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# *Glucose Metabolic Reprogramming of Cancer-Associated Fibroblasts in Lung Cancer Immune Resistance*

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***Abstract.*** Lung cancer is considered significantly lethal and prevalent among all types of cancer, becoming the academic focal point in the oncology circle. As tumor microenvironment (TME) research becomes a core hotspot in oncology, accumulating clinical and basic studies have clarified the intrinsic correlation between the glucose metabolic reprogramming of cancer-associated fibroblasts (CAFs) and malignant lung tumor development, verifying its critical value for developing optimized combined regimens with sustained clinical efficacy. This paper concentrates on glucose metabolic reprogramming in lung cancer-derived CAFs, followed by its regulatory role in tumor immune resistance. Combined with recent high-quality findings on lung cancer metabolic remodeling, this paper elaborates the molecular mechanisms by which CAF glucose metabolic reprogramming triggers immune escape, summarizes potential targeted strategies to reverse CAF-driven immunosuppression, and discusses the existing challenges and future research directions, aiming to provide promising directions and potential for improving immunotherapy efficacy and optimizing clinical treatment strategies for patients.

***Keywords:*** Metabolic reprogramming, lung cancer, glucose metabolism, immunotherapy, tumor microenvironment

## 1. Introduction

With a significantly high incidence and case fatality rate (CFR) each year, lung cancer exerts huge health burden worldwide [1]. Lung cancer has two main subtypes, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) where NSCLC accounts for nearly six times as many cases as the other lung cancer subtype, and its 5-year overall mortality remains over 80% in advanced stages, highlighting the urgency of exploring novel therapeutic targets and strategies [2, 3]. Conventional clinical interventions, including surgical resection, radiotherapy and chemotherapy, have prolonged patient survival to a limited extent, but their efficacy is severely constrained by tumor recurrence, metastasis and therapeutic resistance [4].

Among these regimens, chemotherapy has long served as the mainstream antitumor approach, but tumor heterogeneity and frequent therapeutic resistance severely restrict its long-term benefits [1]. In recent years, PD-1/PD-L1 immune checkpoint inhibitors (ICIs), the most widely recognized and utilized immunotherapy, have successfully transformed lung cancer treatment in the idea of

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reactivating endogenous antitumor immunity, although far fewer than half of patients achieve durable responses due to widespread immunotherapy resistance [1, 2].

The lung cancer TME is an intricate immunosuppressive niche, with CAFs as the most dominant stromal cell subset, accounting for 30% to 50% of stromal cells. CAFs modulate tumor behaviors and immune cell function via multiple pathways, while metabolic reprogramming—especially glucose metabolic remodeling—serves as a core driver of immune suppression and therapeutic resistance. This review integrates latest evidence to elaborate CAF glucose metabolic reprogramming mechanisms, summarize targeted strategies, and provide a theoretical basis for clinical translation.

## 2. CAF metabolic reprogramming mediates immune resistance mechanisms in lung cancer

### 2.1. Mechanisms of glucose metabolic reprogramming in lung cancer

Glucose metabolism plays an indispensable role in maintaining normal physiological activities and supporting malignant progression through offering energy and carbon skeletons for cell survival and proliferation [2, 3]. Under physiological conditions, normal cells primarily rely on oxidative phosphorylation (OXPHOS) in mitochondria to decompose glucose, an efficient way to generate large amounts of ATP [5]. In contrast, malignant tumor cells exhibit the Warburg effect—a special metabolism that activates aerobic glycolysis regardless of oxygen content, without participating in the mitochondrial tricarboxylic acid (TCA) cycle and directly converting glucose to pyruvate in the cytoplasm and then rapidly converting pyruvate to lactate [3]. Although this process is less efficient in ATP production, it enables tumor cells to rapidly obtain energy and a large number of biosynthetic precursors, which is crucial for meeting the needs of rapid proliferation and malignant progression [6].

Lung cancer cells show excessive glucose uptake, which is mainly driven by upregulated GLUT1 expression on the cell membrane. GLUT1, a key member of the glucose transporter family, is in charge of the cross-membrane transportation of glucose, and its overexpression directly accelerates glucose transport efficiency, providing sufficient substrates for sustained glycolysis [7]. A 2024 study published in Front Pharmacol confirmed abnormal GLUT1 overexpression in lung adenocarcinoma tissues [2]. In vitro laboratory experiments further proved that knockdown of GLUT1 can suppress cell proliferation and migration as a result of reduced glucose uptake and glycolytic activity of malignant epithelial cells in lung cancer. This study also revealed that GLUT1 overexpression is related to the PI3K/Akt/mTOR signaling pathway in lung cancer cells; targeting and inhibiting this pathway can downregulate GLUT1 expression and reverse glycolytic metabolic reprogramming.

Glucose metabolism in lung cancer is orchestrated by multiple important molecules, with HIF-1α as the core regulator. Intratumoral hypoxia is a common characteristic of lung cancer, especially in advanced tumors, and it is also an important driving factor for glucose metabolic reprogramming. Hypoxia and excessive reactive oxygen species (ROS) accumulation in the TME stabilize HIF-1α, preventing its ubiquitination and degradation. Stabilized HIF-1α enters the nucleus and binds to the hypoxia response element (HRE) of downstream target genes, transcriptionally upregulating the expression of a series of glycolytic-related molecules, including GLUT1, HK2, PKM2 and LDHA, and elevating overall glycolytic activity significantly. HK2, an enzyme functioning in the glycolytic pathway, decelerates the pathway after it binds to voltage-dependent anion channel (VDAC) via enhancing glycolytic flux and blocking G6P-mediated feedback inhibition [8]. PKM2, the predominant pyruvate kinase isoform in lung cancer, not only modulates glycolytic activity but also

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regulates $CD8^+$ T cell differentiation, as well as tumor sensitivity to PD-1 blockade immunotherapy. LDHA, which is highly expressed in over 90% of NSCLC patients, promotes lactate accumulation in the TME, forming an immunosuppressive barrier. Collectively, these molecules form a HIF-1α-orchestrated regulatory network that links glucose metabolic reprogramming to tumor immune resistance.

## 2.2. Core features and regulatory mechanisms of CAF glucose metabolic reprogramming

CAFs, mainly derived from normal fibroblasts and mesenchymal stem cells, are important stromal cells in the lung cancer TME. The TME undergoes significant glucose metabolic reprogramming due to the presence of complex interactions between diverse factors within the TME, malignant cells, and CAFs. CAF glucose metabolic reprogramming is characterized by a phenomenon termed as the reverse Warburg effect—tumors elicit CAFs to undergo aerobic glycolysis, producing large amounts of lactate and pyruvate, which are then absorbed by tumor cells to meet their biosynthetic and energetic requirements for metabolism, forming a metabolic symbiosis between CAFs and tumor cells [7]. The pattern of this type of metabolism is characterized by enhanced glucose uptake, increased glycolytic activity and massive lactate secretion, which is mainly driven by abnormal GLUT1 expression on CAF membranes.

A 2025 review published in Oncogene confirmed that TGF-β secreted by lung cancer cells can specifically induce GLUT1 overexpression in CAFs, and knockdown of GLUT1 in CAFs significantly reduces glucose uptake and lactate secretion, thereby inhibiting tumor cell proliferation in co-culture experiments [9]. CAFs secrete lactate through the monocarboxylate transporter 4 (MCT4), which is highly expressed on their cell membranes, and tumor cells take up lactate via the monocarboxylate transporter 1 (MCT1), forming a complete lactate exchange pathway between CAFs and tumor cells. Beyond autonomous metabolic reprogramming, CAFs also exert multifaceted regulation on tumor cell metabolism: they directly deliver nutrients such as lactate and pyruvate to tumor cells; transfer non-coding RNAs (e.g., miR-146a) to tumor cells through exosomes, which activate the PI3K/Akt/mTOR signaling pathway and enhance glycolysis of tumor cells; transfer functional mitochondria to tumor cells to improve their OXPHOS capacity; and mediate extracellular matrix (ECM) remodeling under the regulation of HIF-1α, which further affects tumor cell metabolic patterns [10].

The glucose metabolic reprogramming of CAFs is regulated by multiple factors, including tumor-derived cytokines and the hypoxic microenvironment. Expression of glycolytic enzymes, such as HK2 and LDHA, is upregulated by tumor-derived TGF-β and IL-6, which activate the Smad3 and JAK/STAT3 signaling pathways in CAFs, respectively. Hypoxic conditions in the TME stabilize HIF-1α in CAFs, which further upregulates the expression of GLUT1, HK2 and LDHA, enhancing the reverse Warburg effect. This complex regulatory network ensures that CAFs can stably support tumor progression, and the reverse Warburg effect has become the core metabolic feature that distinguishes CAFs from normal fibroblasts.

## 2.3. Mechanisms of immune resistance mediated by CAF metabolic reprogramming

CAF glucose metabolism is a core driver of lung cancer immune resistance, which mainly mediates immunosuppression by reshaping the TME structure, expanding immunosuppressive cell subsets and directly inhibiting the function of antitumor immune cells such as $CD8^+$ T cells and natural killer (NK) cells [9]. This series of changes together form a stable immunosuppressive microenvironment, making tumor cells escape the surveillance and attack of the immune system.

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CAFs and M2-type macrophages (M2-TAMs) form a positive feedback regulatory loop in the lung cancer TME, which significantly strengthens immunosuppression. Metabolically activated CAFs secrete chemokines such as CCL2, anti-inflammatory cytokines such as IL-10, and large amounts of lactate. CCL2 binds to CCR2 on peripheral monocytes, promoting their migration to the tumor site; IL-10, in monocytes, suppresses the expression of pro-inflammatory cytokines, inducing their polarization to M2-TAMs; lactate binds to GPR81 on macrophages, activating the cAMP/PKA signaling pathway, which further promotes M2 polarization. In return, M2-TAMs release IL-6 and SDF-1, which trigger the STAT3 and PI3K/Akt signaling cascades within CAFs. This activation potentiates the reverse Warburg phenotype of CAFs by upregulating the expression of GLUT1, HK2, and LDHA. Moreover, CAFs produce CCL22 to facilitate Treg cross-membrane movement. CCL22 is a chemokine that engages CCR4 on Tregs, and simultaneously enhances the suppressive activity of these regulatory cells through lactate and IL-10. Additionally, CAFs increase the expression of immunosuppressive mediators, including Arg1 and iNOS, via the secretion of CCL2 and CXCL1. Those factors promote the transport of myeloid-derived suppressor cells (MDSCs) from the bone marrow to the tumor site, and lactate and IL-6 both stimulate the STAT3 pathway in MDSCs and further amplify their immunosuppressive potential [11].

In addition to regulating immunosuppressive cells, CAF glucose metabolic reprogramming also directly inhibits the function of antitumor immune cells [12]. The massive accumulation of lactate in the TME lowers the local pH value to 6.0–6.5, an acidic condition that suppresses the surface presentation of crucial activating receptors—notably TCR and NKG2D—on both $CD8^+$ T lymphocytes and NK cells, thereby impairing their activation and cytolytic capacity. Concurrently, lactate stimulates the mTOR signaling cascade in $CD8^+$ T cells, leading to functional exhaustion characterized by increased expression of immune checkpoint molecules such as PD-1, TIM-3, and LAG-3, alongside the downregulation in effector proteins including perforin and granzyme. In addition, CD73 is originated from CAFs, which is an ectonucleotidase that mediates the dephosphorylation of AMP into adenosine. The resulting adenosine accumulation within the TME binds to A2A receptors on $CD8^+$ T cells and NK cells, further delivering an inhibitory signal that curtails antitumor immunity [13]. This complex intercellular crosstalk forms a stable immune evasion loop, which is the key cause of primary and acquired resistance to ICIs in lung cancer.

## 3. CAF metabolic reprogramming mediates targeted strategies for immune resistance in lung cancer

Continuous development of immunotherapy requires in-depth understanding of the relationship between immune resistance and changes in CAFs' metabolism in lung cancer; a series of novel therapeutic strategies have been developed aimed at regaining immune cells' antitumor response, which mainly target CAF-related metabolic molecules and immune regulatory pathways to normalize the immunosuppressive TME. These strategies are categorized into two forms: targeted therapy against metabolic molecules and combined therapeutic strategies, both of which have shown good potential in preclinical and clinical studies.

### 3.1. Potential target in treating lung cancer

The potential targets for reversing CAF glucose metabolic reprogramming mainly include glucose transporters, key glycolytic enzymes and lactate transporters, which are the core molecules that satisfy the energy requirements of cancer and regulate metabolic symbiosis between CAFs and cancer. 2-DG, a classic glycolytic inhibitor, is a structural analog of glucose that is specifically

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utilized by CAFs and tumor cells across the cell membrane via GLUT1. Hexokinase efficiently converts 2-DG into 2-deoxyglucose-6-phosphate, a non-metabolizable metabolite that resists further breakdown and thus accumulates in cells, competitively inhibiting hexokinase activity and blocking the initial step of glycolysis. Preclinical studies have shown that 2-DG can successfully restore the function of $CD8^+$ T cells by effectively inhibiting the glycolytic activity of CAFs and tumor cells, reducing lactate accumulation in the TME. When combined with cisplatin (a classic chemotherapeutic drug) or PD-1 inhibitors, 2-DG shows significant synergistic antitumor effects. Currently, treatment, such as 2-DG, for patients at an early stage of NSCLC has shown positive progress, and preliminary results show that it has a good safety profile and potential therapeutic efficacy.

GLUT1, as the main glucose transporter mediating CAF glucose uptake, is also an important therapeutic target. BAY-876 and STF-31 are selective GLUT1 inhibitors that can specifically bind to GLUT1 and block glucose transport. Recent preclinical studies have proposed potential directions in developing ICIs for lung cancer, and researchers have demonstrated that these inhibitors, BAY-876 and STF-31, can significantly reduce glucose uptake and lactate secretion by CAFs, disrupt the metabolic symbiosis of CAFs and tumor cells. Critical enzymes of glucose metabolism, such as HK2, PKM2 and LDHA are also important targets. Inhibition of HK2 can block CAF glycolysis and induce CAF death via 3-bromopyruvate (3-BP), an inhibitor that can specifically suppress HK2 activity. Shikonin, a PKM2 inhibitor, can inhibit PKM2 activity in CAFs, reduce lactate secretion, and repair the impairment of $CD8^+$ T cells. GSK2837808A, an LDHA inhibitor, can lower the production of lactate, normalize the local pH value, and more importantly enhance the efficacy of PD-1 inhibitors. Furthermore, MCT4 inhibitors (such as AZD3965) can block lactate secretion from CAFs, disrupting the lactate exchange between CAFs and tumor cells, and further weakening the immunosuppressive TME.

### 3.2. New Strategies to overcome immunotherapy resistance

Combined therapeutic regimens are key to overcoming CAF-mediated immunotherapy resistance, as they can simultaneously target multiple links of the immunosuppressive TME and achieve synergistic antitumor effects [4]. Chemoradiotherapy is a conventional combined treatment method with both short-term benefits—directly targeting and eliminating cancer—and long-term benefits as it simultaneously promotes secretion of tumor-associated antigens, triggering a systemic antitumor immune response. In addition, chemoradiotherapy synergizes with ICIs to improve therapeutic efficacy within the TME by inhibiting the cross-membrane movement of immunosuppressive cells such as Tregs and MDSCs and alleviating local immunosuppression. Clinical studies in patients with solid tumors have shown that concurrent chemoradiotherapy combined with PD-1/PD-L1 blockade significantly improves in efficacy and expands patients' lifespan to a encouraging extent [14].

Cytokine-targeted therapy is another important strategy to normalize the TME shaped by glucose metabolism with the help of CAFs. CAFs secrete a variety of cytokines (such as TGF-β, IL-6 and CCL2) to avoid immunosurveillance, targeting and inhibiting these cytokines can effectively reverse the immunosuppressive microenvironment. For example, anti-TGF-β antibodies can inhibit the activation of CAFs and the polarization of M2-TAMs, while anti-IL-6 antibodies can reduce MDSC recruitment and strengthen the ability of $CD8^+$ T cells. Tumor-infiltrating lymphocyte (TIL) therapy, TCR-T therapy and CAR-T/NKT therapy are termed adoptive cellular therapy which shows great potential and promising outcomes for patients with PD-1-resistant lung cancer. TILs derived from tumor tissues can specifically recognize tumor antigens, and their therapeutic effect has been verified in clinical trials. Modified CAR-NKT cells and CAR-NKT extracellular vesicles represent a

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novel therapy for refractory lung cancer, with improved safety and enhanced antitumor immunity in preclinical models of lung cancer [15]. In addition, dual targeting of metabolic and immune checkpoints (such as HIF-1α + PD-L1) can simultaneously block CAF glucose metabolic reprogramming and immune suppression, thereby achieving a more effective reversal of ICI resistance. In NSCLC, inhibiting KEAP1, CPT1A or YAP/TAZ signaling can also boost the effectiveness of anti-PD-L1 monotherapy, providing novel precision treatment directions for clinical practice.

## 4. Conclusion

CAF glucose metabolic reprogramming is a core driver of lung cancer immune resistance, mediating immunosuppression via crosstalk with TAMs, Tregs, MDSCs and direct inhibition of antitumor immune cells. Several promising strategies with strong potential are proposed to successfully reverse resistance such as targeting CAF metabolic molecules (GLUT1, HK2, MCT4) and combining metabolic inhibitors with ICIs, chemoradiotherapy or adoptive cellular therapy. Importantly, future development of treatment should deal with recent hurdles, including CAF heterogeneity and off-target effects of metabolic inhibitors. Further research should put emphasis on identifying specific CAF subtypes, developing selective inhibitors and optimizing combination treatment for individuals. Better outcomes depend on continuous development of techniques that translate preclinical findings into clinical benefits and enhancing the prognostic value of treatments.

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