SPARKLING PUBLISHING GROUP

TYPE Review Article

PUBLISHED 15 June 2025

DOI 10.5883/ctr.2025.6.6.2

CLINICAL AND TRANSLATIONAL REPORTS

OPEN ACCESS

Vol 2, No.1

RUNNING TITLE
Glycolytic switch in cancer

RECEIVED
23 March 2025

REVISED
14 May 2025

ACCEPTED
20 May 2025

PUBLISHED ONLINE
15 June 2025

Targeting the glycolytic switch in cancer: mechanisms, cancer progression and therapeutic challenges

Torsten Lundberg[1], Sigurd Lindholm[1,*]

1 Department of Cell and Molecular Biology, Karolinska Institute, Stockholm, Sweden

* Address for Correspondences:
Sigurd Lindholm
Department of Cell and Molecular Biology, Karolinska Institute, Stockholm, Sweden
E-mail: sigurdlindholm@tutamail.com

Abstract

The Warburg effect, characterized by aerobic glycolysis in cancer cells, represents a metabolic reprogramming mechanism that is critical for sustaining tumorigenesis. In addition to its association with mitochondrial dysfunction, this phenomenon is now recognized as an oncogene-driven adaptation that promotes rapid ATP production, biomass accumulation, and microenvironmental remodeling. Central to glycolytic reprogramming are dysregulated rate-limiting enzymes (including HK2, PFK1/PFKFB3, PKM2, and LDHA), whose activities are regulated by transcriptional networks (e.g. HIF-1α, MYC), post-translational modifications, and isoform switching. Together, these enzymes divert glycolytic intermediates toward anabolic pathways while maintaining redox balance under hypoxic conditions. Tumor progression is further promoted by lactate-mediated extracellular acidification, which reshapes the tumor microenvironment (TME) to promote immunosuppression, angiogenesis, and metastatic dissemination. Glycolytic metabolites also orchestrate epigenetic reprogramming through histone lactylation, forming a feed-forward loop that consolidates the malignant phenotype. Despite advances in therapeutic efforts targeting glycolytic enzymes, challenges remain due to metabolic plasticity, activation of compensatory pathways, and on-target toxicity in normal tissues. Emerging strategies combining glycolytic inhibitors with immunotherapies or microenvironmental modulators have shown promise in preclinical models, but tumor heterogeneity and dynamic metabolic crosstalk still hinder clinical translation. This review synthesizes the mechanistic basis of glycolytic reprogramming, its multifaceted roles in malignancies, and translational barriers that impede therapeutic innovation.

DOI 10.58832/ctr.2025.6.6.2

KEYWORDS

Glycolytic reprogramming; Cancer; Tumor microenvironment; Therapeutic; Metabolic plasticity

Introduction

The biological characteristics of malignant tumors are always closely intertwined with metabolic abnormalities. As one of the hallmark features that distinguishes cancer cells from normal cells, metabolic remodeling of cancer cells not only supports their uncontrolled proliferation and survival needs, but is also deeply involved in malignant processes such as tumor invasion, metastasis, and treatment resistance. Glucose metabolism in cancer cells is mainly characterized by two major biochemical events: increased glucose uptake and aerobic glycolysis, the process of converting glucose into pyruvate, which ultimately leads to the production of lactate (1). In 1927, Otto Warburg first observed that cancer cells preferentially metabolize glucose to lactate via glycolysis, even under oxygen-rich conditions—a phenomenon known as the "Warburg effect." While initially attributed to mitochondrial dysfunction, contemporary studies have revealed that glycolysis is a conscious reprogramming mechanism that supports rapid ATP generation, biomass synthesis, and microenvironmental remodeling.

The core mechanism of aerobic glycolysis in cancer cells begins with the overexpression of glucose transporters (GLUTs), which accelerates the rate of glucose uptake by cancer cells. Intracellular glucose generates glucose-6-phosphate under the catalysis of hexokinase 2 (HK2), which is a key rate-limiting enzyme that promotes glycolytic flux and inhibits mitochondrial apoptosis through physical coupling with the voltage-dependent anion channel (VDAC) of the mitochondrial outer membrane. Subsequently, phosphofructokinase-1 (PFK1) catalyzes the irreversible conversion of fructose-6-phosphate into fructose-1,6-bisphosphate as the rate-limiting enzyme. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is anchored on actin filaments close to the glycolytic fragments occurring in the cytoplasm, generates NADH through oxidation reactions, and participates in the spatial localization of metabolic enzymes on the cytoskeleton (microtubules/microfilaments), which may improve glycolytic efficiency by optimizing enzyme complex assembly. As one of the isoforms of phosphofructokinase (PFK), PFKFB3 affects cancer cell proliferation through its nuclear translocation. Similarly, direct binding of GAPDH to telomeric DNA protects telomeres from rapid degradation caused by chemotherapy. In addition, the end product of glycolysis, pyruvate, is generated under the catalysis of pyruvate kinase M2 (PKM2) and further reduced to lactate by lactate dehydrogenase (LDH), while regenerating NAD+ to maintain the continuation of glycolysis. Pyruvate also enters the mitochondria for the tricarboxylic acid cycle (TCA cycle) to continue to produce energy. Lactate is excreted to the extracellular space through monocarboxylate transporters (MCT), leading to acidification of the tumor microenvironment, a process that is closely related to tumor invasion and immune escape(2, 3) (Figure 1). This metabolic shift is orchestrated by oncogenic signals, hypoxia-inducible factors, and epigenetic modifications, allowing tumors to survive metabolic stress. Understanding glycolytic reprogramming may not only shed light on cancer biology but also reveal therapeutic vulnerabilities. Here, we dissect the molecular mechanisms of glycolytic reprogramming and the mechanistic interplay between it and malignancy and outline the challenges in clinical targeting.

DOI 10.58832/ctr.2025.6.6.2

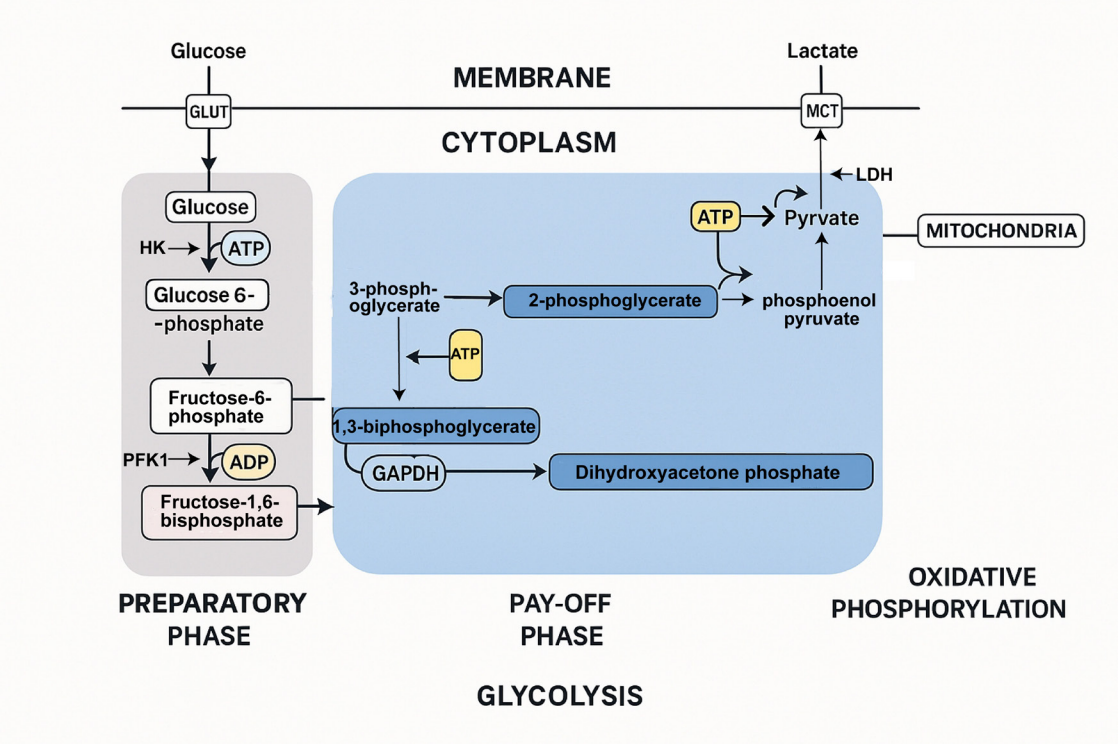

FIGURE 1

Aerobic glycolysis pathway in cancer cells and its regulation in cellular metabolism.

Even under oxygen-sufficient conditions, cancer cells will preferentially break down glucose through glycolysis (rather than efficient oxidative phosphorylation) to obtain energy and produce a large amount of lactic acid. The aerobic glycolysis pathway first absorbs glucose through the GLUT transporter, and then phosphorylates it to 6-phosphate glucose under the catalysis of HK, consumes ATP to start glycolysis, and then isomerizes to fructose-6-phosphate. Fructose-6-phosphate generates fructose-1,6-bisphosphate under the action of PFK1, and then undergoes a series of conversions to generate pyruvate. Among them, the glycolytic flux is controlled by the key rate-limiting enzyme HK, PFK1, and PKM2 regulated by PFKFB3 through 2,6-bisphosphate fructose. The glycolysis process is divided into a "preparation stage" and a "reward stage": in the preparation stage, glucose is gradually broken down into three-carbon sugars (such as dihydroxyacetone phosphate and glyceraldehyde-3-phosphate) and consumes ATP; in the reward stage, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) catalyzes the generation of 1,3-bisphosphoglycerate, which is subsequently phosphorylated at the substrate level to generate ATP and finally form pyruvate. Despite normal mitochondrial function, cancer cells still preferentially reduce pyruvate to lactate through lactate dehydrogenase (LDH) rather than entering mitochondria for oxidative phosphorylation. Finally, lactate dehydrogenase (LDH) converts pyruvate into lactate, promoting its efflux. The massive secretion of lactate leads to a decrease in the pH of the TME, prompting cancer cells to evade immune evasion and enhance invasion and metastasis. GLUT: Glucose transporter; HK: Hexokinase; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PKM2: Pyruvate kinase M2; LDH: Lactate dehydrogenase; PFK1: Phosphofructokinase-1; TME: Tumor microenvironment.

DOI 10.58832/ctr.2025.6.6.2

1.Mechanisms of glycolytic reprogramming

In the occurrence and progression of malignant tumors, metabolic reprogramming has been established as a key feature of cancer cells. The remodeling of glucose metabolic pathways is particularly significant, and tumor cells still rely on glycolysis for energy even under aerobic conditions. Compared with oxidative phosphorylation, the glycolysis rate is significantly increased, lactate is produced in large quantities, and the ATP synthesis efficiency is reduced, but it provides metabolic advantages for rapid cell proliferation. Metabolite intermediates accumulate, and carbon flow is redirected to nucleotide, amino acid and lipid synthesis pathways to meet biosynthesis needs(4, 5). At the same time, glycolysis reprogramming is not only regulated by key enzymes, but also involves the synergistic effects of transcription factors, epigenetic modifications and signaling pathways, driving cells to adapt to changes in the microenvironment(6). Next, we will focus on the core mechanisms of glycolytic reprogramming, including enzyme activity regulation, interactions of key signaling pathways, and epigenetic regulation, to reveal its role in tumorigenesis.

1.1 Key enzymatic drivers

Glycolytic reprogramming in cancer is fundamentally driven by the dysregulation of rate-limiting enzymes that control the flux of the glycolytic cascade. This metabolic shift, a hallmark of malignant progression, arises not only from the availability of passive substrates but also through active oncogenic signaling pathways that hijack enzyme activity(7, 8). Central to this process are HK, PFK1, PKM2, and lactate dehydrogenase A (LDHA), whose expression, localization, and catalytic functions are frequently exploited by tumor cells(9). Their dysregulation is mediated by transcriptional regulation, post-translational modifications, and isoform switching, which together fine-tune glycolytic output to meet biosynthetic and redox demands(10). Crucially, these enzymatic alterations confer selective advantages by maintaining ATP production under hypoxic conditions, diverting intermediates to anabolic pathways, and suppressing oxidative stress. Elucidating the mechanistic interplay between these drivers and the tumorigenic milieu remains critical to identifying exploitable vulnerabilities.

1.1.1 HK

Glycolytic flux in cancer is controlled by rate-limiting enzymes that are overexpressed or overactivated in tumors. HK, as the first rate-limiting enzyme in glycolysis, catalyzes the phosphorylation of glucose to glucose-6-phosphate, allowing glucose to enter the glycolytic flux(11). Overexpression of HK isoforms, especially HK2, is frequently observed in malignant tumors, promoting glucose capture and maintaining elevated glycolytic activity(12). HK2 has been found to be highly expressed in oral squamous cell carcinoma tissues and cell lines, and knocking down HK2 inhibits glycolysis, delays tumor growth, and enhances chemotherapy sensitivity(13). In addition, HK2 also binds to the mitochondrial VDAC to evade the inhibitory feedback of glucose-6-phosphate while increasing the efficiency of ATP generation(12).

1.1.2 PFK1 and PFKFB3

PFK1 is the second rate-limiting enzyme that regulates the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. Studies have shown that cancer cells maintain a high glycolytic rate by maintaining low levels of citrate (a natural inhibitor of PFK1) to relieve the inhibition of PFK1(14). PFK1 has been shown to be highly expressed in colorectal cancer (CRC), and its expression level is associated with radioresistance. Inhibition of PFK1 can enhance the sensitivity of CRC cells to radiotherapy(15). PFK1 activity is regulated by the bifunctional enzyme PFKFB3, which synthesizes fructose-2,6-bisphosphate (F2,6BP), which is a potent allosteric activator of PFK1. For example, the PFKFB3 inhibitor PFK15 inhibits PFK1 activity in breast cancer by reducing F2,6BP levels(16). In addition, in cutaneous squamous cell carcinoma, renal cell carcinoma, and ovarian cancer, PFKFB3 overexpression is closely associated with tumor proliferation, metastasis, and enhanced glycolysis(17, 18). KLF9 inhibits the transcription of PFKFB3 by directly binding to the PFKFB3 promoter. Silencing PFKFB3 can inhibit the proliferation and metastasis of skin squamous cell carcinoma cells(19).

1.1.3 PKM2

PKM2 controls the final rate-limiting step, converting phosphoenolpyruvate to pyruvate. Its low catalytic activity prompts cancer cells to prefer aerobic glycolysis rather than oxidative phosphorylation, thereby accumulating upstream

DOI 10.58832/ctr.2025.6.6.2

glycolytic intermediates for use in anabolic pathways. High expression of PKM2 has been shown to be associated with poor prognosis in patients with brain glioma, breast cancer, etc(20). In other related studies, miR-142-3p inhibits CRC invasion and migration by targeting PKM2(21), while miR-19a-3p enhances PKM2 expression by inhibiting IGFBP3 and promotes glycolysis in ovarian cancer(22). In addition, PKM2 not only acts as a metabolic enzyme, but also has protein kinase activity, regulating gene expression by phosphorylating transcription factors or histone modification proteins (such as HIF-1α or p300), promoting tumor angiogenesis, immune escape and metastasis. For example, PKM2 inhibits CD8+ T cell activity and weakens anti-tumor immune response by upregulating PD-L1 expression in M2 macrophages(23). Under hypoxic conditions, PKM2 enhances the transcriptional activity of HIF-1α through a non-canonical pathway, promoting tumor adaptation to the hypoxic microenvironment.

1.1.4 LDHA

LDHA catalyzes the reduction of pyruvate to lactate, regenerating NAD+ to maintain glycolysis under hypoxic conditions. By enhancing glycolytic flux, LDHA provides cancer cells with rapid ATP generation and synthetic precursors, supporting tumor proliferation and invasion(24). Therefore, its overexpression is associated with an aggressive tumor phenotype and an immunosuppressive microenvironment. YY1 directly binds to the LDHA promoter to promote its transcription, enhancing glycolysis and proliferation of neuroblastoma(25). On the other hand, LDHA-mediated lactate secretion leads to extracellular acidification (pH decrease), promoting tumor immune escape, angiogenesis and metastasis(26).

1.1.5 Triosephosphate isomerase (TPI)

Although TPI is traditionally considered to be a non-rate-limiting enzyme that ensures a rapid balance between dihydroxyacetone phosphate (DHAP) and 3-phosphoglyceraldehyde (GAP), its activity directly affects glycolytic flux, thereby regulating the energy metabolism and biosynthetic capacity of cancer cells(27). For example, in lung adenocarcinoma, TPI1 expression is upregulated, and its knockdown significantly inhibits lung cancer cell migration, colony formation, and xenograft tumor growth(28). At the same time, in lung cancer cells, TPI1 knockdown inhibited glycolysis and reduced the accumulation of metabolites such as lactic acid in the tumor microenvironment, thereby inhibiting tumor growth(29), proving that the activity regulation of TPI may affect the dependence of cancer cells on glycolysis.

1.2 Transcriptional and epigenetic regulation

Transcriptional and epigenetic regulation form a multi-level network in aerobic glycolysis, involving the synergistic effects of metabolic sensors, transcription factors, chromatin modifying enzymes, and non-coding RNA. As an NADH-dependent transcriptional co-regulator, CtBP2 connects metabolic status with epigenetic reprogramming by sensing intracellular NADH levels(30). In breast cancer, it regulates the expression of glycolysis-related genes, promotes pyruvate oxidation and lactate production, and maintains glycolytic flux. HOXA3 recruits histone demethylase KDM6A to the promoter region of glycolytic genes (such as GLUT1 and HK2), removes the inhibitory histone mark H3K27me3, activates transcription and accelerates glycolysis, and promotes glioblastoma proliferation(31). Hypoxia-inducible factor-1 (HIF-1) is one of the key transcription factors that regulates metabolic reprogramming in cancer cells. HIF-1 is stabilized and activated under hypoxic conditions, promoting the expression of glycolysis-related genes and lipid metabolism genes, thereby enhancing the glycolytic capacity and lipid synthesis capacity of cancer cells to adapt to the hypoxic environment(32). HIF-1α transcriptionally activates glycolytic genes (e.g. GLUT1, LDHA) under low oxygen tension, while MYC synergistically enhances mitochondrial biogenesis and glycolysis(33). Mutated p53 is prevalent in invasive cancers and can promote HK2 and G6PD expression, linking glycolysis to redox homeostasis(34). Notably, lactate, a byproduct of glycolysis, can induce histone lactylation and epigenetically regulate immune and fibrotic genes to favor tumor progression.

DOI 10.58832/ctr.2025.6.6.2

2. Glycolysis and cancer malignant progression

The metabolic symbiosis between glycolysis and tumor invasiveness is not limited to energy supply but also includes dynamic interactions with oncogenic signals, microenvironmental adaptation, and therapeutic resistance. Reprogrammed glycolysis, traditionally viewed as an auxiliary pathway for ATP generation under hypoxic conditions, has now emerged as an active builder of the malignant phenotype, promoting proliferation autonomy, invasive potential, and metastatic fitness(35). Elevated glycolytic flux provides biosynthetic precursors for nucleotide, lipid, and protein synthesis while acidifying the extracellular environment through lactate secretion. This acid-mediated extracellular matrix remodeling promotes immune evasion, angiogenesis, and matrix activation, collectively establishing a permissive niche for metastatic dissemination(36). Mechanistically, glycolysis-driven malignant progression is intertwined with transcriptional networks such as HIF-1α stabilization, Myc-driven metabolic amplification, and Ras-mediated signaling rewiring. These pathways not only maintain glycolytic hyperactivity but also coordinate epigenetic reprogramming to lock tumors into an invasive state. Paradoxically, the adaptability of glycolytic metabolism that allows tumors to survive stress also complicates therapeutic targeting, as tumors exploit metabolic plasticity to circumvent pathway inhibition. Uncovering how spatiotemporal regulation of glycolysis intersects with hierarchical tumor evolution remains critical for disrupting the metabolic ecosystem of malignancies.

2.1 TME remodeling

Glycolytic reprogramming in cancer cells extends its oncogenic influence beyond cell-autonomous metabolism, actively shaping the TME, forming a symbiotic ecosystem that perpetuates malignancy. By preferentially exporting lactate through MCTs, glycolytically active tumor cells establish an acidic extracellular microenvironment, which not only suppresses antitumor immunity but also reprograms stromal and immune cell behaviors(37). Lactate-driven acidification polarizes tumor-associated macrophages (TAMs) toward an immunosuppressive phenotype, inhibits cytotoxic T cell function, and upregulates immune checkpoint ligands such as PD-L1(38). At the same time, glycolytic intermediates, including fructose-1,6-bisphosphate and phosphoenolpyruvate, act as signaling molecules to enhance the secretion of matrix metalloproteinases (MMPs), promoting extracellular matrix (ECM) degradation and metastatic dissemination(39). HIF-1α, which is stabilized by glycolytic ATP depletion, further amplifies angiogenic signals through VEGF production, while lactate itself stimulates endothelial cell sprouting(40). This self-reinforcing crosstalk between glycolytic and TME components generates metabolic competition for glucose, creating zones of nutrient deprivation that select for aggressive, therapy-resistant clones.

2.1.1 Formation of acidic microenvironment and immunosuppression

Cancer cells consume large amounts of glucose through aerobic glycolysis, and even in the presence of oxygen, they preferentially produce lactate rather than enter the tricarboxylic acid cycle. Lactic acid is excreted from the cell through MCTs, accompanied by the release of H⊠, resulting in a significant decrease in the pH of the TME (pH 5.5-6.5). Prostate cancer cells can also secrete lactate through glycolysis-associated fibroblasts (CAFs), forming a "symbiotic" metabolic relationship, further exacerbating acidification(41). This acidic environment not only directly promotes tumor cell invasion and metastasis, but also inhibits the function of immune cells (such as T cells and NK cells). Existing studies have pointed out the important role of lactate/lactate anions and glucose in the immunosuppressive activity of regulatory T (Treg) cell subsets with different lactate and glucose affinity metabolism within the TME(42). Lactate, a product of aerobic glycolysis, is secreted into the extracellular space by MCT, and then taken up by MCT1 on the surface of Treg cells, activating the LDHA activity inside the cells, further strengthening the metabolic cycle of lactate, leading to the accumulation of intracellular H+ and the formation of an acidic microenvironment. At the same time, by upregulating immunosuppressive molecules such as PDL1, it promotes the stabilization of the immunosuppressive phenotype of Treg cells(43) (Figure 2).

DOI 10.58832/ctr.2025.6.6.2

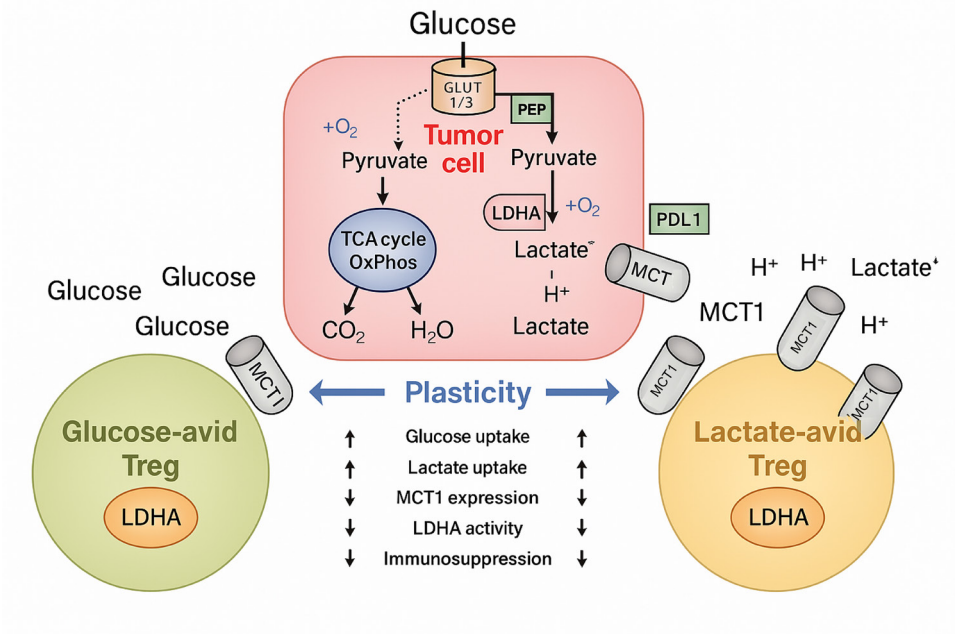

FIGURE 2

Effect of glycolysis-derived extracellular lactate on the plasticity of Treg cells.

Extracellular lactate derived from glycolysis promotes immunosuppression by regulating the metabolism and functional plasticity of Treg cells in the tumor microenvironment. Tumor cells take up glucose through GLUT and rely on LDHA to convert pyruvate into lactate, which is secreted into the extracellular space through MCT; extracellular lactate is taken up by MCT1 on the surface of Treg cells and activates the activity of LDHA inside them, further strengthening the metabolic cycle of lactate. This process enhances the glucose uptake, lactate transport capacity and LDHA activity of Treg cells, leading to the accumulation of intracellular H⊠ and the formation of an acidic microenvironment, while promoting the stabilization of the immunosuppressive phenotype of Treg cells by upregulating immunosuppressive molecules such as PD-L1. The accumulation of lactate can also directly inhibit the function of effector T cells, and through metabolic reprogramming, Treg cells gain a stronger survival advantage in the TME, ultimately forming a vicious cycle of immune escape. Treg cells: Regulatory T cells; GLUT: Glucose transporter; LDHA: Lactate dehydrogenase; PD-L1: Programmed death-ligand 1; MCT: Monocarboxylate transporter; TME: Tumor microenvironment.

2.1.2 Metabolic competition and immune escape

Tumor cells compete with immune cells in the TME for glucose resources through high glycolytic activity, resulting in insufficient energy and dysfunction of the latter. For example, the loss of GLUT1 and HK2 enhances the killing ability of T cells against tumor cells, indicating that cancer cells weaken the immune response through competition for glucose uptake dominated by glycolytic enzymes(44). In addition, glycolysis-related products (such as lactate) promote tumor cell immune escape by upregulating PD-L1 expression. For example, prostate cancer cells induce oxidative tumor cells to form a metabolic symbiosis with cancer-associated fibroblasts (CAFs) by secreting lactate, further exacerbating immunosuppression(45). In breast cancer, HK2 is positively correlated with PD-L1 expression, suggesting that glycolytic activity may promote immune escape by upregulating immune checkpoint molecules(46).

2.2 Metastasis and drug resistance

The accumulation of lactate can acidify the TME, promote matrix remodeling and immune escape, and thus enhance metastatic ability. Key enzymes of glycolysis (such as HK2

DOI 10.58832/ctr.2025.6.6.2

and PFKFB3) can promote cancer cell invasiveness by activating epithelial-mesenchymal transition (EMT)-related signaling pathways. In addition, exosomal miR-620 secreted by esophageal cancer cells can reprogram the glycolysis of lung fibroblasts to create a pre-metastatic microenvironment for their metastasis(47). In other studies on the mechanism of metastasis, neutrophil extracellular traps (NETs) are released in the acidic TME and promote metastasis by activating the EMT pathway(48). In addition, the upregulation of glycolysis also enables cancer cells to resist the cytotoxicity caused by chemotherapy and radiotherapy by regulating the intracellular redox state and energy metabolism, thereby leading to drug resistance problems(49). Enhanced glycolysis leads to lactate accumulation, which promotes the efflux of chemotherapeutic drugs by activating ABC transporters (such as MDR1). Abnormal glycolysis has been shown to be directly related to sorafenib resistance in liver cancer cells(50). Inhibition of HK2 can reverse glycolysis and resistance in triple-negative breast cancer(51). Glycolysis is also key to maintaining the stemness of cancer stem cells (CSCs). ETV4 promotes breast cancer stem cell resistance and metastasis by regulating LDHA. CD44 interacts with PKM2 to enhance antioxidant capacity, leading to chemotherapy resistance in ovarian cancer(52).

2.2.1 Glycolytic enzymes and metastasis regulation

Abnormal expression of key glycolytic enzymes such as HK2, PFKFB3, and LDHA directly promotes tumor cell invasion and metastasis. For example, HK2 enhances EMT and induces prostate cancer metastasis by activating the STAT3 signaling pathway(53). It can also bind to the mitochondrial voltage-dependent anion channel (VDAC) to inhibit apoptosis by isolating pro-death signals. PFKFB3 promotes breast cancer cell extravasation by regulating cytoskeletal reorganization and matrix metalloproteinase (MMPs) secretion(54).

2.2.2 Mechanisms of resistance

Some glycolytic enzymes exhibit atypical functions that directly drive therapeutic resistance. PKM2 enhances chemoresistance through nuclear translocation, where it synergizes with HIF-1α to activate genes involved in drug efflux and DNA repair. Upregulation of GLUT1 not only maintains glycolytic influx but also activates PI3K/AKT/mTOR signaling, establishing a feed-forward loop that amplifies survival pathways under therapeutic stress. Several other studies have found that some genes and pathways are also closely associated with cancer cell glycolysis. For example, KLF9 promotes aerobic glycolysis-induced cisplatin resistance in breast cancer cells through the PI3K/AKT/mTOR signaling pathway(55). Additionally, exosomal miR-21-5p from cisplatin-resistant SKOV3 ovarian cancer cells has been found to promote glycolysis and inhibit the chemosensitivity of their progenitor SKOV3 cells by targeting PDHA1(56).

2.3 Exosome-mediated transmission of malignant phenotypes

As a key medium of intercellular communication, exosomes can regulate the metabolic reprogramming of tumor cells and microenvironments by delivering metabolism-related molecules (such as enzymes, miRNAs, signaling proteins, etc.), thereby affecting cancer progression. Exosomes secreted by cancer cells carry glycolytic enzymes that can directly enhance the glycolytic capacity of recipient cells. For example, miR-620 in esophageal cancer cell exosomes reduces cancer cell glycolysis by inhibiting the FOXM1/HER2 axis(57), but after being delivered to lung fibroblasts (HFL1), it activates its glycolysis and provides energy support for the pre-metastatic microenvironment(58). Breast cancer cell exosomes promote glycolysis through the PI3K/AKT/mTOR signaling pathway, while inhibiting oxidative phosphorylation, leading to cisplatin resistance. In addition, circCDKN2B-AS1 stabilizes HK2 mRNA by binding to IMP3 protein, thereby enhancing the glycolytic activity of cervical cancer cells(59). Exosomes can also regulate TME through metabolic inhibition of immune cells. Tumor exosomes inhibit glycolysis of monocytes through the PD-1/GLUT1/HK2 axis, weakening their immune function. In addition, cancer cell exosomes inhibit the anti-tumor activity of CD8+T cells by downregulating AKT/mTOR signaling, reducing glucose uptake and glycolysis. Exosomes regulate aerobic glycolysis of cancer cells and microenvironment in multiple dimensions, becoming an important direction of tumor metabolism research.

DOI 10.58832/ctr.2025.6.6.2

3.Therapeutic targeting of glycolysis

Cancer cells' dependence on glycolytic reprogramming offers a unique therapeutic opportunity, but translating metabolic vulnerability into clinical efficacy remains fraught with biological and pharmacological complexity. Targeting glycolytic enzymes has emerged as a strategy to disrupt tumor bioenergetics, impair redox homeostasis, and block synthesis of anabolic precursors. Small molecule inhibitors and isoform-specific modulators aim to exploit the differential dependence of malignant versus normal cells on glycolytic flux, taking advantage of oncogene-driven enzyme activation or allosteric dysregulation(60). Combining glycolytic inhibitors with immunotherapy is increasingly being explored to circumvent adaptive escape mechanisms. Given the ubiquity of glycolysis in proliferative tissues, achieving tumor-selective inhibition without exacerbating systemic toxicity remains a challenge.

3.1 Pharmacological inhibitors

Small molecule inhibitors of glycolytic enzymes have shown promise in preclinical settings but still face clinical hurdles. Existing studies have shown that the antipsychotic drug penfluridol directly binds to PFKL to inhibit glucose consumption, lactate and ATP production, leading to nuclear translocation of FOXO3a, followed by transcriptional activation of BIM in an AMPK-dependent manner, thereby inhibiting glycolysis and inducing apoptosis in esophageal squamous cell carcinoma cells(61) (Figure 3). 2-Deoxyglucose (2-DG) is an HK2 antagonist that has shown limited efficacy in trials due to dose-limiting neurotoxicity. 2-DG has been shown to be effective against sorafenib-resistant persistent cancer cells in combination with sorafenib(62). Low, non-cytotoxic doses of 2-DG have been shown to reduce cancer cell invasiveness in aggressive breast cancer cell lines by inhibiting cellular glycolysis(63). 2-DG can also be used as an adjuvant to other anticancer therapies without the common side effects associated with cytotoxic doses. LDHA inhibitors such as GSK2837808A reduce tumor growth in xenografts but can exacerbate acidosis, necessitating combination therapy. CENP-N was confirmed to be a key gene for aerobic glycolysis in nasopharyngeal carcinoma (NPC) cells, and GSK2837808A can block the promotion of aerobic glycolysis in NPC cells induced by CENP-N overexpression, thereby inhibiting cancer progression(64).

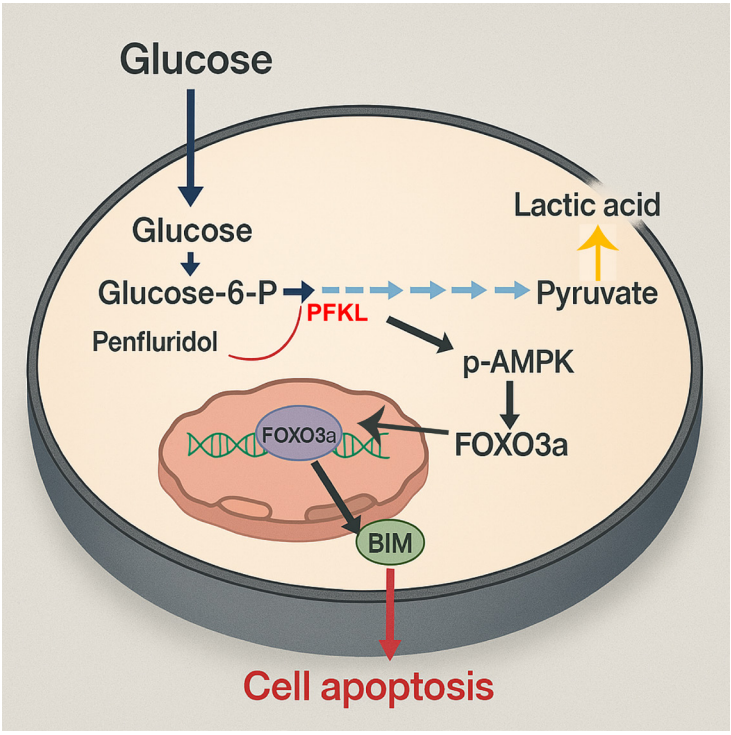

FIGURE 3
Pentaflupiridol inhibits glycolysis and tumorigenesis.

DOI 10.58832/ctr.2025.6.6.2

Pentafluridol inhibits glycolysis and induces apoptosis of tumor cells through a dual mechanism. First, it directly inhibits phosphofructokinase, a key enzyme in glycolysis, and reduces the conversion of glucose-6-phosphate to subsequent metabolic steps, thereby reducing the production of pyruvate and lactate, blocking the way for tumor cells to obtain energy through the Warburg effect. Secondly, pentafluridol activates AMPK (p-AMPK), and phosphorylated AMPK upregulates the expression of the pro-apoptotic protein BIM by enhancing the activity of the transcription factor FOXO3a, ultimately triggering apoptosis of tumor cells.

3.2 Immunometabolic synergy

Glycolysis blockade can reverse T cell exhaustion and enhance anti-PD-1/PD-L1 immunotherapy. For example, previous studies have improved the efficacy of anti-PD-1 immunotherapy in melanoma cells by inhibiting the TCA cycle, affecting ATF3-mediated PD-L1 expression and glycolysis. Lactate generated by aerobic glycolysis is associated with resistance to anti-PD-1/PD-L1 therapy. Lactate accumulation induces the differentiation and activation of M2 macrophages and Treg cells, inhibits the antigen presentation function of DCs, the activation of T cells and NK cells, and promotes the immune escape of tumor cells, thereby forming an immunosuppressive TME and affecting the efficacy of anti-PD-1/PD-L1 therapy. Elevated lactate concentrations also directly interact with intracellular GLUT10 motifs, thereby reducing glucose uptake and anti-tumor function of CD8+ T cells. In addition, in mouse models, LDHA inhibition increased CD8+ T cell infiltration in tumors, resulting in synergistic tumor regression(65). Targeted metabolism combined with immunotherapy can help improve the effectiveness of immunotherapy. Lactate content in the TME can be reduced by affecting key enzymes in lactate metabolism such as LDH or directly consuming lactate. Therefore, nanovaccines have been developed to deliver CaCO3 to tumor tissue to consume lactate(66).

4. Challenges and future perspectives

Therapeutic targeting of glycolytic reprogramming in cancer continues to face multifaceted challenges that require innovative solutions. Despite advances in understanding Warburg effect-driven carcinogenesis, translation of preclinical findings into clinically actionable strategies remains hampered by tumor heterogeneity, metabolic plasticity, and microenvironmental complexity. Current inhibitors targeting glycolytic enzymes such as HK2, PKM2, or LDHA often exhibit limited efficacy due to compensatory activation of alternative metabolic pathways. For example, inhibition of glycolysis often induces adaptive reliance on glutaminolysis or fatty acid oxidation, underscoring the need for combinatorial approaches that simultaneously disrupt parallel energy supply mechanisms(67). Furthermore, the dual roles of glycolytic intermediates in bioenergetics and epigenetic regulation complicate selective pathway inhibition without inducing genome-wide dysregulation.

A key hurdle lies in the dynamic interplay between tumor cells and stromal components within the metabolic niche. Immune cells, fibroblasts, and endothelial cells engage in competitive nutrient consumption while secreting metabolites that reshape therapeutic sensitivity(68). This crosstalk not only exacerbates resistance but also obscures the boundaries of cell-autonomous versus microenvironment-driven glycolytic dependence. Single-cell multi-omics and spatially resolved metabolomics may help unravel these interactions, but technical limitations remain in capturing real-time metabolic fluxes in vivo. Furthermore, the lack of predictive biomarkers for glycolytic addiction hampers patient stratification(69). While elevated FDG-PET affinity or serum lactate levels provide indirect evidence, they cannot distinguish between driving metabolic vulnerability and passenger effects.

Clinical translation of glycolytic inhibitors is further complicated by on-target toxicity arising from the physiological role of glycolysis in normal tissues. Isoform-specific targeting (exploiting differential expression of metabolic enzymes between malignant and healthy cells) has shown promise but requires deeper mechanistic validation(70). For example, selective inhibition of

DOI 10.58832/ctr.2025.6.6.2

tumor-enriched PKM2 isoforms while sparing ubiquitously expressed PKM1 requires precise structural biology insights to avoid off-target effects. Emerging strategies (such as prodrug activation in hypoxic environments or nanoparticle-mediated targeted delivery) can enhance the therapeutic window(71), but scalability and pharmacokinetic optimization remain unresolved. Future studies must address the complexity of metabolic crosstalk and tumor adaptation mechanisms to maximize therapeutic success. A deeper understanding of intratumoral metabolic heterogeneity, coupled with innovative drug development strategies, will pave the way for effective glycolysis-targeted therapies.

Conclusion

Glycolytic reprogramming is one of the important mechanisms by which cancer cells adapt to the harsh microenvironment and promote malignant progression. By deeply studying the molecular mechanisms of the glycolytic pathway and its association with the malignant phenotype of cancer, we can better understand the metabolic vulnerability of cancer and develop new therapeutic strategies targeting these vulnerabilities. Glycolytic reprogramming represents a vulnerability and adaptive shield in cancer biology. Although significant progress has been made in targeting metabolic enzymes and microenvironmental crosstalk, overcoming tumor heterogeneity and plasticity remains critical. Future studies should further explore the interactions between glycolysis and other metabolic pathways, and how these metabolic changes affect cancer immune escape and drug resistance mechanisms, providing new ideas and directions for the precision treatment of cancer.

References

1. Yan L, Raj P, Yao W, Ying H. Glucose metabolism in pancreatic cancer. Cancers. 2019;11(10):1460.

2. Ediriweera MK, Jayasena S. The role of reprogrammed glucose metabolism in cancer. Metabolites. 2023;13(3):345.

3. Spencer NY, Stanton RC, editors. The Warburg effect, lactate, and nearly a century of trying to cure cancer. Seminars in nephrology; 2019: Elsevier.

4. Niu N, Ye J, Hu Z, Zhang J, Wang Y. Regulative roles of metabolic plasticity caused by mitochondrial oxidative phosphorylation and glycolysis on the initiation and progression of tumorigenesis. International Journal of Molecular Sciences. 2023;24(8):7076.

5. Tian H, Zhu X, Lv Y, Jiao Y, Wang G. Glucometabolic reprogramming in the hepatocellular carcinoma microenvironment: cause and effect. Cancer Management and Research. 2020:5957-74.

6. Ge T, Gu X, Jia R, Ge S, Chai P, Zhuang A, et al. Crosstalk between metabolic reprogramming and epigenetics in cancer: updates on mechanisms and therapeutic opportunities. Cancer Communications. 2022;42(11):1049-82.

7. Sun F, Li W, Du R, Liu M, Cheng Y, Ma J, et al. Impact of glycolysis enzymes and metabolites in regulating DNA damage repair in tumorigenesis and therapy. Cell Communication and Signaling. 2025;23(1):44.

8. Crispo F, Condelli V, Lepore S, Notarangelo T, Sgambato A, Esposito F, et al. Metabolic dysregulations and epigenetics: a bidirectional interplay that drives tumor progression. Cells. 2019;8(8):798.

9. Li S, Hao L, Hu X. Natural products target glycolysis in liver disease. Frontiers in Pharmacology. 2023;14:1242955.

10. Afonso J, Gonçalves C, Costa M, Ferreira D, Santos L, Longatto-Filho A, et al. Glucose metabolism reprogramming in bladder cancer: hexokinase 2 (HK2) as prognostic biomarker and target for bladder cancer therapy. Cancers. 2023;15(3):982.

11. Yadav D, Yadav A, Bhattacharya S, Dagar A, Kumar V, Rani R, editors. GLUT and HK: two primary and essential key players in tumor glycolysis. Seminars in cancer biology; 2024: Elsevier.

12. Liu B, Lu Y, Taledaohan A, Qiao S, Li Q, Wang Y. The Promoting Role of HK II in Tumor Development and the Research Progress of Its Inhibitors. Molecules. 2023;29(1):75.

13. Zhu X, Du J, Gu Z. Circ-PVT1/miR-106a-5p/HK2 axis regulates cell growth, metastasis and glycolytic metabolism of oral squamous cell carcinoma. Molecular and Cellular Biochemistry. 2020;474(1):147-58.

14. Icard P, Coquerel A, Wu Z, Gligorov J, Fuks D, Fournel L, et al. Understanding the central role of citrate in the metabolism of cancer cells and tumors: an update. International journal of molecular sciences. 2021;22(12):6587.

15. Tian R-F, Li X-F, Xu C, Wu H, Liu L, Wang L-H, et al. SiRNA targeting PFK1 inhibits proliferation and migration and enhances radiosensitivity by suppressing glycolysis in colorectal cancer. American journal of translational research. 2020;12(9):4923.

16. Kashyap A, Umar SM, Dev JR A, Mathur SR, Gogia A, Batra A, et al. Combination of 3PO analog PFK15 and siPFKL efficiently suppresses

DOI 10.58832/ctr.2025.6.6.2

the migration, colony formation ability, and PFK-1 activity of triple-negative breast cancers by reducing the glycolysis. Journal of Cellular Biochemistry. 2023;124(9):1259-72.

17. Li J, Zhang S, Liao D, Zhang Q, Chen C, Yang X, et al. Overexpression of PFKFB3 promotes cell glycolysis and proliferation in renal cell carcinoma. BMC cancer. 2022;22(1):83.

18. Kotowski K, Rosik J, Machaj F, Supplitt S, Wiczew D, Jabłońska K, et al. Role of PFKFB3 and PFKFB4 in cancer: genetic basis, impact on disease development/progression, and potential as therapeutic targets. Cancers. 2021;13(4):909.

19. Xing J, Jia Z, Xu Y, Chen M, Yang Z, Chen Y, et al. KLF9 (Kruppel Like Factor 9) induced PFKFB3 (6-Phosphofructo-2-Kinase/Fructose-2, 6-Biphosphatase 3) downregulation inhibits the proliferation, metastasis and aerobic glycolysis of cutaneous squamous cell carcinoma cells. Bioengineered. 2021;12(1):7563-76.

20. Ishfaq M, Bashir N, Riaz SK, Manzoor S, Khan JS, Bibi Y, et al. Expression of HK2, PKM2, and PFKM is associated with metastasis and late disease onset in breast cancer patients. Genes. 2022;13(3):549.

21. Ren J, Li W, Pan G, Huang F, Yang J, Zhang H, et al. miR-142-3p modulates cell invasion and migration via PKM2-mediated aerobic glycolysis in colorectal cancer. Analytical cellular pathology. 2021;2021(1):9927720.

22. Du L, Dou K, Zhang D, Xia H, Liang N, Wang N, et al. MiR-19a-3p Promotes Aerobic Glycolysis in Ovarian Cancer Cells via IGFBP3/PI3K/AKT Pathway. Folia Biologica. 2023;69(5/6):163-72.

23. Yu Y, Liang Y, Xie F, Zhang Z, Zhang P, Zhao X, et al. Tumor-associated macrophage enhances PD-L1-mediated immune escape of bladder cancer through PKM2 dimer-STAT3 complex nuclear translocation. Cancer Letters. 2024;593:216964.

24. Mishra D, Banerjee D. Lactate dehydrogenases as metabolic links between tumor and stroma in the tumor microenvironment. Cancers. 2019;11(6):750.

25. Wang Q, Fan W, Liang B, Hou B, Jiang Z, Li C. YY1 transcription factor induces proliferation and aerobic glycolysis of neuroblastoma cells via LDHA regulation. Experimental and Therapeutic Medicine. 2022;25(1):37.

26. Naik A, Decock J. Lactate metabolism and immune modulation in breast cancer: a focused review on triple negative breast tumors. Frontiers in Oncology. 2020;10:598626.

27. Otto AM. Small is beautiful–a glycolytic metabolite signals mTORC1 activation in cancer cell metabolism. Signal transduction and targeted therapy. 2020;5(1):259.

28. Liu P, Sun S-J, Ai Y-J, Feng X, Zheng Y-M, Gao Y, et al. Elevated nuclear localization of glycolytic enzyme TPI1 promotes lung adenocarcinoma and enhances chemoresistance. Cell Death & Disease. 2022;13(3):205.

29. Duan Y, Li J, Wang F, Wei J, Yang Z, Sun M, et al. Protein modifications throughout the lung cancer proteome unravel the cancer-specific regulation of glycolysis. Cell Reports. 2021;37(12).

30. Bonanomi M, Salmistraro N, Fiscon G, Conte F, Paci P, Bravatà V, et al. Transcriptomics and metabolomics integration reveals redox-dependent metabolic rewiring in breast cancer cells. Cancers. 2021;13(20):5058.

31. Yang R, Zhang G, Dong Z, Wang S, Li Y, Lian F, et al. Homeobox A3 and KDM6A cooperate in transcriptional control of aerobic glycolysis and glioblastoma progression. Neuro-oncology. 2023;25(4):635-47.

32. Moldogazieva NT, Mokhosoev IM, Terentiev AA. Metabolic heterogeneity of cancer cells: an interplay between HIF-1, GLUTs, and AMPK. Cancers. 2020;12(4):862.

33. Vallée A, Lecarpentier Y, Vallée J-N. The key role of the WNT/β-catenin pathway in metabolic reprogramming in cancers under normoxic conditions. Cancers. 2021;13(21):5557.

34. Tang Y, Li W, Qiu L, Zhang X, Zhang L, Miyagishi M, et al. The p52-ZER6/G6PD axis alters aerobic glycolysis and promotes tumor progression by activating the pentose phosphate pathway. Oncogenesis. 2023;12(1):17.

35. Miranda-Galvis M, Teng Y. Targeting hypoxia-driven metabolic reprogramming to constrain tumor progression and metastasis. International journal of molecular sciences. 2020;21(15):5487.

36. Singh L, Nair L, Kumar D, Arora MK, Bajaj S, Gadewar M, et al. Hypoxia induced lactate acidosis modulates tumor microenvironment and lipid reprogramming to sustain the cancer cell survival. Frontiers in Oncology. 2023;13:1034205.

37. Li Z, Wang Q, Huang X, Yang M, Zhou S, Li Z, et al. Lactate in the tumor microenvironment: A rising star for targeted tumor therapy. Frontiers in nutrition. 2023;10:1113739.

38. Tao H, Zhong X, Zeng A, Song L. Unveiling the veil of lactate in tumor-associated macrophages: a successful strategy for immunometabolic therapy. Frontiers in Immunology. 2023;14:1208870.

39. Romani P, Valcarcel-Jimenez L, Frezza C, Dupont S. Crosstalk between mechanotransduction and metabolism. Nature Reviews Molecular Cell Biology. 2021;22(1):22-38.

40. Gorski T, De Bock K. Metabolic regulation of exercise-induced angiogenesis. Vascular Biology. 2019;1(1):H1-H8.

41. Chetta P, Sriram R, Zadra G. Lactate as key metabolite in prostate cancer progression: what are the clinical implications? Cancers. 2023;15(13):3473.

42. Hao Z-N, Tan X-P, Zhang Q, Li J, Xia R, Ma Z. Lactate and Lactylation: Dual Regulators of T-Cell-Mediated Tumor Immunity and Immunotherapy. Biomolecules. 2024;14(12):1646.

43. Peng X, He Z, Yuan D, Liu Z, Rong P. Lactic acid: The culprit behind the immunosuppressive microenvironment in hepatocellular carcinoma. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2024:189164.

44. Dong S, Li W, Li X, Wang Z, Chen Z, Shi H, et al. Glucose metabolism and tumour microenvironment in pancreatic cancer: a key link in cancer progression. Frontiers in Immunology. 2022;13:1038650.

45. Iozzo M. Lactate and tumor microenvironment: how prostate cancer and melanoma rely on this oncometabolite. 2023.

46. Lin J, Fang W, Xiang Z, Wang Q, Cheng H, Chen S, et al. Glycolytic enzyme HK2 promotes PD-L1 expression and breast cancer cell immune evasion. Frontiers in Immunology. 2023;14:1189953.

47. Xi Y, Shen Y, Chen L, Tan L, Shen W, Niu X. Exosome-mediated metabolic reprogramming: Implications in esophageal carcinoma progression and tumor microenvironment remodeling. Cytokine & Growth Factor Reviews. 2023;73:78-92.

48. Demkow U. Neutrophil extracellular traps (NETs) in cancer invasion, evasion and metastasis. Cancers. 2021;13(17):4495.

49. Bhardwaj V, He J. Reactive oxygen species, metabolic plasticity, and drug resistance in cancer. International journal of molecular sciences. 2020;21(10):3412.

50. Xia S, Pan Y, Liang Y, Xu J, Cai X. The microenvironmental and metabolic aspects of sorafenib resistance in hepatocellular carcinoma. EBioMedicine. 2020;51.

51. Arundhathi JD, Mathur SR, Gogia A, Deo S, Mohapatra P, Prasad CP. Metabolic changes in triple negative breast cancer-focus on aerobic glycolysis. Molecular Biology Reports. 2021;48(5):4733-45.

52. Papadaki C, Manolakou S, Lagoudaki E, Pontikakis S, Ierodiakonou D, Vogiatzoglou K, et al. Correlation of PKM2 and CD44 protein expression with poor prognosis in platinum-treated epithelial ovarian cancer: a retrospective study. Cancers. 2020;12(4):1013.

DOI 10.58832/ctr.2025.6.6.2

53. Fan Y, Ou L, Fan J, Li L, Wang X, Niu L, et al. PLCε regulates metabolism and metastasis signaling via HIF-1α/MEK/ERK pathway in prostate cancer. Journal of Cellular Physiology. 2020;235(11):8546-57.

54. Wang EJ-Y, Chen I-H, Kuo BY-T, Yu C-C, Lai M-T, Lin J-T, et al. Alterations of cytoskeleton networks in cell fate determination and cancer development. Biomolecules. 2022;12(12):1862.

55. Xu L, Sun J, Guo J, Guo S, Li J, Tang Y, et al. Transcriptional factor KLF9 overcomes 5-fluorouracil resistance in breast cancer via PTEN-dependent regulation of aerobic glycolysis. Journal of Chemotherapy. 2024:1-12.

56. Zhuang L, Zhang B, Liu X, Lin L, Wang L, Hong Z, et al. Exosomal miR-21-5p derived from cisplatin-resistant SKOV3 ovarian cancer cells promotes glycolysis and inhibits chemosensitivity of its progenitor SKOV3 cells by targeting PDHA1. Cell Biology International. 2021;45(10):2140-9.

57. Wang C, Shi Z-Z. Exosomes in esophageal cancer: function and therapeutic prospects. Medical Oncology. 2024;42(1):18.

58. Zhu Y, Li F, Wan Y, Liang H, Li S, Peng B, et al. Cancer-secreted exosomal MiR-620 inhibits ESCC aerobic glycolysis via FOXM1/HER2 pathway and promotes metastasis. Frontiers in Oncology. 2022;12:756109.

59. Zhang Y, Zhao L, Yang S, Cen Y, Zhu T, Wang L, et al. CircCDKN2B-AS1 interacts with IMP3 to stabilize hexokinase 2 mRNA and facilitate cervical squamous cell carcinoma aerobic glycolysis progression. Journal of experimental & clinical cancer research. 2020;39:1-18.

60. Kawatani M, Aono H, Hiranuma S, Shimizu T, Muroi M, Ogawa N, et al. Identification of a small-molecule glucose transporter inhibitor, glutipyran, that inhibits cancer cell growth. ACS Chemical Biology. 2021;16(8):1576-86.

61. JIAJUN C, HAR YP, NG ZX. Research Progress on the Antitumor Mechanism of Penfluridol. Medicine. 2024;4(2).

62. Wang L, Yang Q, Peng S, Liu X. The combination of the glycolysis inhibitor 2-DG and sorafenib can be effective against sorafenib-tolerant persister cancer cells. OncoTargets and therapy. 2019:5359-73.

63. Fujita M, Imadome K, Somasundaram V, Kawanishi M, Karasawa K, Wink DA. Metabolic characterization of aggressive breast cancer cells exhibiting invasive phenotype: impact of non-cytotoxic doses of 2-DG on diminishing invasiveness. BMC cancer. 2020;20:1-13.

64. Qi C-L, Huang M-L, Zou Y, Yang R, Jiang Y, Sheng J-F, et al. The IRF2/CENP-N/AKT signaling axis promotes proliferation, cell cycling and apoptosis resistance in nasopharyngeal carcinoma cells by increasing aerobic glycolysis. Journal of Experimental & Clinical Cancer Research. 2021;40(1):390.

65. Tang Y, Gu S, Zhu L, Wu Y, Zhang W, Zhao C. LDHA: The Obstacle to T cell responses against tumor. Frontiers in Oncology. 2022;12:1036477.

66. Fu B, Hu J, Yu A, Wang Y. Therapeutic nanovaccines reshape the metabolic and immune microenvironment for enhancing immunotherapy of primary and lymphatic metastatic tumors. Advanced Functional Materials. 2024;34(12):2307823.

67. Goetzman ES, Prochownik EV. The role for Myc in coordinating glycolysis, oxidative phosphorylation, glutaminolysis, and fatty acid metabolism in normal and neoplastic tissues. Frontiers in endocrinology. 2018;9:129.

68. Gupta S, Roy A, Dwarakanath BS. Metabolic cooperation and competition in the tumor microenvironment: implications for therapy. Frontiers in oncology. 2017;7:68.

69. Reece AS, Wang W, Hulse GK. Pathways from epigenomics and glycobiology towards novel biomarkers of addiction and its radical cure. Medical hypotheses. 2018;116:10-21.

70. Marczyk M, Gunasekharan V, Casadevall D, Qing T, Foldi J, Sehgal R, et al. Comprehensive analysis of metabolic isozyme targets in cancer. Cancer research. 2022;82(9):1698-711.

71. Hamdy NM, Eskander G, Basalious EB. Insights on the dynamic innovative tumor targeted-nanoparticles-based drug delivery systems activation techniques. International Journal of Nanomedicine. 2022;17:6131.