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REVIEW ARTICLE

A Review of Metabolic Reprogramming in Cancer

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Abstract: Cancer cells exhibit distinct metabolic adaptations that support their rapid proliferation and survival in hostile microenvironments. The fundamental alterations in cellular metabolism, first described by Otto Warburg, have emerged as crucial hallmarks of cancer progression. Malignant cells preferentially utilize glucose through aerobic glycolysis while simultaneously maintaining oxidative phosphorylation, enabling them to meet their enhanced bioenergetic and biosynthetic demands. Recent advances in cancer metabolism research have unveiled complex metabolic networks involving glucose, glutamine, and lipid metabolism that contribute to tumor growth and metastasis. These metabolic alterations present unique therapeutic opportunities, as cancer cells often develop dependencies on specific metabolic pathways. Novel therapeutic strategies targeting key metabolic enzymes and transporters have shown promising results in preclinical and clinical studies. However, metabolic plasticity and heterogeneity within tumors pose significant challenges, often leading to drug resistance. The identification of reliable metabolic biomarkers has facilitated better patient stratification and treatment response monitoring. Emerging approaches combining metabolic inhibitors with conventional therapies, immunotherapy, or other targeted agents demonstrate enhanced efficacy. The continued elucidation of cancer metabolic reprogramming mechanisms and their clinical implications will be crucial for developing more effective therapeutic strategies and improving patient outcomes.

Keywords: Cancer metabolism; Warburg effect; Metabolic targeting; Drug resistance; Biomarkers.

1. Introduction

Cellular metabolism represents a complex network of biochemical reactions that maintain life processes through energy production and biomolecule synthesis. In cancer, these metabolic networks undergo profound alterations, enabling malignant cells to meet their heightened energetic and biosynthetic demands [1]. The significance of metabolic alterations in cancer has evolved from early observations of increased glucose fermentation to our current recognition of extensive metabolic rewiring as a fundamental characteristic of malignant transformation [2]. Historical perspectives trace back to Otto Warburg's seminal discoveries in the 1920s, which identified unusual glucose metabolism patterns in cancer cells [3]. Modern technological advances have since revealed that metabolic reprogramming extends far beyond glucose metabolism, encompassing complex alterations in amino acid utilization, lipid metabolism, and nucleotide synthesis [4]. These metabolic adaptations support not only energy generation but also provide building blocks for cellular components and maintain redox balance [5].

The molecular basis of metabolic reprogramming involves intricate interactions between oncogenic signaling pathways and metabolic networks. Mutations in key oncogenes and tumor suppressors, including PI3K, p53, and MYC, directly influence metabolic enzyme expression and activity [6]. Furthermore, the tumor microenvironment exerts significant pressure on cancer cell metabolism, driving adaptations to hypoxia, nutrient limitation, and pH changes [7].

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Recent advances in metabolomics, genomics, and proteomics have enhanced our ability to map cancer-specific metabolic alterations at unprecedented resolution [8]. These technological developments have revealed remarkable heterogeneity in metabolic profiles across different cancer types and even within individual tumors [9]. The emergence of single-cell analysis techniques has further highlighted the complexity of metabolic regulation in cancer, demonstrating significant metabolic plasticity and adaptation capabilities [10]. The clinical significance of cancer metabolism extends beyond basic biology to therapeutic applications. Metabolic alterations influence treatment responses, disease progression, and patient outcomes [11]. PET imaging utilizing glucose analogs represents a prime example of how understanding cancer metabolism translates into clinical practice [12]. Moreover, the identification of cancer-specific metabolic vulnerabilities has spurred the development of novel therapeutic strategies targeting key metabolic pathways [13]. The integration of metabolism with other cancer hallmarks, including sustained proliferation, metastasis, and immune evasion, highlights its central role in malignancy [14]. Metabolic interactions between cancer cells and the tumor microenvironment, including immune cells and stromal components, add another layer of complexity to cancer metabolism [15].

2. Cancer metabolism

2.1. Warburg Effect

The Warburg effect, characterized by increased glucose uptake and fermentation to lactate even in the presence of oxygen, remains a central paradigm in cancer metabolism [16]. This metabolic phenotype serves multiple purposes beyond ATP generation, providing essential precursors for biosynthetic pathways and creating a favorable microenvironment for tumor progression [17].

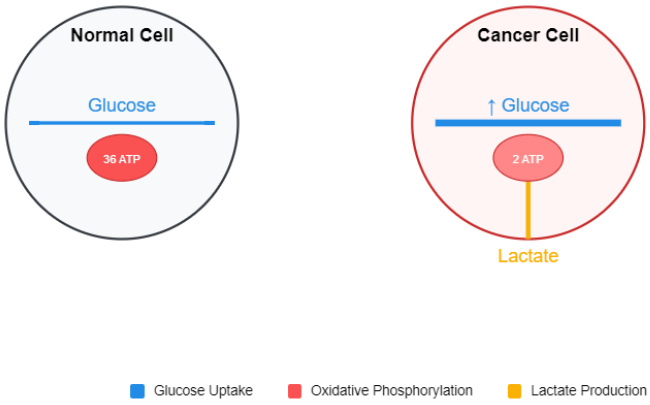

Figure 1. The Warburg Effect and Metabolic Reprogramming in Cancer Cells

2.1.1. Molecular Mechanisms

The molecular underpinnings of aerobic glycolysis involve coordinated changes in multiple cellular processes. Enhanced glucose uptake is facilitated by upregulation of glucose transporters, particularly GLUT1, through transcriptional activation by oncogenic signaling pathways [18]. The main glycolytic enzymes, including hexokinase II (HK-II), phosphofructokinase-1 (PFK1), and pyruvate kinase M2 (PKM2), undergo isoform switching and activity modulation to support the glycolytic phenotype [19].

Table 1. Metabolic Pathways Altered in Cancer

Metabolic Pathway	Enzymes/Transporters	Major Alterations	Clinical Significance
Glycolysis	HK2, PKM2, PFKFB3, GLUT1	↑ Glucose uptake, ↑ Lactate production	Diagnostic imaging (FDG-PET), therapeutic targeting
Glutamine Metabolism	GLS1, GLUD1, ASCT2	↑ Glutamine consumption, ↑ Anaplerosis	Glutamine addiction, therapeutic vulnerability
Lipid Metabolism	FASN, ACLY, ACC	↑ De novo lipogenesis, ↑ FAO	Membrane synthesis, energy source
One-Carbon Metabolism	SHMT1/2, MTHFD1/2	↑ Nucleotide synthesis, ↑ Methylation	Therapeutic targeting, biomarker potential
TCA Cycle	IDH1/2, SDH, FH	Altered flux, oncometabolite production	Diagnostic markers, targeted therapy

HK2: Hexokinase 2; PKM2: Pyruvate Kinase M2; GLUT1: Glucose Transporter 1;
GLS1: Glutaminase 1; FASN: Fatty Acid Synthase; IDH: Isocitrate Dehydrogenase

The role of mitochondria in the Warburg effect extends beyond reduced oxidative phosphorylation. Cancer cells maintain functional mitochondria, which participate in biosynthetic processes and redox homeostasis [20]. The preferential channeling of pyruvate to lactate, catalyzed by lactate dehydrogenase A (LDHA), supports NAD+ regeneration and contributes to microenvironmental acidification [21].

2.1.2. Regulation of Metabolic Reprogramming

Multiple signaling pathways orchestrate metabolic reprogramming in cancer cells. The PI3K/AKT/mTOR pathway promotes glucose uptake and glycolysis through direct phosphorylation of metabolic enzymes and transcriptional regulation [22]. Hypoxia-inducible factors (HIFs) play crucial roles by activating genes involved in glucose metabolism and angiogenesis [23].

The c-MYC oncogene serves as a master regulator of cancer metabolism, coordinating glucose and glutamine metabolism [24]. p53 mutations not only remove metabolic checkpoints but also actively promote metabolic rewiring through altered expression of metabolic enzymes and transporters [25].

2.1.3. Metabolic Consequences

Enhanced glycolysis generates various metabolic advantages for cancer cells. The rapid ATP production, although less efficient than oxidative phosphorylation, supports high-energy demands during proliferation [26]. Glycolytic intermediates feed into various biosynthetic pathways, including the pentose phosphate pathway for nucleotide synthesis and the serine biosynthesis pathway [27].

The production of lactate creates an acidic microenvironment that facilitates tumor invasion and immunosuppression [28]. Additionally, the reduced dependence on oxygen allows cancer cells to survive in hypoxic regions, contributing to therapy resistance [29].

2.1.4. Interconnection with Other Metabolic Pathways

The Warburg effect interfaces with numerous other metabolic pathways critical for cancer cell survival. Glutamine metabolism complements glucose utilization by providing carbon and nitrogen sources for biosynthesis [30]. Lipid metabolism undergoes significant alterations, with enhanced fatty acid synthesis supporting membrane biogenesis and signalling molecule production [31].

2.2. Metabolic Pathways in Cancer

2.2.1. Glutamine Metabolism

Glutamine serves as a critical nutrient in cancer cells, functioning beyond its role as a protein building block. Enhanced glutamine uptake through upregulated transporters, particularly SLC1A5 (ASCT2), supports various metabolic processes [32]. Glutaminase (GLS) catalyzes the conversion of glutamine to glutamate, which enters the TCA cycle through α-ketoglutarate, supporting cellular bioenergetics and biosynthesis [33].

Cancer cells exhibit "glutamine addiction," particularly in MYC-driven tumors, where glutamine metabolism supports redox homeostasis through NADPH production and glutathione synthesis [34]. The anaplerotic role of glutamine maintains TCA cycle functionality when glucose-derived carbons are diverted to biosynthetic pathways [35].

2.2.2. Lipid Metabolism

Altered lipid metabolism represents a crucial adaptation in cancer cells. De novo lipid synthesis is enhanced through increased expression of key enzymes including fatty acid synthase (FASN), ATP citrate lyase (ACLY), and acetyl-CoA carboxylase (ACC) [36]. These alterations support membrane biogenesis, energy storage, and signaling molecule production [37].

Fatty acid oxidation (FAO) provides an alternative energy source, particularly important during nutrient stress conditions. Enhanced FAO activity, regulated by carnitine palmitoyltransferase 1 (CPT1), supports cancer cell survival during glucose limitation [38].

2.2.3. One-Carbon Metabolism

One-carbon metabolism, encompassing folate and methionine cycles, plays essential roles in cancer progression. This pathway supports nucleotide synthesis, methylation reactions, and NADPH production [39]. Serine and glycine metabolism, closely linked to one-carbon metabolism, contribute to cellular redox state maintenance and epigenetic regulation [40].

2.2.4. Nucleotide Metabolism

Cancer cells require enhanced nucleotide synthesis to support rapid proliferation. Both de novo synthesis and salvage pathways undergo significant upregulation [41]. The pentose phosphate pathway provides ribose-5-phosphate for nucleotide synthesis while generating NADPH for redox balance [42].

2.2.5. TCA Cycle Alterations

The TCA cycle undergoes significant remodeling in cancer cells, shifting from its classical role in energy production to supporting biosynthetic processes [43]. Oncogenic mutations in TCA cycle enzymes, including IDH1/2 and SDH, produce oncometabolites that influence cellular signaling and epigenetic regulation [44].

2.2.6. Amino Acid Metabolism

Beyond glutamine, cancer cells exhibit altered metabolism of various amino acids. Serine and glycine synthesis pathways are frequently upregulated, supporting one-carbon metabolism and protein synthesis [45]. Branched-chain amino acid metabolism contributes to protein synthesis and serves as an alternative energy source [46].

2.2.7. Redox Metabolism

Cancer cells maintain complex redox balance mechanisms to manage increased oxidative stress. Enhanced NADPH production through multiple pathways supports antioxidant systems and biosynthetic processes [47]. Glutathione metabolism undergoes significant alterations to combat elevated reactive oxygen species levels [48]

2.3. Metabolic Vulnerabilities

2.3.1. Cancer Cell Dependencies

Metabolic adaptations in cancer cells create specific dependencies that represent potential therapeutic targets. Glucose addiction, characterized by enhanced sensitivity to glucose deprivation, emerges from the commitment to aerobic glycolysis [49]. Similarly, glutamine dependency varies across cancer types, with particular prominence in MYC-driven tumors [50].

Specific metabolic vulnerabilities arise from oncogenic signaling. KRAS-mutant cancers exhibit heightened dependence on pathways including macropinocytosis and glutamine metabolism [51]. PIK3CA mutations create dependencies on specific lipid metabolism pathways, offering therapeutic opportunities [52].

2.3.2. Synthetic Lethal Interactions

Metabolic synthetic lethality occurs when simultaneous disruption of complementary metabolic pathways leads to cell death. For instance, cells with defective mitochondrial function become critically dependent on glycolysis [53]. Understanding these interactions has revealed novel therapeutic strategies, particularly in cancers with specific genetic alterations [54].

2.3.3. Redox Vulnerabilities

Cancer cells maintain delicate redox balance, creating targetable vulnerabilities. Enhanced oxidative stress renders cancer cells dependent on antioxidant systems, particularly glutathione and thioredoxin pathways [55]. Disruption of NADPH production mechanisms can selectively impact cancer cell survival [56].

2.3.4. Nutrient Availability Dependencies

Spatial and temporal variations in nutrient availability create context-dependent vulnerabilities. Hypoxic regions within tumors force adaptation to limited oxygen availability, affecting metabolic pathway utilization [57]. Nutrient competition within the tumor microenvironment influences cellular dependencies and survival strategies [58].

2.3.5. Cell State-Specific Vulnerabilities

Different cellular states within tumors exhibit distinct metabolic vulnerabilities. Cancer stem cells often display unique metabolic requirements, including enhanced mitochondrial function [59]. Metastatic cells show specific dependencies during different stages of the metastatic cascade [60].

2.3.6. Therapeutic Window

Exploitable differences between normal and cancer cell metabolism create therapeutic windows. Cancer-specific isoform expression of metabolic enzymes offers opportunities for selective targeting [61]. Differential requirements for specific nutrients between normal and cancer cells can be therapeutically leveraged [62].

2.3.7. Microenvironmental Dependencies

The tumor microenvironment creates unique metabolic vulnerabilities. Acidic pH conditions influence metabolic pathway utilization and drug sensitivity [63]. Metabolic interactions between cancer cells and stromal components, including immune cells, present additional therapeutic opportunities [64].

2.3.8. Compensatory Mechanisms

Initial metabolic adaptations to therapeutic pressure can create new dependencies [65]. Sequential targeting of primary and compensatory pathways represents a promising therapeutic strategy [66]

3. Current treatment

3.1. Targeting Glucose Metabolism

Glycolysis inhibition represents a fundamental approach in metabolic targeting. 2-deoxy-D-glucose (2-DG), a glucose analog, competitively inhibits hexokinase, disrupting the initial step of glycolysis [67]. Lonidamine, targeting mitochondria-bound hexokinase II, shows enhanced efficacy in combination with conventional therapies [68].

Table 2. Current Metabolic Targeting Agents in Clinical Development

Drug Class	Example Compounds	Target	Clinical Phase	Cancer Types
Glycolysis Inhibitors	2-DG, Lonidamine	HK2, GLUT1	Phase II/III	Solid tumors
Glutaminase Inhibitors	CB-839, BPTES	GLS1	Phase II	TNBC, RCC
FASN Inhibitors	TVB-2640	FASN	Phase II	Solid tumors
IDH Inhibitors	Ivosidenib, Enasidenib	IDH1/2	FDA Approved	AML, Glioma
Metformin	Metformin HCl	Complex I	Phase III	Multiple

TNBC: Triple Negative Breast Cancer; RCC: Renal Cell Carcinoma

GLUT1 inhibition, using compounds such as WZB117 and BAY-876, reduces glucose uptake in cancer cells [69]. These agents demonstrate particular efficacy in tumors with high glucose dependence, though careful patient selection remains crucial [70].

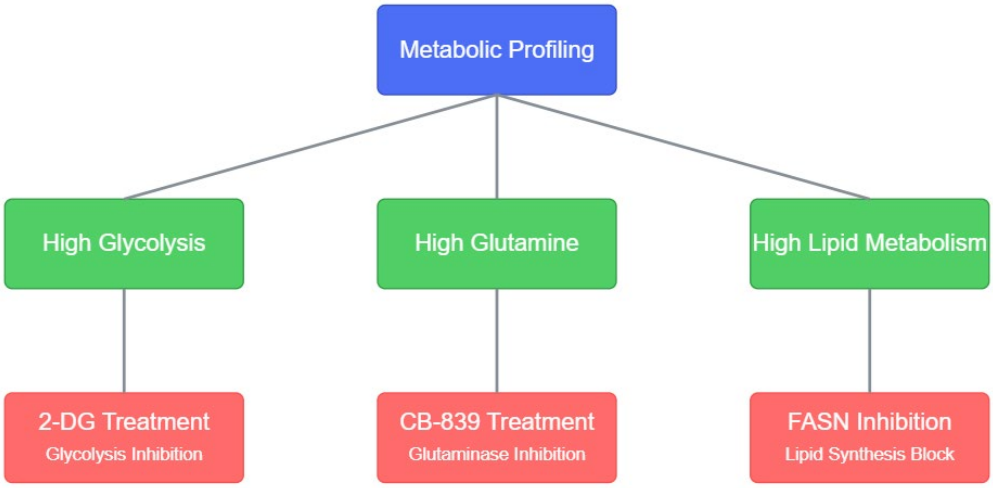

Figure 1. Metabolic Pathway Decision Tree for Therapeutic Targeting

3.2. Glutamine Metabolism Inhibitors

Glutaminase inhibitors have emerged as promising therapeutic agents. CB-839 (Telaglenastat), a selective GLS1 inhibitor, shows clinical efficacy in various cancer types [71]. Combination strategies with conventional chemotherapy or targeted agents enhance therapeutic outcomes [72].

Novel approaches targeting glutamine transporters, particularly ASCT2, demonstrate potential in preclinical models [73]. Dual inhibition of glutamine metabolism and complementary pathways addresses potential resistance mechanisms [74].

3.3. Lipid Metabolism Targeting

FASN inhibitors, including TVB-2640, target de novo lipid synthesis in cancer cells [75]. These agents show particular promise in lipid-dependent malignancies, with several compounds advancing through clinical trials [76].

Strategies targeting lipid uptake and fatty acid oxidation provide additional therapeutic opportunities. CPT1 inhibitors, limiting fatty acid oxidation, demonstrate efficacy in specific cancer contexts [77].

3.4. Metabolic Enzyme Inhibitors

IDH inhibitors, approved for IDH-mutant cancers, represent successful implementation of metabolism-targeted therapy [78]. Additional enzyme-specific inhibitors, targeting PKM2, LDHA, and other key metabolic enzymes, are under development [79].

3.5. Novel Delivery Approaches

Nanoparticle-based delivery systems enhance the efficacy of metabolic inhibitors [80]. Smart delivery platforms, responding to tumor-specific metabolic conditions, improve therapeutic targeting [81].

3.6. Combination Strategies

3.6.1. Integration with Standard Therapies

Metabolic inhibitors enhance the efficacy of conventional chemotherapy and radiation [82]. Careful timing and sequencing of combination approaches maximize therapeutic benefit while minimizing toxicity [83].

3.6.2. Immunotherapy Combinations

Metabolic targeting can enhance immunotherapy response through multiple mechanisms [84]. Modulation of tumor metabolism influences immune cell function and anti-tumor immunity [85].

3.6.3. Resistance Management Strategies

Dual targeting of primary and compensatory metabolic pathways prevents resistance development [86]. Adaptive treatment protocols, based on metabolic monitoring, optimize therapeutic outcomes [87].

3.6.4. Metabolism-Based Patient Selection

Metabolic profiling guides patient stratification for targeted therapies [88]. Integration of molecular and metabolic markers improves treatment selection and monitoring [89]

4. Imaging Biomarkers

4.1. Nuclear Medicine Approaches

18F-FDG PET imaging remains the gold standard for assessing glucose metabolism in tumors [90]. Advanced quantitative analysis methods enhance diagnostic accuracy and treatment response monitoring [91]. Novel radiotracers targeting specific metabolic pathways, including 11C-glutamine and 18F-acetate, provide complementary metabolic information [92].

4.2. Magnetic Resonance Spectroscopy

MR spectroscopy enables non-invasive assessment of metabolite profiles in tumors [93]. Dynamic nuclear polarization techniques enhance sensitivity for metabolic imaging [94]. Real-time monitoring of metabolic flux provides insights into treatment response [95].

4.3. Circulating Biomarkers

4.3.1. Metabolomics-Based Markers

Plasma metabolomic profiling reveals cancer-specific metabolic signatures [96]. Circulating metabolites serve as early detection markers and indicators of disease progression [97]. Integration of metabolomics with other molecular markers improves diagnostic accuracy [98].

4.3.2. Circulating Enzymes and Metabolic Products

Serum lactate dehydrogenase levels correlate with disease burden and prognosis [99]. Circulating fatty acids and amino acids reflect altered tumor metabolism [100]. Novel blood-based metabolic markers enable non-invasive monitoring [101].

4.4. Tissue-Based Biomarkers

4.4.1. Metabolic Enzyme Expression

Immunohistochemical analysis of key metabolic enzymes guides therapeutic decisions [102]. Spatial distribution of metabolic markers reveals intratumoral heterogeneity [103].

Table 3. Metabolic Biomarkers in Cancer

Biomarker Type	Examples	Detection Method	Clinical Application
Imaging	FDG uptake, Glutamine tracers	PET/CT, MRS	Diagnosis, monitoring
Circulating Metabolites	2-HG, Lactate, Glutamine	LC-MS, NMR	Disease monitoring
Enzyme Expression	PKM2, GLS1, FASN	IHC, Western blot	Prognosis, stratification
Genetic Markers	IDH1/2 mutations, PKM2 variants	NGS, PCR	Treatment selection
Metabolic Signatures	Glucose/glutamine ratio	Metabolomics	Response prediction

4.4.2. Metabolic Gene Signatures

Transcriptional profiles of metabolic pathways predict treatment response [104]. Integration of metabolic signatures with molecular subtypes enhances prognostication [105].

4.5. Novel Biomarkers

4.5.1. Single-Cell Metabolomics

Advanced technologies enable metabolic profiling at single-cell resolution [106]. Spatial metabolomics reveals metabolic heterogeneity within tumor microenvironments [107].

4.5.2. Real-Time Monitoring

Biosensor technologies enable continuous monitoring of metabolic parameters [108]. Implantable devices measure key metabolites in tumor environments [109].

4.6. Clinical Applications

4.6.1. Treatment Response Monitoring

Early metabolic changes predict therapeutic efficacy [110-114]. Dynamic monitoring guides treatment adaptation and resistance management [115].

4.6.2. Disease Progression Markers

Metabolic alterations signal disease recurrence and metastatic spread [116]. Integration of multiple metabolic markers improves progression monitoring [117].

5. Drug Resistance Mechanisms

5.1. Metabolic Adaptation

5.1.1. Primary Resistance Mechanisms

Cancer cells exhibit intrinsic metabolic flexibility, enabling rapid adaptation to metabolic inhibitors [118]. Alternative pathway activation maintains essential metabolic functions during therapeutic pressure [119]. Pre-existing metabolic heterogeneity contributes to treatment resistance [120].

5.1.2. Acquired Metabolic Resistance

Prolonged exposure to metabolic inhibitors induces compensatory pathway upregulation [121]. Epigenetic modifications alter metabolic enzyme expression patterns [122]. Mitochondrial dynamics and function undergo significant adaptations during resistance development [123].

Table 4. Resistance Mechanisms to Metabolic Targeting

Resistance Type	Mechanism	Example	Therapeutic Usage
Primary Resistance	Metabolic flexibility	Substrate switching	Combination therapy
Acquired Resistance	Pathway compensation	Alternative enzyme isoforms	Sequential targeting
Microenvironmental	Stromal support	CAF metabolic symbiosis	Microenvironment targeting
Genetic Adaptation	Enzyme mutations	IDH inhibitor resistance	Second-generation drugs
Phenotypic Plasticity	Cell state switching	EMT-mediated changes	Multi-modal therapy

CAF: Cancer-Associated Fibroblasts; EMT: Epithelial-Mesenchymal Transition; ICI: Immune Checkpoint Inhibitors

5.2. Molecular Mechanisms of Resistance

5.2.1. Signaling Pathway Alterations

Activation of PI3K/AKT/mTOR signaling promotes metabolic adaptation [124]. AMPK-mediated stress responses enable survival under metabolic pressure [125]. Enhanced HIF signaling facilitates metabolic reprogramming during treatment [126].

5.2.2. Transcriptional Regulation

Modified expression of metabolic enzymes through transcriptional adaptation [127]. Enhanced activity of metabolic master regulators, including MYC and PGC-1α [128]. Epigenetic modifications affect metabolic gene expression patterns [129].

5.3. Microenvironmental Factors

5.3.1. Stromal Cell Interactions

Cancer-associated fibroblasts provide metabolic support during therapy. Metabolic symbiosis between tumor and stromal cells promotes resistance [130].

5.3.2. Hypoxia-Mediated Resistance

Hypoxic regions foster resistance through metabolic adaptation. HIF-dependent metabolic reprogramming supports survival under therapy [131].

5.4. Transport-Mediated Resistance

5.4.1. Metabolite Transporter Modifications

Altered expression of nutrient transporters affects drug efficacy. Enhanced metabolite exchange between cellular compartments [132].

5.4.2. Drug Efflux Mechanisms

ATP-dependent transporters affect metabolic inhibitor distribution. Membrane composition changes influence drug uptake and retention [133].

5.5. Compensatory Metabolic Pathways

5.5.1. Alternative Substrate Utilization

Shift to alternative nutrient sources during pathway inhibition. Enhanced fatty acid oxidation compensates for glucose restriction [134].

5.5.2. Metabolic Network Rewiring

Reorganization of metabolic flux distributions. Development of bypass pathways maintaining essential functions [135].

5.6. Cell State Transitions

5.6.1. Phenotypic Plasticity

Transition to drug-tolerant persister states. Metabolic adaptation in cancer stem cell populations [136].

5.6.2. Stress-Induced Responses

Activation of survival pathways under metabolic stress. Enhanced autophagy and metabolic recycling mechanisms [137].

6. Clinical Applications

6.1. Resistance Monitoring

Metabolic biomarkers indicate emerging resistance. Real-time monitoring of metabolic adaptation [138].

6.2. Treatment Strategies

Sequential targeting of primary and compensatory pathways [139]. Rational combination approaches preventing resistance development [140].

Table 5. Recent Therapeutic Strategies in Cancer Metabolism

Strategy	Approach	Examples	Current Status
Combination Therapy	Metabolic + Standard care	CB-839 + Paclitaxel	Clinical trials
Immunometabolic	Metabolism + Immunotherapy	PKM2 inhibitors + ICIs	Early phase trials
Synthetic Lethality	Genetic vulnerability	PARP + Metabolic inhibitors	Preclinical
Smart Drug Delivery	Targeted nanoparticles	Metabolic-responsive carriers	Development
Metabolic Editing	CRISPR-based	Enzyme modification	Preclinical

7. Conclusion

Metabolic reprogramming in cancer involves interconnection between cellular pathways, microenvironmental factors, and systemic influences. The expanding knowledge of cancer metabolism has revealed numerous therapeutic opportunities, yet challenges remain in developing effective targeting strategies. The emergence of resistance mechanisms and metabolic plasticity necessitates innovative approaches, including combination therapies and precision medicine strategies. Advanced technologies in metabolomics, imaging, and artificial intelligence continue to enhance our understanding and therapeutic targeting capabilities. Combined usage of metabolic targeting with immunotherapy and conventional treatments shows promise for improving patient outcomes.

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