



“GLUCOSE METABOLIC REPROGRAMMING IN CANCER CELLS: MOLECULAR BASIS, REGULATORY NETWORKS, AND THERAPEUTIC OPPORTUNITIES”

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<https://doi.org/10.5281/zenodo.18954529>

ARTICLE INFO

Qabul qilindi: 07-mart 2026 yil

Ma'qullandi: 09-mart 2026 yil

Nashr qilindi: 11-mart 2026 yil

KEYWORDS

cancer metabolism, Warburg effect, glycolysis, oncogenes, metabolic reprogramming, glucose, transporter.

ABSTRACT

Metabolic reprogramming is a defining hallmark of cancer, enabling malignant cells to sustain rapid proliferation, resist apoptosis, and adapt to hostile microenvironments. One of the most prominent metabolic alterations is the preferential utilization of aerobic glycolysis, known as the Warburg effect. Despite its lower ATP yield compared to oxidative phosphorylation, glycolysis provides essential metabolic intermediates required for anabolic growth and redox homeostasis. This review examines the molecular mechanisms underlying glucose metabolic reprogramming in cancer cells, including the roles of oncogenes, tumor suppressors, hypoxia signaling, and key glycolytic enzymes. Furthermore, the clinical implications of altered glucose metabolism are discussed, highlighting its utility in diagnostic imaging and targeted therapeutic strategies. Understanding cancer glucose metabolism provides critical insights into tumor biology and reveals novel avenues for precision oncology.

Introduction

Cancer is characterized not only by genetic mutations but also by profound metabolic alterations that support uncontrolled cell proliferation. Unlike normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation (OXPHOS) for ATP generation, cancer cells exhibit increased glucose uptake and preferentially convert glucose into lactate, even under normoxic conditions. This metabolic phenotype, first described by Otto Warburg in 1924, is now recognized as aerobic glycolysis or the Warburg effect (Warburg, 1956).

Main part

Although aerobic glycolysis produces significantly less ATP than oxidative phosphorylation (2 ATP vs. approximately 36 ATP per glucose molecule), it provides essential

intermediates for nucleotide synthesis, amino acid production, and lipid biosynthesis. These anabolic processes are crucial for rapidly dividing cancer cells (Vander Heiden et al., 2009).

Recent advances in cancer biology have demonstrated that metabolic reprogramming is not merely a consequence of malignant transformation but a regulated process driven by oncogenic signaling pathways and tumor suppressor gene dysfunction.

Increased Glucose Uptake and Transporter Regulation

One of the earliest metabolic changes observed in cancer cells is increased glucose uptake. This is primarily mediated by overexpression of facilitative glucose transporters, particularly GLUT1 and GLUT3.

GLUT1 expression is upregulated in many cancers, including lung cancer, breast cancer, and glioblastoma (Zhao et al., 2013). Increased GLUT expression ensures continuous glucose supply necessary to sustain elevated glycolytic flux.

This process is regulated by oncogenic pathways including:

PI3K/AKT pathway

MYC oncogene activation

HIF-1 α stabilization

Loss of p53 tumor suppressor function

Activation of PI3K/AKT signaling promotes glucose transporter translocation to the plasma membrane and enhances glycolytic enzyme activity (Robey and Hay, 2009).

The Warburg Effect and Aerobic Glycolysis

Under normal physiological conditions, glucose is metabolized via glycolysis into pyruvate, which enters mitochondria and undergoes oxidative phosphorylation. However, cancer cells preferentially convert pyruvate into lactate through the action of lactate dehydrogenase A (LDHA), even when oxygen is available.

This metabolic shift provides several advantages:

1. Rapid ATP generation

Although inefficient, glycolysis produces ATP faster than oxidative phosphorylation.

2. Biosynthetic precursor generation Glycolytic intermediates are diverted into anabolic pathways, including:

* Pentose phosphate pathway (nucleotide synthesis)

* Lipid biosynthesis

* Amino acid synthesis

3. Maintenance of redox balance

Glycolysis supports NAD⁺ regeneration, essential for continued metabolic flux.

4. Tumor microenvironment modification

Lactate accumulation acidifies the extracellular environment, promoting invasion, angiogenesis, and immune evasion (Pavlova and Thompson, 2016).

Molecular Regulation of Glycolysis in Cancer

Multiple oncogenes and tumor suppressors regulate cancer metabolism.

Oncogenes

MYC promotes transcription of glycolytic enzymes, including:

* Hexokinase 2 (HK2)

* Phosphofructokinase (PFK)

* Enolase

MYC also enhances mitochondrial biogenesis and glutamine metabolism (Dang, 2012).

Hypoxia-inducible factor (HIF-1 α)

HIF-1 α plays a critical role in adapting cancer cells to hypoxic environments. It increases expression of:

- * GLUT1
- * LDHA
- * Glycolytic enzymes

HIF-1 α also inhibits mitochondrial respiration, reinforcing glycolytic dependence.

Tumor suppressor p53

The p53 protein normally inhibits glycolysis and promotes oxidative phosphorylation. Loss of p53 function results in enhanced glycolysis and tumor progression (Vousden and Ryan, 2009).

Role of Key Glycolytic Enzymes

Several glycolytic enzymes play critical roles in cancer progression.

Hexokinase II (HK2)

HK2 catalyzes the first step in glycolysis and is often overexpressed in tumors. It also inhibits apoptosis by interacting with mitochondrial membranes.

Pyruvate kinase M2 (PKM2)

PKM2 regulates metabolic flux and promotes anabolic metabolism. It also functions as a transcriptional regulator in cancer cells (Israelsen and Vander Heiden, 2015).

Lactate dehydrogenase A (LDHA)

LDHA converts pyruvate into lactate and supports continuous glycolytic flux.

Clinical Implications

Diagnostic applications

Cancer cells' increased glucose uptake forms the basis of FDG-PET imaging, widely used in oncology for tumor detection and staging.

Therapeutic targeting

Metabolic targeting represents a promising cancer treatment strategy.

Potential targets include:

- * GLUT inhibitors
- * HK2 inhibitors
- * LDHA inhibitors
- * PI3K/AKT/mTOR pathway inhibitors

These therapies aim to selectively disrupt cancer metabolism while sparing normal cells.

Discussion

Metabolic reprogramming provides cancer cells with significant survival advantages. Rather than maximizing ATP production efficiency, cancer cells prioritize biosynthesis and redox stability.

Importantly, metabolic plasticity allows cancer cells to adapt to environmental stress, including hypoxia and nutrient deprivation.

Targeting metabolic vulnerabilities represents a promising therapeutic approach. However, metabolic heterogeneity among tumors remains a significant challenge.

Future research should focus on identifying tumor-specific metabolic dependencies and developing precision metabolic therapies.

Conclusion

Glucose metabolic reprogramming is a fundamental hallmark of cancer that supports tumor growth, survival, and progression. The Warburg effect provides essential biosynthetic intermediates and facilitates adaptation to the tumor microenvironment.

Understanding the molecular mechanisms underlying altered glucose metabolism offers promising opportunities for diagnostic and therapeutic advancements in oncology.

Targeting cancer metabolism represents a rapidly evolving frontier in precision medicine.

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