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REVIEW

Lactate and lactylation in breast cancer: current understanding and therapeutic opportunities

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ABSTRACT Breast cancer (BC) has the highest prevalence among cancers specific to women, and its incidence rates are increasing in many countries. Subtypes of BC, including HER2-positive or triple-negative BC, exhibit differing treatment responses; consequently, demand for personalized therapy is increasing, and relevant precision medicine strategies are under development. Aerobic glycolysis in cancer cells can lead to excessive lactate production, which in turn promotes lactylation and influences tumor cell behavior. Epigenetic alterations and metabolic reprogramming are prominent characteristics of tumors. Because lactate and lactylation are important in cancer, further investigation of the mechanisms underlying lactate metabolism and lactylation, and the development of therapeutic strategies targeting these processes, are topics of increasing interest. This review describes current research on lactate metabolism and lactylation in BC, thus offering new perspectives for advancing treatment and management toward more precise and personalized approaches that will ultimately increase BC survival rates and patient quality of life.

KEYWORDS Lactate; lactylation; breast cancer; tumor metabolism; immunotherapy prognosis

Introduction

Breast cancer (BC), a major public health challenge globally, is a life-threatening disease and a major cause of mortality in women[1-4]. BC also shows high heterogeneity, and aggressive and complex biological characteristics[5,6]. Various treatments, such as immunotherapy, emerging targeted inhibitors, antibody-drug conjugates, nanoparticles (such as albumin-based, metal-based, lipid-based, polymer-based, and micelle-based nanoparticles), and therapeutics targeting BC stem cells, are available for treating BC[7-10]. However, effective treatment of BC faces numerous challenges, including the poor prognosis and drug resistance associated with triple-negative BC (TNBC)[11-13]. Additionally, neglected self-examination and clinical breast screening often lead to diagnosis of BC in late stages[14,15]. Recent progress in genomics has enhanced understanding of the molecular pathways involved in BC pathogenesis, and enabled the discovery of novel biomarkers for diagnosis and the development of targeted therapies. Continuing studies on BC epidemiology have further refined knowledge regarding screening practices, the implementation of adjuvant therapies, and evolving risk factors[16,17]. Although the use of precision medicine has expanded therapeutic options for patients with BC, it has concurrently introduced new complexities in clinical management.

Metabolic reprogramming has been extensively investigated in the context of cancer, and disordered cell metabolism has been demonstrated to promote tumor development and dissemination in adverse microenvironments[18-22]. Metabolic reprogramming and its corresponding byproducts exert complex effects on tumor cell functions. Many studies have demonstrated that lactate, the glycolytic metabolic byproduct present in BC cells, has important effects as a metabolic substrate and

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signaling molecule in cancer biology[23-26]. Tumor cells rely primarily on glycolysis for energy production. Lactate accumulation stimulates the glycolytic pathway through feedback mechanisms, thus leading to activation of signaling pathways such as the HIF-1α pathway, which promotes the growth and survival of tumor cells[27,28]. Acidification of the tumor microenvironment (TME) through lactate accumulation suppresses immune cell activity, stimulates cancer cells' immune escape, and increases their invasive and metastatic capabilities[23,29]. Additionally, lactate interacts with other metabolic pathways, including amino acid metabolism and fatty acid oxidation, thereby exerting complex effects on angiogenesis and immune regulation[24,30]. These interactions activate multiple oncogenic pathways while concurrently inhibiting immune cell function. Targeting lactate production or its metabolic byproducts has recently shown potential value as a therapeutic strategy against BC and may contribute to the development of novel antitumor agents[25,31,32]. Consequently, lactate metabolism has emerged as a promising target for innovative anti-BC therapies.

Lactylation, a recently identified post-translational protein modification, has garnered increasing attention in cancer research, because of its complex roles in regulating cellular functions and metabolic pathways[33,34]. Lactylation influences gene expression through changes in histone modification status. Histone modification may promote the expression of oncogenes or suppress the expression of tumor suppressors, thus triggering tumor occurrence and development[35,36]. Several groundbreaking research findings regarding lactylation in various cancer fields have been reported in recent years. For example, lactate is used in the lactylation of PIK3C3/VPS34 at lysine residues 356 and 781 *via* the acyltransferases KAT5/TIP60. The hyperlactylation of PIK3C3/VPS34 triggers autophagy and has crucial roles in maintaining skeletal muscle homeostasis and cancer progression[37]. In contrast, inhibiting histone lactylation efficiently restrains tumorigenesis and the development and prognosis of metastatic colorectal cancer in hypoxic environments[38,39]. Recent findings indicating that global lactylation is considerably elevated in colorectal cancer have established its role as an independent predictor of cancer prognosis[40]. Elevated global lysine lactylation and histone H3 lysine 18 lactylation (H3K18la) in non-small cell lung cancer tissues have been shown to positively correlate with poor patient prognosis[41]. Moreover, lactylation and lactylation-related molecules are involved in various pathways that promote BC proliferation, invasion, and metastasis,[42,43] and have substantial research value, particularly in the TNBC subtype[44]. Analysis of lactylation-associated gene levels and mutations in BC, combined with insights from databases and datasets, has been found to improve diagnosis and prognosis management, and enhance treatment outcomes for patients with BC[45]. Thus, lactylation notably illustrates interactions between tumor epigenetic modifications and metabolic reprogramming, and may be targeted through new strategies to enhance antitumor effects[46,47]. Continued investigation of lactylation-specific targets may yield novel strategies for improving outcomes in BC and other malignancies.

Relationship between lactate and lactylation in the TME

Lactate is closely associated with lactylation in the TME. As a principal byproduct of glycolytic metabolism in mammals, lactate is markedly elevated under various pathological conditions[48]. Beyond its metabolic role, lactate directly modulates protein functions, thereby influencing cell growth and cell cycle regulation[49,50]. In cancer cells, lactate is produced in large quantities as a consequence of the "Warburg effect", a metabolic hallmark of malignancy[51-53]. Multiple studies have established correlations of lactate levels with tumor prognosis, metastasis, and overall survival outcomes[52,54-56]. Furthermore, lactate exerts immunomodulatory effects within the TME and affects various immune cell functions[57,58]. Notably, recent findings have demonstrated that lactate enhances $CD8^+$ T cell stemness and potentiates anticancer immune responses. Additionally, lactate regulates Foxp3-dependent RNA splicing through CTLA-4 signaling, thereby preserving the phenotypic and functional integrity of tumor-infiltrating regulatory T cells (Tregs)[59,60]. These observations underscore the multifaceted roles of lactate in shaping antitumor immunity and highlight its potential as a therapeutic target in cancer immunotherapy.

Emerging evidence suggests that lactate drives the formation of a novel histone post-translational modification known as lysine lactylation (Kla). This modification involves alteration of lysine residues in proteins *via* lactate addition, and subsequently affects protein function and various physiopathological events in cells[61]. Lactylation of lysine residues on substrate proteins is catalyzed by acetyltransferases, potentially p300. The p300 enzyme, a histone acetyltransferase, facilitates the transfer of the acetyl group from acetyl-CoA to lysine residues on histones, thus resulting in histone acetylation[48,61,62]. AARS1 has been reported to be a lactate sensor mediating global lysine

lactylation while catalyzing the production of lactate-AMP and the subsequent transfer of lactate to lysine acceptor residues[63]. The research group led by Professor Zhaocai Zhou at Fudan University has confirmed that lactate is recognized and bound by AARS1, which, in the presence of ATP, is converted to a high-energy intermediate that catalyzes the lactylation of substrate proteins[64]. The finding that lactylation induced by lactate is necessary for modulating gene transcription has suggested new perspectives regarding the nonmetabolic activities of lactate in the TME[61]. The liver, a central organ in lipid and glucose metabolism, exhibits elevated lactate accumulation because of the Warburg effect[65]. Recent studies have revealed extensive lactate-driven lactylation modifications affecting key metabolic enzymes involved in the tricarboxylic acid cycle; glucose and fatty acid metabolism; and nucleotide and amino acid metabolism[66,67].

Importantly, the intracellular and extracellular concentrations of lactate, the principal donor for lactylation modification, directly influence the frequency and extent of these modifications[68]. In the TME, high lactate levels provide sufficient substrate to facilitate widespread lactylation. Among the factors influencing the TME, lactate and lactylation have multiple effects[69,70]. For example, excessive lactate secretion by metabolically reprogrammed cancer cells leads to extracellular acidification, thereby creating an acidic environment that promotes tumor cell proliferation and metastasis[71,72]. In addition, acidification of the local tumor environment decreases the binding activity of cell integrins to the extracellular matrix (ECM); leads to downregulation of the expression of E-cadherin; and triggers activation of proteinases such as MMP-9, hyaluronidase-2, and cathepsin B, which are produced by cancer cells and facilitate tumor cell invasion[73,74]. Lactate binds the G protein-coupled receptor GPR81, which transmits intracellular signals, thereby affecting the downstream signal transduction molecules cAMP and Ca^{2+}. This interaction inhibits protein kinase A (PKA) pathway activation by decreasing cAMP levels. High levels of GPR81 in tumor cells, in association with lactate, correlate with tumor growth, invasion, and immunosuppression in the TME[75,76]. Lactate further influences protein function and localization through lactylation modifications, thus promoting tumor initiation and progression[77]. Lactate and lactylation modifications help tumors evade the immune system, and lactylation is a key mechanism underlying lactate's immunosuppressive effects in the TME. Lactylation affects the functions of key transcription factors and regulatory proteins necessary for maintaining the immune balance within T cells[78]. Lactate promotes immune escape of cancer cells, including T cells, dendritic cells, and myeloid-derived suppressor cells, by influencing the activation and activity of immune cells[47,48]. D-lactate has been found to modulate M2 tumor-associated macrophages while remodeling the immunosuppressive TME *via* the phosphatidylinositol 3-kinase/protein kinase B pathway[79]. Elevated lactate levels in the TME affect $CD8^+$ T-cell migration and infiltration in glioblastoma[80]. Moreover, lactate has been found to promote carcinogenesis by regulating MOESIN lactylation and stimulating the TGF-β pathway in Tregs[81]. Lactylation modification levels are closely associated with function and metabolism in immune cells, such as macrophages. This modification either sustains or exacerbates the immunosuppressive state in the TME, and consequently facilitates cancer formation and progression[61,82]. Lactate and lactylation modifications are associated with the regulation of metabolic reprogramming in tumor cells. Lactate, an essential metabolite linking glycolysis and oxidative phosphorylation, has crucial roles in energy supply and metabolic regulation in tumor cells. Lactylation modulates metabolic pathways and energy utilization in tumor cells by influencing the activity and stability of metabolic enzymes, thus affecting tumor cell development[83,84].

In summary, lactate is intricately associated with lactylation in the TME (**Figure 1**). The generation of lactate supplies the substrates necessary for lactylation, a process that regulates cancer cell metabolism, proliferation, invasion, and migration by modulating protein function and localization. This bidirectional interaction promotes tumor progression and has provided valuable insights into the molecular mechanisms governing the TME.

Roles of lactate in BC

Lactate accumulation in the TME contributes to tumor progression

Through glycolysis, BC cells can increase glucose uptake and lactate production, even in aerobic environments[85,86]. The accumulation of lactate, driven by active metabolic reprogramming, facilitates sustained cancer cell proliferation and malignant progression[87,88]. Tumor hypoxia is a major factor associated with the BC microenvironment, in which metabolic adaptations induced by hypoxia-inducible factor 1 (HIF-1) inhibit the citric acid cycle and cause accumulation of large amounts of lactate in hypoxic tumors[89]. Elevated lactate

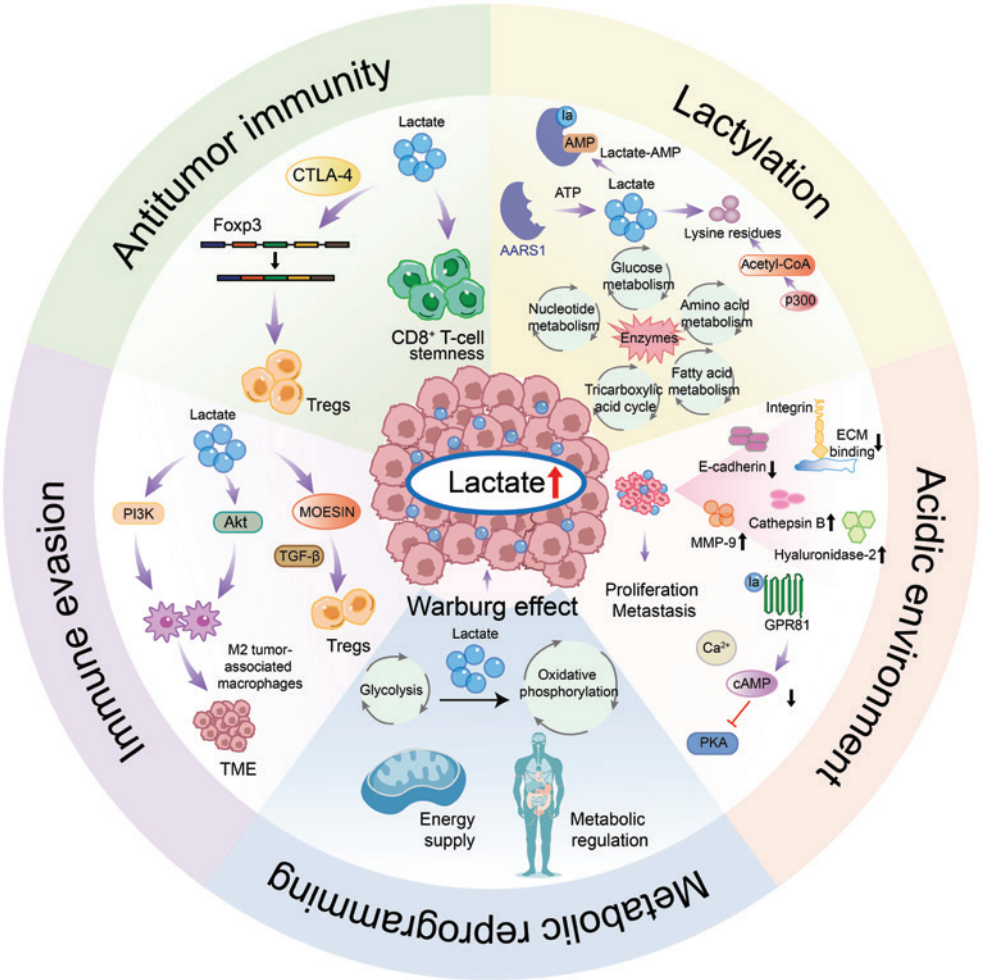


Figure 1 Interplay between lactate and lactylation in the TME. Lactylation: In the tumor microenvironment (TME), lactate is produced through the "Warburg effect". AARS1 acts as a lactate sensor that mediates global lysine lactylation in tumor cells. This enzyme binds lactate and catalyzes the conversion of lactate to lactate-AMP in the presence of ATP, and subsequently transfers lactate to the lysine acceptor residue. The p300 enzyme is a histone acetyltransferase that catalyzes the transfer of an acetyl group from acetyl-CoA to lysine residues on histones, thus resulting in histone acetylation, and is considered a "writer" of histone lactylation. Acidic environment: Acidification of the TME decreases integrin binding to the ECM and E-cadherin expression, and activates proteinases such as MMP-9, cathepsin B, and hyaluronidase-2, thus facilitating tumor cell invasion. Lactate also binds GPR81, thereby influencing cAMP and Ca^{2+} levels. Metabolic reprogramming: As a key metabolite linking glycolysis and oxidative phosphorylation, lactate is notably involved in energy supply and metabolic regulation in tumor cells. Immune evasion: Lactate also modulates M2 tumor-associated macrophages and leads to remodeling of the immunosuppressive tumor microenvironment through the PI3K/Akt pathway, promotes tumorigenesis by altering MOESIN lactylation, and enhances TGF-β signaling in Tregs. Antitumor immunity: Lactate enhances $CD8^+$ T-cell stemness and regulates Foxp3-dependent RNA splicing *via* CTLA-4, thereby maintaining Treg phenotype and function. Akt, protein kinase; AARS1, alanyl-tRNA synthetase 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; cAMP, cyclic adenosine monophosphate; ECM, extracellular matrix; GPR81, G protein-coupled receptor 81; MMP-9, matrix metalloproteinase 9; PI3K, phosphatidylinositol 3-kinase; TGF-β, transforming growth factor-β; Tregs, regulatory T cells.

content and induced overexpression of HIF-1α synergistically promote the dissemination of MDA-MB-231 cells and their stromal metastasis. Lactate accumulation enhances the gene expression heterogeneity in BC, thus facilitating tumor growth and decreasing patient survival rates[27]. In an investigation of glucose metabolism in human TNBC *via* ^{13}C glucose isotope tracing, Ghergurovich et al. have found high local lactate accumulation in human breast tumors after intravenous injection of ^{13}C glucose[30]. This accumulation facilitates the proliferation and survival of BC cells, by promoting tumor growth and

metastasis[85,90,91]. An analysis of a BC dataset from the cancer genome atlas (TCGA) by Zong et al. has revealed that patients with wild-type p53 who exhibited gene expression profiles indicative of elevated serum lactate (high-lactate clusters) had significantly lower p53 pathway scores compared with low-lactate clusters. Consequently, lactate in cancers decreases p53 activity. In a BC mouse model generated *via* the MMTV-PyMT transgenic system, lactate levels in tumors have been found to increase during tumorigenesis and positively correlate with tumor burden; therefore, intracellular lactate accumulation might promote BC progression[63]. Further investigations have revealed that lactate modulates the malignant BC cell phenotype *via* GPR81, a lactate sensor highly expressed in BC tissues and cells but not healthy mammary epithelial cells[90]. In contrast, GPR81 knockout decreases BC cell growth and tumor development[92]. Recent single-cell in situ analyses of BC MCF-7 cells have revealed upregulation of GPR81-regulated genes in identical cell clusters. The Notch pathway, particularly the Notch ligand Delta-like-4 (DLL4), is significantly downregulated after GPR81 knockdown. Moreover, this knockdown induces spheroid necrosis while inhibiting invasion, similarly to observations after GPR81 knockdown[31].

Moreover, several key glycolytic enzymes and lactate production-associated transport proteins, such as lactate dehydrogenase (LDH), monocarboxylate transporter (MCT), and glucose transporter, are upregulated in breast tumors[93]. LDH-5 is overexpressed in cancer cells, whereas elevated LDH-A mRNA and protein levels are observed in a substantial percentage of BC cases and are associated with poor patient prognosis[23,94]. MCTs catalyze the efflux of lactate (accumulating within cells) contributing to maintaining an intracellular neutral pH while favoring extracellular acidosis. Consequently, MCTs, particularly MCT1 and MCT4, might be closely associated with the hyperglycolytic phenotype of tumor cells[23,95]. Some studies have shown that BC cells activate GPR81 in sensory neurons through lactate release mediated by MCT4, thereby inducing BC-related bone pain. These changes adversely affect quality of life and prognosis in patients with BC[32]. Cancer-associated fibroblasts (CAFs) are the predominant cell type in the breast TME. Hypoxia-induced oxidized ATM promotes glycolytic activity of CAFs by phosphorylating GLUT1 at S490 and increasing PKM2 expression. Moreover, lactate derived from hypoxic CAFs, acting as a metabolic coupling between CAFs and breast cancer cells, promotes breast cancer cell invasion by activating the TGFβ1/p38 MAPK/MMP2/9 signaling axis and fueling the mitochondrial activity in cancer cells[96]. The lactate G-protein coupled receptor hydroxycarboxylic acid receptor 1 (HCAR1) is highly expressed in BC cells. HCAR1 regulates cell development and migration, and maintains cancer-specific energy metabolism in BC cells[25].

Collectively, these findings underscore lactate's critical role as a tumor-promoting metabolite in BC. Lactate's downstream metabolic products and associated signaling pathways play a critical role in tumor development, invasion, and immune modulation.

Immune suppression and angiogenesis

Glucose-derived lactate provides energy for BC cells and facilitates immune escape by suppressing immune function[97,98] (**Figure 2**). First, lactate inhibits the function of intratumoral plasmacytoid dendritic cells (pDCs)[99]. Moreover, lactate suppresses type I interferon induction *via* pDCs, either through intracellular Ca^{2+} mobilization initiated by the cell surface GPR81 receptor. In the pDC cytoplasm, lactate promotes kynurenine generation and tryptophan catabolism, and consequently enhances immunosuppressive Treg expansion[99]. In addition, lactate modulates macrophage polarization in BC tissues by suppressing polarization toward the M1 phenotype and accelerating polarization toward the alternatively activated (M2) phenotype through activation of GPR132 in macrophages[85,100]. Tumor-derived lactate also promotes M2 polarization of macrophages through activation of the ERK/STAT3 pathway in BC[101]. Additionally, BC cells exhibiting ectopic Zeb1 expression produce lactate in the acidic TME and consequently induce the M2 phenotype by stimulating the PKA/cAMP response element-binding protein (CREB) signaling pathway[102]. Single-cell transcriptomic analysis of integrated clinical data has revealed that expression of the lactate transporter SLC16A3 is correlated with BC molecular subtypes and immune infiltration. The proportion of M1 macrophages is decreased in the group with high SLC16A3 expression. *In vitro* studies have verified lactate's effects on inhibiting the mRNA and protein levels of M1 macrophage markers[85]. Because M1 macrophages generally have anticancer effects, whereas M2 macrophages are often associated with immune evasion and tumor growth, lactate-mediated modulation of macrophages stimulates BC cell invasion, migration, and adhesion[103]. Additionally, lactate's activation of GPR81 in dendritic cells inhibits the antigen-presenting capacity of tumor cells to other immune cells, and allows BC cells to evade immune recognition and destruction[90]. Lactate also

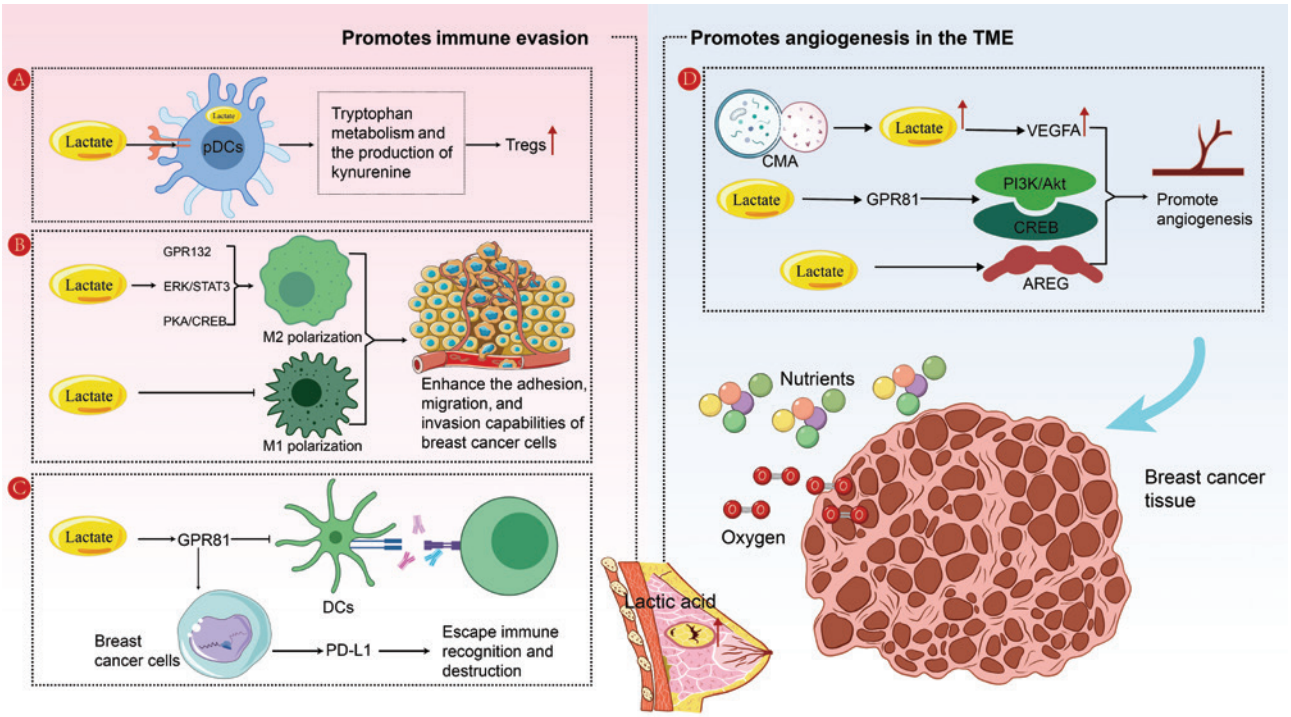


Figure 2 Lactate promotes immune escape and enhances angiogenesis in breast cancer. Glucose-derived lactate not only facilitates tumor immune evasion by inhibiting immune system function but also promotes the progression of breast cancer by enhancing angiogenesis in the TME. (A) In the context of the immune evasion, lactate transport into the cytoplasm in pDCs enhances tryptophan catabolism and kynurenine production, and consequently promotes Treg expansion. (B) Lactate regulates macrophage polarization in breast cancer tissues, thereby inhibiting macrophage polarization toward the M1 phenotype and promoting polarization toward the M2 phenotype by activating GPR132 in macrophages or the ERK/STAT3 signaling pathway in breast cancer. Lactate's modulation of macrophages enhances the adhesion, migration, and invasion of breast cancer cells. (C) Lactate activates GPR81 in dendritic cells and impairs their ability to present tumor antigens to other immune cells. Lactate also induces the production of PD-L1 in breast cancer cells through GPR81 activation, thereby further facilitating immune evasion by these cancer cells. (D) Lactate stimulates angiogenesis through GPR81 signaling, which in turn activates the PI3K/Akt-CREB pathway and results in increased secretion of AREG. Additionally, lactate production is upregulated by CMA, which enhances the expression of VEGFA in breast cancer cells. AREG, amphiregulin; CMA, chaperone-mediated autophagy; cAMP, cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; ERK, extracellular regulated protein kinase; GPR132, G protein-coupled receptor 132; GPR81, G protein-coupled receptor 81; PD-L1, programmed cell death ligand 1; PKA, protein kinase A; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; STAT3, signal transducer and activator of transcription 3; Tregs, regulatory T cells; VEGFA, vascular endothelial growth factor A.

triggers programmed death ligand-1 (PD-L1) production in BC cells by activating GPR81, thus further facilitating immune escape by BC cells[90]. Notably, recent studies have demonstrated that TNBC cells exhibit significantly higher intracellular lactate levels than other BC subtypes. RNA sequencing analyses have identified 14 differentially expressed lactate-related genes (LRGs) under various lactate conditions in TNBC cells. The association of this LRG signature with dysregulation of the interleukin-17 (IL-17) signaling pathway indicates a direct link between lactate metabolism and immune dysfunction. Importantly, the LRG signature has enabled the classification of TNBC into 2 distinct molecular subtypes: subtype A, characterized by an immunosuppressive profile, and subtype B, associated with immune activation. Given the molecular heterogeneity of BC, and the consequent wide variations in prognosis and treatment response, elucidating lactate's role in driving this heterogeneity might uncover novel therapeutic targets and inform personalized treatment stratification strategies[104].

Beyond its roles in immune suppression and metabolic regulation, lactate significantly contributes to BC progression by promoting angiogenesis within the TME[105-107] (**Figure 2**). Lactate stimulates angiogenesis through GPR81 signaling, which in turn activates the PI3K/Akt-CREB pathway and increases the secretion of amphiregulin (AREG, a

proangiogenic factor). Subsequently, promotion of angiogenesis provides breast tumors with additional nutrients and oxygen[105]. Chaperone-mediated autophagy (CMA) increases the expression of VEGFA in BC xenograft models and BC cells by increasing lactate production. Additionally, lactate modulation in BC cells depends on hexokinase 2 (HK2); silencing of HK2 decreases the CMA-mediated angiogenic ability of human umbilical vein endothelial cells. These findings suggest that CMA promotes angiogenesis in breast tumors by enhancing lactate-mediated signaling pathways[106].

Therapeutic targets and prognostic assessment

Given the multifaceted roles of lactate in promoting BC cell survival, invasion, immune evasion, metastasis, and angiogenesis, targeting lactate metabolism and its associated enzymes might provide a promising therapeutic strategy (**Table 1**). Examination of fibroblasts isolated from patients with benign breast tissue and BC, as well as various animal models, has indicated that CAFs can undergo a metabolic shift toward the production of lactate and pyruvate, thereby supporting cancer cells' biosynthetic pathways. Depleting or inhibiting lactate production in CAFs alters tumor metabolic profiles and slows tumor growth[114,115]. Moreover, inhibiting the key signaling molecules ERK/STAT3 in the lactate signaling pathway decreases tumor development and angiogenesis through the elimination of lactate-mediated polarization of M2 macrophages. Studies on the natural product withanolide D have revealed that the ERK/STAT3 pathway might provide a target for BC prevention and treatment[101]. Kar et al. have reported that PFKFB4 enhances lactate-induced migration of BC cells, given that silencing of PFKFB4 decreases lactate levels and BC cell invasion[108]. Zhang et al. have used a polyphenol nanocomplex to inhibit LDH activity, decrease lactate production, and alleviate the acidic immune-suppressive TME. This polyphenol nanocomplex has been found to elicit effective antitumor immunity in a BC mouse model[109]. Analysis of paired biopsy samples from BC tissue and cancer-associated adipose tissue from overweight/obese and normal-weight premenopausal women has revealed that elevated lactate levels in tumor tissues are accompanied by changes in the isozyme pattern to "muscle-type" LDH, and associated alterations in LDH A and B protein levels. In contrast, the considerably elevated LDH activity in cancer-associated adipose tissue suggests that LDH activity primarily facilitates lactate oxidation[116]. In contrast, treatment with various inhibitors of LDH activity decreases lactate levels outside cells, cell growth, motility, and migration in estrogen receptor-positive (ER+) and -negative (ER–) BC cells[110]. These findings highlight that LDH, along with its isoforms, may be used for BC treatment and that significant differences exist among BC tissues in various regions, thus providing promising directions for future BC diagnostic research. Additionally, targeted knockdown of MCT4 *via* miR-425-5p decreases lactate secretion from CAFs and impairs their ability to support BC cell angiogenesis, invasion, survival, and proliferation[111]. Combined therapy with the MCT inhibitor quercetin and doxorubicin inhibits lactate metabolism, suppresses the HIF-1α/VEGF pathway and angiogenesis, and repolarizes tumor-associated macrophages[24]. The tamoxifen-resistant BC cell line MCF-7 (TAMR-MCF-7) shows elevated conversion of lactate to pyruvate—a process in which MCT1 and LDHB have critical roles. In contrast, the MCT1 inhibitor AR-C155858 effectively inhibits TAMR-MCF-7 cell growth, invasion, spheroid formation, and tumor development *in vivo*. Therefore, targeting MCT1-mediated and LDHB-mediated lactate production is a promising modality for treating tamoxifen-resistant BC[112]. Tang et al. have developed nanoparticles containing vascular endothelial growth factor (VEGF) siRNA (siVEGF) and lactate oxidase/catalase for delivery into 4T1 cells. This approach promotes lactate consumption and silences VEGF expression, thereby synergistically inhibiting TNBC proliferation and angiogenesis[107]. To further ameliorate the breast TME and overcome immune evasion, Tang et al. have developed nanoparticles containing lactate oxidase and PD-L1 siRNA (siPD-L1). This technique regulates the acidic TME in TNBC by depleting lactate, thereby ameliorating the immunosuppressive TME through activating exhausted $CD8^+$ T cells and decreasing the percentage of immunosuppressive Tregs. Additionally, siPD-L1 administration synergistically enhances the therapeutic effect of PD-1/PD-L1 blockade on TNBC[113].

Precision medicine in BC requires biomarkers that are sensitive to early treatment responses. Clinically, the lactate concentration measured in whole-breast tumors *via* double quantum filtering and magnetic resonance spectroscopy is significantly sensitive to tumor grade and patient prognosis[91]. A novel gene signature associated with lactate metabolism and hypoxia has recently been developed for predicting prognosis, treatment response, and the immune microenvironment in patients with BC. A research group led by Jia Li has collected genes associated with lactate metabolism and hypoxia from public data and identified differentially expressed genes (DEGs) with the edgeR R package. The researchers conducted univariate Cox

Table 1 Potential biomarkers and therapeutic targets for breast cancer therapies based on lactate

Potential biomarkers or targets	Therapeutic methods related with lactate	Effects	References
ERK/STAT3 pathway	Inhibition of the key signaling molecules ERK/STAT3 in the lactate signaling pathway Elimination of lactate-mediated polarization of M2 macrophages	Decreased tumor development and angiogenesis	101
PFKFB4	Decreased lactate levels through PFKFB4 silencing	Decreased invasion	108
Polyphenol nanocomplex	Inhibition of LDH activity; decreased lactate production	Alleviation of the acidic immune-suppressive TME; promotion of effective antitumor immunity	109
Various inhibitors of LDH activity	Decreased lactate levels outside cells	Inhibition of cell growth, motility, and migration in estrogen receptor-positive (ER+) and -negative (ER−) BC cells	110
Knockdown of MCT4 *via* miR-425-5p	Decreased lactate secretion by cancer-associated fibroblasts	Impaired cell angiogenesis, invasion, survival, and proliferation	111
Combined therapy with the MCT inhibitor quercetin and doxorubicin	Inhibition of lactate metabolism; suppression of the HIF-1α/VEGF pathway	Suppressed angiogenesis; repolarization of tumor-associated macrophages	24
MCT1 inhibitor AR-C155858	Decreased conversion of lactate to pyruvate	Inhibition of TAMR-MCF-7 cell growth, invasion, spheroid formation, and tumor development	112
Nanoparticles containing lactate oxidase, lactate oxidase/catalase, and siPD-L1 or siVEGF	Promotion of lactate consumption; silencing of VEGF expression	Regulation of the acidic TME; inhibition of TNBC proliferation and angiogenesis; improved therapeutic effects of PD-1/PD-L1 blockade in TNBC	107,113

regression, stepwise multivariate Cox regression, and random survival forest analyses to construct a hypoxia-lactate metabolism-related prognostic model. In total, 181 differentially expressed hypoxia- and lactate metabolism-related genes were identified, 24 of which were deemed valuable prognostic genes. Risk score analysis indicated that patients in low-risk groups had more favorable responses to common chemotherapeutic and immunotherapeutic agents than high risk groups. This model integrates lactate metabolism with hypoxia to predict overall survival, treatment response, and immune status in patients with BC, thus offering new insights for personalized treatment[117]. Another study has used quantitative nuclear magnetic resonance spectroscopy to investigate the metabolic components in 22 patients with HER2-positive BC. Patients with higher lactate levels had higher HER2 transcript levels. Furthermore, TCGA dataset analyses and metabolic assessments have confirmed significantly greater glycolytic metabolic activity in cells with high *vs.* low HER2 transcript levels. This study has provided compelling evidence that noninvasive intratumoral lactate detection can serve as a metabolic biomarker for HER2 addiction and trastuzumab response, and suggested the feasibility of *in vivo* imaging for assessing lactate levels and identifying HER2-positive patients with BC who stand to benefit from anti-HER2 therapies[118].

Extensive bioinformatics research has further highlighted the prognostic and immunological significance of lactate metabolism-related genes (LMRGs) in BC. By using RNA sequencing data and clinical parameters from the TCGA and Gene Expression Omnibus databases, researchers have identified LMRGs and DEGs and constructed risk prediction models through univariate analysis, LASSO Cox regression, and multivariate Cox regression. These models yielded a lactate metabolism-associated risk signature and a nomogram to predict survival probability in patients with BC. Functional enrichment analyses—including Gene Ontology and KEGG pathway analyses—have revealed a strong association between the risk signature and immune responses. Notably, significant correlations were observed between prognostic LMRGs and

tumor mutation burden, immune checkpoint molecules, and immune cell infiltration[119]. These findings suggest that lactate metabolism-associated risk signatures can aid in prognostic assessment and therapeutic decision-making, particularly in the context of immunotherapy[120]. Despite the promising findings, these studies also present certain limitations and challenges. Bioinformatics analyses are highly dependent on the availability of high-quality, large-scale genomic datasets. However, data sourced from public repositories such as TCGA and Gene Expression Omnibus might be affected by technical variability, sample heterogeneity, and missing data, thus compromising the robustness and reproducibility of the analytical outcomes. Moreover, bioinformatics studies often prioritize computational prediction over experimental validation. Without corroborative *in vitro* and *in vivo* evidence, bioinformatically identified genes and pathways might lack clinical relevance and translational applicability. Therefore, computational findings must be complemented by rigorous experimental studies to validate gene functions and confirm their therapeutic or diagnostic potential in BC.

Lactylation plays major roles in various pathways modulating BC progression

BC is the most common malignant tumor globally and the main factor causing cancer-associated mortality in women[121,122]. Since the discovery of protein lactylation, research on this modification in cancer has increased. This newly identified epigenetic mark influences various aspects of cell fate, including carcinogenesis. Determining the relationship between lactylation and cancer characteristics might aid in the development of novel treatments or dual-targeting approaches, including those for BC treatment. Lactylation is closely associated with BC occurrence and development, and strongly affects multiple mechanisms and pathways involved in BC proliferation and migration[45,46].

An analysis of lactylation-related gene expression and mutations in BC in the TCGA database and the GSE20685 dataset, including mRNA expression, copy number variation, somatic mutation, and correlation network data, has revealed that lactylation-related genes have crucial roles in BC by affecting tumor growth, treatment response, and the immune microenvironment[42]. Recent studies have indicated that AARS1, a sensor and transporter of L-lactic acid in cells, mediates p53 lactylation in BC. The lactylation of p53 at certain lysine residues in the DNA-binding domain mitigates liquid-liquid phase separation and DNA binding, thus decreasing the tumor-suppressing effects of p53 *in vitro* and *in vivo*, and promoting tumorigenesis in BC[63]. Additionally, potassium 2 pore domain channel subfamily K member 1 (KCNK1) is significantly upregulated in human BC and is predictive of extremely poor prognostic outcomes in patients. Further investigations have revealed that KCNK1 binds to and activates LDHA, thus enhancing LDHA function and promoting lactate production. Additionally, KCNK1 catalyzes H3K18 lactylation in target genes in BC cells while increasing the number of histone lactylation modifications in LDHA. Consequently, sustained LDHA expression establishes a positive feedback mechanism, thereby explaining the persistently elevated lactate generation in BC cells, and the subsequent upregulation of KCNK1 and facilitation of BC occurrence[123]. Immunoblot analysis of 15 breast tumor samples has indicated elevated abundance of H3K18la, and expression of SRSF10 and c-Myc, in BC tissues. In an ongoing clinical study examining treatment of various cancer types, treatment of wild-type BBS cells with a p300 inhibitor has been found to significantly decrease SRSF10 and c-Myc levels. These findings further highlight the importance of H3K18la-mediated epigenetic c-Myc modulation. Therefore, restricting key glycolytic enzyme activities might affect the c-Myc-SRSF10 axis and subsequently inhibit BC cell growth[43]. Moreover, alterations in H3K18la and its downstream transcription factor PPARD have been found to stimulate BC cell survival under anaerobic glycolytic conditions: PPARD facilitates the transcription and phosphorylation of AKT and consequently accelerates the proliferation of BC cells[124].

Notably, TNBC, characterized by its notable aggressiveness among BC subtypes, making it highly valuable for research on lactylation. CAFs have been found to inhibit ferroptosis, thus leading to doxorubicin resistance in TNBC through upregulation of ZFP64 mediated by histone lactylation; inhibition of lipid peroxidation induced by GCH1; and intracellular Fe^{2+} consumption induced by FTH1[125]. Comprehensive transcriptomic analysis has indicated significantly elevated pan-lysine lactylation levels in the cytoplasm and nucleus in TNBC cells. Nuclear lactylation pathways include ribosomal subunit biosynthesis/assembly and aminoacyl-tRNA biosynthesis, both of which contribute to the tumor-promoting mechanisms of lactylation[126]. A research team led by Jingyi Li, through immunohistochemical staining of 60 TNBC samples, has recently discovered that pan-acylated protein levels are higher in tumor

tissues than normal tissues. The researchers have identified acylation at the H4K12 site of histone proteins, which is associated with the progression of TNBC. In addition, CUT&Tag sequencing and luciferase reporter assays have confirmed that lactate-induced H4K12 lactylation in TNBC cells inhibits the expression of SLFN5, thus promoting TNBC malignancy[44]. Similarly to the aforementioned findings, a comprehensive analysis of lactylated proteomes has revealed greater levels of lactylated lysine at position 12 (H4K12lac) within the histone H4 domain in TNBC tissues than in matched non-carcinoma tissues. Further investigations have shown that H4K12lac is highly upregulated in TNBC, with positive rates of 93.19% (137/147) and 92.93% (92/99) in TNBC tissue chip and validation cohorts[127]. These studies have revealed an important histone lactylation-mediated oncogenic pathway in TNBC and have highlighted that lactylation can be further assessed in this context.

Lactylation may serve as a diagnostic and therapeutic target in BC

The past several decades have witnessed a BC oncology revolution, as local treatments such as surgery and radiotherapy have become less invasive and more precise. With increasing knowledge of the molecular and biological characteristics of BC, along with advancements in scientific methods and precision medicine, new treatment approaches continue to emerge[128]. The performance of targeted lactylation therapy in BC clinical trials is particularly notable. Recent studies involving radiotherapy and chemotherapy have analyzed lactylated proteomes and revealed that several DNA repair-associated proteins undergo lactylation in resistant cancer cells, particularly in various solid tumors. Lactylation has been found to significantly affect the regulation of DNA repair. TIP60, a lysine lactyltransferase that mediates NBS1 lactylation at lysine 388 (K388), is an important residue at the interaction interface between NBS1 and MRE11. This modification is essential for the formation of the MRN complex and efficient DNA repair. These findings further underscore the role of lactate as a protective metabolite that enhances cancer cell survival in the presence of genotoxic agents—thereby promoting DNA repair and facilitating chemoresistance—and that exerts a crucial role in maintaining genomic integrity. Given that chemotherapy is a primary treatment for malignant tumors, including BC, targeting lactate metabolism is a potential approach to enhance chemotherapy efficacy and improve patient survival[129]. Because inhibition of key glycolytic enzyme activities influences the c-Myc-SRSF10 axis, thereby suppressing the growth of BC cells, chemotherapy is a feasible approach to decrease the glycolytic rate. This approach hinders the c-Myc-SRSF10 axis and consequently restricts BC progression[43]. To therapeutically exploit this mechanism, researchers are exploring the development of inhibitors targeting TIP60 or NBS1 to impair DNA repair in cancer cells, thereby increasing sensitization to chemotherapeutic agents. The combination of such inhibitors with standard chemotherapy has potential for overcoming resistance and increasing therapeutic efficacy. Furthermore, integrating immune checkpoint inhibitors with glycolytic enzyme inhibitors offers a dual strategy to suppress tumor growth while disrupting the metabolic plasticity of cancer cells, thereby enhancing immune-mediated tumor eradication. Inhibitors of lactate metabolism, such as those targeting LDHA, have shown promise in decreasing chemoresistance and potentiating the cytotoxic effects of chemotherapy. Moreover, decreasing lactate levels might ameliorate the TME and augment the effectiveness of immunotherapeutic approaches. Importantly, to validate the therapeutic potential and safety of these combinatorial strategies—targeting DNA repair, metabolic regulation, and immune modulation—well-designed, systematic clinical trials will be essential. Such trials should include diverse BC subtypes, to accurately assess treatment outcomes and establish subtype-specific therapeutic protocols. Through personalized treatment plans based on patients' molecular characteristics, the success rate of treatment may be increased.

A research team led by Jian Deng has analyzed 1,073 BC samples and 112 normal control samples and identified 257 Kla-specific DEGs in BC. The study also revealed significant associations of Kla with the immune microenvironment, drug treatment, and immunotherapy in patients with BC. Kla is associated with various KEGG pathways in BC. Because Kla has also been implicated in drug resistance and adverse immune responses, thus exerting important effects on BC prognosis, it therefore might serve as a novel anti-BC therapeutic target[45]. An RNA sequencing study of BC samples to assess lactylation-related gene levels has revealed markedly greater expression of HDAC2 in BC samples than in matched non-carcinoma samples, and considerable downregulation of SIRT1, SIRT2, SIRT3, and CREBBP in BC samples. HDAC2 was identified as a poor prognostic factor in invasive breast carcinoma. Therefore, considerable

potential exists for further research examining the association between lactylation-related genes and the prognosis in patients with BC[130]. An analysis by Jiao et al., examining lactylation-related genes' expression levels and mutations in BC data from TCGA and the GSE20685 dataset, has identified a seven-gene biomarker for predicting survival prognosis in patients with BC. Prognostic scoring indicated this biomarker's significant prognostic value in predicting treatment response[42]. Additionally, lactylation-related lncRNAs can be used to develop prognostic models for BC. Lin et al. have analyzed BC tissues, including tumor and non-carcinoma tissues obtained from the TCGA database, then used XGBoost methods and Cox regression to identify lncRNAs associated with Kla. On this basis, the researchers developed a prognostic model, which was validated across training, testing, and overall cohorts. Eight lncRNAs associated with immune function and immune cell infiltration were identified and selected for the risk model. Patients with higher risk scores had greater tumor mutation burden but lower tumor immune dysfunction and exclusion (TIDE) scores. This study not only highlights the potential relationship of Kla-associated lncRNAs with BC but also provides innovative therapeutic insights for the management of this disease[131]. Other studies examining treatment prognosis for TNBC have indicated a positive relationship between H4K12lac expression correlated positively with Ki-67 and inversely with overall survival (OS) in TNBC (HR [hazard ratio] = 2.813, 95% CI [credibility interval]: 1.242–6.371, $P = 0.0164$), suggesting its potential as an independent prognostic marker (HR = 3.477, 95% CI: 1.324–9.130, $P = 0.011$)[127]. Another study has indicated elevated histone H4K5lac in both BC tissues and peripheral blood mononuclear cells, according to immunohistochemistry and immunoblotting. Furthermore, H4K5lac expression positively correlates with the percentage of lymph nodes, Ki-67 expression, serum lactate, and carcinoembryonic antigen levels. In contrast, H4K5lac expression is negatively associated with overall survival in both TNBC and non-TNBC cases[132]. Overall, research on lactylation in the field of BC clinical treatment has increased. The promising potential of lactylation for BC treatment might include identifying biomarkers associated with lactylation or the construction of prognostic models (**Table 2**). Concurrently, an urgent need exists for additional clinical BC samples, particularly from patients with advanced TNBC, to ensure the stability and precision of treatment strategies and to support further optimization of therapeutic approaches.

Conclusion, limitations, and perspective

Recent studies on the role of lactate and lactylation in BC have provided novel insights into the interplay between metabolism and epigenetics. Lactate not only is a byproduct of cellular energy metabolism but also plays a major role in the TME. Lactylation, a newly discovered epigenetic modification, influences cancer cell metabolism, cell behavior, and gene expression. However, the mechanisms through which these processes operate in BC remain under investigation. With advances in liquid biopsy technologies, lactate and its associated metabolites in sera may be applied as biomarkers for BC, thus aiding in early diagnosis and prognostic assessment. Additionally, intervention strategies targeting lactylation might emerge as new therapeutic avenues, particularly for challenging subtypes such as TNBC, which have relatively poor prognosis.

Nonetheless, several limitations and challenges persist in this field of research. Lactate, although often regarded as a tumor-promoting metabolite within the TME, might also exert context-dependent tumor-suppressive effects. Elucidating its precise role across different stages and molecular subtypes of BC remains a critical area of investigation. Similarly, although lactylation has been shown to influence protein function and stability, the identification of specific protein targets and the mechanistic pathways through which lactylation contributes to BC pathogenesis remain to be fully delineated. Therapeutically, the metabolic heterogeneity across BC subtypes requires a nuanced understanding of lactate and lactylation dynamics; consequently, determining whether their roles vary among major subtypes—such as luminal A, luminal B, HER2-enriched, basal-like, and Claudin-low—is a key future research direction. Developing subtype-specific therapeutic interventions targeting lactate metabolism or lactylation also poses substantial challenges, particularly in the context of personalized medicine. Furthermore, despite the therapeutic promise of targeting lactate and lactylation, rigorous assessment of the safety and efficacy of such interventions across diverse patient populations will be essential. The potential for tumor cells to develop resistance necessitates carefully designed clinical trials to evaluate both risks and benefits. Translating these molecular insights into clinical practice will involve additional hurdles, including the accurate quantification of lactate levels and lactylation status in patient samples,

Table 2 A lactylation modifications and their potential therapeutic evidence in breast cancer

Lactylation modifications	Related molecules or pathways	Functions	Potential therapeutic evidence	References
p53	AARS1 functions as a lactate sensor that mediates global lysine lactylation. Lactylation of p53 at the K120 and K139 residues impairs p53 liquid-liquid phase separation and DNA binding.	Promotes tumorigenesis	AARS1 expression and p53 lactylation are associated with a poor prognosis among cancer patients carrying wild type p53	63
H3K18la	H3K18la modification of target genes is catalyzed by KCNK1, thus increasing histone lactylation modifications of LDHA and promoting lactate production in breast cancer cells with high expression of KCNK1.	Facilitates progression and survival	H3K18la is significantly upregulated in breast cancer, and is associated with poor prognosis in breast cancer patients	43,123,124
	H3K18la-dependent epigenetic regulation of c-Myc, the abundance of H3K18la, and the expression of c-Myc and SRSF10 increased.	Promotes proliferation	Restricted activity of key glycolytic enzymes may affect the c-Myc-SRSF10 axis; p300 inhibitor treatment is currently under clinical trial	
H4K12la	H4K12la induced by lactate in TNBC cells specifically suppresses SLFN5 expression.	Contributes to TNBC malignancy	Correlated with TNBC progression H4K12lac expression positively correlates with Ki-67 and negatively correlates with overall survival	44,127
H4K5lac	Histone H4K5lac is upregulated in both triple-negative breast cancer (TNBC) and non-TNBC tissues.	N/A	H4K5lac expression correlates with the percentage of lymph nodes, Ki-67 expression, carcinoembryonic antigen levels, and overall survival	132
NBS1 at lysine 388	TIP60 acts as a lysine lactyltransferase facilitating the lactylation of NBS1 at lysine 388, an essential residue located at the interaction interface between NBS1 and MRE11.	Enhances DNA repair processes and facilitates resistance to chemotherapy	Targeting lactate metabolism may be a promising approach to enhance chemotherapy efficacy and survival rates	129
Kla-specific genes (DEKlaGs)	Kla is associated with various KEGG pathways.	Correlates with the immune microenvironment, drug treatment, and immunotherapy	Associated with drug resistance and detrimental immune responses, thus playing a crucial role in prognosis	45
Related genes	Expression of HDAC2 is significantly upregulated; expression of SIRT1, SIRT2, SIRT3, and CREBBP is notably downregulated.	HDAC2 is a poor prognostic factor	Can help establish a prognostic model to predict survival prognosis and treatment response	42,130
Related lncRNAs	N/A	Correlates with immune cell infiltration and immune function	Can be used to construct prognostic models; patients with higher risk scores exhibit greater tumor mutation burden and lower TIDE scores	131

and the integration of these biomarkers into clinical decision-making frameworks.

Overall, as precision medicine continues to evolve, patients with BC will have a range of treatment options. The primary challenge in the field of cancer treatment lies in providing patients with precise and tailored therapy. Therefore, various diagnostic and prognostic models must be developed. In summary, increasing research on lactate and its related lactylation modifications in BC may yield new insights and methods for diagnosis and treatment.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Lan Huang, Xuemei Chen, Jian Wu.
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Contributed data or analysis tools: Ze Xiang, Jian Wu.
Performed the analysis: Lan Huang, Xuemei Chen.
Wrote the paper: Lan Huang, Xuemei Chen.

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