glycolysis and then generate lactic acid. Malignant tumor cells often exhibit obvious aerobic glycolysis, which leads to excessive dependence on glucose, referred to as 'glucose addiction'. To meet the demand for glucose for rapid proliferation, tumor cells overexpress glucose transporter protein (GLUT) to accelerate the transmembrane transport of glucose (64). After glucose is transported to cancer cells, it is transformed into lactate through a cascade of enzymes.

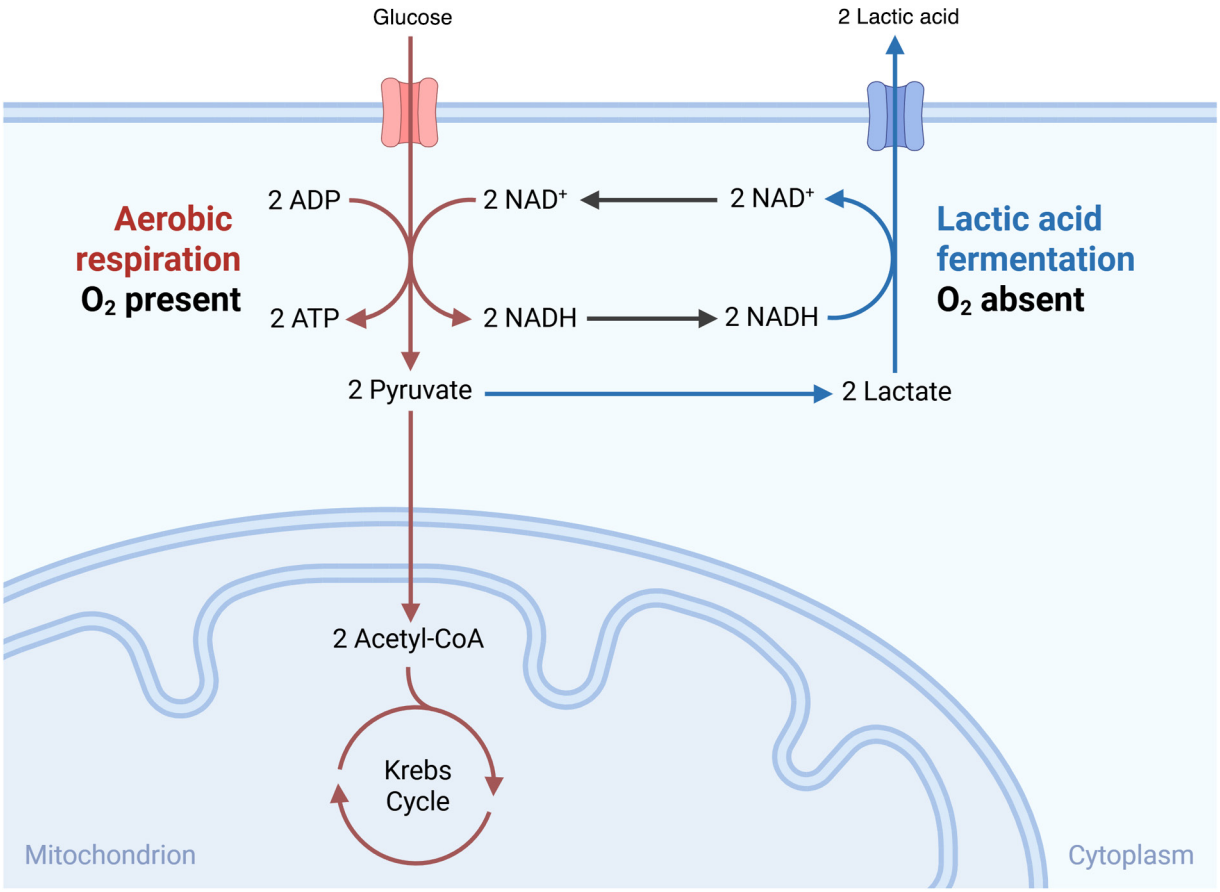

Figure 4. Process of lactic acid production.

Therefore, it may be hypothesized that directly blocking tumor cell glycolysis through inhibition of glucose transport and inactivating enzymes of glycolysis could effectively reduce lactate levels in the TME.

Currently, numerous drugs targeting GLUT and enzymes of the glycolytic pathway, such as hexokinase 2 inhibitors (3-bromopyruvate), LDHA suppressors (GNE-140), etc., are receiving extensive attention (65-67). However, these drugs face serious challenges in clinical translation, such as high body-wide adverse effects and poor therapeutic efficacy. The fundamental properties of nanoparticles, such as tumor-targeting capacity, blood circulation steadiness and ability to modulate enzyme activities, render them appropriate for targeted suppression of tumor cell glycolysis. Researchers have engineered various nanoplatforms to suppress lactic acid generation in tumor cells via diverse intervention approaches, including blockade of glucose uptake (68), alleviation of tumor oxygen deprivation (69) and reduction in enzymatic activities in the glycolytic pathway (70,71). These nano-systems have been demonstrated to disrupt tumor cell energy metabolism and remodel the TME, thus inhibiting tumor expansion.

Promoting lactic acid catabolism. Owing to elevated glycolytic activity in tumor cells, lactic acid levels in tumor tissues markedly increase over normal tissue levels. The exocytosis of proton-coupled lactate from tumor and stromal cells promotes the creation of an acidic tumor-promoting milieu that facilitates tumor proliferation, invasion, angiogenesis, metastasis, drug resistance and immune escape. Therefore, enhancing lactate catabolism within tumors is an attractive strategy to increase the efficacy of tumor therapy. Currently, a range of micro/nano-systems have been engineered to promote lactic acid catabolism, which could be categorized into three main groups: Native bio-enzyme nano-systems, man-made nano-enzymes and living bacteria. Lactate oxidase (LOX) and LDHB are common natural enzymes involved in lactate catabolism (72,73). Researchers have engineered a range of nano-enzymes with LOX- or LDHB-like catalytic activities (74), for example, SnSe nanosheets, NiO@Au nanocomposites and Co_4N/C (75). In addition to nano-enzymes, lactic acid can be used as a metabolic substrate by some microorganisms in nature, such as *Acidobacter oxidans* (76), Snapper (77), *Fusobacterium harzianum* (78), *Anaerobacter* spp. and *Veillonella atypica* (79). Compared with natural enzymes, live bacteria have better *in vivo* stability and higher catalytic efficiency than artificial nanozymes (80). Critically, some bacteria are naturally tumorophilic and can actively penetrate into the tumor and enrich the tumor site, thus enhancing the antitumor effect.

Blocking lactate transmembrane transport. Abnormally high expression of MCT on tumor cell membranes efficiently mediates lactate transmembrane transport and enhances the interaction among cancer cells and the adjacent microenvironment. In solid malignancies, internal hypoxic tumor cells accelerate glycolysis to generate substantial lactate, which is exported to the extracellular compartment through overexpressed MCT4. By contrast,

peripheral oxygen-enriched tumor cells highly express MCT1, which takes up lactic acid and converts it to pyruvic acid, which acts as an energy source for energy metabolism. This metabolic heterogeneity triggered by differences in oxygen and nutrient supplies ensures the fuel sustenance of neoplastic cells from different ecological niches under unfavorable conditions and facilitates metabolic symbiosis among tumor cells. Current studies have confirmed that a number of tumor cells overexpress MCT. For instance, in tumors such as glioblastoma and colon and breast cancers, MCT1/MCT4 expression in terms of mRNA and protein are significantly elevated, which contributes to driving tumor progression, enhancing chemotherapy resistance and inducing immunosuppression (81). From a therapeutic perspective, blocking lactate transmembrane transport to disrupt metabolic symbiosis stands out as a powerful and innovative method for treating tumors. Specifically, the lactate supply between cancer cells can be blocked by targeting MCT4-mediated lactate outflow in hypoxic zones or MCT1-mediated lactate inflow in aerobic tumor regions. This approach can disrupt the competitive metabolic edge of tumoral cells in a harsh environment and thereby suppress tumor expansion.

Over the past few years, various nanoparticle-based formulations that target lactate transmembrane transport have been published, and these drugs have exhibited significant antitumor effects. For example, several small-molecule inhibitors of MCT4, including lonidamine (LND), pyrazole derivatives and singolapine, have been developed. To optimize the pharmacokinetic properties of LND and facilitate its precise tumor targeting, Zhao *et al* (82) developed a self-assembled nanodrug system named TerBio, which is formed by Ce6, SB505124 and LND. In addition, to enable regulated drug release, a smart-responsive nanoplatform 'HMON@HCPT-BSA-PEI-CDM-PEG' was constructed, which was able to provide good stability, safety and targeting ability for therapeutic agents by progressively reacting to the low-pH TME and glutathione-dependent intracellular redox environments to achieve controlled drug release (83).

Although inhibiting MCT4 is a highly promising antitumor strategy, the complex structural composition of solid tumors makes it hard for nanotherapeutic agents to access the target organ and release the drug. Therefore, well-designed nano-system structures are still needed to increase the efficacy of MCT4 inhibitors.

5. Conclusions and outlook

The current review presents the processes of lactic acid production, transport and accumulation in cancerous tissues and describes the effects of lactate on tumor progression through multifaceted mechanisms. In addition, it provides insights into the associations among lactic acid, drug insensitivity and the immune response in tumors and analyzes the therapeutic potential of lactate in clinical applications. With the continuous progress in modern disciplines, the research and development of small-molecule and biomacromolecule antineoplastic agents has entered a phase of rapid development. To date, a variety of small molecule inhibitors and gene drugs that target lactic acid metabolism in tumors have arisen as potential tumor therapies, showing significant advantages. However, these drugs generally have several shortcomings, such as poor circulatory stability, poor bioavailability, difficulty in effectively reaching the tumor site and off-target effects, which severely restrict their clinical translational applications. In recent years, nanoscience and nanotechnology have made rapid progress and are revolutionizing the delivery of antitumor drugs. Studies have shown that nano-formulations can effectively optimize the pharmacokinetic properties of lactic acid metabolism-targeted drugs, significantly enhance the agent's pharmacokinetic profile, mitigate off-target toxicity and enable a theranostic approach that combines both therapy and diagnostics.

In conclusion, although the regulation of lactate metabolism in antitumor therapy is challenging, various types of nano-systems represent a promising class of materials that offer a viable pathway to boost bioavailability and improve the safety profile, thereby increasing their clinical viability. After a comprehensive review and a deep dive into numerous recent advances in this domain, the present review expects to establish a foundation for understanding the future development of high-performance nanomaterials that interfere with lactic acid metabolism and develop more effective nano-formulations that enhance cancer therapy. Furthermore, dissecting the role of lactate metabolism in the immunoregulation of the TME may be helpful for the clinical application of immunotherapy.

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Authors' contributions

ML performed the literature search, selection and collation of information, writing-original draft and writing-review and editing. KS was responsible for supervision, conceptualization, project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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