Research progress of abnormal lactate metabolism and lactate modification in immunotherapy of hepatocellular carcinoma

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Tumors meet their energy, biosynthesis, and redox demands through metabolic reprogramming. This metabolic abnormality results in elevated levels of metabolites, particularly lactate, in the tumor microenvironment. Immune cell reprogramming and cellular plasticity mediated by lactate and lactylation increase immunosuppression in the tumor microenvironment and are emerging as key factors in regulating tumor development, metastasis, and the effectiveness of immunotherapies such as immune checkpoint inhibitors. Reprogramming of glucose metabolism and the "Warburg effect" in hepatocellular carcinoma (HCC) lead to the massive production and accumulation of lactate, so lactate modification in tumor tissue is likely to be abnormal as well. This article reviews the immune regulation of abnormal lactate metabolism and lactate modification in hepatocellular carcinoma and the therapeutic strategy of targeting lactate-immunotherapy, which will help to better guide the medication and treatment of patients with hepatocellular carcinoma.

KEYWORDS

lactate metabolism, lactylation, immune regulation, immunotherapy, hepatocellular carcinoma

Introduction

Lactate has previously been mistakenly thought to be a metabolic waste product of glycolysis under hypoxic conditions. However, the lactate shuttle hypothesis proposed by Brooks in 1985 describes the role of lactate as fuel to coordinate systemic metabolism and as signaling molecules to coordinate signaling between different cells, tissues, and organs

(1, 2). As an important carbon source for cell metabolism, lactate is involved in carbon cycling *in vivo*, and is also an important signaling molecule in inflammatory and cancerous tissues (3). Cancer cells metabolize glucose differently than normal cells. Normal cells produce large amounts of lactate only under hypoxic conditions, whereas tumor cells tend to convert pyruvate to lactate even when sufficient oxygen is present through the mitochondrial TCA cycle to support oxidative phosphorylation to generate ATP, the process is an aerobic glycolysis, also known as the "Warburg effect" (4, 5). Lactylation is a novel post-translational modification (PTM) that includes histone lactylation and non-histone lactylation (6–9). The large amount of lactate produced by tumor tissue through aerobic glycolysis provides a substrate for lactylation. The biological function of lactylation in a range of diseases and cancers is being investigated.

The occurrence, metastasis, invasion and drug resistance of hepatocellular carcinoma (HCC) are largely influenced by the tumor microenvironment, which contains complex interactions between various immune or non-immune cells (10–14). Lactate has emerged as a key regulator in maintaining cancer initiation, progression, and immune escape, and lactate accumulation and lactylation in HCC enhance the immunosuppressive properties of tumor microenvironment(TME). The lactate metabolic crosstalk in the TME may be an important factor affecting the progression, immunotherapy and prognosis of HCC. By targeting lactate metabolism and restoring the metabolic adaptability of host anti-tumor immunity, the therapeutic effect of cancer immune checkpoint blockade can be further improved. Therefore, anti-lactate therapy combined with immunotherapy has broad prospects.

Reprogramming of glucose metabolism in HCC promotes lactate production

Metabolic associated fatty liver (MAFLD) has been proposed as a more appropriate new nomenclature for nonalcoholic fatty liver disease (NAFLD) that more accurately reflects the drivers of the disease (15). Altered liver metabolism is critical to the development of liver disease, contributing to the progression of NAFLD and nonalcoholic steatohepatitis (NASH), which progressively become major risk factors for hepatocellular carcinoma (16). Lactate levels in the blood and liver also increase with the severity of liver disease, particularly from steatosis to NASH (17, 18). HCC cells are metabolically different from normal hepatocytes. In order to meet the demands of tumor tissue for energy, redox, and biosynthesis, HCC cells exhibit active anaerobic glycolysis and aerobic glycolysis (Warburg effect). In addition, metabolism-related enzymes and transport proteins are reprogrammed (19, 20). Upregulated glucose transporters (GLUTs) promote glucose uptake, increased

expression of hexokinase (HK), phosphofructokinase 1 (PFK1) and pyruvate kinase (PKM) accelerates glycolysis, and overexpression of lactate dehydrogenase (LDH) drives the rapid conversion of pyruvate to lactate (21). Ultimately one of the results of this metabolic reprogramming is the production of large amounts of lactate.

Production of lactate

Lactate is produced through abundant pathways in tumor tissue, such as pentose phosphate pathway, malate-mediated glutamine pathway, and citrate-mediated pyruvate production, which ultimately lead to the secretion of lactate salts (Figure 1). Glucose is transported into cancer cells by GLUT1/3 transporters and then undergoes glycolysis to produce pyruvate. Under positive oxygen conditions, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase and releases carbon dioxide (CO_2), which enters the tricarboxylic acid (TCA) cycle. Under anaerobic conditions, glucose is metabolized to pyruvate by phosphoenolpyruvate (PEP), which is then converted to lactate by lactate dehydrogenase A (LDHA). Tumor cells meet the energy requirements for growth and proliferation of cancer cells by increasing glycolysis, while glucose is metabolized at a higher rate by aerobic glycolysis (Warburg effect) (5). Compared with lactate produced by complete oxidation of glucose in mitochondria, tumor tissue produces 10-100 times more lactate through aerobic glycolysis (22).

Glucose is the main metabolic substrate for lactate production, and glutamine is also an important substrate for lactate production. Tumor cells have a clear Warburg effect, which is enough to support most of the requirements of the cell for ATP synthesis, and the construction of lipids, proteins, and nucleotides required for cell growth mainly comes from the TCA cycle. But in these cells, their TCA cycle is intact, and this requirement is met by high glutamine metabolism. They can utilize the carbon backbone of glutamine as a respiratory substrate, activate the NADPH-producing pathway, and restore oxaloacetate to continue TCA cycle function (23, 24). Continued glutamine metabolism provides an intermediate for the TCA cycle and also makes aerobic glycolysis the best choice for cancer growth (25). Glioblastomas, for example, convert about 90 percent of glucose and 60 percent of glutamine to lactate (24). Glutamine is converted to glutamate by glutaminase, glutamate is converted to α-ketoglutarate by glutamate dehydrogenase (GDH) in mitochondria, and then α-ketoglutarate is converted to malate and then transported out of the mitochondria, oxidized to pyruvate in the cell matrix, and finally lactate is produced under the action of LDHA (26). Glutamine can also provide carbon in the form of mitochondrial oxaloacetate to generate citrate in the first step of the TCA cycle, mediating lactate and lipid biosynthesis.
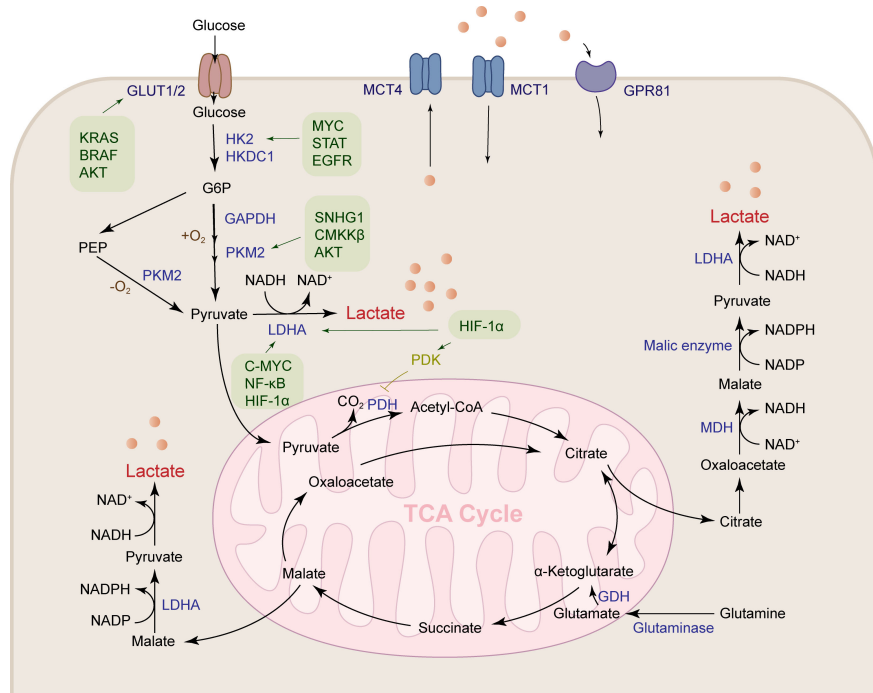
FIGURE 1

Lactate is produced by a variety of pathways. Lactates are mainly produced by the aerobic glycolysis pathway and the glutamine pathway. Glucose metabolism reprogramming in HCC promotes glucose uptake by the glucose transporter GLUT1/2. HK2, GAPDH, PKM2 and LDHA are upregulated under the regulation of a variety of cytokines to accelerate lactate production. Glutamine is transported into mitochondria, where it produces α-ketoglutaric acid under the action of GDH, followed by participation in the TCA cycle to produce malate, and finally transported out of the mitochondria to produce lactate.

Glutamine also provides a carbon source to support the TCA cycle during glucose starvation (27).

In addition to the above methods, activated immune cells can also metabolize lactate, such as dendritic cells (DC) depending on the Warburg effect (28). CD28-stimulated T cells rapidly increase the expression of glucose transporters and the rate of glycolysis (29, 30). In macrophages, monocarboxylate transporter 4 (MCT4) is upregulated by the stimulation of TLR2 and TLR4, activating an inflammatory response to increase the rate of glycolysis to produce lactate (31). But they contribute less to lactate in the tumor microenvironment because it depends on the number of immune cells in the tumor microenvironment and their activation status. In conclusion, the accumulation of lactate in HCC tumor tissue is largely due to its active production pathway.

Metabolic reprogramming promotes lactate production in HCC

To meet the demands for energy and biosynthesis, HCC tumor tissues metabolically reprogram key enzymes of their glycolysis. HCC tumors enhance glucose uptake by upregulating

the glucose transporters GLUT1 and GLUT2 (32, 33), and HIF-1 is an important accelerator of this process (34). In addition, KRAS mutation, BRAF mutation and activated AKT cascade increased GLUT1 expression (35, 36).

Glucose is converted into glucose-6-phosphate by hexokinase (HK) after entering cells. Among HK family members, HK2 and HKDC1 are up-regulated in HCC and are associated with poor prognosis (37, 38). Silencing HK2 and HKDC1 inhibited lactate flux, inhibited HCC cell proliferation and migration *in vitro*, increased oxidative phosphorylation, and metformin sensitivity (38, 39). The expression of HK2 is induced in HCC by multiple mechanisms and oncogenic transcription factors. HK2 was recently identified as a downstream target of ZMYND8 in HCC cells, and high expression of ZMYND8 in HCC was associated with glucose consumption, increased lactate, and ATP production in HCC cells, and was associated with patients with unfavorable clinicopathological features and poor prognosis. Silencing ZMYND8 inhibited the proliferation and migration of HCCLM3 cells *in vivo (40)*. MACC1 and STAT3 also enhance glucose metabolism and lactate production through HK2 (41, 42). Blockade of FOXK1, EGFR, C-MYC signaling inhibits HK2-mediated glycolysis (42–44).

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been considered as a stably expressed reference gene in the past, and GAPDH has been reported to be up-regulated in various cancers (45). The interaction of GAPDH with hepatitis viruses (HBV and HCV) induces hepatitis, as well as metabolically enhances glycolytic capacity (46, 47).

The pyruvate kinase isoform PKL is an important enzyme involved in the final step of glycolysis in normal hepatocytes, while pyruvate kinase 2 (PKM2) is overexpressed in HCC cells and is an independent predictor of recurrence and survival (48, 49). As an active protein kinase, PKM2 promotes hepatocellular carcinoma cell proliferation by upregulating HIF-1α, Bcl-xl and Gli1 expression (50). PKM2 plays a synergistic effect with ODC1, which is an important enzyme involved in polyamine metabolism (51), and is also affected by various signals such as SNHG1 and CaMKKβ, as well as the AKT pathway (52–54). Genes related to polyamine metabolism are overexpressed in HCC patients, which also links polyamine metabolism to abnormal lactate metabolism promoting poor prognosis. Decreased expression of PKM2 inhibits glucose uptake by HCC cells and inhibits aerobic glycolysis (48). Altered expression of the aforementioned enzymes supports glucose flux in the glycolytic pathway, leading to an increase in the end product of glycolysis, pyruvate, which is available for the TCA cycle as well as lactate production.

The Warburg effect is a key event in hepatocarcinogenesis, where pyruvate tends to be converted to lactate catalyzed by lactate dehydrogenase (LDH) even under aerobic conditions. In hepatocellular carcinoma cells, LDHA is overexpressed due to downregulation of miR-383, triggering increased cell proliferation, invasion and glycolysis (55), MYC, NFκB, HIF-1α-mediated signaling enhances glycolysis in HCC by promoting upregulation of LDHA (56–58). In contrast, knockdown of LDHA significantly inhibited tumor growth and metastasis of hepatocellular carcinoma as well as the Warburg-like metabolic signature of mouse HCC (59, 60). LDH levels in serum have been regarded as a prognostic indicator in HCC patients treated with sorafenib, transarterial-chemoembolization (TACE), and partial hepatectomy (61–63). In addition to these enzymes as important regulators of the Warburg effect, the Warburg effect is also regulated by other complex mechanisms, such as the transcriptional activation of PFKM by ZEB1 and the direct targeting of FBP1 by miR-517a to enhance the Warburg effect of liver cancer (64, 65); PGC1α inhibits the Warburg effect by regulating the WNT/β-catenin/PDK1 axis (66).

Transport of lactate

Lactate is mainly transported by the monocarboxylate transporter (MCT) on the cell membrane, MCT1 (SLC16A1) mainly imports lactate, and MCT4 (SLC16A3) mainly exports lactate. MCT1 can also mediate lactate export under hypoxic conditions (67–69). It has been reported that MCT4 is highly expressed in HCC and promotes tumor progression (70), and inhibition of CD147 or MCT1 inhibits lactate export and glucose metabolism, and inhibits HCC proliferation (71). The poor prognosis of multiple types of cancers is associated with high expression of MCT1 and MCT4, such as glioma (72), breast cancer (73), non-small cell lung cancer (74), colorectal cancer (75), gastric cancer (76), cervical cancer (77) and neuroblastoma (78).

G protein-coupled receptor 81 (GPR81) is a lactate-selective receptor that is highly expressed in many tumor cell lines, such as breast, colon, lung, hepatocellular, salivary gland, cervical, and pancreatic cancers. The expression level of GPR81 affects tumor growth and metastasis, and knockdown of GPR81 results in significantly reduced growth and metastasis of pancreatic cancer cells and breast cancer cells (79, 80). Inhibition of GPR81 signaling and thus angiogenesis is mediated by PI3K/AKT-cAMP in response to CREB (81). Activation of GPR81 aggravates hepatic ischemia-reperfusion injury-induced remote organ injury (82).This suggests that GPR81 is essential for cancer cells to regulate lactate transport, tumor growth and metastasis, angiogenesis, and lipolysis inhibition (79).

Lactate homeostasis and metabolic abnormalities

Cells in humans typically have lactate concentrations of 1-3 mM at rest, and transiently increase to 15 mM during exercise, however, in highly glycolytically active tumor cells, lactate concentrations even reach 30-40 mM (83). Lactate is not only a substrate for glycolysis, but also the main fuel for maintaining the carbon cycle, and is rapidly exchanged in the body to provide an energy substrate for cellular metabolism. Studies have shown that, in addition to the brain, the contribution of glucose to the tissue TCA cycle is indirect, but mainly through circulating lactate. In genetically engineered lung and pancreatic cancer tumors in fasted mice, lactate was the main source of carbon for the TCA cycle (84). In addition, lactate and pyruvate together act as a circulating redox buffer, balancing the NADH/NAD ratio (85). Lactate is also reused by different cell subsets in the TME, a phenomenon known as metabolic symbiosis (86). The function of lactate depends on its concentration in the organism, and the normal production and transport of lactate is the basis for maintaining the lactate cycle in the body. Under the coordinated action of oncogenes and tumor suppressors, tumor cells produce a large amount of lactate through aerobic glycolysis, local TME acidification, and the homeostasis of lactate is severely disrupted in the TME. HIF-1α, c-MYC, PI3K/AKT increase glycolytic flux by increasing the expression of glucose transporter, hexokinase, phosphofructokinase (26).

Pyruvate dehydrokinase (PDK) inhibits the activation of pyruvate dehydrogenase (PDH) by phosphorylation, preventing pyruvate from entering the mitochondria and being converted to acetyl-CoA for the TCA cycle. Hypoxia-inducible factor 1α (HIF-1α) stimulates the expression of PDK and LDHA, resulting in the conversion of pyruvate to lactate (87). C-MYC is an oncogene that stimulates glycolysis as well as the expression of LDHA. LDHA is one of the key enzymes in the conversion of glucose and glutamine to lactate. Increased activity of LDHA, increased glycolysis, and increased production of lactate, inhibiting LDHA activity affects cancer cell proliferation (88).

Lactate accumulation in tumor tissue is a combined result of increased production and decreased clearance. The net clearance of lactate by the healthy liver accounts for 70% of the systemic clearance, showing higher clearance than other organs (89). P300/CBP-associated factor (PCAF)-mediated acetylation of LDHB reduces LDHB activity and inhibits lactate clearance, leading to lactate accumulation, which exacerbates lipid deposition and inflammatory responses in NAFLD and NAFLD progression (90). In conclusion, the abnormal metabolism of lactate is regulated by a complex network of genes. In addition to genes that directly regulate glucose metabolism and lactate formation, oncogenes and tumor suppressor genes such as HIF-1 and MYC are also involved in glucose metabolism reprogramming during carcinogenesis (21), the interaction of these genes is shown in Figure 2.
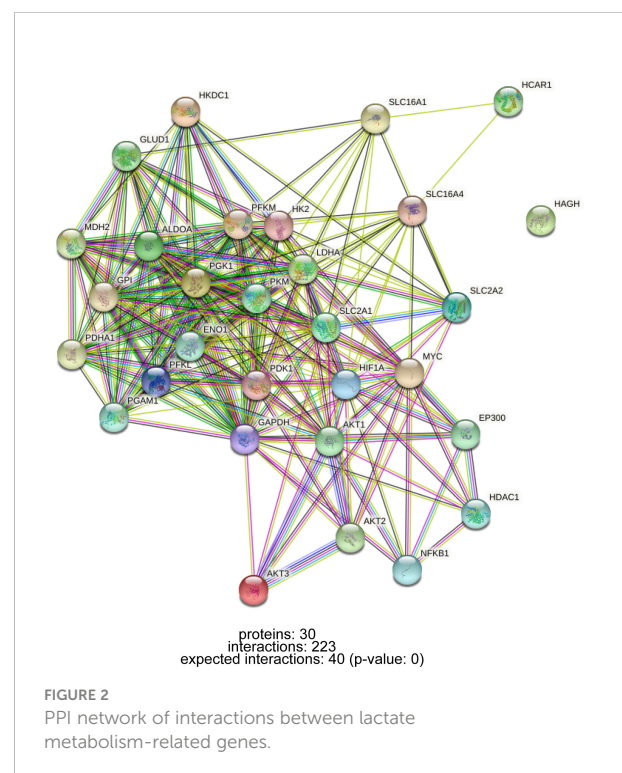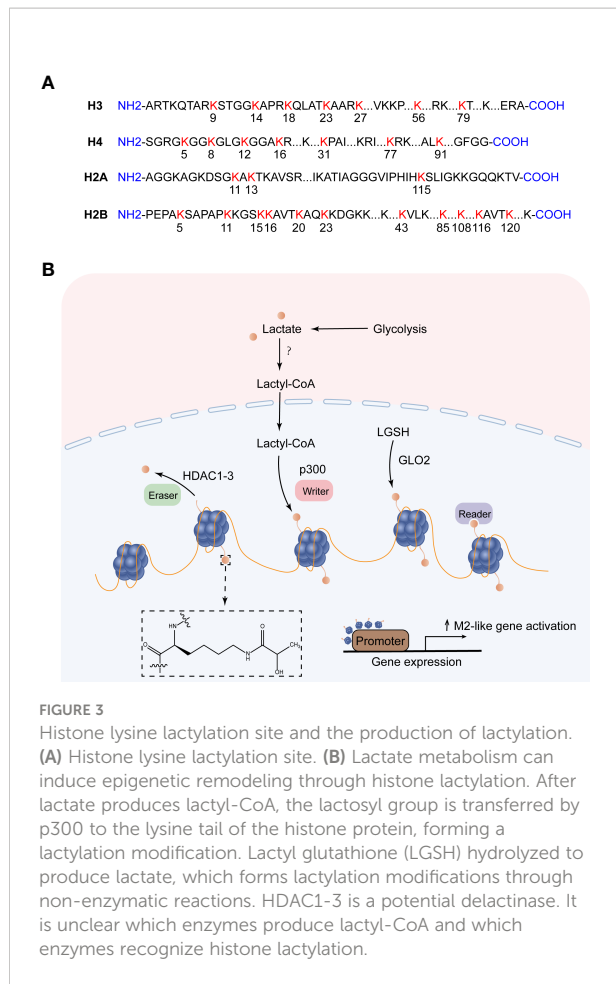
Lactylation of HCC

Histone lactylation

Post-translational modifications of histones, such as methylation, acetylation, phosphorylation, and ubiquitination, maintain homeostasis by regulating DNA transcription, replication, and repair, and their misregulation is closely related to the occurrence and development of many diseases (91). With the application of high-sensitivity mass spectrometry, some new short-chain Lys acylations of histones have been discovered, such as propionylation (Kpr), butyrylation (Kbu), 2-hydroxyisobutyrylation (Khib), Succinylation (Ksucc) et al (92). Zhang et al. first predicted and identified lysine lactylation (Kla) as a novel histone modification stimulated by endogenous lactate. They used MS/MS analysis to identify 26 and 16 histone Kla sites from human MCF-7 cells and mouse bone marrow-derived macrophages (BMDM), respectively (9) (Figure 3A). Yang et al. identified 27 histone Kla sites from gastric cancer AGS cells (8). Mouse cancer models show that the expression of the M2-like gene Arg1 is positively correlated with histone Kla levels. Zhang et al. knocked down LDHA or used glycolysis inhibitors during M1 polarization of macrophages induced by lipopolysaccharide (LPS) and interferon gamma

(IFN-γ). The results showed decreased lactate production as well as global histone Kla levels, decreased ARG1 expression, and decreased histone Kla levels at the ARG1 promoter (9). Stefanie Dichtl et al. also confirmed that the expression of ARG1 in LPS-stimulated cells was mediated by IL-6, and the increase of ARG1 was dependent on the increase of lactate levels (93). The study identified four pathways of increased histone lactylation (1): Increased glucose to increase glycolysis; (2) Rotenone, an inhibitor of the mitochondrial respiratory chain complex I, drives glycolysis; (3) Hypoxia; (4) M1 macrophage polarization (9).

So how does lactate mediate histone lactylation modification, and how does histone lactylation change the transcriptional landscape? Existing studies have shown that lactoyl-CoA produced by endogenous or exogenous (mostly endogenous) lactate, the acetyltransferase p300 acts as a writer to transfer the lactosyl group to the lysine tails of histones to create a modification called lactylation (9). Both lactylation and acetylation prefer lysine (Lys) as a residue of epigenetic modifications, and they compete for the same enzyme p300. However, how these enzymes decide which epigenetic modification to encode in histones remains a mystery, possibly regulated by differential recruitment of cofactors in response to cellular metabolic dynamics (94). In addition to the enzymatic transfer of lactyl-CoA to lysine, lactyl-glutathione (LGSH) is hydrolyzed by glyoxalase 2 (GLO2) to generate glutathione and D-lactate, the lactate moiety is nonenzymatically transferred from LGSH to lysine residues to form lactylation

FIGURE 2

PPI network of interactions between lactate metabolism-related genes.

FIGURE 3

Histone lysine lactylation site and the production of lactylation. **(A)** Histone lysine lactylation site. **(B)** Lactate metabolism can induce epigenetic remodeling through histone lactylation. After lactate produces lactyl-CoA, the lactosyl group is transferred by p300 to the lysine tail of the histone protein, forming a lactylation modification. Lactyl glutathione (LGSH) hydrolyzed to produce lactate, which forms lactylation modifications through non-enzymatic reactions. HDAC1-3 is a potential delactinase. It is unclear which enzymes produce lactyl-CoA and which enzymes recognize histone lactylation.

modifications (95). Recent studies have shown that Class I histone deacetylases (HDAC1-3) act as erasers to exhibit delactylase activity *in vitro* (96, 97), Sirtuins are potential non-histone delactate enzymes (98). However, it is not clear which enzymes produce the intermediate molecule Lactyl-CoA, which enzymes recognize histone lactylation as "readers", and more "writers" and "eraser" are yet to be discovered (Figure 3B). ChIP-seq data showed that H3K18la, like H3K18ac, was enriched in the promoter region (± 2 kb around the transcription start site) and indicated steady-state mRNA levels. In contrast to H3K18ac, the increased H3K18la marked more genes than the decreased H3K18la, and most genes marked by elevated H3K18la were specific. Zhang et al. took advantage of a cell-free, recombinant chromatin-templated histone modification and transcription assay, and they demonstrated that histone Kla plays a direct role in transcriptional regulation. In this assay, acetyl-CoA is replaced by L-lactyl-CoA, showing strong p53-dependence, p300-mediated H3 and H4 lactate salting, and effects on transcription. The H3 and H4 mutations eliminate p300 and p53-dependent transcription. These findings suggest that transcription is directly mediated by histone lactylation rather than mediating other transcription factors in the nucleus

(9). Furthermore, H3K18la is enriched not only at the promoter but also at the active enhancer in a tissue-specific manner (99). Eva Galle et al. calculated ChromHMM state enrichment over ENCODE's database of cell type agnostic candidate cis-regulatory elements (cCRE). They found that each ChromHMM state enriched with a distal enhancer-like sequence (dELS) was always marked with H3K18la. H3K18la marks active promoters and active enhancers, which are typically marked by H3K27ac (typical mark of active promoters and activity enhancers). And a considerable part of the presumed dELS only H3K18la peak marker, but not H3K27ac peak marker, indicating that dELS has additional H3K18la-specific effects. Research on histone lactylation is still in its infancy, and delving into how this post-translational modification affects the transcriptional landscape will broaden our horizons in the treatment of disease (99).

Current studies have demonstrated that various disease states are regulated by histone lactylation. Increased histone lactylation correlates with inflammation-induced macrophage death. Phosphoinositide 3-kinase (BCAP) promotes the transition of macrophages from an inflammatory state to a repair state through histone lactylation in response to microbial ligands and various deleterious signals (100). Lung myofibroblasts promote the fibrotic activity of macrophages through lactate-induced histone lactylation in macrophage profibrotic gene promoters (101). A clinical study by Chu et al. showed that histone H3K18 lactylation aggravated the severity of septic shock in patients (102). Macrophages can take up lactate through MCT and promote HMGB1 lactylation through the p300/CBP pathway. Inhibiting lactate levels *in vivo* or inhibiting lactate signaling can reduce exosomal HMGB1 lactylation levels, thereby ameliorating multiple microbial sepsis (103). Yang et al. further identified the lactylation modification site HMGB1-K43la in HMGB1 (8). Glis1 acts as a reprogramming factor to promote somatic reprogramming by enhancing histone acetylation (H3K27ac) and lactylation (H3K18la) at pluripotent gene loci (104). Histone Kla is also widely distributed in the brain, and the level of histone H1Kla in the brain increases in response to the expression of the neuronal activity marker c-Fos and the neural excitation induced by Repeated social defeat stress (SDS) (105). H3K18la is involved in remodeling transcriptome expression and activates transcription in brain neurons (97).

Cancer cells produce more lactate than normal cells through the "Warburg effect", so it is likely that histone lactylation in tumors is abnormal (106) (Table 1). Yu et al. found for the first time that the level of histone lactylation was significantly up-regulated in ocular melanoma, and inhibition of histone lactylation could effectively inhibit tumor progression. Their study found that histone lactylation promotes YTHDF2 expression in ocular melanoma, and that YTHDF2 binds to m⁶A sites on the mRNAs of PER1 and TP53 to mediate RNA degradation, thereby driving carcinogenesis (107). Lactate in the

TABLE 1 Lactylation in Disease.

Disease	Modification site	Cell	Protein targets	Gene targets	Reference
Lung fibrosis	Lysine	Macrophages			(101)
Septic shock	H3K18 HMGB1-K43	Macrophages			(8, 102, 103)
Ocular melanoma	K3K18		YTHDF2	m^6A	(107)
Colon cancer	H3K18	TIMs	METTL3	m^6A	(108)
NSCLC	Lysine		HK-1 IDH3G		(109)
ccRCC	Lysine	Macrophages	PDGFRβ		(110)
HCC HCC	MOESIN-Lys72 H3K9la, H3K56la	Tregs			(111) (112)

TME induces METTL3 expression in tumor-infiltrating myeloid cells (TIMs) through histone lysine K18 lactylation, METTL3 lysine K281 and K235 lactylation-mediated RNA m6A modification leads to tumor immune escape by promoting the immunosuppressive function of TIM (108). Disturbed lactate metabolism in non-small cell lung cancer (NSCLC) mediates the expression of genes such as HK-1 and IDH3G through histone lactylation, regulating mitochondrial homeostasis as well as cellular metabolism (109). Inactive von Hippel-Lindau (VHL) is an important factor in the pathogenesis of clear cell renal cell carcinoma (ccRCC), which exerts oncogenic effects by inducing histone lactylation to activate platelet-derived growth factor receptor beta (PDGFRβ) expression. In turn, PDGFRβ positively feedback regulates histone lactylation (110). Histone lactylation at the promoter of Gram-negative bacteria-derived lipopolysaccharide in colorectal tumor tissues reduces the binding efficiency of the inhibitory factor YY1, resulting in the overexpression of LINC00152 to promote colorectal cancer cell migration and invasion (97).

Lactate can induce the expression of liver injury-related genes, leading to acute liver failure (113). Accumulation of lactate is responsible for histone lactylation in inflammation and cancer. The formation of histone lactylation modification mainly depends on the enzymatic transfer of lactyl-CoA, Varner et al. first quantitatively measured lactyl-CoA in hepatoma cells. They showed that lactyl-CoA is quantifiable at 1.14×10^{-8} pmol per cell in HepG2 cell culture and 0.0172 pmol mg^{-1} tissue wet weight in mouse heart. These leves are similar to crotonyl-CoA, but significantly less 20-350 times less than majo acyl-CoAs including acetyl-, propionyl- and succinyl-CoA (114). Pan et al. isolated liver cancer stem cells (LCSCs) from MHCCLM3 and Hep3B cell lines with significantly higher lactate levels than those in HCC cells. They identified that the increase of two histone H3 lactylation sites (H3K9la, H3K56la) effectively promoted the progression of HCC. The levels of Pan Kla and histones H3K9la and H3K56la in liver cancer were positively correlated with the expression of cancer malignancy markers

(the stemness marker CD133, the proliferation marker BCL2, the cancer cell proliferation marker Ki67, and the glycolysis enzyme LDHA). Inhibition of LDHA was able to reduce lactate levels in LCSCs and inhibit lactylation. Demethylzeylasteral (DML) inhibits LCSC-induced tumorigenicity by inhibiting histone H3 lactylation (112). Intracellular lactate production and histone lactylation levels are elevated under hypoxic conditions, inhibition of pyruvate dehydrogenase and lactate dehydrogenase activities using sodium chloroacetate and sodium oxalate, respectively, could attenuate the hypoxia-induced elevation effect. Under positive oxygen conditions, human lactate production and histone lactylation were completely inhibited in HepG2 cells after knockdown of LDHA and LDHB (9).

Non-histone lactylation

During the dynamic metabolic homeostasis of tissues, part of the lactate produced by the cells is involved in metabolism, while the other part is received to participate in epigenetic modification and non-histone lactylation. Lactylation was originally discovered on human histones (9), and recent studies have shown that lactylation is a gross modification of human cells and tissues. Digging of the Meltome Atlas revealed that glycolytic enzymes in human cells are heavily lactated, particularly K147 of fructose-bisphosphate aldolase A (ALDOA) (7). Yang et al. identified 2375 Kla sites in 1014 proteins in gastric cancer AGS cells (8). Gu et al. established a solid tumor model of liver cancer by subcutaneously injecting Hepa1-6 cells into B6 mice, and injected lactate dehydrogenase inhibitor (LDHi) to reduce LDH activity. It was found that the lactate concentration in the tumor of the mice was significantly reduced, and the immunomodulatory effect of Treg cells in the TME was inhibited. Lactate levels are elevated, and lactate levels are elevated in Treg cells. Lactate enhances TGF-βR1-mediated TGF-β signaling by regulating the lactylation of Lys72 residues

in MOESIN, which is involved in the metabolic reprogramming of Treg cells (111).

Abnormal lactate metabolism is an important feature of liver cancer, and NMR analysis showed that HCC displayed high levels of lactate and low levels of glucose compared with distant non-tumor tissues (NTT) (115). The elevated lactate concentration detected in the serum of HCC patients also confirmed that this is the result of abnormal lactate metabolism in liver cance (116). Taken together, this abnormal lactate metabolism is critical for the maintenance of tumor growth and progression in HCC, and plays an important role in the lactylation of tumor cells histones as well as non-histone proteins.
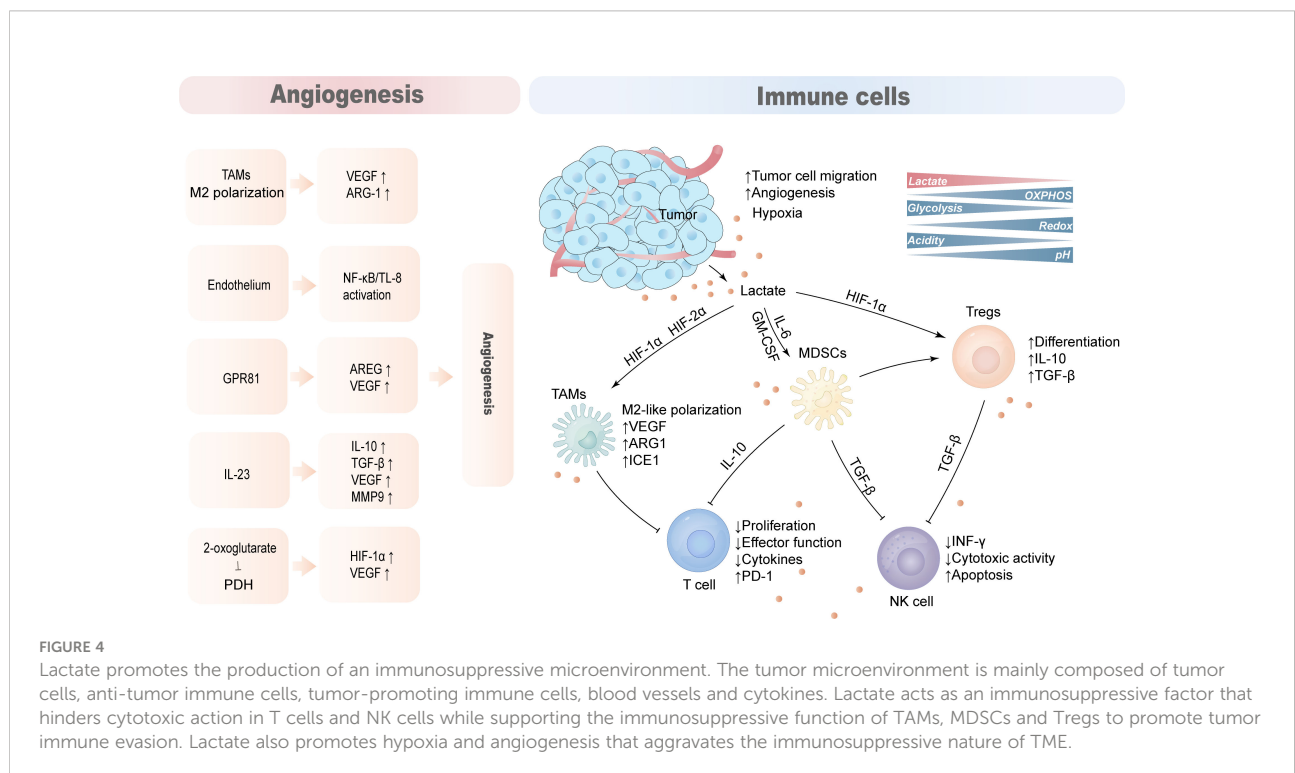
Lactate promotes immunosuppressive TME

The TME of HCC is composed of complex components such as tumor cells, immune cells, stromal cells, and blood vessels. Due to the Warburg effect, tumor cells secrete lactate into the TME, reducing the pH of the TME. Lactate acts as an immunosuppressive factor to promote tumor progression by hindering T cell and natural killer (NK) cell function or supporting the suppression of TAMs, MDSCs, and regulatory T cells (Tregs) (Figure 4).

T cell

The rate of lactate production and secretion by tumor cells and activated T lymphocytes was significantly increased, and the large amount of lactate and increased acidity of the TME inhibited the proliferation of activated T cells and the production of cytokines (117). Lactate secreted by tumor cells hinders T cell function, especially the lytic function of CD8 T cells, by modulating the redox state of nicotinamide adenine dinucleotide (NAD) and (NADH) (118). Lactate inhibits the proliferation and cytokine production of 95% of human cytotoxic T lymphocytes (CTLs) and reduces cytotoxicity by 50%. A high lactate environment in the TME blocks monocarboxylate transporter-1 (MCT-1) export resulting in abnormal CTL lactate metabolism and impaired function (117).

NK cell

High levels of lactate in the TME interfere with the secretion of the antitumor cytokines INF-γ, perforin, and granzyme B in T cells and NK cells, thereby promoting tumor immune escape and growth. Lactate-pretreated NK cells inhibited NK cell cytotoxicity by downregulating the expression of NKp46 (119, 120). In addition, high levels of acidic lactate environments are not conducive to the proliferation of natural killer T cells (NKTs) and affect their activity and function (121).

FIGURE 4
Lactate promotes the production of an immunosuppressive microenvironment. The tumor microenvironment is mainly composed of tumor cells, anti-tumor immune cells, tumor-promoting immune cells, blood vessels and cytokines. Lactate acts as an immunosuppressive factor that hinders cytotoxic action in T cells and NK cells while supporting the immunosuppressive function of TAMs, MDSCs and Tregs to promote tumor immune evasion. Lactate also promotes hypoxia and angiogenesis that aggravates the immunosuppressive nature of TME.

TAMs

Macrophages regulate immune responses to pathogens, maintain tissue homeostasis and participate in tissue repair and remodeling (122). M1-type macrophages tend to be more pro-inflammatory phenotypes, whereas M2-type macrophages primarily play a role in immune regulation, tissue remodeling, and tumor progression (123). Tumor-associated macrophages (TAMs) typically exhibit pro-inflammatory and anti-tumor activities, and gradually polarize to the M2 phenotype as tumors progress. MCTs take up tumor-derived lactate on the cell membrane of TAMs to induce vascular endothelial growth factor (VEGF), L-arginine arginase-1(ARG1) and the expression of the transcriptional repressor ICER through HIF-1α, and promoting M2-like polarization of TAMs. This process can support tumor growth and suppress antitumor immune responses (124, 125).

MDSCs

MDSCs are the most prominent myeloid-derived cell population that exerts extensive immunosuppressive functions, inhibiting innate immunity and adaptive immunity in the TME by preventing dendritic cell maturation, inhibiting NK cell toxicity and T cell activation, and promoting Tregs differentiation (126). The number of myeloid-derived suppressor cells (MDSC) is reduced in LDHA knockdown mice, and exogenous lactate increases MDSCs production mediated by GM-CSF and IL-6, and these cells have significant NK inhibitory activity (120). Lactate increases MDSCs activity through GPR81/mTOR/HIF-1α/STAT3 pathway and its inhibition of NK cell, antitumor T cell activity (120, 127).

Tregs

Regulatory T cells (Tregs) are significantly enriched within tumors, and tumor-infiltrating Tregs require lactate uptake to support their proliferative and immunosuppressive functions (128). Lactate-activated Tregs have reduced glucose uptake, and instead show increased MCT1 to accelerate lactate uptake, increased LDHA activity, and enhanced immunosuppressive capacity (129).

Lactate mediates the expression of immunosuppressive molecules and their receptors

PD-1, as a surface molecule that transmits immunosuppressive signals, is expressed on the surface of immune cells such as activated

T cells, B cells, and NK cells (130). Activated PD-1 promotes tumor immune escape by inhibiting the activation of immune cells and the secretion of related antitumor factors (131). PD-1 expression is complexly regulated, and its expression is rapidly induced after T cell receptor (TCR) activation (132). The TGF-β/Smad pathway plays an important role in this process, and blocking TGF-β can significantly inhibit the expression of PD-1 (133). NFATc1 is activated after TCR activation, then NFATc1 enters the nucleus and binds to DHS-C region within the conserved region C (CR-C) located at the transcription initiation point 5', thereby activating Pdcd1 transcription (134, 135). Blimp-1 inhibits the expression of NFATc1 and displaces it from CR-C, thereby removing the induction effect after TCR activation, resulting in inhibition of PD-1 gene transcription (136). TCR can also promote the expression of PD-1 and attenuate the T cell response in conjunction with IFN-α (137). In macrophages and T cells, IFN-α can promote PD-1 expression through the JAK/STAT signaling pathway (138). IFN-α increases PD-1 expression by activating JAK1 and TYK2 and inducing the binding of ISGF3 complexes (STAT1/STAT2/IRF9) to ISRE located at the promoter CR-C (139). In addition, IL-6 or IL-12 enhances PD-1 expression by changing the structure of chromatin and activating STAT3 and STAT4. Other cytokines in the tumor microenvironment are also able to regulate PD-1 expression, such as gamma-chain cytokines IL-2, IL-7, IL-15, and IL-21. Although these cytokines-induced PD-1 expression does not affect the expansion and survival of peripheral T cells, it can inhibit cytokine secretion in T lymphocytes when TCR is involved (140) (Figure 5).

PD-L1 on tumor cells binds to PD-1 on immune cells and mediates negative feedback for various lymphocyte activation (141). In TME, to avoid T cell attack, cancer cells hijack inflammatory factors IFN-γ, TNF-α, IL-6-mediated inflammatory pathways to enhance PD-L1 expression (142–144). IFN-γ is often considered an inducer of PD-L1 and is produced in large quantities when T cells and NK cells are activated (145). IFN-γ binds to its receptor to activate the JAK/STAT pathway, preferentially inducing the expression of the transcription factor interferon response factor 1 (IRF1) *via* STAT1 (146). IRE1/2 constitutes the binding site of IRF1 in the PD-L1 promoter and regulates the transcription of PD-L1 in HCC (147). In addition, the PI3K/AKT pathway, activated by IFN-γ, also upregulated the expression of PD-L1 in tumors (148). IFN-γ can also activate the NF-κB pathway, which in turn mediates the expression of PD-L1 (149). TNF-α can be released by activated TAMs, which is a major driver of inflammation, while it also drives EMTs to regulate PD-L1 expression (150). In addition to EMT, TNF-α upregulates PD-L1 expression by activating NF-κB and ERK1/2 signals (143). The inflammatory factor IL-6 triggers the expression of PD-L1 in the JAK/STAT3 and MEK/ERK signaling pathways (144, 151). Previous studies have also demonstrated that increased IL-6 in HCC activates the STAT3/c-MYC/miR-25-3p pathway, resulting in a decrease in protein tyrosine phosphatase receptor

O (PTPRO), which downregulates PD-L1 expression by regulating JAK2-STAT1/3 activation (152). In addition, STAT3 can act directly on the promoter of PD-L1 to regulate the expression of PD-L1 (153).
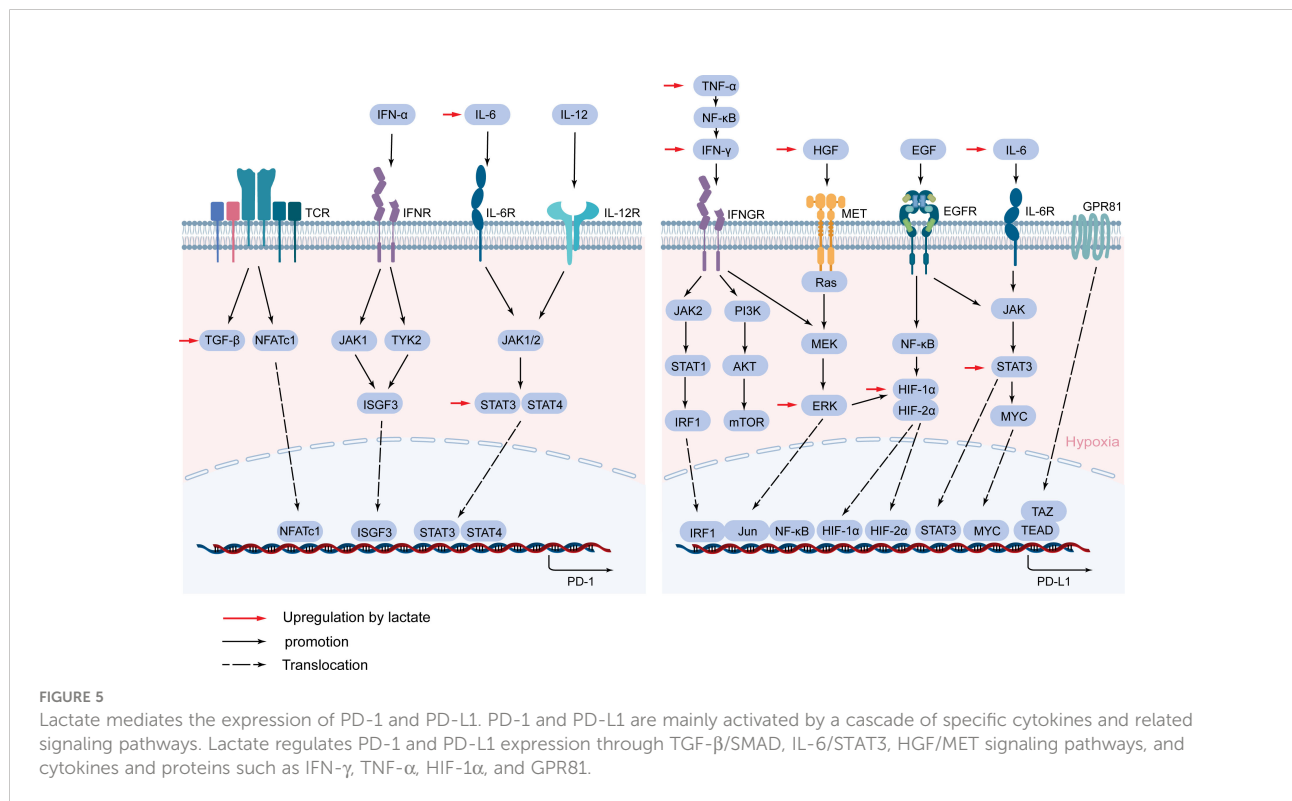
In addition to the inflammatory signaling pathway, RAS/MEK/ERK signaling can regulate the expression of the PD-L1 gene through crosstalk with inflammatory signaling (132). When MEK is inhibited, IFN-γ-induced STAT1 phosphorylation and PD-L1 transcription are also inhibited (154). Conversely, activation of the MEK/ERK pathway increases PD-L1 expression (132). Hepatocyte growth factor (HGF) activates Met and epidermal growth factor receptor (EGFR) activation also regulate PD-L1 expression through the RAS/MEK/ERK pathway (154–156).

Studies have shown that certain oncogenic signaling pathways can also promote tumor immune escape by driving the expression of PD-L1. Chromatin Immunoprecipitation (ChIP) analysis showed that the oncogene MYC bound to the PD-L1 promoter and directly regulated the expression of PD-L1 at the transcription level (157), and Kim et al. also confirmed that positive expression of MYC correlated with PD-L1 expression in NSCLC (158). The pharmacological inactivation of MYC weakens mRNA levels of PD-L1 and re-establishes anti-tumor immunity in TME (159). Hypoxia is typical of most tumor microenvironments and is achieved by activating a range of hypoxia-inducible factors (HIFs), and this response can also

lead to increased expression of PD-L1 (160). Specifically, the promoter of PD-L1 contains HIF-1α response elements, and HIF-1α and HIF-2α have been shown to interact with the hypoxia response element (HRE) in the PD-1 promoter (161, 162), and it have been demonstrated in a variety of tumors (163, 164). NF-κB can induce HIF-1α by directly binding to the promoter of HIF-1α, so the NF-κB pathway can enhance the expression of PD-L1 in synergy with HIF-1α (156, 165). In addition, the interaction of TAZ with the transcription factor TEAD directly regulates the transcription of PD-L1 (166) (Figure 5).

Lactate regulates the expression of PD-1 and PD-1

In TME with high glycolysis in hepatocellular carcinoma, lactate inhibits the function of effector T cells as well as activates the function of immunosuppressive cells (e.g., Treg) by directly upregulating the expression of PD-1 and PD-L1 (167). In addition to direct regulation, the expression of PD-1 and PD-L1 is mainly activated by the cascade of the above cytokines and related signaling pathways, while lactate has been shown to be involved in multiple signaling pathways that can activate PD-1 and PD-L1 expression(Figure 5).

FIGURE 5
Lactate mediates the expression of PD-1 and PD-L1. PD-1 and PD-L1 are mainly activated by a cascade of specific cytokines and related signaling pathways. Lactate regulates PD-1 and PD-L1 expression through TGF-β/SMAD, IL-6/STAT3, HGF/MET signaling pathways, and cytokines and proteins such as IFN-γ, TNF-α, HIF-1α, and GPR81.

TGF-β/SMAD pathway

TGF-β is involved in regulating PD-1 transcription, its expression increases in cancer in a lactate-dependent manner, accumulates in the tumor microenvironment, and TGF-β function is also increased by the increase of lactate (168, 169). Lactate upregulates the TGF-β/Smad pathway and coordinates the expression of TGF-β1/Snail and TZ/AP-1 to activate EMT-related genes (170, 171). Lactate-induced oxidoreductase NOX2 mediates TGF-β activation, promotes phosphorylation of TGF-β receptors and subsequent Smad 2/3-Smad4 colocalization (172). TGF-β attenuates tumor response to PD-L1 blockade by promoting the exclusion of T cells. In mice with progressive liver metastases, blocking TGF-β signaling increased tumor sensitivity against PD-1/PD-L1 therapy, promoting T cell penetration into tumor centers to function (173, 174). In addition, lactate regulates TGF-β and downstream SMAD3 signaling in regulatory T cells through MOESIN lactylation (111). In summary, there may be a regulatory cascade between lactate and PD-1 or PD-L1, with TGF-β functioning as an intermediate molecule. As a positive feedback loop that promotes lactate-TGF-β signaling cycling as a danger signal, tumor cells may produce more TGF-β promote PD-1 expression, thus evading immune surveillance (168).

IL-6/STAT3

High concentrations of IL-6 in the tumor microenvironment were identified as one of the main causes of cancer growth, and lactate plays an important role in the expression of IL-6 and the activation of the STAT3 signaling pathway. Extensive studies have shown that lactate-induced acidosis promotes IL-6 expression, possibly due to acidosis activating ERK1/2 and p38 signaling in cells (175, 176). Lactate mediates partial crosstalk between tumor cells and macrophages, and also promotes the secretion of IL-6 and upregulates the expression of HIF1α (177). Higher IL-6 levels were also detected in patients with high expression of H3K18la, indicating that lactate and lacttylation modifications jointly regulate IL-6 secretion (102). In addition, a significant correlation was observed between IL-6 and lactate dehydrogenase (178). Lactate-induced IL-6/STAT3 signaling in inflammatory macrophages occurs simultaneously with histone lactylation (93), and when the IL-6/STAT3 pathway is inhibited, lactate production is reduced in turn (179).

Lactate also activates the STAT3 signaling pathway independently of IL-6, and lactate enhances STAT3 expression through ERK1/2 as well as phosphorylation of EZH2 enhancers (180, 181). Lactate not only enhances mRNA levels of TGF-β, but also promotes M2 macrophage polarization by accelerating p-STAT3, while STAT3 inhibitors eliminate this lactate salt-

mediated macrophage polarization (169). Whole-cell lysates that block STAT3 stimulate the activation of T cells and NK cells and enhance the infiltration of toxic CD8 T cells in HCC tumor tissue, also reducing TGF-β production (182).

HGF/MET

HGF and its receptor MET play a key role in the occurrence and metastasis of liver cancer, and lactate can regulate the expression of HGF (183). Lactate produced by tumors leads to an increase in HGF in NF-κB in cancer-associated fibroblasts, which in turn activates MET/Ras/REK signaling in tumors (184, 185). MCT1 regulates lactate transport and knocks down the expression of MCT1, resulting in blockage of signaling of HGF receptor MET. How lactate regulates the expression of PD-L1 through HGF/MET deserves further study (186).

IFN-γ

IFN-γ appears to play a dual role in the tumor microenvironment, synergistic with granzyme B-mediating tumor killing of toxic T cells (187). On the other hand, IFN-γ also mediates the expression of immunosuppressive molecules to promote tumor immune escape, and lactate participates in regulating this process (145). In HCC, tissues with high IFN-γ characteristics are often accompanied by elevated expression of PD-L1 (145). Lactate accumulation at the site of chronic inflammation not only directly promotes PD-1 expression, but may also upregulate PD-1 by promoting IFN-γ transcription (188). In tumors, lactate significantly upregulated IFN-γ levels of M2 tumor-associated macrophages and promoted apoptosis of T cells through the PD-1/PD-L1 pathway (189). LDHA is a rate-limiting enzyme for lactate production processes, and LDHA promotes IFN-γ expression through histone acetylation in epigenetic modifications (190).

TNF-α

In solid tumors, lactate accumulation leads to acidification of the tumor microenvironment, affecting the function and phenotype of cells in the microenvironment (177). Among them, lactate-mediated acidic environment significantly upregulates the expression of TNF-α, an inflammatory mediator, and activates ERK1/2 signaling (175). HCC tumor tissues with high glycolytic macrophages showed higher glycolysis rates, produced more lactate, and mediated the upregulation of PD-L1 induced by inflammatory factors such as TNF-α, blocking TNF-α which could inhibit the expression of PD-L1 in 40%-50% of tumor macrophages (191).

HIF-1α

In HCC tumor tissues, PD-L1 is produced in a HIF-1α-dependent manner by macrophages with a high glycolytic phenotype (191). Even if tumor cells metabolize glucose through the "Warburg effect", the accumulation of its product lactate salts will further induce hypoxia, which in turn will further promote lactate production, and HIF-1α is an important regulator of this process (192). The expression of HIF-1α protein increased significantly in THP-1 macrophages co-cultured with cancer cells treated with lactate, and the HIF-1α pathway was involved in coordinating PD-L1-mediated immune escape. After transfection of THP-1 cells with HIF-1α siRNA, the redistribution of M2-TAM subsets and the expression of PD-L1 were reversed (189). HIF-1α is essential for lactate-mediated activation of GPR81/mTOR/HIF-1α/STAT3 pathway, and inhibition of lactate production in tumor cells or HIF-1α expression in MDSC can restore the immune response of antitumor T cells (127). When the immunosuppressive factor macrophage migration inhibitor (MIF) is inhibited, the lactate production of melanoma cells is significantly reduced, and the expression of HIF-1α and PD-L1 is also significantly reduced (193).

GPR81

Lactate evades the surveillance of the immune system by activating GPR81 in tumor cells to induce the production of PD-L1 in tumor cells (194). Lactate-mediated activation of GPR81 reduces intracellular cAMP levels and inhibits protein kinase A (PKA) activity, leading to activation of the transcriptional coactivator TAZ, while TAZ/YAP/TEAD enhances PD-L1 promoter activity (195). The double blockade of lactate/GPR81 and PD-1/PD-L1 significantly increased the antitumor effect of metformin and even caused tumor regression (196). In addition, lactate-activated STAT3 is also able to directly activate the GPR81 promoter and activate its expression (181). This also proves that as a powerful transcription factor, lactate-mediated STAT3 can not only directly induce the expression of PD-1 and PD-L1, but also activate the expression of PD-1 and PD-L1 by other regulatory genes.

Lactate promotes hypoxia and angiogenesis

In the hypoxic tumor microenvironment, hypoxia-inducible factor 1 (HIF1) promotes hypoxic glycolysis and angiogenesis by binding to its receptor, which in turn further aggravates hypoxia. Lactate released by tumor cells activates angiogenesis-promoting signaling and is a well-established promoter of angiogenesis. Overall, lactate is involved in angiogenesis through the following mechanisms (1): Induced polarization of TAMs to M2 phenotype, increased expression of VEGF and Arg1, and thus stimulated angiogenesis (197) (2); MCT1-mediated activation of the NF-κB/IL-8 pathway in endothelial cells drives endothelial cells to form blood vessels (198) (3); Activation of GPR81 increases the secretion of AREG, which further increases the production of VEGF and promotes angiogenesis (79) (4); Stimulate the production of cytokine IL-23, which further induces the expression of IL-10, TGF-β, VEGF and MMP9 (199, 200) (5); Support the activation of HIF-1α and upregulate VEGF by inhibiting prolyl hydroxylase (PHD) through 2-oxoglutarate (192, 201).

The future of anti-lactate combined with immunotherapy for HCC

The efficacy and safety of immunotherapy in the treatment of solid tumors make it an ideal treatment option for the treatment of HCC. So far, a variety of immunotherapies have been clinically tested and achieved effective results, such as immune checkpoint inhibitors (ICIs), which have become mature HCC treatments (202).

Immune checkpoints are surface molecules that transmit inhibitory signals on the surface of immune cells, including but not limited to programmed cell death protein-1 (PD-1), cytotoxic T lymphocyte antigen 4 (CTLA-4), T cell Ig and ITIM domain (TIGIT), T cell immunoglobulin domain and mucin domain-3 (TIM-3), Lymphocyte activation gene 3 (LAG3), B and T lymphocyte attenuator (BTLA) (203). Solid tumors, including HCC, evade antitumor immune responses through such inhibitory immune receptors (204). PD-1 and CTLA-4 are members of the CD28 family, expressed on most immune cells, and by binding to their ligands, transmit inhibitory signals to T cells to promote tumor immune escape (205, 206). ICIs are monoclonal antibodies that can block the binding of immune checkpoints to their ligands and block the transduction of inhibitory signals, thereby restoring the activity of T cells to exert immune recognition and immune attack to enhance anti-tumor immune responses. The PD-1 inhibitors nivolumab (207) and pembrolizumab (208), PD-L1 inhibitor atezolizumab (209), and the CTLA-4 inhibitors ipilimumab (210) and tremelimumab (211) have been tested individually or in combination in large clinical trials. The results suggest that some patients have lower response rates to ICI therapy alone due to a lack of tumor-infiltrating T cells. The immunotherapy effect of single ICIs has not been satisfactory, and the above findings suggest that lactate modulates the immune response in the TME by modulating the pH of the TME, lactate-dependent pathways, lactate-mediated signaling, and histone modifications.

Therefore, anti-lactate combined with immunotherapy has broad prospects (Figure 6; Table 2).
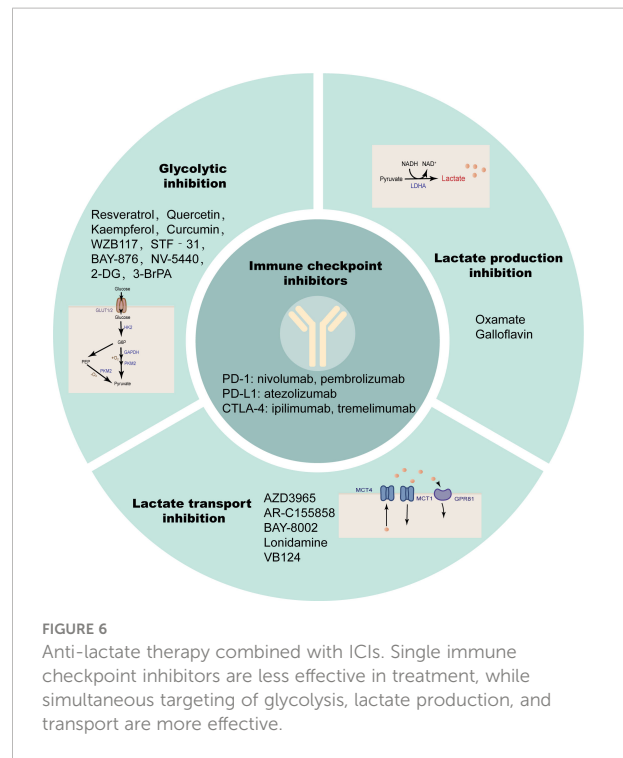
Targeting glycolysis

Active glycolysis is an important source of lactate, and inhibition of glycolysis appears to be more capable of suppressing lactate due to the "Warburg effect" in cancer cells. Glucose uptake is the first rate-limiting step in glycolysis, and inhibition of glucose transporters may have therapeutic benefits in the treatment of hyperglycolytic tumors. Small-molecule GLUT1 inhibitors such as the natural products Resveratrol (227, 228), Quercetin (229, 230), Kaempferol (231) and Curcumin (232), and the non-natural products WZB117 (233, 234), STF-31 (235, 236), BAY-876 (237), NV-5440 (238) can effectively inhibit the progression of various cancers including HCC. 2-Deoxy-D-glucose (2-DG) as a glucose analog is a competitive inhibitor of glucose metabolism (239). Studies have shown that 2-DG and sorafenib synergistically inhibit the proliferation of HCC cells and sorafenib resistance (212, 213). 3-Bromopyruvate(3-BrPA), a HK2 inhibitor, reduces the proliferation and motility of HCC cells. It is also able to enhance the efficacy of sorafenib in an *in vivo* model of HCC and can also be considered as a potential clinical chemosensitizer to optimize the index of CNU treatment (214–216). These glycolysis inhibitors also require extensive clinical trials to evaluate their safety and efficacy in patients.

Target lactate synthesis

Lactate accumulation mediated by abnormally high expression of LDHA is a common and major feature of cancer metabolism (240), so targeting LDHA is a safe and effective strategy that has been tested clinically. Oxamate as an inhibitor of LDHA enhanced the antitumor activity of sorafenib, imatinib and sunitinib in HCC (217). Quinoline-3-sulfonamides and Galloflavin, which are inhibitors of LDHA, can inhibit HCC tumor proliferation (218, 219). LDH levels can also predict the prognosis of patients with a variety of ICI-treated tumors, such as patients with advanced esophageal squamous cell carcinoma (ESCC) and non-small cell lung cancer (241, 242).

Target lactate transport

MCT1/4 and GPR81 mediate the exchange of lactate on the tumor cell membrane and are also important factors in tumor aggressiveness, and blocking lactate transport is a potential target for cancer therapy (79, 243). Dual blockade of the lactate/GPR81 pathway and the PD-1/PD-L1 pathway significantly inhibits tumor growth and induces tumor

FIGURE 6
Anti-lactate therapy combined with ICIs. Single immune checkpoint inhibitors are less effective in treatment, while simultaneous targeting of glycolysis, lactate production, and transport are more effective.

regression, while increasing the number of CD8 T cells in tumor tissue and increasing IFN-γ secretion in lymph nodes (196). In lactate-mediated TME, PD-1 is more expressed in Tregs than in effector T cells. MCT1 upregulation in Tregs and its downstream lactate signaling promote resistance to anti-PD-1 therapy in HCC patients (244). MCT1 inhibitor AZD3965 was combined with anti-ICIs to enhance the immunity of antigen-specific CD8 T cells to tumors, effectively inhibiting tumor growth (220). AR-C155858, BAY-8002 and Londonamine (LND) also showed effective MCT1 inhibitory and immunomodulatory activities, and the cytotoxicity of some anti-tumor drugs (such as anti-PD-1) of HCC was increased after LND treatment (221–225). MCT4 targeted inhibition destroys intracellular pH homeostasis and initiates self-apoptosis of HCC cells (245), and MCT4 inhibitor VB124 enhances T cell infiltration and the potency of anti-PD-1 immunotherapy in HCC mice (226).

In addition to targeting glycolysis, lactate production and transport, targeting mTOR pathways also play an important role in regulating lactate metabolism. Water-soluble rapamycin analogues (temsirolimus, everolimus), ATP-competitive mTOR inhibitors (MLN0128, AZD2014, PP242), and dual PI3K/mTOR inhibitors (NVP-BEZ235, LY3023414, PQR309, XH00230381967, SN20229799306, GSK2126458, PKI-587) have been used to treat a variety of cancers (246). Although the efficacy of mTOR inhibitors alone is limited, mTOR inhibitors exert anti-HCC tumor activity in synergy with anti-PD-1 therapy (247). The concentration of lactate in the tumors of HCC individuals who responded to PD-1 inhibitor therapy

TABLE 2 Some of the anti-lactate drugs that have been reported.

Type	Inhibitors	Targets	Reference
glycolysis	2-DG	HK2	(212, 213)
glycolysis	3-BrPA	HK2	(214–216)
lactate production	Oxamate	LDHA	(217)
lactate production	Quinoline-3-sulfonamides	LDHA/LDHB	(218)
lactate production	Galloflavin	LDHA	(219)
lactate transport	AZD3965	MCT1	(220)
lactate transport	AR-C155858	MCT1	(221)
lactate transport	BAY-8002	MCT1	(222)
lactate transport	Lonidamine	MCT1/4	(223–225)
lactate transport	VB124	MCT1	(226)

and the level of MOESIN lactylation in Treg cells were lower than in the unresponsive individuals. Anti-lactate combined with immunotherapy has a stronger anti-tumor effect, so ICIs and anti-lactate combination therapy is a potential treatment direction (111).

Conclusion

Multiple evidence shows that lactate plays an important role in regulating tumor cell metabolic reprogramming, remodeling TME, and regulating anti-tumor immunity, and lactate modification is an important way for lactate to function. Metabolic reprogramming resulting in active glycolysis increases lactate levels and lactylation in the TME. The production and accumulation of lactate plays a key role in HCC. We believe that accelerated uptake of glucose and aerobic glycolysis in tumor tissue increases the production, accumulation and release of lactate. Acidification of the TME and persistently high lactate levels lead to abnormal signaling that promotes the formation of an immunosuppressive tumor microenvironment, thereby supporting tumor immune escape. One of the consequences of abnormal lactate metabolism is an abnormal increase in lactylation levels, and the increase in lactylation levels can be observed in a variety of diseases and cancers.

Cancer immunotherapy seems to be one of the most promising treatment modalities over the past decade. At present, immune checkpoint PD-1/PD-L1 inhibitors have been studied in multiple clinical trials, but only a few patients have benefited from them. Lactate not only plays a role in TME as an immunosuppressive molecule, but also participates in regulating the expression of other immunosuppressive molecules such as PD-1 and PD-L1, thereby exerting immunosuppressive effects and affecting the therapeutic effect of immune checkpoint inhibitors. Therefore anti-lactate combined immunotherapy

appears to be a more promising treatment modality. In addition to targeting glycolysis, lactate synthesis and transport, epigenetic modifying enzymes may also be new therapeutic targets. Overall, targeting lactate metabolic pathways combined with immune checkpoint inhibitors may be able to more selectively modulate immune cell activity, and lactate modification may be beneficial for in-depth study of more diseases and their processes.

These findings about lactylation are still in their infancy, only lactylation is known to be written into enzyme p300, it is not clear which enzymes recognize lactylation, and more lactylation "writers" as well as "readers" and "erasers" have yet to be discovered. Studies have shown that in a variety of cancers, key enzymes involved in glucose metabolism are rich in non-histone lactate salt modifications, how do they in turn regulate lactate metabolism? Is there crosstalk between lactate modifications and other PTMs? These details all deserve further study.

Author contributions

YX collected the related papers and drafted the manuscript. XH, YR, QX, and XL participated in the design of the review. SS and YW initiated the study and revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

PTM	Post-translational modification
HCC	Hepatocellular carcinom
TME	Tumor microenvironment
MAFLD	Metabolic associated fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
CO2	Carbon dioxide
TCA	Tricarboxylic acid
PEP	Phosphoenolpyruvate
LDHA	Lactate dehydrogenase A
GDH	Glutamate dehydrogenase
DC	Dendritic cells
MCT	Monocarboxylate transporter
HK	Hexokinase
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
PKM2	Pyruvate kinase 2
LDH	Lactate dehydrogenase
TACE	Transarterial-chemoembolization
GPR81	G protein-coupled receptor 81
PDK	Pyruvate dehydrokinase
PDH	Pyruvate dehydrogenase
HIF-1α	Hypoxia-inducible factor 1α
PCAF	P300/CBP-associated factor
NK	Natural killer
Tregs	Regulatory T cells
CTLs	Cytotoxic T lymphocytes (CTLs)
NKTs	Natural killer T cells
TAMs	Tumor-associated macrophages
VEGF	Vascular endothelial growth factor
ARG1	Arginase-1
MDSCs	Myeloid-derived suppressor cells
PHD	Prolyl hydroxylase
BMDM	Bone marrow-derived macrophages
INF-γ	Interferon gamma
LGSH	Lactyl-glutathione
GLO2	Glyoxalase 2
	(Continued)

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HDAC	Class I histone deacetylases
BCAP	Phosphoinositide 3-kinase
TIMs	Tumor-infiltrating myeloid cells
NSCLC	Non-small cell lung cancer
VHL	Inactive von Hippel-Lindau
ccRCC	Clear cell renal cell carcinoma
PDGFRβ	Platelet-derived growth factor receptor beta
LCSCs	Liver cancer stem cells
ALDOA	Aldolase A
LDHi	Lactate dehydrogenase inhibitor
NTT	Non-tumor tissues
PD-1	Programmed cell death protein-1
CTLA-4	Cytotoxic T lymphocyte antigen
TIGIT	T cell Ig and ITIM domain
TIM-3	T cell immunoglobulin domain and mucin domain-3
LAG3	Lymphocyte activation gene 3
BTLA	B and T lymphocyte attenuator
2-DG	2-Deoxy-D-glucose
3-BrPA	3-Bromopyruvate
ESCC	Esophageal squamous cell carcinoma