Research progress on lactate metabolism in lung cancer: Tumorigenesis, drug resistance and clinical translation (Review)

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Abstract. Therapeutic resistance is the main obstacle to long-term survival in lung cancer, with metabolic reprogramming identified as a key factor in this failure. Accumulating evidence suggests that metabolic reprogramming, particularly the aberrant metabolism of lactate, plays a crucial role in the progression of lung cancer and the failure of treatment. Beyond its traditional characterization as a metabolic byproduct, lactate is increasingly recognized as a multifunctional signaling metabolite that connects tumor-intrinsic metabolic adaptation with the remodeling of the tumor microenvironment. In the context of lung cancer, an increase in aerobic glycolysis and dysregulated lactate transport result in the persistent accumulation of lactate and extracellular acidification. This metabolic environment fosters tumor invasion, epithelial-mesenchymal transition and the acquisition of cancer stemness, in part through lactylation-mediated epigenetic reprogramming. Importantly, emerging research indicates that lactate metabolism serves as a unifying mechanism underlying resistance to chemotherapy, targeted therapy, immunotherapy and radiotherapy in lung cancer. Lactate-driven metabolic support, signaling pathways and epigenetic modifications collectively establish a self-reinforcing network of resistance across multiple treatment modalities. Key metabolic enzymes and transporters, such as lactate dehydrogenase and monocarboxylate transporters, function as critical regulatory nodes in this process. The present review aimed to summarize recent advancements in lactate production, transport and signaling in lung cancer, with a particular focus on the remodeling of the tumor microenvironment and pan-therapeutic resistance. The present review discusses novel lactate-related biomarkers and treatment approaches, focusing on their existing translational limitations.

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Abbreviations: ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ATP, adenosine triphosphate; CAF, cancer-associated fibroblast; DCA, dichloroacetate; DC, dendritic cell; EGFR, epidermal growth factor receptor; GLUT, glucose transporter; HIF, hypoxia-inducible factor; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; MCT, monocarboxylate transporter; MDSC, myeloid-derived suppressor cell; MET, MET receptor tyrosine kinase; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDK, pyruvate dehydrogenase kinase; SCLC, small cell lung cancer; SUVmax, maximum standardized uptake value; TAM, tumor-associated macrophage; TKI, tyrosine kinase inhibitor; Treg, regulatory T-cell

Key words: lactate metabolism, lung cancer, tumor microenvironment, therapeutic resistance, clinical translation

Contents

1. Introduction

Ranking first in global cancer morbidity and mortality, lung cancer remains the most lethal malignancy worldwide. In 2022, it accounted for ~2.5 million new cases (12.4% of all cancers) and 1.8 million deaths (18.7% of total cancer mortality) (1). Clinically, while cytotoxic chemotherapy, epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint blockade have significantly improved outcomes for certain patient groups, the therapeutic landscape of advanced-stage lung cancer still faces considerable challenges. These challenges include high rates of acquired resistance across various treatment modalities, modest response rates to immunotherapy and poor 5-year survival rates, particularly among patients with distant metastases. This ongoing therapeutic stalemate highlights the urgent need for novel intervention targets identified through a systems-level perspective, particularly within the tumor microenvironment that supports malignant cell survival. Among the shared biological programs underlying treatment failure, lactate metabolism has emerged as a clinically relevant link between tumor-intrinsic adaptation, microenvironmental remodeling, and therapeutic resistance. While numerous recent reviews have discussed lactate metabolism, tumor immunometabolism, or lactylation in cancer, the majority of these have concentrated on general cancer biology, tumor immune metabolism, or isolated molecular mechanisms such as lactate-mediated immune modulation and histone lactylation (2-8). Although there have been recent lactylation-related reviews in lung cancer, a unified framework connecting lactate production and transport, intercellular lactate shuttling, lactylation-mediated epigenetic regulation, tumor-stromal-immune crosstalk, pan-therapeutic resistance and clinical translation remains to be inadequately synthesized (9,10). Therefore, the primary objective of the present review was to establish a lung cancer-specific lactate-centered framework that amalgamates these processes into a cohesive regulatory network, while also critically assessing the current translational barriers of lactate-associated biomarkers and lactate-targeting therapeutic strategies.

2. Core mechanisms of lactate metabolism in the lung tumor microenvironment

The Warburg effect in lung cancer and the regulation of lactate generation. First characterized by Warburg in 1923, the Warburg effect refers to the tendency of cancer cells to preferentially metabolize glucose to lactate through the process of aerobic glycolysis. This metabolic reprogramming is mediated by a coordinated cascade of rate-limiting enzymes, which include glucose transporters (GLUTs), hexokinase (HK), phosphofructokinase (PFK), pyruvate kinase M2 and lactate dehydrogenase (LDH). Collectively, these enzymes facilitate the efficient production of lactate (11). This enzymatic cascade is regulated by multiple layers of molecular control, with upstream signaling pathways precisely modulating downstream lactate production. Intratumoral hypoxia or Von Hippel-Lindau loss-of-function mutations stabilize hypoxia-inducible factor (HIF)-1α. This stabilization leads to the transcriptional upregulation of glycolytic enzymes (HK2, PFK1, LDHA and GLUT1) and the lactate exporter, monocarboxylate transporter (MCT)4, while simultaneously repressing genes involved in mitochondrial oxidative phosphorylation, such as cytochrome *c* oxidase subunit 4 isoform 1. As a result, there is a forced diversion of metabolic flux toward lactate generation (12). MYC proto-oncogene (MYC) amplification or activation, a common oncogenic event in lung cancer, directly transactivates glycolytic genes, including HK2 and LDHA, while simultaneously repressing mitochondrial biogenesis genes, such as mitochondrial transcription factor A. This dual action synergistically enhances glycolytic flux and lactate efflux (13). The aberrant activation of the PI3K/AKT/mTOR pathway, a common oncogenic event, directly accelerates glycolytic flux. This activation also promotes the translocation of GLUT1 and GLUT3 to the plasma membrane, which enhances glucose uptake and supports increased lactate synthesis (14,15). Beyond these canonical oncogenic pathways, the Warburg effect is modulated by additional transcription factors (e.g., p53 and NF-κB) and non-coding RNAs (e.g., lncRNAs, miRNAs and circRNAs). In addition to transcriptional and post-transcriptional controls, genetic mutations, tumor microenvironment remodeling and interactions with the immune system all play a crucial role in shaping the metabolic phenotype of the tumor (16). Notably, the generation of lactate is intricately connected to a larger adaptive metabolic framework. In situations where the production or transportation of lactate through glycolysis is inhibited tumor cells have the ability to channel their metabolic flow towards alternative pathways such as glutaminolysis, fatty acid oxidation, mitochondrial oxidative phosphorylation, acetate utilization, or nutrient recycling via autophagy. The mechanisms and potential therapeutic applications of this compensatory adaptability are elaborated upon in below.

Molecular mechanisms and functional characteristics of MCT1/4. MCTs, the principal transmembrane lactate carriers, are central orchestrators of lactate metabolism in lung tumors (17). MCT expression demonstrates pronounced histological heterogeneity, with MCT1 levels being significantly elevated in squamous cell carcinoma relative to adenocarcinoma. A high GLUT1/MCT4 co-expression predicts diminished disease-specific survival in adenocarcinoma, whereas this prognostic association is not observed in squamous cell carcinoma (18,19). Small cell lung cancer (SCLC) is characterized by a unique MCT expression profile. Of note, ~21% of tumors demonstrate MCT1 expression in hypoxic regions, without a detectable MCT4 expression. Furthermore, elevated MCT1 levels are linked to a worse prognosis, whereas MCT4 is positively associated with the hypoxia marker, carbonic anhydrase IX (CAIX) (20). Beyond these histological distinctions, MCT1 and MCT4 exhibit cell-type-specific distributions and functional specializations within the tumor microenvironment (21). In non-small cell lung cancer (NSCLC), MCT1 is primarily found on the cell membranes of both tumor and stromal cells. By contrast, MCT4 is predominantly expressed

on the cell membranes of tumor cells (22). The distribution patterns suggest distinct functional roles: Both MCT1 and MCT4 are proton-linked bidirectional transporters; however, MCT1 and MCT4 serve as proton-linked bidirectional transporters. MCT1 primarily facilitates lactate uptake in oxidative cells, while MCT4, characterized by a low affinity and high capacity, mainly enables lactate efflux from highly glycolytic cells. MCT4 has a lower substrate affinity but a greater transport capacity (23). This functional specialization has critical pathological implications, as the low-affinity, high-capacity profile of MCT4 is ideally suited for functioning in the lactate-rich tumor microenvironment.

These transport processes are further regulated by CD147, an essential chaperone for the functionality of MCT1 and MCT4. CD147 controls both the plasma membrane trafficking and catalytic stability of these transporters. Its expression directly influences membrane localization and transport activity; conversely, depletion of CD147 markedly impairs the membrane localization of MCT1/4 and reduces lactate transport activity (24). Within tumor cells, CD147-MCT4 interactions are particularly significant. The elevated expression of CD147 facilitates the translocation of MCT4 from the cytosol to the membrane, which in turn enhances glycolytic flux and lactate efflux in NSCLC (25).

Carbonic anhydrases function synergistically to enhance MCT4-mediated lactate export by coordinating intracellular pH dynamics. The primary pathway for cytosolic lactate extrusion involves upregulated MCT4, which operates alongside H^+ transporters and the carbonic anhydrases, CAII and CAIX. These carbonic anhydrases catalyze the hydration of metabolically generated CO_2, resulting in the formation of H^+ and bicarbonate (26).

Dysregulated lactate transport and pH regulation create a metabolically conducive microenvironment that supports tumor advancement, suppresses the immune system and confers resistance to therapy.

Compensatory metabolic crosstalk and subtype-specific plasticity. Inhibiting lactate production or transport therapeutically may not inevitably result in a sustained bioenergetic crisis as lung cancer cells have the ability to reroute metabolic flux through alternate pathways. The suppression of LDHA-mediated pyruvate-to-lactate conversion could lead to an increased dependence on mitochondrial oxidative phosphorylation, as evidenced by the metabolic transition from glycolysis to oxidative phosphorylation observed following the combined pyruvate dehydrogenase kinase (PDK)1 and LDHA inhibition in lung adenocarcinoma models (27). In addition, glutamine metabolism and fatty acid oxidation can offer alternative bioenergetic and biosynthetic support in NSCLC cells (28). These pathways have the potential to replenish tricarboxylic acid cycle intermediates and facilitate adenosine triphosphate (ATP) production, maintain redox homeostasis, support glutathione synthesis and enable macromolecular biosynthesis, ultimately diminishing the efficacy of single-agent LDHA or glycolysis inhibition.

Adenocarcinoma and squamous cell carcinoma exhibit differences in the expression and spatial distribution of GLUT1 and MCT4. Moreover, a subset of SCLC demonstrates an MCT1-high/MCT4-low phenotype (18-20). In addition, inhibiting MCT1 may prompt oxidative tumor cells to enhance glucose utilization instead of causing total metabolic collapse (29). These results suggest that the response to LDHA or MCT inhibition relies on histological subtype, transporter profile, mitochondrial capacity and the predominant compensatory pathway.

3. Intercellular lactate transport and metabolic networks in the lung tumor microenvironment

In the lung tumor microenvironment, lactate serves not only as a metabolic byproduct, but also as a crucial signaling molecule. It orchestrates a complex intercellular network among various cell populations, actively promoting malignant progression through signal transduction and immunomodulation.

Vascular endothelial cells. Central to this intercellular network is the tumor-endothelial lactate shuttle, which exemplifies the metabolic symbiosis in the lung tumor microenvironment. Tumor cells release substantial amounts of lactate through the highly expressed MCT4. This lactate is subsequently taken up by vascular endothelial cells via MCT1, establishing the canonical lactate shuttle paradigm (23). MCT1 serves as the main pathway for lactate uptake in oxygenated tumor cells. Inhibition of MCT1 in murine lung cancer models leads to a metabolic shift from lactate-driven respiration to glycolysis, significantly hindering tumor growth (29). Beyond its role in oxygenated tumor cells, endothelial lactate uptake has multifaceted biological significance. It serves as an energy source to fuel endothelial proliferation and angiogenesis. At the same time, it activates HIF-1α, which upregulates pro-angiogenic factors, such as basic fibroblast growth factor and VEGF receptor 2 (30,31) (Fig. 1). This reciprocity creates a positive feedback loop in which tumor-derived lactate promotes angiogenesis. In turn, the newly formed blood vessels provide metabolic substrates that support tumor expansion.

Cancer-associated fibroblasts (CAFs). CAFs engage in context-dependent and potentially bidirectional lactate exchange with lung cancer cells. In the classical 'reverse Warburg effect', glycolytic CAFs upregulate HK2, LDHA and MCT4, export lactate, and provide an oxidative substrate that is absorbed by MCT1-expressing tumor cells to facilitate mitochondrial oxidative phosphorylation and biosynthesis (32). Immunohistochemical analyses of some NSCLC specimens have revealed glycolytic tumor-cell regions and comparatively oxidative stromal regions, indicating that stromal cells may also utilize tumor-derived lactate under specific spatial and metabolic conditions (22) (Fig. 1). Therefore, the direction of the tumor-CAF lactate shuttle is influenced by oxygen availability, tumor genotype, mitochondrial capacity, and the relative expression of MCT1 and MCT4, rather than adhering to a universally fixed pattern. In addition to substrate exchange, CAF-derived lactate can serve as a signaling and epigenetic regulator. The methyltransferase-like 3/zinc finger protein 384/RNA polymerase III subunit G axis activated by lactate promotes epithelial-mesenchymal transition in lung cancer cells, while CAF signaling dependent on lactate contributes to the establishment of an immunosuppressive

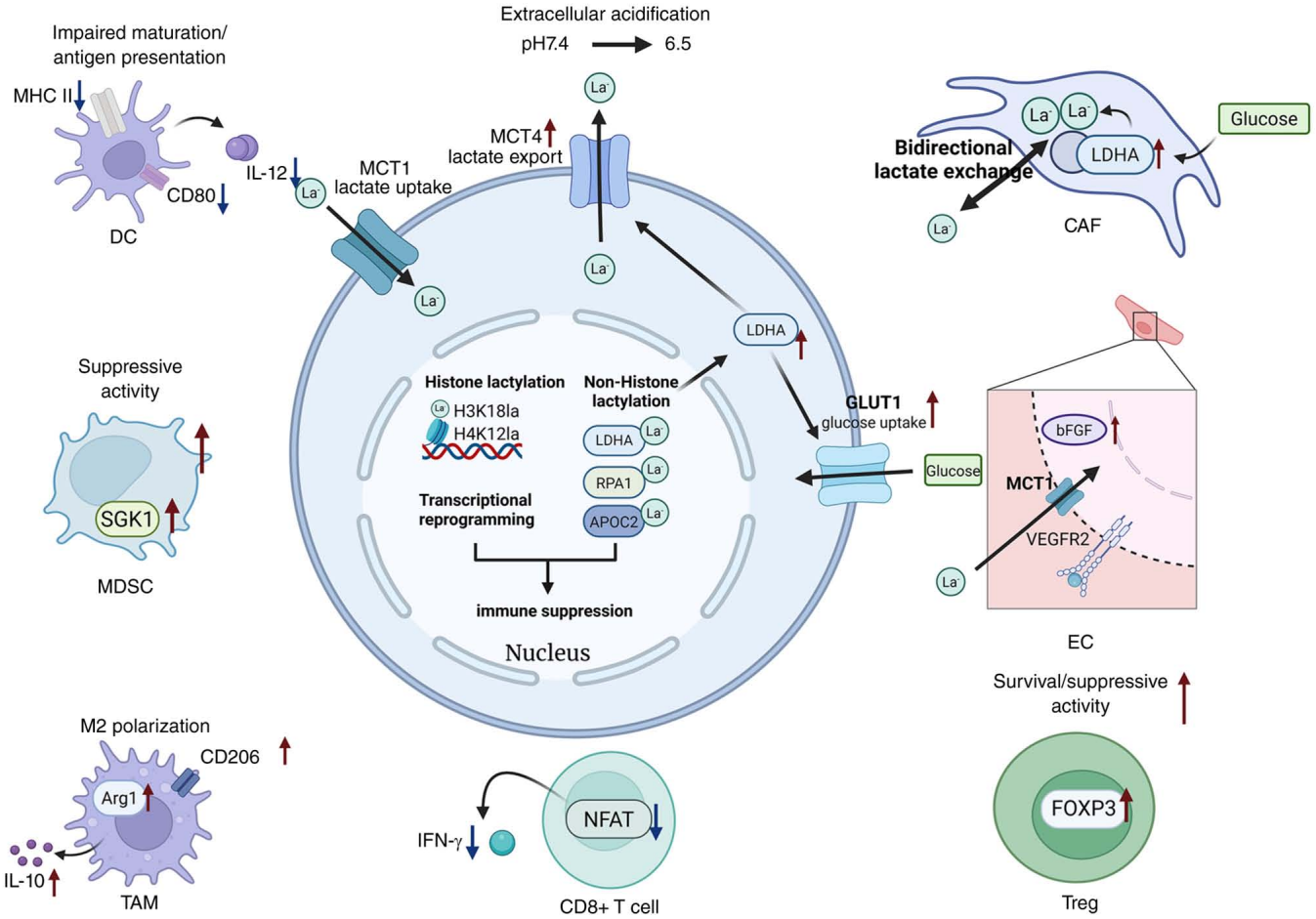

Figure 1. Lactate-mediated metabolic crosstalk in the lung tumor microenvironment. Tumor-derived lactate is transported through MCT1/4 and promotes extracellular acidification, CAF-tumor metabolic exchange, angiogenesis, immune-cell dysfunction and immunosuppressive cell activity. Histone and non-histone lactylation further contribute to transcriptional reprogramming and immune suppression. CAF, cancer-associated fibroblast; MCT, monocarboxylate transporter; MHC, major histocompatibility complex; DC, dendritic cell; SGK1, serum/glucocorticoid-regulated kinase 1; MDSC, myeloid-derived suppressor cell; Arg1, arginase 1; TAM, tumor-associated macrophage; IFN, interferon; H3K18la, histone H3 lysine 18 lactylation; H4K12la, histone H4 lysine 12 lactylation; LDHA, lactate dehydrogenase A; RPA1, replication protein A1; APOC2, apolipoprotein C-II; NFAT, nuclear factor of activated T-cells; GLUT1, glucose transporter 1; bFGF, basic fibroblast growth factor; EC, endothelial cell; Treg, regulatory T-cell; FOXP3, forkhead box P3. The figure was created in BioRender [Zhang Y (2026) https://BioRender.com/b8eadbd].

microenvironment (33,34). These discoveries establish CAFs as dynamic regulators of both metabolic symbiosis and lactate-dependent tumor signaling.

Immune cells. Immune cells are essential components of the immunosuppressive tumor microenvironment, where the uptake and utilization of lactate play a crucial role in determining their functional phenotype. Tumor cells, through MCT4-mediated lactate efflux, create a high-lactate environment that infiltrating immune cells primarily absorb via MCT1. This process leads to metabolic reprogramming and skews these immune cells toward an immunosuppressive state (35).

The impact of lactate on T-cells varies depending on the context, rather than being uniformly stimulatory or suppressive. In specific *in vitro* activation models under buffered, near-neutral conditions, lactate anions may promote $CD8^+$ T-cell proliferation, cytotoxicity and the production of IFN-γ, IL-2 and TNF-α (36) (Fig. 1). By contrast, the chronically lactate-rich and acidic tumor microenvironment restricts lactate efflux from activated T-cells, disrupts glycolytic homeostasis, and diminishes their proliferative and effector capacity. Elevated lactate levels in combination with extracellular acidosis therefore impede cytotoxic T-lymphocyte function and cytokine production *in vivo*. In NSCLC models, decreasing tumor-cell glycolysis or LDHA activity can enhance $CD8^+$ T-cell cytotoxicity and reduce immune escape (35). Lactic acid production dependent on LDHA also inhibits nuclear factor of activated T-cells activity in T-cells and natural killer cells, thereby reducing IFN-γ production (37) (Fig. 1).

Regulatory T-cells (Tregs) exhibit a notable ability to uphold their metabolic robustness in glucose-poor, lactate-rich settings, potentially granting them a competitive edge over traditional effector T-cells. The presence of lactate can support Treg survival, suppressive capabilities and the presence in the tumor microenvironment, consequently dampening antitumor defenses. Nonetheless, the specific outcomes are contingent upon lactate levels, extracellular pH, and the metabolic condition of the T-cell population. In NSCLC, the overexpression of circRUNX1 stimulates glycolytic activity and lactate production, thereby enabling Treg infiltration and immune evasion (38).

Lactate has particularly complex effects on macrophages, driving their polarization toward the M2 (pro-tumor) phenotype. Following MCT1-mediated internalization, tumor-associated macrophages (TAMs) activate ERK/STAT3 signaling, culminating in the upregulation of M2 markers including CD206, arginase 1 and IL-10 (39) (Fig. 1). Tumor-derived lactate activates cancer-associated fibroblasts, which then secrete IL-8. This secretion orchestrates the recruitment of TAMs and promotes M2 polarization (40). Furthermore, lactate enhances macrophage-derived VEGF production through HIF-2α stabilization, thereby promoting angiogenesis (41).

Dendritic cells (DCs), the professional antigen-presenting cells, orchestrate adaptive immunity by priming T-lymphocyte responses (42). However, this sentinel function is significantly impaired in lactate-enriched microenvironments, where lactate suppresses lipopolysaccharide-induced DC maturation. This suppression is evidenced by the downregulation of CD80 and major histocompatibility complex class II molecules (43). Lactate within the lung tumor microenvironment attenuates DC secretion of IL-12 and type I interferons, curtails antigen cross-presentation, and accelerates antigen degradation (44) (Fig. 1).

Myeloid-derived suppressor cells (MDSCs), critical mediators of immune suppression in the tumor microenvironment, are also modulated by lactate, which enhances their immunosuppressive capacity through ten-eleven translocation 2-mediated demethylation and upregulation of serum/glucocorticoid-regulated kinase 1 (SGK1) (45) (Fig. 1). Cumulatively, tumor-derived lactate differentially influences the functions of various immune cell subsets. This modulation contributes to the creation of a metabolic and immunosuppressive microenvironment that promotes tumor growth and facilitates immune evasion.

4. Role of lactate metabolism in lung cancer therapeutic resistance

Lactate metabolism establishes a pan-therapeutic resistance network. In addition to serving as a metabolic fuel, lactate orchestrates a complex defense network against therapeutic interventions. It achieves this by remodeling the tumor microenvironment, activating pro-survival signaling cascades and inducing epigenetic reprogramming.

Chemotherapeutic resistance. Platinum-based and other cytotoxic regimens remain crucial components of lung cancer treatment; however, metabolic adaptation can gradually diminish their effectiveness. In NSCLC, lactate promotes cisplatin resistance through the YTH N^6-methyladenosine RNA-binding protein 2-mediated N^6-methyladenosine regulation of the forkhead box O3/MAGI1 intronic transcript 1/miR-664b-3p/IL-6R axis (46) (Fig. 2). At the post-translational level, LDHA lactylation increases LDHA activity and fosters cisplatin resistance by facilitating DNA non-homologous end joining (47). Lactate also contributes to etoposide resistance through various mechanisms. It boosts glutathione peroxidase 4 (GPX4) expression and activates the p38-SGK1 pathway, which decreases NEDD4-like E3 ubiquitin protein ligase-mediated GPX4 ubiquitination and inhibits ferroptosis. Additionally, lactate induces multidrug resistance-associated protein 1/ATP-binding cassette subfamily C member 1 expression via TGF-β1/Snail and transcriptional coactivator with PDZ-binding motif/activator protein 1 signaling, thereby enhancing drug efflux (48,49). Resistance to pemetrexed is linked to aldo-keto reductase family 1 member B10-driven glycolysis and H4K12 lactylation-mediated cyclin B1 transcription in lung cancer brain metastases (50). Forkhead box P3-mediated kinesin family member 5A activation likewise elevates lactate production and contributes to docetaxel resistance in lung adenocarcinoma (51). Collectively, these findings suggest that lactate-dependent chemoresistance involves epigenetic rewiring, DNA repair, ferroptosis suppression and drug efflux, with the dominant mechanism varying based on the drug and histological subtype.

Targeted therapeutic resistance. With the emergence of precision medicine, targeted therapy has become essential to lung cancer management, establishing the standard of care for advanced NSCLC with actionable driver mutations (e.g., EGFR and anaplastic lymphoma kinase). However, acquired resistance remains a common clinical challenge, increasingly attributed to lactate metabolic reprogramming (52). Under chronic tyrosine kinase inhibitor (TKI) treatment, EGFR- or MET receptor tyrosine kinase (MET)-addicted tumor cells experience a significant metabolic shift toward aerobic glycolysis and increased lactate production (53). The resultant lactate acts as a signaling metabolite that activates G protein-coupled receptor 81 (GPR81), which in turn transactivates pro-survival cascades, such as AKT. This mechanism creates a bypass signaling axis that avoids the inhibited oncogenic driver pathways (54) (Fig. 2). CAFs constitute another critical component in maintaining resistance, orchestrating resistance to TKIs through two complementary mechanisms: NF-κB-driven hepatocyte growth factor production activates MET signaling in tumor cells, while concurrent lactate provision via the 'Reverse Warburg Effect' supports their metabolic demands (55) (Fig. 2). These mechanisms create a self-reinforcing feedback loop between lactate and CAFs. Collagen triple helix repeat containing 1 (CTHRC1)-expressing CAFs enhance tumor cell glycolysis through TGF-β/Smad3 activation. In turn, the excess lactate leads to histone lactylation, which reciprocally upregulates CTHRC1, thus maintaining resistance to EGFR-TKIs (56). Parallel feedback architectures, encompassing the nicotinamide N-methyltransferase (NNMT)-mediated early growth response 1 (EGR1)-lactate circuit (EGR1/NNMT/EGR1) and the NNMT/aldehyde dehydrogenase 3 family member A1/lactate/NNMT axis, further buttress this resistance-conferring metabolic network (57). Recent investigations have revealed deeper resistance mechanisms involving lactate. Specifically, the HIF1A-solute carrier family 16 member 3 (SLC16A3)-lactate axis significantly inhibits ferroptosis in lung adenocarcinoma. This discovery establishes a connection between MCT4-dependent lactate export and the evasion of ferroptosis. It also provides a mechanistic rationale for the combination of lactate-transport inhibition with EGFR-targeted therapy in metabolically selected tumors (58).

Resistance to immunotherapy. Although immune checkpoint inhibitors have fundamentally revolutionized cancer

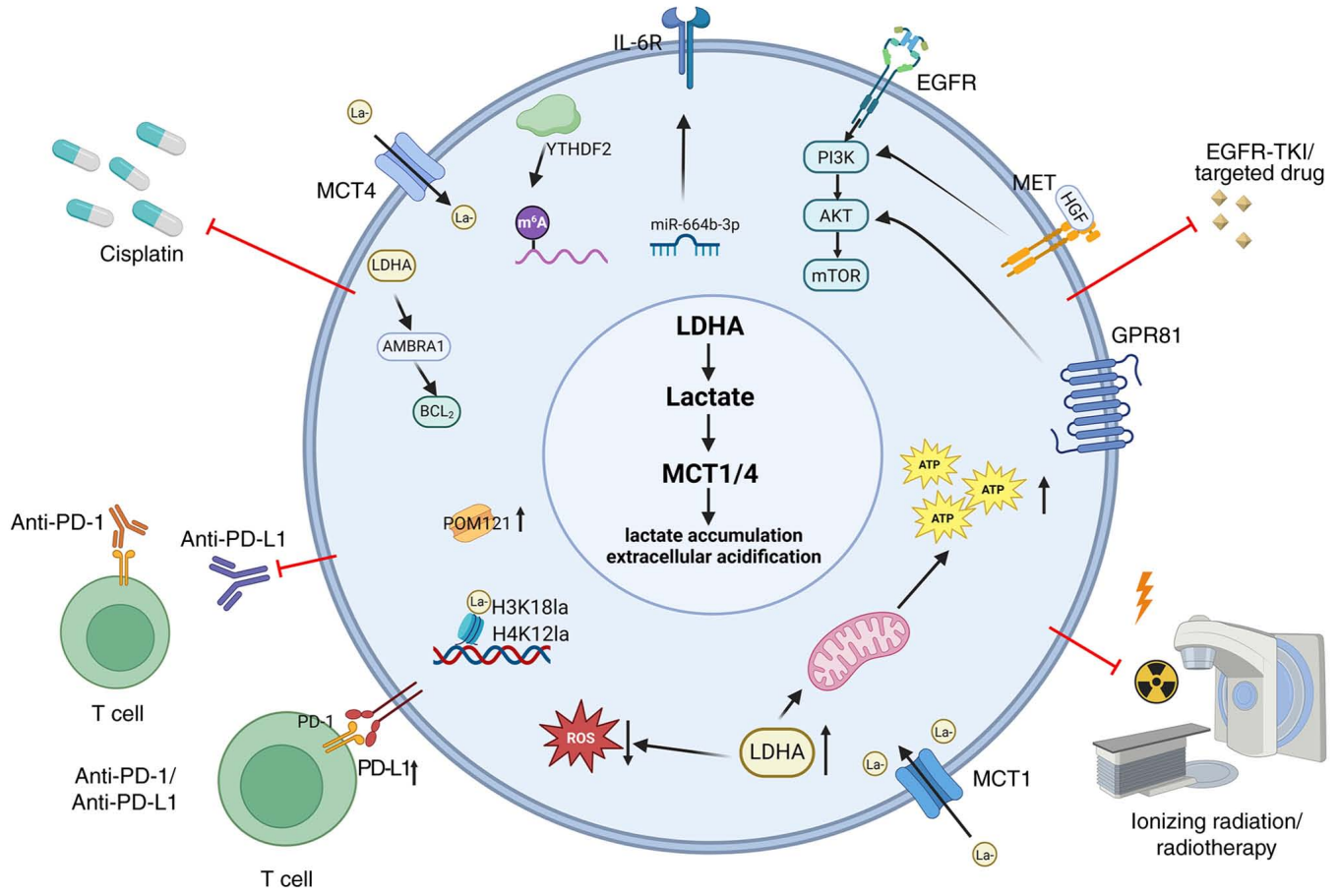

Figure 2. Lactate-mediated pan-therapeutic resistance in lung cancer. The LDHA-lactate-MCT1/4 axis forms a central resistance hub connecting metabolic support, prosurvival signaling, lactylation, immune escape and redox regulation, thereby promoting resistance to chemotherapy, targeted therapy, immunotherapy and radiotherapy. LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; YTHDF2, YTH N^6-methyladenosine RNA-binding protein 2; m^6A, N^6-methyladenosine; AMBRA1, autophagy and beclin 1 regulator 1; POM121, POM121 transmembrane nucleoporin; H3K18la, histone H3 lysine 18 lactylation; H4K12la, histone H4 lysine 12 lactylation; ROS, reactive oxygen species; ATP, adenosine triphosphate; mTOR, mechanistic target of rapamycin; MET, MET receptor tyrosine kinase; HGF, hepatocyte growth factor; GPR81, G protein-coupled receptor 81. The figure was created in BioRender [Zhang Y (2026) https://BioRender.com/f5p2epm].

immunotherapy, their clinical efficacy is often limited by acquired resistance. Within this clinical framework, PD-1/PD-L1-targeted therapies have become integral to lung cancer management. Accumulating evidence suggests that lactate metabolism plays a critical role in shaping the immunosuppressive microenvironment and facilitating immune evasion. Through excessive lactate production and efflux, particularly via SLC16A3 (MCT4) overexpression, tumor cells directly weaken anti-tumor immunity by inducing M2 macrophage polarization and suppressing $CD8^+$ T-cell function, thereby compromising the efficacy of anti-PD-1 therapy (19,59) (Fig. 2). At the epigenetic level, lactate-induced histone H3 lysine 18 lactylation transcriptionally upregulates POM121 transmembrane nucleoporin, thereby amplifying MYC activity and PD-L1 expression to further entrench the immunosuppressive phenotype in NSCLC (35) (Fig. 2). Beyond direct transcriptional modulation, lactate indirectly promotes immunosuppression by remodeling lipid metabolism through post-translational modifications. Specifically, intracellular lactate facilitates the lactylation of apolipoprotein C-II (APOC2) at K70, which enhances protein stability and drives extracellular lipolysis. The free fatty acids released as a result provide metabolic support to suppressive immune populations, such as Tregs, thereby promoting their recruitment and function. This process ultimately contributes to immunotherapy resistance and metastasis (60).

Resistance to radiotherapy. Resistance to radiotherapy is a major factor contributing to local recurrence and distant metastasis in NSCLC. Lactate metabolism plays a crucial role in enhancing radioresistance through various mechanisms, including energetic support, regulation of DNA damage repair and the remodeling of the tumor microenvironment. When exposed to ionizing radiation, lung cancer cells increase the expression of LDHA, which boosts glycolytic flux and lactate production. As a result, inhibiting LDHA reduces ATP levels and leads to the accumulation of reactive oxygen species, thereby enhancing radiation-induced apoptosis and autophagy (61) (Fig. 2). Consistently, pharmacological inhibition of glycolysis with dichloroacetate (DCA) reverses the Warburg phenotype and augments radiation-induced cell death in radioresistant NSCLC cell lines (A549 and H1299 cells) (62). Radiotherapy primarily works by inducing DNA damage, but lactate metabolism plays a crucial role in supplying the energy and functional support needed for DNA repair. In this context, histone acetyltransferase 1 functions as a lactyltransferase that

facilitates the lactylation of replication protein A1 (RPA1). This modification increases the binding affinity of RPA1 for single-stranded DNA and the MRE11-RAD50-NBS1 complex (Fig. 2). As a result, it promotes homologous recombination repair and strengthens the radioresistance of tumor cells (63).

The lactate-driven regulation of redox homeostasis, the DNA damage response and tumor hypoxia in the context of radioresistance parallels critical resistance mechanisms identified in chemotherapy, targeted therapy and immunotherapy.

A unified lactate-centered hub underlying pan-therapeutic resistance. Lactate-mediated therapeutic resistance should not be regarded as four separate, treatment-specific processes. Instead, resistance to chemotherapy, targeted therapy, immunotherapy and radiotherapy all stem from a common lactate-centered network consisting of four interconnected layers.

At the metabolic level, increased LDHA activity and lactate exchange through MCT1/4 sustain ATP production, redox balance and metabolic symbiosis. Concurrently, compensatory glutaminolysis, fatty acid oxidation and oxidative phosphorylation maintain metabolic efficiency when the lactate pathway is inhibited. On the signaling front, lactate triggers activation of GPR81, HIF-1α, PI3K/AKT, MET, TGF-β and NF-κB-associated pathways, empowering tumor cells to circumvent treatment-induced signaling inhibition.

At the epigenetic and post-translational levels, lactylation of both histone and non-histone proteins, such as histone H3 lysine 18 lactylation, histone H4 lysine 12 lactylation, RPA1, LDHA and APOC2, connects lactate buildup to processes, such as transcriptional reprogramming, DNA repair, ferroptosis regulation and lipid remodeling. At the microenvironmental layer, lactate promotes CAF activation, TAM polarization, Treg and MDSC function, DC cell dysfunction and $CD8^+$ T-cell suppression.

These layers cooperate with each other instead of working separately. For example, lactate-dependent signaling can enhance glycolytic gene expression, while lactylation and immune suppression help to maintain the resistant metabolic state. This comprehensive framework clarifies why blocking a single lactate-related molecule may have only temporary or restricted effects. It also endorses the use of combination strategies guided by biomarkers that target both the lactate axis and the primary compensatory resistance pathway.

5. Progress in the clinical translation of lactate metabolism in lung cancer

Given these mechanistic insights, lactate metabolism has attracted increasing interest as a source of biomarkers and therapeutic targets in lung cancer. However, the majority of lactate-related biomarkers and strategies for targeting lactate are still in the exploratory or early translational stages. Consequently, this section provides an overview of the current biomarker evidence, therapeutic strategies and available clinical data, with a focus on their translational limitations.

Lactate-associated candidate biomarkers for prognosis, treatment stratification and monitoring. Lactate-associated biomarkers vary significantly in clinical maturity and should not be considered a uniform group (Table I). The serum LDH blood test is widely available and exhibits consistent prognostic associations in advanced NSCLC. However, it primarily serves as a non-specific marker for disease burden and systemic tissue injury rather than a direct measure of intratumoral lactate metabolism (64-66). The Lung Immune Prognostic Index (LIPI), which combines pre-treatment LDH with the derived neutrophil-to-lymphocyte ratio, provides prognostic stratification for patients receiving ICIs (64,67,68). Nevertheless, there is insufficient evidence to support the notion that LDH or LIPI can accurately predict the differential benefits of a specific treatment. Therefore, these markers should be regarded as mainly prognostic rather than definitively predictive. The tissue expression of LDHA/LDH5, MCT4 and CD147 may indicate tumor glycolysis, hypoxia, lactate export and an immunosuppressive microenvironment. Nevertheless, their clinical utility is limited by the reliance on biopsies, spatial heterogeneity, variable antibodies and non-standardized immunohistochemical scoring. Circulating tumor cell-derived MCT4, exosomal lactate-metabolism-related cargo, and lactylation-related gene signatures have been evaluated in exploratory observational, exosome-based, and transcriptomic/computational biomarker studies rather than in prospective interventional clinical trials (69-72). Any proposed diagnostic or treatment-monitoring roles for these markers require independent external validation, assay standardization and prospective evaluation prior to clinical implementation. Imaging biomarkers provide complementary, yet indirect metabolic information. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) maximum standardized uptake value (SUVmax) reflects glucose uptake and glycolytic activity rather than lactate itself, and its prognostic performance is affected by inflammation, tumor size, scanner calibration, image reconstruction and respiratory motion (73,74). Hyperpolarized ^{13}C magnetic resonance spectroscopy (MRS)/magnetic resonance imaging (MRI) provides a non-invasive method to evaluate pyruvate-to-lactate label exchange and lactate-related metabolic responses. In preclinical lung cancer models, this method identified decreased lactate-to-pyruvate signals after pharmacological LDH inhibition or LDHA ablation, indicating its promise for assessing metabolic target engagement and treatment-response assessment (75). Specific constraints related to markers are outlined in Table I, while overarching obstacles to clinical adoption are deliberated below in the section entitled '*Current challenges in clinical translation*'.

Therapeutic strategies targeting lactate metabolism in lung cancer. Therapeutic strategies targeting lactate metabolism can be categorized into three groups: Direct synthetic inhibitors of lactate production or transport, repurposed or indirect metabolic modulators and natural compounds with lactate-related activity. While some agents have exhibited antitumor effects in lung cancer models, the majority of evidence is preclinical. Only a limited number of agents have progressed to early-phase trials in unselected advanced solid tumors (Table II).

The direct inhibition of LDHA is considered a viable approach to reduce lactate production and disrupt glycolytic adaptation. While GSK2837808A, NHI-Glc-2 and other experimental LDHA inhibitors have demonstrated the ability to suppress lactate production and inhibit tumor growth

Table I. Lactate-associated candidate biomarkers in lung cancer: Evidence, potential applications and translational limitations.

Biomarker	Detection method	Clinical significance	Application context	Limitations for clinical application	(Refs.)
Serum LDH	Serum biochemical assay	Accessible prognostic marker associated with tumor burden, survival, and longitudinal treatment response	Advanced NSCLC and SCLC across chemotherapy, immunotherapy, and chemoimmunotherapy	Non-specific; influenced by tumor burden, inflammation, liver injury, hemolysis, and treatment-related tissue damage; cut-off values and sampling time points vary across studies	(64-66, 76,77)
LIPI score	Composite score based on pretreatment LDH and dNLR	Prognostic stratification in patients receiving immune checkpoint inhibitors; strictly predictive value remains uncertain	Advanced NSCLC treated with ICIs, with or without chemotherapy	Mainly supported by retrospective cohorts; prognostic rather than definitively predictive; cut-off and applicability across treatment lines remain inconsistent	(67,68)
Tumor LDHA/ LDH5 expression	Tissue IHC or transcriptomic profiling	Associated with glycolysis, hypoxia, poor prognosis, and potential radioresistance	Exploratory tissue biomarker in NSCLC, particularly lung adenocarcinoma	Requires tissue sampling; affected by intratumoral heterogeneity, sampling bias, antibody variability, and non-standardized positivity thresholds	(78)
MCT4/CD147	Tissue IHC, transcriptomics, or multiplex immunostaining	Lactate-export phenotype associated with extracellular acidification, immune suppression, aggressive behavior, and poor prognosis	Exploratory prognostic and treatment-resistance marker in NSCLC, particularly LUAD and LKB1-deficient tumors	Marked spatial and histological heterogeneity; variable antibodies and scoring methods; no prospectively validated threshold for treatment selection	(79)
CTC-derived MCT4	CTC detection	Exploratory indicator of a lactate-export and metastatic phenotype in circulating tumor cells	Research-stage assessment of metastatic risk and longitudinal treatment response in NSCLC	Low and variable CTC abundance; platform-dependent isolation; uncertain concordance with tumor tissue; no prospective clinical validation	(69)
Lactylation-related gene signature	Transcriptomic profiling and risk-score model	Research-grade computational model associated with prognosis and immune-infiltration patterns	Exploratory risk stratification in lung adenocarcinoma	Predominantly derived from TCGA/GEO datasets; gene composition and coefficients vary between studies; risk of overfitting; no locked assay or prospective validation	(70)
Exosomal lactate-metabolism-related cargo	Exosome isolation with RT-qPCR, ELISA, western blotting, or RNA profiling	Potential liquid-biopsy indicator of lactate-related metabolic remodeling	Exploratory diagnosis, prognosis, or recurrence monitoring in LUAD	Limited direct clinical evidence; exosome isolation, normalization, source attribution, and quantitative thresholds are not standardized	(71,72)
^{18}F-FDG SUVmax	PET/CT	Indirect surrogate of glucose uptake and glycolytic activity; may complement serum LDH for prognostic stratification	Staging, response evaluation, and exploratory prognostic assessment	Not lactate-specific; affected by inflammation, tumor size, scanner calibration, reconstruction protocols, uptake time, and respiratory motion	(74)

Table I. Continued.

Biomarker	Detection method	Clinical significance	Application context	Limitations for clinical application	(Refs.)
Hyperpolarized ^{13}C MRS/MRI	Hyperpolarized magnetic resonance spectroscopy/ imaging	Research imaging approach for assessing pyruvate-to-lactate label exchange and metabolic target engagement	Preclinical lung cancer metabolic imaging and exploratory treatment-response assessment	Requires specialized on-site polarization equipment; high cost; short signal lifetime; complex acquisition and reconstruction; limited spatial resolution; thoracic motion artifacts; insufficient multicenter standardization	(75)

LDH and LIPI are clinically accessible but are predominantly prognostic. All other biomarkers listed in the table remain under investigation and have not been prospectively validated for routine treatment selection. LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; dNLR, derived neutrophil-to-lymphocyte ratio; MCT, monocarboxylate transporter; IHC, immunohistochemistry; LUAD, lung adenocarcinoma; HIF, hypoxia-inducible factor; LKB1, liver kinase B1; CTC, circulating tumor cell; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; TME, tumor microenvironment; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; SUVmax, standardized uptake value maximum; PET/CT, positron emission tomography/computed tomography; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging.

in preclinical models, questions remain regarding their selectivity, pharmacokinetic properties, systemic toxicity and *in vivo* therapeutic windows (27,80,81). Stiripentol, an approved antiepileptic agent, has been suggested as a potential LDH inhibitor for repurposing; however, its use in antitumor therapy remains under investigation (82). Allosteric inhibitors that interfere with LDHA tetramer formation show promise in enhancing tumor selectivity; however, further validation is needed to determine their therapeutic window (83). Although experimental allosteric inhibitors may enhance target selectivity, existing evidence mainly originates from non-lung cancer models; thus, this evidence should be viewed as proof of concept rather than lung cancer-specific efficacy.

MCT1 and MCT4 serve as alternative targets for disrupting lactate transport and metabolic symbiosis. AZD3965 has exhibited activity in MCT1-high/MCT4-low preclinical models, notably in SCLC, and has progressed to first-in-human phase I evaluation in patients with advanced solid tumors or lymphoma (20). The trial illustrated pharmacodynamic target engagement, yet encountered dose-limiting toxicities such as reversible ocular changes, cardiac troponin elevation and acidosis. Notably, no lung cancer-specific clinical efficacy has been definitively established (84). Moreover, selective MCT4 inhibitors, such as VB-124 are still in the preclinical stage, and the existing evidence on their antitumor and immune-remodeling properties is primarily drawn from non-lung cancer models (85).

Several approved or previously investigated agents have been shown to indirectly decrease lactate production. For example, DCA inhibits PDK and shifts pyruvate towards mitochondrial oxidation. Despite the ability of DCA to enhance the radiosensitivity of NSCLC cells in preclinical models (62), a previous phase I study involving 24 patients with advanced-stage solid tumors revealed no significant objective responses (86). Only 8 cases of stable disease were observed, with dose escalation being restricted due to side-effects, such as fatigue, neuropathy, nausea, vomiting and diarrhea. Notably, the specific clinical efficacy of DCA in lung cancer has not yet been demonstrated (86).

The benserazide-mediated inhibition of HK2 may decrease glycolytic flux and enhance cisplatin cytotoxicity in NSCLC models (87). PX-478 indirectly suppresses lactate-related metabolism by inhibiting HIF-1α and has demonstrated preclinical activity in lung adenocarcinoma and SCLC models (88,89). However, its early-phase clinical evaluation in advanced solid tumors did not establish lung cancer-specific efficacy; thus, it cannot be promoted as a clinically validated lung cancer therapy.

Natural compounds, such as emodin and formosanin C inhibit the MCT/CD147 lactate-export axis, thereby suppressing NSCLC progression in preclinical models (90,91). Ginsenoside Rh2 modulates the HIF-1α/PDK4 axis, redirecting metabolism away from aerobic glycolysis, while cinobufagin affects HIF-1α-dependent metabolic reprogramming in tumor-associated macrophages (92,93). These compounds provide valuable mechanistic insight, but should be distinguished from clinically developed synthetic inhibitors. Their translation is hindered by issues, such as variable purity, low or inconsistent bioavailability, uncertain target specificity, formulation differences, and limited pharmacokinetic and toxicological characterization.

Table II. Lactate-metabolism-targeting strategies in lung cancer: Evidence and translational status.

Target/ pathway	Agent/strategy	Category	Mechanism	Lung cancer evidence	Clinical trial/phase and lung cancer-specific data	Major translational limitations	(Refs.)
LDHA	GSK2837808A, NHI-Glc-2	Synthetic LDHA inhibitors	Inhibit lactate production and enhance chemo-/ radiosensitivity	Suppress lung cancer cell growth, reduce lactate production, and enhance therapy sensitivity in preclinical models	Preclinical only; no reported lung cancer-specific clinical efficacy data	Selectivity, drug-like properties, systemic toxicity, and *in vivo* efficacy require validation	(27,81)
LDHA	Stiripentol	Drug repurposing LDH inhibitor	Reduces LDH-dependent lactate generation and tumor growth	Mainly preclinical or extrapolated evidence; direct lung cancer evidence is limited	Approved antiepileptic agent; antitumor use remains investigational, with no established oncology dose or lung cancer-specific efficacy	Repurposing dose, pharmacodynamics, tumor selectivity, and combination safety remain unclear	(82)
PDK	DCA	PDK inhibitor/ metabolic modulator	Activates PDH, promotes pyruvate entry into TCA cycle, reduces lactate production	Reverses Warburg-like metabolism and radiosensitizes NSCLC cells; clinical activity appears limited	Phase I evaluation in 24 patients with advanced solid tumors; no objective responses and eight cases of stable disease; no established lung cancer-specific clinical efficacy	Peripheral neuropathy, fatigue, gastrointestinal toxicity, variable pharmacokinetics, modest monotherapy activity, and lack of biomarker-guided patient selection	(62,86)
MCT1	AZD3965	Synthetic MCT1 inhibitor	Blocks MCT1-mediated lactate transport and disrupts metabolic symbiosis	Preclinical SCLC activity, especially in MCT1-high/MCT4-low models	First-in-human phase I trial in advanced solid tumors/lymphoma (NCT01791595); pharmacodynamic target engagement demonstrated, but no established lung cancer-specific clinical efficacy	MCT4-mediated bypass, reversible ocular toxicity, cardiac troponin elevation, risk of acidosis, and absence of validated MCT1-high/ MCT4-low patient-selection criteria	(84)
MCT4	VB-124	Synthetic MCT4 inhibitor	Blocks lactate export and may reverse lactate-driven immunosuppression	Direct lung cancer evidence is limited; antitumor and immune-remodeling effects are mainly preclinical	Preclinical only; immune-remodeling evidence is mainly derived from non-lung cancer models, with no completed lung cancer-specific trial	Selectivity, pharmacokinetics, toxicity, and predictive biomarkers need validation	(85)
MCT4/ CD147	Emodin, Formosanin C	Natural compounds	Inhibit the MCT4/ CD147 lactate-export axis and reduce extracellular lactate accumulation	Formosanin C inhibits NSCLC progression via MCT4/CD147 blockade; emodin evidence is mainly preclinical	Preclinical NSCLC evidence; no robust lung cancer-specific clinical trial	Multi-target effects, low bioavailability, uncertain specificity, and lack of standardized formulation	(90,91)

Table II. Continued.

Target/ pathway	Agent/strategy	Category	Mechanism	Lung cancer evidence	Clinical trial/phase and lung cancer-specific data	Major translational limitations	(Refs.)
HIF-1α	PX-478	Synthetic HIF-1α inhibitor	Suppresses HIF-1α and downregulates glycolytic enzymes	Shows antitumor activity in preclinical lung adenocarcinoma models	Completed early-phase evaluation in advanced solid tumors/lymphoma; no established lung cancer-specific efficacy	Broad pathway inhibition, potential off-target effects, and undefined optimal combinations	(88,89)
HIF-1α/ PDK4	Ginsenoside Rh2	Natural compounds	Regulates the HIF-1α/PDK4 axis and shifts metabolism away from aerobic glycolysis	Suppresses aerobic glycolysis and malignant progression in preclinical NSCLC models	Preclinical NSCLC evidence; no robust lung cancer-specific clinical trial	Variable purity, pharmacokinetics, target specificity, and translational reproducibility	(92)
HK2	Benserazide	Repurposed metabolic agent	Inhibits HK2-dependent glycolysis and reduces lactate-generating metabolic flux	Enhances cisplatin cytotoxicity in NSCLC cell models	Approved for neurological indications; antitumor use remains preclinical	Uncertain tumor exposure, target selectivity, effective oncology dose, and combination safety	(87)
HIF-1α/ macrophage glycolysis	Cinobufagin	Natural compound	Promotes HIF-1α degradation and reprograms glycolytic metabolism in tumor-associated macrophages	Preclinical NSCLC evidence involving macrophage metabolic and PD-L1 regulation	Preclinical; no established lung cancer-specific clinical efficacy	Narrow therapeutic window, uncertain target specificity, formulation variability, and limited pharmacokinetic standardization	(93)

LDHA, lactate dehydrogenase A; PDK, pyruvate dehydrogenase kinase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; DCA, dichloroacetate; MCT1/4, monocarboxylate transporter 1/4; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; PD-L1, programmed death-ligand 1.

Current evidence collectively does not endorse unselected lactate-targeting monotherapy in lung cancer. Clinical development should focus on metabolically selected patients, confirming target inhibition pharmacodynamically, and developing combinations guided by mechanism that effectively suppress the lactate axis and the primary compensatory pathway.

6. Research challenges and future perspectives

Current challenges in clinical translation. Despite the increasing amount of mechanistic evidence underscoring the significance of lactate metabolism in lung cancer, its clinical application is constrained by various interconnected challenges. These obstacles can be broadly classified as metabolic heterogeneity, compensatory metabolic adaptability, therapeutic specificity and toxicity, standardization of biomarkers, and technical constraints in real-time lactate monitoring.

Lactate metabolic regulation varies substantially across lung cancer histological subtypes, molecular backgrounds and treatment states (94,95). Adenocarcinoma, squamous cell carcinoma, SCLC, EGFR-mutant tumors, liver kinase B1 (LKB1)-deficient tumors, hypoxic tumors and therapy-resistant clones may demonstrate distinct dependencies on glycolysis, lactate production, MCT1/MCT4-mediated transport, and mitochondrial oxidative metabolism. This heterogeneity hampers the effectiveness of indiscriminate lactate-targeting approaches and adds complexity to patient classification in clinical trials. Hence, forthcoming research endeavors are warranted to integrate single-cell sequencing, spatial metabolomics and functional metabolic imaging to elucidate subtype-specific and patient-specific lactate metabolic states.

Another significant translational barrier is the limited tumor selectivity of lactate-targeting therapies. Core lactate metabolic enzymes and transporters, such as LDHA, MCT1 and MCT4, are also expressed in normal tissues. This raises concerns about on-target toxicity, systemic metabolic disturbance, myopathic fatigue, anemia, ocular toxicity and other adverse events (96). Moreover, the majority of LDHA-, MCT-, PDK- and HIF-1α-targeting agents have primarily exhibited efficacy in cell-line or xenograft models, with limited robust lung cancer-specific clinical efficacy data. Therefore, future drug development should prioritize tumor-selective inhibition, optimized pharmacokinetic and pharmacodynamic profiles, as well as rational delivery systems to enhance the therapeutic window.

Lactate metabolism does not operate in isolation. Inhibiting lactate production or transport could lead to the compensatory activation of other bioenergetic pathways, such as glutaminolysis, fatty acid oxidation, mitochondrial oxidative phosphorylation, acetate utilization and autophagy-mediated nutrient recycling. These adaptive responses enable tumor cells to sustain ATP production, redox balance, and biosynthetic precursor supply during metabolic stress, potentially reducing the effectiveness of targeting LDHA or MCT inhibition (27,28). This situation underscores the need to pursue combination strategies guided by biomarkers rather than relying solely on monotherapy.

Current lactate-associated biomarkers face significant clinical limitations. Serum LDH blood tests and LIPI are convenient and widely available; however, they lack specificity and may be affected by factors, such as systemic inflammation, liver injury, hemolysis, tumor burden and treatment-related tissue damage. Tissue markers, such as LDHA, MCT4 and CD147 are impacted by intratumoral spatial heterogeneity, sampling bias, antibody variability and inconsistent immunohistochemistry scoring systems (78,79). Imaging parameters, such as ^{18}F-FDG SUVmax indirectly reflect glucose uptake and glycolytic activity. However, they are not lactate-specific and may be influenced by factors, such as tumor size, inflammation, scanner protocols, image reconstruction, and respiratory motion. In addition, these biomarkers may exhibit limited predictive performance in early-stage lung cancer, where systemic lactate-related changes are less apparent and capturing intratumoral heterogeneity is more difficult. While hyperpolarized 13C MRS/MRI shows promise for monitoring pyruvate-to-lactate conversion and metabolic flux, its routine clinical application in lung cancer remains challenging.

Major barriers to the implementation of hyperpolarized MRS/MRI include the short lifetime of the hyperpolarized signal, the requirement for specialized on-site polarization infrastructure, high costs, complex acquisition and reconstruction protocols, limited spatial resolution, challenges posed by respiratory motion in thoracic imaging, and a lack of multicenter standardization. Moreover, differentiating tumor-derived lactate metabolism from inflammatory, stromal, or treatment-induced metabolic signals continues to present challenges. Addressing these technical limitations is crucial before hyperpolarized MRS/MRI can be widely utilized for monitoring treatment responses or predicting recurrences in lung cancer.

Future research directions and clinical translational prospects. Future research is warranted to shift its focus to transforming lactate metabolism from a theoretical concept into a practical clinical framework. In order to address metabolic heterogeneity, it is recommended to combine multi-omics profiling, single-cell sequencing, spatial metabolomics, and functional imaging to pinpoint tumor subgroups that rely on lactate. This type of categorization could prove beneficial in identifying patients who are most suitable for treatments targeting LDHA, MCT1/4, PDK, or HIF-1α.

To enhance therapeutic specificity, forthcoming drug advancement should give precedence to allosteric LDHA inhibitors, specific MCT4 antagonists, dual-action compounds addressing both lactate production and export, and potential tumor-directed delivery systems such as nanocarriers, exosomes, antibody-drug conjugates, or locally activated prodrugs. While natural compounds with multitarget characteristics could offer valuable foundational frameworks, their pharmacokinetics, bioavailability, target specificity, purity and formulation consistency necessitate thorough refinement before progressing to clinical translation.

Given the compensatory activation of glutamine metabolism, fatty acid oxidation, and oxidative phosphorylation following the inhibition of the lactate pathway, future

therapeutic approaches should transition from empirical combinations to combinations guided by mechanisms. Potential strategies may involve combining inhibitors of lactate metabolism with immune checkpoint blockade in tumors with high lactate levels that exhibit immunosuppression, with EGFR-TKIs in resistant clones dependent on glycolysis, with radiotherapy in tumors demonstrating LDHA-driven redox adaptation or DNA repair, and with inhibitors of glutamine or fatty acid oxidation in tumors undergoing compensatory metabolic rewiring.

For the development of biomarkers, it is essential to conduct prospective multicenter studies to standardize cut-off values, detection platforms, immunohistochemistry scoring systems, and imaging acquisition protocols. Instead of focusing solely on individual markers, such as LDH, MCT4, or SUVmax, future research should aim to create comprehensive biomarker panels that include serum markers, tissue metabolic markers, imaging parameters, circulating tumor cells, exosomal cargo and lactylation-related gene signatures. In the case of hyperpolarized MRS/MRI, the establishment of standardized procedures for acquisition, reconstruction, quantification, and quality control is imperative before its integration into regular clinical trials.

7. Conclusion

Lactate serves as a central hub for metabolism, signaling and epigenetics in lung cancer rather than merely being a byproduct of glycolysis. Its role in resistance to chemotherapy, targeted therapy, immunotherapy and radiotherapy involves metabolic adaptation, signaling pathway bypasses, lactylation-induced remodeling and immune suppression. Challenges, such as histological variations, alternate substrate usage, redundant transporters, non-specific markers and limited treatment specificity currently hinder clinical progress. Advancements will rely on identifying lactate-dependent tumor subgroups, validating the inhibition of pharmacodynamic targets, and implementing combination strategies guided by mechanisms in prospective trials enriched with biomarkers.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests

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