Review Article

Lactic acid: a narrative review of a promoter of the liver cancer microenvironment

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Background and Objective: Lactic acid is a metabolite of glycolysis produced in the body, and its production is thought to be a mechanism by which cancer cells evade immune surveillance. Immune evasion and metabolic changes are well established as basic hallmarks of cancer. Although lactate has long been considered a waste product, it is now generally recognized to be a versatile small-molecule chemical that plays an important part in the tumor microenvironment (TME), with increased lactate production linked to the development of human malignancies. Metabolism in liver cancer is redirected toward glycolysis, which enhances the production of metabolic compounds used by tumor cells to produce proteins, lipids, and nucleotides, enabling them to maintain high proliferation rates and to establish the TME. Dysregulation of metabolic activity in liver cancer may impair antitumor responses owing to the immunosuppressive activity of the lactate produced by anaerobic glycolytic rates in tumor cells. This review primarily explores the link connection between lactic acid and the TME; evaluates the role of lactic acid in the occurrence, metastasis, prognosis, and treatment of liver cancer. Additionally, it investigates the associated pathways as potential targets for liver cancer treatment.

Methods: Literature searches were conducted in PubMed, Web of Science, and Google Scholar, with the publication date of the most recent article included being January 2024. After eliminating duplicate articles and less relevant articles through titles and abstracts, we selected 113 articles for this review. We categorized references into two categories. One is to classify the content into lactate-related, liver cancer-related and tumor metabolism-related. The other is to classify the article types, which are divided into reviews, research articles and clinical trials. Additionally, we consulted the reference lists of the relevant articles to ensure coverage was comprehensive and unbiased.

Key Content and Findings: The connection between lactic acid and the TME has recently become an area of intense research interest, and many related articles have been published in this field. The main finding of this review is to summarize the proven link between lactate and the TME and its possible impact on the TME of liver cancer. And analyzed the potential of lactate in liver cancer treatment and prognosis prediction.

Conclusions: Lactate may be key to developing novel approaches in the future treatment of liver cancer. Related research on the combination of classic therapies and molecular targeted drugs may provide innovative medicines that more selectively regulate immune cell activity.

Keywords: Lactic acid; liver cancer; tumor microenvironment (TME); cancer metabolism; immune cells

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Introduction

Background

Liver cancer is among the most common fatal cancers worldwide, with its incidence being higher in developing countries and increasing year by year (1,2). The causes of liver cancer include hepatitis B virus, hepatitis C virus, fatty liver disease, alcohol-related cirrhosis, and smoking (3). A study shows that only 5% to 15% of patients are suitable for surgical resection, all of whom have early-stage disease. Therefore, patients with liver cancer have poor prognosis, with fewer than one-third being able to benefit from treatment owing to the weakened regenerative capacity of the liver (4). Due to low efficacy of the currently available treatment options, research is needed to develop more effective approaches in the treatment of treat liver cancer.

Tumor-induced recruitment of immune cells is an early response to incipient disease and leads to immune-mediated facilitation of tumor cell proliferation, survival, and angiogenesis through the initiation of oncogenic inflammation (5). If the early influx of immune cells successfully detects an abnormality and mounts an immune response, the malignant cells will be eliminated directly. However, if insufficient signaling or response results in immune evasion, tumors can develop and begin to grow locally, eventually spreading to distant sites. The development of a tumor is accompanied by a cascade of soluble factors that promote the influx of nonmalignant cells, blood vessels, and stroma, which together form the tumor microenvironment (TME) (6). As tumors progress, the TME gradually changes and may become highly complex. Research into the nature of the TME can thus be expected to result in new interventions for improving treatment response.

Lactic acid was first discovered in sour milk by Karl Wilhelm Scheele in 1780 (7). In normal tissue, lactate concentrations range from 1.5 to 3 mM, whereas in tumor tissue, concentrations may be as high as 10 to 30 mM (8,9). The energy consumed by tumor cells derives mainly from the conversion of glucose to lactate through glycolysis, whereas normal cells use glucose for oxidative phosphorylation (OXPHOS) to produce adenosine 5'-triphosphate (ATP) (10). Glutamine can also be enzymatically converted to lactate. Isotope analysis using U-13C-labeled lactic acid has demonstrated that when cells are starved of glucose, a number of tricarboxylic acid (TCA) intermediates are instead produced from lactic acid (11,12). Lactate is normally produced by glycolytic cancer cells and cancer-associated fibroblasts (CAFs) in tumor tissue (13).

Objective

The aim of this study was to examine the connection between lactate and the TME; evaluate the role of lactate in the occurrence, metastasis, prognosis, and treatment of liver cancer; and identify related pathways that may serve as potential targets for liver cancer treatment. We present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-368/rc).

Methods

Literature searches were conducted in PubMed, Web of Science, and Google Scholar, with the publication date of the most recent article included being January 2024. The keywords used for these searches were as follows: lactic acid, lactate, TME, liver cancer, metabolism, immune cell, macrophage, Warburg effect, cancer metabolism, and hepatocellular carcinoma (HCC). After eliminating duplicate articles and less relevant articles through reading the titles and abstracts, we selected 113 articles for this review. Additionally, we consulted the reference list of the relevant articles to ensure coverage was comprehensive and unbiased (*Tables 1*,*2*).

The lactic acid and the metabolic needs in the TME

Lactate within the TME contributes to multiple manifestations of tumor progression, including cell proliferation, migration, angiogenesis, therapy resistance,

Table 1 The search strategy summary

Items	Specification
Date of search	Feb 1st, 2024
Databases and other sources searched	PubMed, Web of Science, and Google Scholar
Search terms used	Lactic acid, lactate, TME, liver cancer, metabolism, immune cell, macrophage, Warburg effect, cancer metabolism, and HCC (filters: review, clinical trial, free full text, full text, 2023, and 2024)
Timeframe	1924–2024
Inclusion and exclusion criteria	Inclusion: original articles, clinical trials, and reviews were included. In addition, we consulted the reference lists of relevant articles
	Exclusion: non-English articles were excluded
Selection process	J.C., G.H., and D.C. conducted the selection and completed the screening; consensus was reached through discussion among all authors

TME, tumor microenvironment; HCC, hepatocellular carcinoma.

Table 2 Search strategy of PubMed

Items	Specification
Database	PubMed
Keywords	Lactic acid, lactate, TME, liver cancer, metabolism, immune cell, macrophage, Warburg effect, cancer metabolism, and HCC
Filters	Review, clinical trial, free full text, full text, 2023, and 2024

TME, tumor microenvironment; HCC, hepatocellular carcinoma.

and evasion of immune surveillance. The metabolic control systems of tumor cells determine when nutrients are required to create components for new cells. When nutrition is scarce, the cells stop production of biomass and adjust their metabolism to survive. Different regulatory mechanisms control cellular metabolism in proliferating versus nonproliferating cells, reflecting fundamental differences in metabolic requirements. Glucose metabolism utilizes energy in the form of ATP through the oxidation of carbon bonds. In mammals, the product of this process is lactic acid, which is completely oxidized to carbon dioxide—a process that is critical to sustaining life. Among cells that are proliferating or developing, even if there is sufficient oxygen and mitochondria, the intake rate of glucose increases significantly and large amounts of lactic acid are simultaneously produced, which is known as the Warburg effect.

Sources of lactic acid

During aerobic glycolysis, most of the carbon involved in the process is not retained, being mainly excreted in the form of lactic acid (14). However, higher rates of glucose metabolism occurring via aerobic glycolysis can result in 10- to 100-fold higher rates of lactate production compared with complete oxidation via mitochondrial metabolism. Therefore, lactic acid is also a hallmark of the Warburg effect.

The increased demand for ATP metabolism in tumor cells promotes aerobic glycolysis, which leads to high levels of glycolysis, such that lactate concentrations inside and outside the cells are higher than those of cells in a resting state. Accumulation of lactic acid in the TME is also a characteristic of inflammatory diseases (15) (*Figure 1*).

The emerging role of the Warburg effect in the TME

Most cells receive a constant nutrient supply. When nutrient availability exceeds the level required for cell division, cell proliferation occurs abnormally. Some of these pathways constantly activate nutrient intake and metabolism, thereby promoting cell survival and refueling cell growth (16,17). As evidence accumulates, it is becoming increasingly clearer that oncogenic mutations in cells lead to excessive glucose uptake to meet or exceed the bioenergetic needs of cell

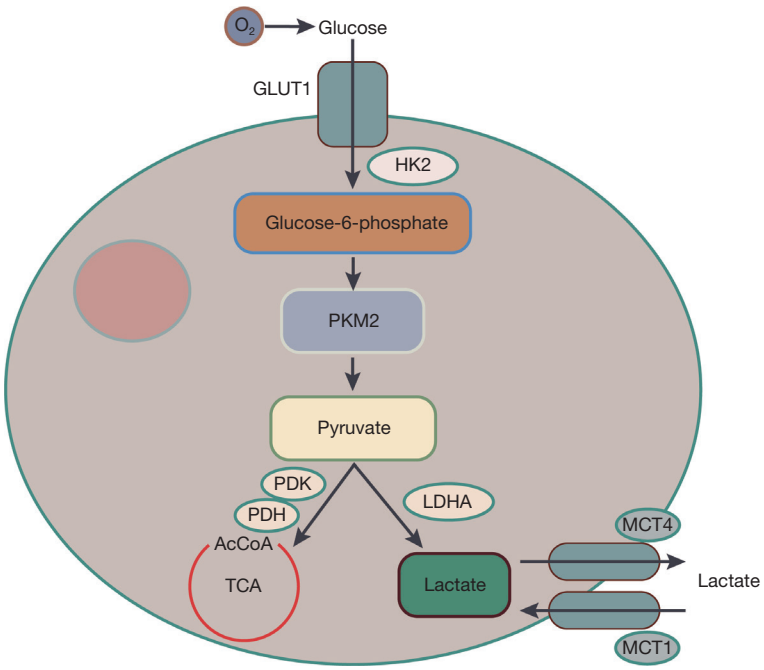

Figure 1 Production and reduction mechanism of lactate. Classical intracellular pathways of lactate production from proteomic, genomic, and transcriptomic domains are shown. GLUT1, glucose transporter 1; HK2, hexokinase 2; PKM2, pyruvate kinase M2; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter.

growth and proliferation. In 1924, Otto Warburg discovered that cancer cells metabolize glucose differently compared to normal tissue cells (18,19). Unlike most normal tissues, cancer cells preferentially convert glucose into lactate even when sufficient oxygen is available to support mitochondria for OXPHOS. The energy demands of proliferation can be better met by maximizing ATP production by utilizing mitochondrial OXPHOS, which enables the complete catabolism of glucose.

The Warburg effect is an adaptive mechanism that can generate lactic acid to meet the growth needs of tumor cells (20). The glucose in the TME can serve as the carbon source of synthetic metabolic processes for the synthesis of nucleotide, lipids, and proteins (16,21). The Warburg effect increases nicotinamide adenine dinucleotide phosphate (NADPH) synthesis to manage the excessive oxidative stress in tumor cells (10,22). In addition to NADP+ and NADPH, the conversion from pyruvate to lactic acid requires NADH, which requires the regeneration of NAD+ to avoid excessive accumulation of NADH. NADH and NAD+ are also critical elements in mitochondria for regulating tumor cell oxidation and restoration (23).

Of note, the Warburg effect can be regulated by methylation (24). Methylation regulates metabolism by changing the activity and state of DNA, RNA, and proteins. DNA methylation is among the causes of glucose metabolism abnormalities in cancer and further promotes the production of lactic acid (25). A study has demonstrated that hexokinase 2 (HK2) upregulation can be mediated through hypomethylation of its promoter, thereby promoting HK2 expression and tumor progression (26). DNA methylation in cancer can also upregulate the expression of hypoxia-inducible factor (HIF)-1α and the activity of the HIF pathway (25). In addition, glycolytic enzymes such as lactate dehydrogenase A (LDHA) and pyruvate kinase M2 (PKM2) can be methylated by methyltransferases, which changes their activity (27,28). Methylation thus plays an important part in the regulation of glycolytic metabolism in cancer cells.

TME and its constituent immune cell populations

The completion of metabolic reactions in the TME relies on various immune cells (29,30). The TME is composed

of tumor cells, endothelial cells, CAFs, and immune cells, in addition to a noncancerous cellular matrix containing a variety of peptide components such as growth factors, chemokines, cytokines, and antibodies (31). Tumor cells may exert a significant impact on energy expenditure, as tumor cells often require increased glycolysis rates to meet their energy needs. As an energy source, signaling molecule, and key tumor immunosuppressor, lactate can affect a variety of cellular activities in the TME (32). The extracellular TME is usually slightly acidic because cancer cells overuse glucose, which causes lactic acid to accumulate, in turn promoting tumor spread, treatment resistance, and immunosuppression (33,34). The production of lactate also promotes tumor growth by reducing the ability of natural killer (NK) cells and NK T cells to fight cancer. NK T cells are antitumor immune cells that produce cytokines in adaptive immune response (35-37). Inflammatory cytokines are essential for the polarization of T helper cells and the differentiation of inflammatory dendritic cells (DCs), with the slightly acidic environment of the TME inhibiting their release (38). Lactic acid increases immunosuppression and cancer growth by inhibiting T-lymphocyte proliferation and cytokine release and by inhibiting DC differentiation and inducing tolerance (39,40). Increased interleukin (IL)-10 production enables evasion of immune surveillance by NK cells. Treg cells take up lactate through MCT1, promote the nuclear translocation of nuclear factor of activated T cells 1 (NFAT1), and then enhance their own programmed cell death 1 (PD-1) expression. This symbiotic relationship in which tumor cell-derived lactic acid serves as an important energy substance for Treg cells illustrates that PD-1 blockade can rejuvenate PD-1-expressing Treg cells, leading to the failure of immunotherapy. Two types of tumor-associated macrophages (TAMs) have been identified in the TME—the traditional M1 phenotype that inhibits cancer cell proliferation and the M2 phenotype with the opposing function—both of which can promote cancer cell growth and metastasis. Lactate increases tumor cell proliferation and migration by stimulating ERK/STAT3 signaling (41,42). TAMs can increase the polarization of the M2 phenotype of macrophages in a monocarboxylate transporter (MCT)-dependent manner, but their function is inhibited by tumor-derived lactate (43). The phenomenon in which CAFs use mitochondrial OXPHOS to maintain tumor growth and metastasis while transporting lactate to oxidized tumor cells through TCA is called the anti-Warburg effect (44). CAFs are tumor tissue cells that figure prominently in tumor development, invasion, and metastasis via paracrine pathways (45). Changing the immune status of tumor-infiltrating immune cells is a means to influencing tumor growth pathways. When lactic acid accumulates, the Warburg effect and lactic acid shuttle occur, which can lead to acidosis and immunosuppression and promote tumor cell proliferation and survival. Overall, lactate in the TME can reduce immune cell activity and allow tumor cells to evade immune responses to promote growth (*Figure 2*). In addition to the tumor cells themselves, lactate also affects stromal cells in the tumor microenvironment. It can inhibit the killing function of immune cells, regulate the metabolism of tumor-related fibroblasts, and coordinate the "metabolic symbiosis" between cells. This helps tumor cells adapt to immune and stromal cells. Lactic acid can serve as a metabolic link between tumor cells and other TME cells, helping tumors better adapt to the environment and evade immune attack.

Macrophages

Macrophages are important innate immune effector cells derived from monocytes, which migrate through the circulatory system to virtually every tissue in the body (46-48). Macrophages generally adopt an M1 or M2 phenotype in response to their microenvironment. M1 macrophages can directly target cancer cells, exerting proinflammatory or phagocytic functions to release or engulf cytokines, respectively (49). They can also indirectly target cancer cells, which requires the recruitment of chemokines and the use of cytokines to activate other immune effector cells.

M2 macrophages are critical for tumor initiation and progression and exert the opposite function compared to M1 macrophages. They release a variety of cytokines and growth factors to promote immune suppression, angiogenesis, tumor cell invasion, and metastasis (50). Both the acidic TME and increased lactate levels affect macrophages, and a study has demonstrated alterations in macrophage phenotype and function due to the low pH in the TME (51). Moreover, lactate secreted by tumor cells can transmit key signals that induce M2 polarization in the TME. One study reported that when M1 and M2 macrophages were incubated at pH 7.4 and 6.8, respectively, M2 macrophages showed increased viability and better adaptability under lower pH conditions, and the expression of M2 markers under acidic pH conditions was even higher than that under alkaline pH conditions (52).

Lactate in macrophages has a direct effect on M2 marker

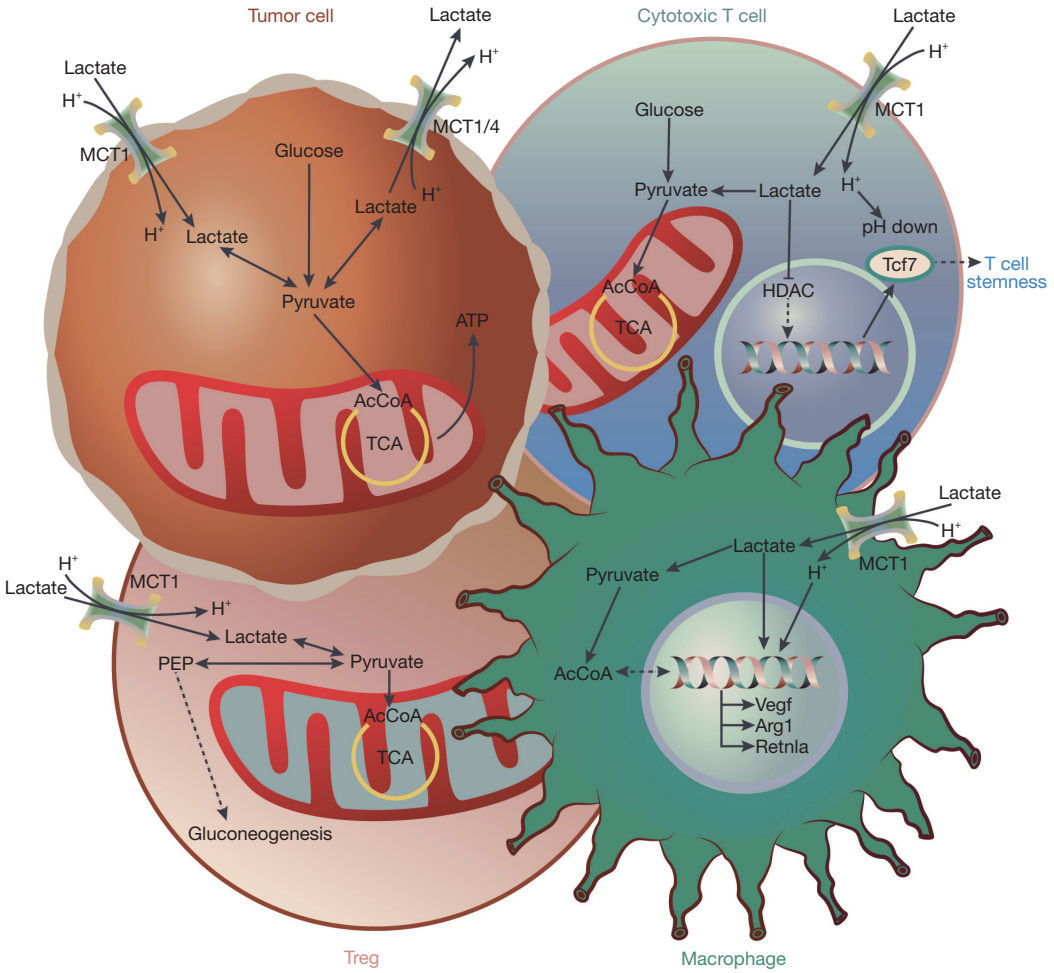

Figure 2 Effects of lactic acid and lactate in the TME. Lactate can be exported simultaneously with protons through MCT1 or 4 and acidify the extracellular space in vitro. Cells acquire lactate through MCT1 and then convert it to pyruvate to produce TCA. Extracellular lactic acid regulates the transcription of genes such as *VEGF*, *ARG1*, and *Retnla* in macrophages, which affects their anti-inflammatory differentiation. Lactate can enter the cytosol of cytotoxic T cells and lower intracellular pH. Acidification inhibits cellular glycolysis, proliferation, and cytokine production. Lactate can also be taken up by cells via MCT1 and fuel the TCA cycle. Lactate acts as a HDAC inhibitor at high concentrations, thereby increasing Tcf7 transcription. The exposure to lactic acid is also closely related to the proliferation and inhibitory function of regulatory T cells. MCT, monocarboxylate transporter; ATP, adenosine 5'-triphosphate; TCA, tricarboxylic acid; PEP, phosphoenolpyruvate; HDAC, histone deacetylase; TME, tumor microenvironment.

arginase 1 (*ARG1*) and neovascularization factor vascular endothelial growth factor (*VEGF*), levels of which change as lactate levels decrease or increase (42,53). Therefore, the expression of the M2 macrophage-related homeostasis genes is closely related to lactate.

NK cells

NK cells are innate immune cells that are well-documented to exert antitumor effects and strong cytolytic activity (54-56). NK cells participate in early tumor immune surveillance and can produce and release perforin, granzymes, and cytokines, and their therapeutic role in solid tumors is being explored (57). Lactate-induced extracellular acidosis in the TME inhibits the antitumor activity of NK cells, and elevated lactate levels reduce NK cell activity and increase tumor size. However, the effects of the acidic TME on NK cells are reversible in various cancers. Increasing the pH of the TME from an acidic pH of 6.5–6.9 to a more physiological pH of 7.2–7.5 can increase the interferon (IFN)-γ production of NK

cells and delay tumor growth (58). Downregulation of MCT4 decreases extracellular lactate concentration in the TME, thereby increasing pH. Reversing TME acidity has been shown to enhance NK cell activation and degranulation, as evidenced by increased perforin and CD107a expression (59). Lactate dehydrogenase (LDH) generated from lactic acid can spontaneously release activity, which is related to NK cell dysfunction. Tumor-derived lactate can inhibit the cytolytic function of human NK cells and reduce NK cell toxicity, which is usually accompanied by a decrease in the expression of perforin and granzymes in NK cells. Therefore, the inhibition of NK cell function by lactate in the acidic TME can be functionally reversed via changes in pH.

DCs

DCs are responsible for activating the adaptive immune response and can connect the innate and the adaptive immune systems. Monocytes that serve as macrophage precursors can differentiate into monocyte-derived DCs, which can not only activate naive T cells but also induce antigen-specific T cell-mediated immune responses (60,61). As T cells are critical for antitumor immune responses and as sufficient DC activity is required for T-cell activation, the functions of cancer-associated DCs can be inhibited by an acidic TME (62). A study has found that TME-rich immunosuppressive factors limit the immunostimulatory capacity of DCs and that high levels of lactic acid in an acidic environment inhibit DC differentiation and maturation (63). When IL-4 and granulocyte macrophage colony-stimulating factor (GM-CSF) are secreted by different tumor cell lines, the DC front ends did not express CD1A and fail to differentiate into DC. Although acid poisoning in an acid-induced TME damages the differentiation of monocyte cells into DCs, as is the case with other congenital immune cells, the inhibitory effect of lactic acid can be reversed (64). The accumulation of lactic acid in the tumor microenvironment can affect the differentiation and antigen presentation functions of DCs. Lactic acid also weakens the release of interferon-alpha (IFN-α) by plasmacytoid DCs by affecting the cellular metabolism required for the activation of plasmacytoid DCs, affecting the anti-tumor immune response. At the same time, lactic acid enhances the tryptophan production of plasmacytoid DCs. Acid metabolism and L-kynurenine production contribute to the induction of the major immunosuppressive immune cell subset in the tumor microenvironment. The impact of lactic acid accumulation on DCs plays a negative role in the antigen presentation process and hinders tumor immunity. Therefore, enhancing DC function can be used as a method to overcoming immune suppression in cancer immunotherapy.

Neutrophils

Neutrophils, whose functions include secreting cytokines and phagocytosis, participate in exerting immunity against invading pathogens and against cancer progression and metastasis (65,66). Neutrophils, similarly to macrophages, exhibit two phenotypes, N1 and N2, with the N1 phenotype having the potential to kill tumor cells (67,68). The N2 phenotype is capable of inducing immunosuppression in the TME owing to the higher expression of arginase and tumor-promoting factors (69), and N2 neutrophils in the TME have a protumor phenotype. A key regulator of apoptosis and neutrophil function is extracellular acidosis, which is caused by the secretion of lactate produced by tumor cells (70). Neutrophil apoptosis can be delayed by a decrease in intracellular pH via extracellular acidosis (71). The decrease in intracellular pH caused by the acidic TME affects the activity of various intracellular enzymes. Lactic acid in the acidic environment promotes the differentiation of neutrophils into the N2 phenotype, thereby promoting their alternative functions, inhibiting the production of reactive oxygen species (ROS), and reducing their phagocytic function. Tumor-associated neutrophils in the acidic TME promote the growth and metastasis of tumor cells by, among other processes, inhibiting T cells, producing angiogenic factors, and secreting proteases. They can also express high levels of β2 integrin and CD11b/CD18, indicating that TME acidity significantly enhances the tumor-promoting function of tumor-associated neutrophils (72).

Myeloid-derived suppressor cells (MDSCs)

Under normal circumstances, bone MDSCs can differentiate into granulocytes, macrophages, or DCs. However, this differentiation is compromised under acidic conditions, leading to the accumulation of MDSCs, which in turn can induce strong immunosuppressive effects, resulting in the expression of multiple cytokines and immunodynamic regulatory molecules. MDSCs can inhibit lymphocytes that are vital to T-cell function and deplete metabolic products, thereby stimulating other immunosuppressive cells to express adenosine metabolism

and generate extracellular enzymes that produce active oxygen (73). The accumulation of MDSCs in tumor cells is thought to promote immunosuppression in the TME (63). In the acidic TME, the lactate-induced HIF-1α pathway enhances MDSC activity, which leads to increased expression of programmed death ligand 1 (PD-L1) and bone marrow cell death (74). Tumor-derived lactate indirectly inhibits NK cell function by increasing the number of MDSCs that can inhibit NK cell toxicity. In addition, MDSCs can also initiate the formation of a tumor cell premetastatic niche, which increases angiogenesis and enhances tumor cell stemness (75).

The role of lactic acid in liver cancer

Under normal conditions, liver cells' use of glucose can markedly change throughout the day depending on whether the organism is in a fed or fasted state. Epithelial cells and liver cells slowly and effectively produce ATP from glucose through oxide acidification (76). However, tumor cells switch from OXPHOS to aerobic glycolysis as the primary mode of glucose metabolism to meet increased energy and biomolecule conversion demands (77-80). Under normal circumstances, OXPHOS can produce 36 molecules of ATP. The efficiency of ATP production during glycolysis is much lower, with each glucose molecule generating only two molecules of ATP. However, aerobic glycolysis skips the OXPHOS pathway and can rapidly generate ATP and a host of anabolic and biosynthetic biomolecules involved in the production of new structures for cell growth and proliferation (81-83). The pentose phosphate pathway is a key process through which the intermediate metabolite of glycolysis, glucose-6-phosphate, is converted into ribulose-5-phosphate, which ultimately becomes a new nucleotide. The NADPH produced in this process is subsequently used for lipid synthesis (84).

Characteristics of the TME of liver cancer cells

Cancer cells are not isolated in the human body; rather, they communicate with the surrounding matrix cells, immune cells, and other cancer cells; detect changes in the extracellular environment; and make corresponding adjustments (85). These interactions result in ecosystems in which cancer cells and nontumor cells coexist, increasing the diversity of tumor metabolism (23,86). Nonmalignant cells in the TME typically exert a tumor-promoting effect in all stages of cancer development by stimulating uncontrolled cell proliferation (87,88). Malignant cells invade healthy tissues and spread to other parts of the body via the lymphatic or circulatory system.

The TME contains various cellular components. One of these is endothelial cells, which contribute significantly to tumor development and the protection of tumor cells against the immune system. These cells provide nutritional support for tumor growth and development by influencing angiogenesis (32). Immune cells constitute another component of the TME and participate in various types of immune response and activity, with macrophages in the TME exerting multiple functions related to the initiation and progression of cancer. For instance, they promote the infiltration of cancer cells into distant parts of the body, resulting in the establishment of metastatic colonies (87,89,90). TAMs can enhance, mediate, or antagonize the antitumor activity of radiation, cytotoxic drugs, and checkpoint inhibitors. The final component of the TME is fibroblasts (91-93), which allow tumor cells to migrate from the primary tumor site into the bloodstream for systemic metastasis.

A heterogeneous TME causes hypoxia, extracellular acidosis, and nutrient deficiency, thereby significantly changing the proportion of immune cells and inducing metabolic reprogramming of stromal cells and immune cells (94,95). Glycolytic metabolism also reshapes the TME. Lactic acid can promote tumor cells and TAMs to secrete a series of factors that support vascular production, and endothelial cells can detect levels of extracellular lactic acid, which promotes their proliferation. CAFs and cancer cells can also promote each other's degrees of glycolysis. In addition, some tumor cells in the TME can take up lactic acid and undergo oxidative metabolism, which is known as the reverse Warburg effect.

Lactic acid metabolic regulation as a component of the liver cancer cell machinery

The glycolytic shift in tumor cells involves multiple pathways, including HIF, p53, and Ras, among others (96). A dramatic increase in glucose metabolism causes its end products to accumulate in the TME and triggers the immunomodulatory functions of intertumoral NK cells. Free adenosine in tumor cells is generated by the cleavage of extracellular ATP by CD39 and CD73, thereby initiating these cells' anti-inflammatory response. Following glucose uptake, glycolytic conversion to pyruvate occurs via increased glucose transporter 1/3 (GLUT1/3) expression.

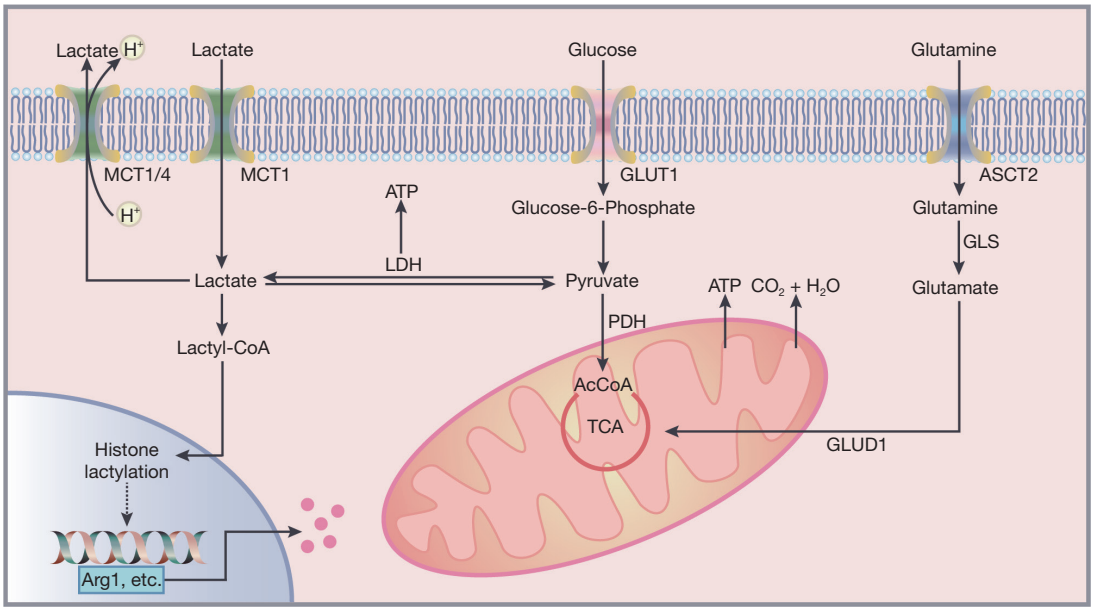

Figure 3 Lactate metabolism in the TME of liver cancer. Lactate is catabolized in cells through a variety of pathways. Lactic acid can be transferred to oxidic tumor cells with MCT1 being used as the fuel. In the cytoplasm, lactate is transported into the cell via MCT and is produced by glycolysis or glutaminolysis, thus generating energy via OXPHOS. Lactic acid can be converted into lactyl-CoA and participates in the lactylation of histones and nonhistone proteins. After oxidation of lactic acid to pyruvate, acetic acid enters the mitochondria and metabolizes the cyclical cycle through triacetic acid. Under different circumstances, lactate is also converted to glucose via gluconeogenesis. Glucose metabolism mainly includes sugar and TCA cycles in mitochondria. The cells mainly generate energy through the cyclical cycle, and under hypoxic conditions, a large amount of lactic acid will be generated. The large amount of lactate produced by glycolysis in tumor cells is eventually transported to the TME through MCT1 or MCT4. MCT, monocarboxylate transporter; ATP, adenosine 5'-triphosphate; GLUT1, glucose transporter 1; ASCT2, alanine serine cysteine transporter 2; TCA, tricarboxylic acid; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; GLS, glutaminase; GLUD1, glutamate dehydrogenase 1; TME, tumor microenvironment; OXPHOS, oxidative phosphorylation.

Excess pyruvate is converted to lactate and exported via MCT4 or retained in the cytoplasm, which lowers cellular pH and thus generates ROS. These intermediates can be used to generate ATP (97). A key intermediate, pyruvate, can be transported into mitochondria for use in the citric acid cycle and converted into fatty acids or carbohydrates through gluconeogenesis. In hypoxic environments and transformed cells, most pyruvate will be converted into lactate-by-LDH (44). MCTs pump excess lactic acid out of the cells, and under normal circumstances, the human liver is the main site for absorption of lactic acid (98). However, in liver cancer, lactate clearance is reduced while lactate production is increased. This causes lactic acid to accumulate in the liver (99). When intracellular lactate levels are high, hepatotoxic lymphocytes are inactivated, and the expression of related cytokines is downregulated (100) (*Figure 3*).

Lactic acid and the prognosis and treatment of liver cancer

Elevated tumor lactate levels are an indicator of poor prognosis in many types of cancer, including liver cancer (99,101). Lactic acid is an immune regulator in the TME that can polarize macrophages and neutral granulocytes, inhibit DC activity, and dysregulate the death of T cells and NK cells (39,64,100,102). Lactic acid is also an internal cell death signal in NK cells in hepatoma. Lymphocytes maintain intracellular pH at a certain level under acidic conditions, facilitate most of the buffering capabilities in cells, and produce HCO from CO_2 produced by mitochondrial respiration. Cells with a larger mitochondrial mass and more active TCA cycles are therefore able to produce more carbon dioxide and host a greater buffering capacity (103). The mitochondrial mass of NK cells is significantly reduced in liver cancer, and mitochondria

have a reduced ability to produce CO_2 owing to increased ROS production, rendering them more susceptible to pH changes in the TME. The recurrence rate of liver cancer after successful resection may be as high as 70%, which shows that the liver's immune system remains impaired even after tumor removal. Recurrence of cancer is more strongly associated with reduced numbers of NK cells in tumors than with a reduced number of T cells (104).

Treatments that target lactate production may benefit patients with liver cancer after tumor resection to improve the liver's immune system and limit possible tumor recurrence. The immune mechanism of tumor cell glucose suppression via lactate-mediated tumor cell glucose represents a novel means for the targeting of specific metabolic pathways. However, it is challenging to specifically inhibit tumor growth while avoiding harm to immune cells by targeting this pathway. In recent preclinical tests, drugs targeting GAPDH (koningic acid) and LDH (FX11) were found to effectively limit tumor growth (105-108). The use of systemic bicarbonate buffering has been reported to reduce tumor aggressiveness while neutralizing tumor acidity, thus improving NK cell immune responses; however, patient adherence to long-term treatment can be a limiting factor to treatment (58). Some drugs (AZD3965, NCT01791595) can specifically target lactate transport to prevent tumor cells from releasing lactate, which forces it to accumulate in tumor cells, subsequently reducing tumor cell growth and inducing apoptosis (109-111).

Discussion

Rates of successful treatment for advanced-stage cancer are notoriously low. In recent years, cancer immunotherapy has emerged as a promising treatment modality. However, the currently available immunotherapies are typically aimed at a single immune cell type and only focus on specific components in the restoration or enhancement of the immune system. Lactic acid exerts complex effects on a variety of congenital and adaptive immune cells that contribute to anticancer immunity. It has been long acknowledged as a key tumor metabolic product and is known to be a critical component of cancer biology, both directly and through the acidified TME. Excessive production of lactic acid in cancer cells and acidification of the TME inhibit the congenital and adaptive immune cells of the entire host, thereby curbing immune-cell proliferation and altering cell function. Effector functions inhibited by lactate and an acidic TME are reversible in multiple immune cell types across different cancers. This knowledge can be potentially used in the development of highly effective immunotherapies.

Lactate, generated through aerobic glycolysis, serves as both an energy reservoir and a signaling agent for tumor cells, capable of interfering with immune reactions. Within tumor-stroma interplay, lactic acid assumes a crucial role and can serve as a gauge for the aggressiveness of tumor cells. Furthermore, it functions as a metabolic resource and a signaling messenger in the process of cellular oncogenesis (112). Due its relevance in the TME, lactate is associated with tumor growth and metastasis, patient prognosis, cancer therapy, and histone modifications. In liver cancer specifically, lactate is closely related to tumor growth, metastasis, and long-term prognosis, and acidification of the TME can also affect the malignant progression of tumors (113). Lactic acid can promote tumor cell proliferation, inhibit ferroptosis, anoikis and other programmed cell death processes, and at the same time promote epithelial-mesenchymal transition and tumor angiogenesis of tumor cells to help tumor metastasis. Furthermore, through the remodeling of the tumor microenvironment, lactic acid also improves the resistance of tumor cells to chemotherapy and immunotherapy, which has profound clinical significance. Inhibiting lactate production could represent a new approach to treating liver cancer, and the discovery of histone lactonization modifications may lead to further insights into the Warburg effect. As research continues, the role of lactic acid in the development of liver cancer will become clearer, and new advances will be made in the concepts and technologies related to tumor identification and targeted therapies. In addition, the upregulation of key proteins involved in lactate-mediated immune responses has been shown to have clinical prognostic value and may be a potential target for tumor treatment. Therefore, inhibiting lactate production should provide more effective treatment options.

Conclusions

Lactate represents a potential starting point from which future liver cancer treatments can be developed, and lactate signaling inhibitors should be further explored in terms of their clinical applicability. Research into combining traditional therapies key with molecularly targeted drugs synergistically affecting metabolic pathways should lead to the innovation of treatments capable of more selectively targeting the activity of both cancer and pro-tumoral immune cells.

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Footnote

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