Targeting Cancer Metabolism With Small Molecules: A Review

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Abstract

Cancer metabolism has emerged as a promising area for therapeutic intervention, given the unique metabolic reprogramming that occurs in tumor cells. The targeting of cancer metabolism with small molecules offers a novel approach to disrupt the altered metabolic pathways that sustain cancer growth and survival. This research explores the development and application of small molecule inhibitors that specifically target key enzymes and pathways in cancer metabolism, such as glycolysis, the tricarboxylic acid cycle, and lipid metabolism. By inhibiting these critical metabolic routes, small molecules can effectively reduce tumor proliferation and enhance the efficacy of existing treatments. This study also discusses the challenges and opportunities in the design of selective and potent metabolic inhibitors, as well as their potential for personalized medicine. The findings underscore the importance of further research into metabolic vulnerabilities of cancer cells, paving the way for new, targeted cancer therapies.

Keywords: Cancer Metabolism, Small Molecules, Metabolic Reprogramming, Tumor Growth, Glycolysis Inhibition, Lipid Metabolism, Enzyme Inhibitors.

Cibler le métabolisme du cancer avec des petites molécules : Une revue

Résumé

Le métabolisme du cancer est devenu un domaine prometteur pour l'intervention thérapeutique, étant donné la reprogrammation métabolique unique qui se produit dans les cellules tumorales. Cibler le métabolisme du cancer avec des petites molécules offre une approche novatrice pour perturber les voies métaboliques altérées qui soutiennent la croissance et la survie du cancer. Cette recherche explore le développement et l'application d'inhibiteurs de petites molécules qui ciblent spécifiquement des enzymes et des voies clés du métabolisme du cancer, telles que la glycolyse, le cycle de l'acide tricarboxylique et le métabolisme des lipides. En inhibant ces voies métaboliques critiques, les petites molécules peuvent réduire efficacement la prolifération tumorale et améliorer l'efficacité des traitements existants. Cette étude aborde également les défis et les opportunités dans la conception d'inhibiteurs métaboliques sélectifs et puissants, ainsi que leur potentiel pour la médecine personnalisée. Les résultats soulignent l'importance de recherches supplémentaires sur les vulnérabilités métaboliques des cellules cancéreuses, ouvrant la voie à de nouvelles thérapies ciblées contre le cancer.

***Mots-clés** : Métabolisme du cancer, petites molécules, reprogrammation métabolique, croissance tumorale, inhibition de la glycolyse, métabolisme des lipides, inhibiteurs enzymatiques.*

ملخص

ظهر التمثيل الغذائي للسرطان كمجال واعد للتدخل العلاجي، بالنظر إلى إعادة البرمجة الأيضية الفريدة التي تحدث في الخلايا السرطانية. يوفر استهداف استقلاب السرطان بجزيئات صغيرة نهجًا جديدًا لتعطيل المسارات الأيضية المتغيرة التي تحافظ على نمو السرطان والبقاء على قيد الحياة. يستكشف هذا البحث تطوير وتطبيق مثبطات الجزيئات الصغيرة التي تستهدف على وجه التحديد الإنزيمات والمسارات الرئيسية في استقلاب السرطان، مثل تحلل السكر ودورة حمض ثلاثي الكربوكسيل واستقلاب الدهون. من خلال تثبيط طرق التمثيل الغذائي الحرجة هذه، يمكن للجزيئات الصغيرة أن تقلل بشكل فعال من تكاثر الورم وتعزز فعالية العلاجات الحالية. تناقش هذه الدراسة أيضًا التحديات والفرص في تصميم مثبطات التمثيل الغذائي الانتقائية والفعالة، بالإضافة إلى قدرتها على الطب الشخصي. تؤكد النتائج على أهمية إجراء مزيد من الأبحاث حول نقاط الضعف الأيضية للخلايا السرطانية، مما يمهد الطريق لعلاجات جديدة وموجهة للسرطان.

الكلمات الرئيسية: استقلاب السرطان، الجزيئات الصغيرة، إعادة البرمجة الأيضية، نمو الورم، تثبيط تحلل السكر، استقلاب الدهون، مثبطات الإنزيم.

Introduction

Cancer metabolism has emerged as a critical area of research, revealing how cancer cells adapt their metabolic pathways to support rapid growth and survival in hostile environments. Unlike normal cells, which primarily rely on oxidative phosphorylation for energy production, many cancer cells exhibit a preference for glycolysis, even in the presence of oxygen a phenomenon known as the Warburg effect (Warburg, 1956). This metabolic reprogramming not only provides ATP but also generates intermediates for biosynthesis, thus supporting the anabolic demands of proliferating tumors (Pavlova and Thompson, 2016).

Recent advances in small molecule inhibitors targeting specific metabolic pathways have opened new avenues for therapeutic intervention. For instance, inhibitors of key glycolytic enzymes, such as hexokinase and lactate dehydrogenase, have shown promise in preclinical models for reducing tumor growth and enhancing the efficacy of existing therapies (Zhao et al., 2021). Moreover, the modulation of mitochondrial metabolism through small molecules like metformin, traditionally used as an antidiabetic agent, has garnered attention for its potential to inhibit cancer cell proliferation and induce apoptosis (Fresneau et al., 2022).

With the increasing understanding of the interplay between cancer metabolism and tumor microenvironments, targeting metabolic vulnerabilities with small molecules represents a compelling strategy in cancer therapy. This review will discuss recent developments in small molecule interventions that target cancer metabolism, highlighting their mechanisms of action, therapeutic potential, and the challenges that lie ahead in translating these findings into clinical practice.

Cancer is a complex disease characterized not only by uncontrolled cell proliferation but also by profound alterations in cellular metabolism. This metabolic reprogramming is essential for cancer cells to sustain their rapid growth and survival, even in hostile environments such as low oxygen (hypoxia) or nutrient-deprived conditions. Understanding the metabolic shifts that cancer cells undergo is crucial for developing new therapeutic strategies, particularly in targeting metabolic pathways that are essential for tumor growth and progression.

One of the most well-known features of cancer metabolism is the Warburg effect, a phenomenon where cancer cells preferentially utilize glycolysis for energy production, even in the presence of sufficient oxygen. This is in stark

contrast to normal cells, which primarily rely on oxidative phosphorylation under aerobic conditions. Glycolysis in cancer cells leads to the production of lactate, which is then secreted, creating an acidic tumor micro environment that further promotes cancer cell invasion and immune evasion. While less efficient in terms of ATP production, glycolysis provides cancer cells with metabolic intermediates needed for biosynthesis and rapid growth. This metabolic reprogramming allows cancer cells to meet the increased demands for energy and biomass during uncontrolled proliferation.

Cancer cells exhibit a variety of metabolic adaptations beyond the well-known Warburg effect, including significant changes in lipid metabolism, amino acid metabolism, and nucleotide biosynthesis. These alterations are driven by mutations in oncogenes and tumor suppressor genes, which reprogram cellular metabolic networks to promote tumor growth and survival. This metabolic rewiring allows cancer cells to become less dependent on normal metabolic regulation and adapt to hostile conditions, facilitating their proliferation and progression (Pavlova and hompson, 2016).

These unique metabolic needs of cancer cells present opportunities for therapeutic interventions. Targeting key enzymes and pathways involved in cancer metabolism using small molecules has emerged as a potential strategy to selectively eliminate cancer cells without damaging normal tissues. Small molecule inhibitors can disrupt the upregulated metabolic pathways in cancer cells, such as glycolysis, fatty acid synthesis, or glutaminolysis, effectively cutting off their energy supply and impairing biosynthesis (Vander Heiden & DeBerardinis, 2017). Furthermore, targeting cancer metabolism with these inhibitors has shown potential to overcome resistance to conventional therapies and enhance the effectiveness of treatments like chemotherapy and immunotherapy (Ngo, Yang, & Ellis, 2019).

Mechanisms of Cancer Metabolism

Cancer metabolism is defined by significant reprogramming of multiple pathways, including glycolysis, oxidative phosphorylation (OXPHOS), fatty acid metabolism, and amino acid metabolism. This reprogramming is essential for supporting the increased proliferative and survival demands of cancer cells. Cancer cells demonstrate remarkable metabolic flexibility, enabling them to switch between these pathways depending on nutrient availability and oxygen levels, which helps them thrive in diverse microenvironments (Pavlova & Thompson, 2016). Understanding the biochemical mechanisms underlying these metabolic changes is key to identifying potential therapeutic targets.

Under normal physiological conditions, cells tightly regulate their metabolic processes, maintaining a balance between energy production, biosynthesis, and growth. This balance ensures that energy demands are met without compromising cellular function. However, cancer cells disrupt this balance through metabolic rewiring, prioritizing pathways that enhance their growth and survival. One prominent example is the shift toward aerobic glycolysis, known as the Warburg effect, where cancer cells preferentially generate energy through glycolysis even in the presence of oxygen (Vander Heiden et al., 2009). This allows cancer cells to meet their high energy and biosynthetic demands while generating metabolic intermediates needed for rapid proliferation.

In addition to glycolysis, cancer cells also alter OXPHOS, allowing for increased flexibility in energy production, particularly under nutrient-poor or hypoxic conditions (Martinez-Outschoorn et al., 2017). Fatty acid metabolism is reprogrammed as well, with many cancer cells upregulating fatty acid synthesis to support membrane production and energy storage, while also enhancing fatty acid oxidation when necessary to meet energy demands (Carracedo et al., 2013).

Amino acid metabolism, especially glutaminolysis, is another critical component of cancer metabolism. Glutamine serves as a key substrate for the tricarboxylic acid (TCA) cycle and provides nitrogen for nucleotide and amino acid biosynthesis (DeBerardinis & Cheng, 2010). Cancer cells often become dependent on glutamine to fuel anabolic processes and maintain redox balance, making glutamine metabolism a promising target for therapy.

Glycolysis and the Warburg Effect

One of the key metabolic adaptations in cancer cells is the Warburg effect. Normally, cells under aerobic conditions utilize oxidative phosphorylation (OXPHOS) in the mitochondria to produce ATP efficiently. However, cancer cells preferentially rely on glycolysis for ATP production, even when oxygen is available. This process is known as aerobic glycolysis.

$$\text{Glucose}(C_6H1_2O_6)+2NAD++2ADP+2Pi \rightarrow 2\text{Pyruvate}(C_3H4O_3)+2NADH+2ATP+2H_2O$$

Overall reaction of oxidative phosphorylation

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 36ATP$$

OXPHOS is highly efficient, generating much more ATP per glucose molecule than glycolysis. Some cancers, particularly those with cancer stem cells or in environments with limited glucose, continue to rely on OXPHOS to meet

Even though glycolysis produces only 2 ATP molecules per glucose, compared to 36 ATP molecules from oxidative phosphorylation, cancer cells favor glycolysis due to its faster rate and ability to generate biosynthetic intermediates. For example, intermediates like dihydroxyacetone phosphate (DHAP) are diverted into lipid biosynthesis, while glucose-6-phosphate (G6P) enters the pentose phosphate pathway to produce ribose-5-phosphate for nucleotide synthesis.

Lactate production (end product of glycolysis under the Warburg effect)

$$\text{Pyruvate}+NADH+H+\rightarrow\text{Lactate}+NAD+$$

Lactate is exported from the cancer cell, acidifying the tumor microenvironment, promoting invasion, and suppressing immune responses. This entire glycolytic pathway is often upregulated in cancer cells due to the activation of oncogenes like MYC and RAS and the inactivation of tumor suppressors like p53.

Oxidative Phosphorylation

Despite the shift to glycolysis, many cancer cells retain functional oxidative phosphorylation (OXPHOS). OXPHOS takes place in the mitochondria, where electrons are transferred through the electron transport chain (ETC), ultimately reducing oxygen to water and driving the phosphorylation of ADP to produce ATP.

their energy demands. In these cells, the switch between glycolysis and OXPHOS represents a form of metabolic plasticity, enabling cancer survival under fluctuating oxygen and nutrient levels.

Fatty Acid Metabolism

Fatty acid metabolism plays a critical role in cancer by providing the necessary lipids for membrane synthesis and serving as an alternative energy source through fatty acid oxidation (FAO). Many cancer cells upregulate fatty acid synthesis (FAS) to meet the demand for lipid biosynthesis required for rapid cell growth.

Fatty acid synthesis reaction (simplified)

$$\text{Acetyl-CoA} + 7\text{Malonyl CoA} + 14\text{NADPH} \rightarrow \text{Palmitate}(C_{16}H_{32}O_2) + 7CO_2 + 14NADP^+$$

The enzyme fatty acid synthase (FASN) catalyzes this reaction, producing palmitate, a 16-carbon saturated fatty acid that serves as the precursor for more complex lipids. Overexpression of FASN is common in many aggressive cancers and is associated with poor prognosis.

In addition to synthesis, cancer cells can also rely on fatty acid oxidation to generate ATP, particularly under nutrient-scarce conditions. In FAO, fatty acids are broken down in the mitochondria to acetyl-CoA, which enters the TCA cycle to produce ATP.

Beta-oxidation of fatty acids

$$\text{Palmitate} + 7\text{NAD}^+ + 7\text{FAD} + 7H_2O \rightarrow 8\text{Acetyl-CoA} + 7\text{NADH} + 7\text{FADH}_2$$

The acetyl-CoA produced then enters the citric acid cycle (TCA), contributing to ATP production via oxidative phosphorylation.

Amino Acid Metabolism

Amino acids play vital roles in cancer metabolism, beyond their function as building blocks for proteins. Glutamine is one of the most important amino acids in cancer cells, serving as both a carbon and nitrogen source. Cancer cells use glutaminolysis, where glutamine is converted to glutamate, which then enters the TCA cycle to fuel energy production and biosynthesis.

Glutaminolysis (initial step)

$$\text{Glutamine}(C5\ H10\ N2\ O3) + H_2O \rightarrow \text{Glutamate}(C_5H_9NO_4) + NH_3$$

Glutamate is further converted to α-ketoglutarate, a TCA cycle intermediate that helps sustain anabolic processes like nucleotide and lipid biosynthesis.

Conversion of glutamate to α-ketoglutarate

$$\text{Glutamate} + \text{NAD}^+ \rightarrow \alpha-\text{Ketoglutarate} + \text{NADH} + NH3$$

In addition to glutamine, cancer cells also upregulate the uptake of other amino acids, such as serine, which is essential for nucleotide synthesis and one-carbon metabolism. Some cancer cells, especially leukemias, rely heavily on asparagine for survival, which has led to the development of the enzyme asparaginase as a therapeutic approach to starve these cells of asparagine.

Metabolic Flexibility and Adaptability in Tumors

A hallmark of cancer metabolism is its **metabolic flexibility**, allowing cancer cells to adapt to the changing tumor microenvironment. This flexibility is crucial for tumor survival in conditions of fluctuating oxygen and nutrient levels, such as hypoxic or nutrient-deprived regions within a tumor. Under hypoxic conditions, cancer cells upregulate glycolysis and reduce their reliance on oxidative phosphorylation. Conversely, in regions with sufficient oxygen but limited glucose, they may switch to fatty acid oxidation or rely on amino acid metabolism (e.g., glutaminolysis) to meet their energy and biosynthetic needs. This adaptability is a major reason why tumors can be resistant to therapies targeting single metabolic pathways, as they can activate alternative routes to survive.

Small Molecule Inhibitors in Cancer Metabolism

Targeting cancer metabolism with small molecule inhibitors has gained significant interest as a therapeutic approach due to the metabolic reprogramming that distinguishes cancer cells from normal cells. By disrupting key metabolic pathways that cancer cells rely on for growth and survival, small molecule inhibitors offer a potential strategy to selectively kill cancer cells. This section will provide an overview of various small molecule targets in cancer metabolism, focusing on glycolysis, mitochondrial function, and fatty acid synthesis, along with preclinical and clinical evidence of their efficacy.

Small Molecule Targets in Metabolic Pathways

Cancer cells exhibit altered metabolic pathways, including increased glycolysis (Warburg effect), fatty acid synthesis, and mitochondrial reprogramming. Small molecule inhibitors are designed to target specific enzymes or pathways involved in these metabolic changes, blocking the cancer cells' ability to generate energy or produce building blocks needed for growth. The primary categories of these inhibitors include:

Glycolytic Enzyme Inhibitors

The glycolytic pathway is upregulated in many cancers to support their rapid growth, making it an attractive target for inhibition.

Hexokinase Inhibitors

Hexokinase (HK) is the enzyme that catalyzes the first step of glycolysis, converting glucose to glucose-6-phosphate (G6P). In cancer cells, hexokinase 2 (HK2) is often overexpressed and associated with mitochondrial membranes, where it helps drive glycolysis and prevent apoptosis.

$$\text{Glucose} + \text{ATP} \rightarrow \text{Glucose-6-phosphate (G6P)} + \text{ADP}$$

Inhibitors like 2-deoxyglucose (2-DG) mimic glucose and competitively inhibit hexokinase, reducing the production of G6P and thereby slowing glycolysis. 2-DG has shown efficacy in preclinical

studies, although its use is limited due to toxicity at higher doses.

Lactate Dehydrogenase (LDH) Inhibitors

Lactate dehydrogenase (LDH) catalyzes the conversion of pyruvate to lactate, a critical step in the Warburg effect that cancer cells rely on for energy production and to regenerate NAD^+ for continued glycolysis.

$$Pyruvate + NADH + H^+ \rightarrow Lactate + NAD^+$$

Inhibitors like FX11 specifically target LDH-A, the isoform predominant in cancer cells. By inhibiting LDH, these molecules prevent the regeneration of NAD^+, halting glycolysis and leading to cancer cell death under hypoxic conditions. LDH inhibitors have shown promise in preclinical models but require further investigation in clinical settings.

Mitochondrial Inhibitors

Mitochondrial function is essential for ATP production, reactive oxygen species (ROS) generation, and the regulation of apoptosis. Some cancers, particularly those resistant to glycolysis inhibitors, rely on mitochondrial oxidative phosphorylation (OXPHOS), making it a target for small molecule inhibitors.

Metformin

Metformin, widely used as an anti-diabetic drug, inhibits mitochondrial complex I of the electron transport chain (ETC), reducing ATP production and increasing AMP levels, which activates AMP-activated protein kinase (AMPK).

$$NADH + H^+ \text{ Coenzyme Q} \rightarrow NAD^+ + CoQH2$$

By inhibiting complex I, metformin reduces oxidative phosphorylation, making it harder for cancer cells to sustain energy production, particularly in glucose-deprived environments. Metformin has demonstrated anti-tumor effects in preclinical studies and is currently undergoing clinical trials for its use in cancer therapy, especially in combination with other agents.

Oligomycin

Oligomycin is an inhibitor of ATP synthase (Complex V) in the mitochondrial ETC, blocking ATP production by preventing proton flux through the enzyme.

$$ADP + Pi \rightarrow ATP$$

By inhibiting ATP synthase, oligomycin starves cancer cells of ATP, particularly under hypoxic conditions where glycolysis alone is insufficient for energy production. Oligomycin is primarily used in research settings due to its toxicity, but it provides insight into how mitochondrial inhibitors could be leveraged in cancer treatment.

Fatty Acid Synthesis Inhibitors

Many cancer cells rely on de novo fatty acid synthesis for membrane production, energy storage, and signaling molecules, making this pathway another therapeutic target.

Fatty Acid Synthase (FASN) Inhibitors

Fatty acid synthase (FASN) is responsible for catalyzing the production of palmitate from acetyl-CoA and malonyl-CoA, providing the building blocks for membrane lipids and signaling molecules.

$$\text{Acetyl-CoA} + 7\text{Malonyl CoA} + 14NADPH \rightarrow \text{Palmitate } (C_{16}H_{32}O_2) + 7CO_2 + 14NADP^+$$

Inhibitors like orlistat and C75 target FASN, leading to the accumulation of toxic lipid intermediates and reduced cell growth. Preclinical studies have shown that FASN inhibitors can reduce tumor growth in various cancer models, and these compounds are being evaluated for clinical development.

Mechanisms of Action of Small Molecule Inhibitors

The mechanism of action for small molecule inhibitors in cancer metabolism generally revolves around:

Starvation of energy
Inhibiting key enzymes like HK2 or LDH-A disrupts ATP production, making it harder for cancer cells to sustain their rapid growth and division.
Disruption of biosynthesis
Blocking enzymes involved in fatty acid or amino acid metabolism prevents the production of crucial building blocks required for cell proliferation.
Induction of metabolic stress
Compounds like metformin increase AMPK activity, promoting catabolic processes that inhibit cancer growth while sensitizing cells to metabolic stress.

Preclinical Studies and Clinical Trials

Preclinical studies have shown the potential of these small molecule inhibitors across various cancer models. 2-DG has demonstrated the ability to inhibit tumor growth in glycolysis-dependent cancers, although its toxicity at high doses remains a concern. FX11, an LDH inhibitor, has shown efficacy in reducing tumor growth in models of lymphoma and pancreatic cancer. Metformin has shown promising results in preclinical studies, particularly in combination with chemotherapy or targeted therapies, and is now being tested in multiple clinical trials for various cancers, including breast and colorectal cancers. FASN inhibitors like orlistat have reduced tumor growth in preclinical models of prostate and breast cancer, and some of these inhibitors are in early-phase clinical trials.

Challenges and Limitations in Targeting Cancer Metabolism

Targeting cancer metabolism with small molecule inhibitors has emerged as a promising therapeutic approach, yet several challenges and limitations must be overcome for these strategies to be fully effective. These challenges include drug resistance mechanisms, tumor heterogeneity, off-target effects, and metabolic plasticity. Below is a comprehensive discussion of each of these issues.

Drug Resistance Mechanisms
Cancer cells have shown a remarkable ability to develop resistance to therapies targeting their metabolic pathways. Several mechanisms can contribute to this resistance, including:

Activation of alternative pathways
When cancer cells face metabolic inhibition, they often upregulate compensatory pathways. For instance, blocking glycolysis may lead cancer cells to increase their reliance on mitochondrial oxidative phosphorylation (OXPHOS) or other metabolic routes to maintain energy production and survival.

Genetic adaptations
Mutations in the genes coding for metabolic enzymes can reduce the efficacy of small molecule inhibitors. Alterations in the target enzymes can prevent the drugs from binding effectively, diminishing their therapeutic effect.

Upregulation of survival pathways
Cancer cells can activate survival signaling pathways, such as the

PI3K/AKT pathway, in response to metabolic stress. These pathways promote glucose uptake and allow cancer cells to overcome the metabolic blockade, leading to continued growth and survival despite treatment.

Tumor Heterogeneity

Tumor heterogeneity poses a significant challenge in targeting cancer metabolism. Cancer is not a uniform disease; even within a single tumor, cells can vary greatly in their metabolic profiles. This heterogeneity complicates treatment because:

Different subpopulations of cancer cells may depend on distinct metabolic pathways. For example, while some cells may predominantly rely on glycolysis, others might use oxidative phosphorylation or fatty acid metabolism for energy production and growth.

Cancer stem cells within tumors may exhibit unique metabolic properties, making them more resistant to metabolic inhibitors. These cells can shift their metabolic reliance depending on the tumor environment, making it difficult to target them with a single metabolic inhibitor. Tumor microenvironment influences metabolic activity as well. Hypoxic regions of a tumor may be more glycolysis-dependent, while oxygenated regions could rely more on mitochondrial respiration. The complexity of the tumor microenvironment makes it challenging to target all metabolic dependencies within a tumor effectively.

Off-Target Effects and Toxicity

Another limitation of targeting cancer metabolism is the risk of off-target effects and toxicity. Since many metabolic pathways targeted by cancer therapies are also crucial for normal cell function, inhibiting these pathways can lead to unintended side effects in healthy tissues.

Metabolic pathways shared with normal cells

Pathways such as glycolysis and oxidative phosphorylation are fundamental processes for all cells, not just cancer cells. Inhibiting key enzymes in these pathways can impair the function of healthy tissues, particularly those with high energy demands, such as the brain, muscles, and heart.

Mitochondrial toxicity

Mitochondrial inhibitors can disrupt ATP production in normal cells, leading to side effects like muscle weakness, fatigue, or cardiac issues. Since mitochondria are essential for energy generation in all cells, targeting them poses a challenge in avoiding damage to non-cancerous tissues.

Accumulation of toxic intermediates

Some metabolic inhibitors can cause the buildup of intermediate molecules that are toxic to healthy cells, leading to organ damage, particularly in the liver or kidneys, which are involved in detoxification and excretion processes.

Metabolic Plasticity and Adaptation

Cancer cells are highly adaptable and exhibit metabolic plasticity, allowing them to survive despite significant metabolic stress. This plasticity is a major challenge in targeting metabolism because:

Flexibility in metabolic states

Cancer cells can switch between glycolysis and oxidative phosphorylation depending on environmental conditions and therapeutic pressure. This flexibility allows them to bypass the effects of metabolic inhibitors and continue to proliferate even when one pathway is blocked.

Use of alternative nutrients

When deprived of glucose or fatty acids, cancer cells can shift to utilizing other

nutrients, such as amino acids or ketone bodies, to fuel their growth. This metabolic adaptability makes it difficult to completely starve cancer cells of the resources they need to survive.

Support from the tumor micro environment

Cancer cells can also engage in metabolic crosstalk with surrounding stromal cells or immune cells within the tumor microenvironment. For example, cancer-associated fibroblasts can provide lactate or other metabolites to tumor cells, allowing them to thrive even when their primary metabolic pathways are blocked.

Conclusion

While small molecule inhibitors targeting cancer metabolism hold great potential, significant challenges must be addressed to fully realize their therapeutic benefits. Drug resistance, tumor heterogeneity, off-target effects, and the adaptability of cancer cells make it difficult to achieve durable responses with current metabolic therapies. To overcome these limitations, future approaches may involve combination therapies that target multiple metabolic pathways simultaneously, personalized treatments based on the metabolic profile of individual tumors, and strategies to reduce off-target toxicity while enhancing selectivity for cancer cells.

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