Molecular Cancer

REVIEW

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Altered metabolism in cancer: insights into energy pathways and therapeutic targets

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Abstract

Cancer cells undergo significant metabolic reprogramming to support their rapid growth and survival. This study examines important metabolic pathways like glycolysis, oxidative phosphorylation, glutaminolysis, and lipid metabolism, focusing on how they are regulated and their contributions to the development of tumors. The interplay between oncogenes, tumor suppressors, epigenetic modifications, and the tumor microenvironment in modulating these pathways is examined. Furthermore, we discuss the therapeutic potential of targeting cancer metabolism, presenting inhibitors of glycolysis, glutaminolysis, the TCA cycle, fatty acid oxidation, LDH, and glucose transport, alongside emerging strategies targeting oxidative phosphorylation and lipid synthesis. Despite the promise, challenges such as metabolic plasticity and the need for combination therapies and robust biomarkers persist, underscoring the necessity for continued research in this dynamic field.

Keywords Cancer metabolism, Glycolysis, Oxidative phosphorylation, Glutaminolysis, Lipid metabolism

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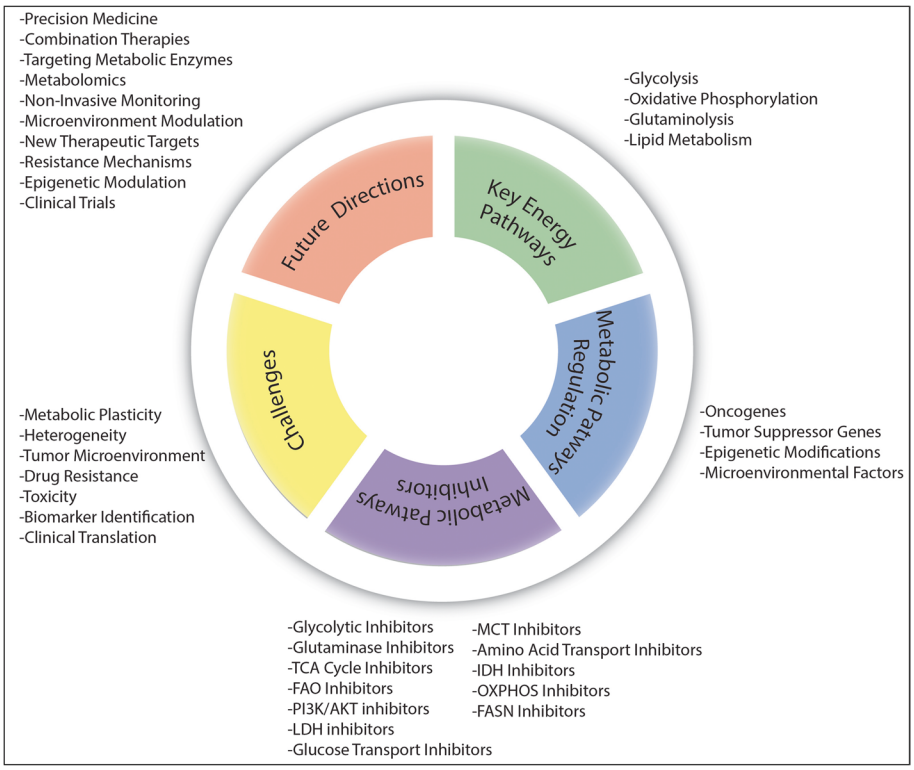
Graphical Abstract



Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide. Despite significant advancements in our understanding and treatment of cancer, the complexity and adaptability of malignant cells continue to pose ongoing challenges [1, 2]. One of the hallmark features of cancer cells is their altered metabolism, which supports rapid growth and survival in hostile environments [3, 4]. The study of cancer metabolism dates back to the early 20th century, when Otto Warburg first observed that cancer cells preferentially utilize glycolysis for energy production, even in sufficient oxygen – a phenomenon now known as the Warburg effect [5]. Warburg's discovery was revolutionary, challenging the prevailing belief that oxidative phosphorylation in mitochondria was the primary energy source for all cells, including cancerous ones. Over the decades, subsequent research has expanded our understanding of the metabolic reprogramming in cancer cells, revealing a complex network of altered pathways that contribute to tumorigenesis and cancer progression.

The metabolic reprogramming in cancer cells is not limited to enhanced glycolysis. It encompasses a range of alterations in various metabolic pathways, including increased glucose uptake and lactate production even under aerobic conditions (aerobic glycolysis) [6], dependency on glutamine for anaplerosis and biosynthesis (glutaminolysis) [3], enhanced lipogenesis and altered fatty acid oxidation (lipid metabolism) [3], and changes in the metabolism of amino acids like serine and glycine [3]. Despite the emphasis on glycolysis, many cancer cells still rely on mitochondrial respiration for survival and proliferation. These alterations are driven by oncogenes and tumor suppressor genes, which rewire cellular metabolism to meet the demands of rapid cell division, resist cell death, and adapt to hypoxic conditions within the tumor microenvironment (TME) [7].

At the molecular level, several key regulators orchestrate the metabolic reprogramming in cancer cells. Oncogenes such as MYC and RAS promote anabolic processes and increase the uptake and utilization of nutrients [8]. When lost, tumor suppressor genes like TP53 and LKB1 can enhance glycolysis and biosynthetic pathways [9, 10]. Hypoxia-inducible factors (HIFs) induce the expression of glycolytic enzymes and glucose transporters in response to low oxygen levels [11, 12]. The

AMP-activated protein kinase (AMPK) acts as a cellular energy sensor and regulator, balancing energy supply and demand [13, 14], while the mTOR signaling pathway promotes protein synthesis and cell growth, integrating signals from nutrients and growth factors [15].

Recognizing altered metabolism as a cancer hallmark has opened new avenues for therapeutic intervention [16, 17]. Targeting metabolic pathways offers the potential to disrupt the energy supply and biosynthetic processes essential for tumor growth [18, 19]. Some promising therapeutic strategies include inhibitors of glycolysis that target key glycolytic enzymes such as hexokinase and lactate dehydrogenase, glutamine antagonists that inhibit glutamine uptake or metabolism, lipid metabolism inhibitors that target fatty acid synthesis and oxidation pathways, and mitochondrial metabolism modulators that disrupt mitochondrial function and oxidative phosphorylation. Clinical trials are exploring these and other metabolic targets to develop effective treatments with minimal toxicity to normal cells.

This review aims to provide a detailed and integrated overview of the current understanding of altered metabolism in cancer. It explores key energy pathways, including glycolysis, oxidative phosphorylation, glutaminolysis, and lipid metabolism, highlighting their roles and regulatory mechanisms in cancer cells. The review also examines the regulation of these pathways by oncogenes and tumor suppressors, epigenetic modifications, and microenvironmental factors. Furthermore, it discusses therapeutic targets in cancer metabolism, including glycolysis inhibitors, oxidative phosphorylation, glutaminase, and lipid metabolism. Finally, it addresses challenges and future directions in overcoming metabolic plasticity, developing combination therapies, and identifying biomarkers for metabolic targeting, aiming to inform the development of novel therapeutic approaches.

Metabolic reprogramming in cancer

Cancer cells exhibit profound alterations in their metabolism, supporting their rapid growth, survival, and ability to adapt to diverse and often hostile environments. Herein, we shed light on two critical aspects of metabolic reprogramming in cancer: the Warburg effect and additional metabolic pathways that extend beyond this well-known phenomenon.

The Warburg effect is one of cancer cells' most well-characterized metabolic alterations. Warburg observed that cancer cells favor glycolysis for energy production, even with adequate oxygen [20]. This preference for glycolysis over oxidative phosphorylation, despite its lower efficiency in ATP production, is a hallmark of many types of cancer [21].

In normal cells, glycolysis is typically followed by oxidative phosphorylation in the mitochondria under aerobic conditions, yielding up to 36 molecules of ATP per glucose molecule [22]. In contrast, glycolysis alone produces only 2 ATP molecules per glucose molecule. However, cancer cells compensate for this inefficiency by upregulating glucose transporters and glycolytic enzymes, leading to an increased glycolytic flux [22, 23]. This metabolic reprogramming supports rapid cell proliferation by providing both ATP and metabolic intermediates for biosynthetic processes, such as nucleotide and lipid synthesis.

Various oncogenic signals and mutations in tumor suppressor genes drive the Warburg effect. For instance, activating oncogenes like MYC and RAS enhances glycolytic enzyme expression [24], while mutations in tumor suppressors like TP53 and PTEN further promote glycolysis [25, 26]. Additionally, HIFs, which are stabilized in low oxygen conditions commonly found in tumors, increase the expression of glycolytic enzymes and glucose transporters, further reinforcing the Warburg effect [24].

While the Warburg effect is central to cancer metabolism, it is not the sole metabolic alteration observed in cancer cells. Several other metabolic pathways are reprogrammed to support the unique demands of tumor growth and survival. Glutaminolysis highlights cancer cells' dependence on the amino acid glutamine, serving as a key nitrogen donor for nucleotide and amino acid biosynthesis and replenishing tricarboxylic acid (TCA) cycle intermediates. Enzymes such as glutaminase (GLS) are frequently upregulated, indicating potential therapeutic targets [27, 28]. Alterations in lipid metabolism, including enhanced de novo lipogenesis and changes in fatty acid oxidation, provide essential components for membrane biogenesis and additional energy sources. Despite the Warburg effect suggesting a reduced reliance on oxidative phosphorylation, many cancer cells still utilize mitochondrial respiration to meet energy demands and support biosynthetic pathways, playing crucial roles in apoptosis regulation and reactive oxygen species (ROS) production [29]. Beyond glutamine, other amino acids like serine and glycine are critical, with the serine-glycine-one-carbon (SGOC) metabolism pathway supporting nucleotide synthesis and redox balance. Enzymes such as serine hydroxymethyltransferase (SHMT) and glycine decarboxylase (GLDC) are often upregulated, underscoring their importance in cancer metabolism [29, 30].

While the Warburg effect has been widely studied, it is important to consider the interconnectedness of metabolic pathways such as glutaminolysis, lipid metabolism, and SGOC metabolism, which cancer cells utilize to meet their biosynthetic and energy demands. Targeting single pathways, like inhibiting GLS in glutaminolysis, has

shown potential in certain cancers, but a combined therapeutic approach could yield better results. For example, combining glycolysis inhibitors with mitochondrial respiration inhibitors could cut off cancer cells' access to multiple energy sources. Moreover, further research into how cancer cells switch between these pathways in response to treatments is crucial, as understanding this metabolic plasticity may reveal new vulnerabilities.

Metabolic synthetic lethalities in cancer

Metabolic synthetic lethality refers to the concept where the combination of a genetic mutation and a metabolic vulnerability leads to cancer cell death, while each factor alone does not. In cancer, this approach exploits the specific metabolic dependencies of tumor cells to induce selective cell death. Tumor cells often have altered metabolic pathways that can create unique vulnerabilities [31, 32].

Metabolic synthetic lethality offers a promising strategy for targeting tumors with specific genetic alterations, particularly those affecting the TCA cycle. This approach capitalizes on the unique metabolic dependencies created by mutations in key TCA cycle enzymes, leading to vulnerabilities that can be therapeutically exploited. Among the enzymes frequently mutated in various cancers are succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH). These mutations result in profound metabolic alterations that create therapeutic opportunities. Understanding how these mutations influence tumor metabolism is crucial for developing targeted treatments.

SDH mutations are genetic alterations that lead to the accumulation of succinate, disrupting the TCA cycle and causing metabolic imbalances in tumor cells. Mutations in SDH result in the accumulation of succinate, which profoundly alters tumor metabolism and creates several vulnerabilities. One significant adaptation in SDH-deficient tumors is an increased reliance on glycolysis for energy production. This heightened glycolytic activity represents a potential therapeutic target; inhibitors of glycolytic enzymes or glucose transporters may selectively affect these tumors [33, 34]. For example, in SDH-deficient tumors, which rely heavily on glycolysis due to TCA cycle impairment, WZB117, a GLUT1 inhibitor, can effectively reduce glucose uptake, decrease intracellular ATP, downregulate glycolytic enzymes, and inhibit tumor growth, making it a promising candidate for enhancing treatment outcomes and sensitizing tumors to other therapies [35]. Additionally, to compensate for the disrupted TCA cycle, SDH-mutant cells often become heavily dependent on glutamine metabolism. Targeting enzymes involved in glutamine utilization, such as glutaminase, could selectively impair these cancer cells. For instance, studies indicate that SDHB knockout cells exhibit heightened sensitivity to GLS-1 inhibitors, suggesting that targeting this enzyme could selectively impair the growth of SDH-mutant tumors [36, 37]. Moreover, the accumulation of succinate and subsequent disruptions in cellular redox balance can lead to increased oxidative stress. Therapeutic strategies that further elevate reactive oxygen species levels might overwhelm the oxidative stress tolerance of these cells, leading to selective cell death.

FH mutations cause fumarate accumulation, leading to distinct metabolic dependencies and vulnerabilities. One notable consequence is the upregulation of heme synthesis, as FH-mutant cells attempt to manage excess fumarate. Targeting heme oxygenase-1 (HO-1), which is involved in heme degradation, has shown potential in selectively targeting FH-deficient tumors [38, 39]. Another vulnerability arises from the dependency of some FH-deficient cells on argininosuccinate synthase to handle excess fumarate. Inhibiting this enzyme could provide a synthetic lethal approach. Additionally, like SDH-deficient tumors, FH-deficient cells often exhibit impaired oxidative phosphorylation and increased reliance on glycolysis [38, 39]. Combining glycolysis inhibitors with other agents could be a potent strategy against tumors. For example, recent studies demonstrated that combining arsenic trioxide (ATO) with HO-1 inhibitors enhances cytotoxicity, induces apoptosis, and modulates autophagy via an ROS-dependent mechanism in pancreatic ductal adenocarcinoma (PDAC) cells [40], while simultaneously targeting HO-1 and σR proteins with novel hybrid compounds shows enhanced antiproliferative activity in DU145 prostate and U87MG glioblastoma cells, highlighting promising strategies for developing more effective and less toxic anticancer therapies [41].

Moreover, mutations in IDH lead to the production of 2-hydroxyglutarate (2-HG), which induces distinctive metabolic changes in tumors. One major alteration is NAD + depletion, a consequence of altered metabolic pathways. IDH-mutant tumors are particularly sensitive to further NAD + depletion, suggesting that targeting NAD + salvage pathways could selectively impair these cells [42, 43]. Such as, treatment with NAMPT inhibitors resulted in significant reductions in intracellular NAD + levels and induced cell death specifically in IDH1/2-mutant cancer cell lines. The depletion of NAD + activated the energy sensor AMPK, triggered autophagy, and ultimately led to cytotoxicity in these cancer cells. This demonstrates a clear therapeutic strategy: by inhibiting NAMPT, which is already compromised in IDH1-mutant cells, it is possible to selectively target and kill these cancer cells while sparing normal cells that do not share this metabolic vulnerability [44, 45]. Furthermore, many IDH-mutant tumors become

dependent on glutamine as a source of α-ketoglutarate to produce 2-HG [43, 46]. Targeting glutamine metabolism in these cancers could therefore be an effective therapeutic strategy. Additionally, IDH mutations can alter lipid metabolism, affecting lipid synthesis and fatty acid oxidation. Exploiting these metabolic changes through inhibition of key lipid metabolism enzymes might offer further therapeutic opportunities [43].

Overall, metabolic synthetic lethality offers a promising approach for cancer treatment by targeting the unique metabolic dependencies caused by TCA cycle mutations, enabling greater selectivity and reduced toxicity to normal cells. This strategy also has the potential to overcome resistance to conventional therapies and enhance efficacy when combined with targeted treatments or immunotherapies. Moreover, identifying specific TCA cycle mutations as biomarkers can help tailor therapies to patients most likely to benefit, making this approach a significant advancement in developing personalized and more effective cancer treatments.

Key energy pathways

Glycolysis

Glycolysis, the central metabolic pathway that converts glucose into pyruvate, plays a pivotal role in the altered metabolism of cancer cells [47, 48]. This process, fundamental to normal and malignant cells, has been extensively studied for its implications in cancer biology and therapeutic targeting. In cancer, glycolysis operates under significantly different dynamics than normal cells, often called the Warburg effect.

Cancer cells undergo significant metabolic alterations to support rapid growth and proliferation [49, 50]. One of the most notable changes is the upregulation of glucose transporters, particularly GLUT1, which enhances glucose influx into the cells [51, 52]. For example, a recent study has reported that GLUT1 is highly expressed in lung adenocarcinoma (LUAD), and its elevated levels are associated with poor patient survival. Functional studies have demonstrated that GLUT1 plays an oncogenic role in LUAD, as its knockdown results in decreased cell proliferation, colony formation, migration, and invasion while also inducing apoptosis in LUAD cells. Mechanistically, GLUT1 interacts directly with phosphorylated epidermal growth factor receptor (p-EGFR), preventing EGFR protein degradation via ubiquitin-mediated proteolysis [53]. These findings suggest that targeting GLUT1 could be a promising therapeutic strategy. Notably, combining GLUT1 inhibitors with EGFR-tyrosine kinase inhibitors (TKIs) like Gefitinib may enhance therapeutic efficacy in treating LUAD [53]. This increased glucose uptake is the foundation for 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, a common technique used in cancer diagnosis. In addition to increased glucose uptake, cancer cells exhibit an enhanced glycolytic flux. This is characterized by higher glycolysis rates than normal cells, facilitated by upregulating key glycolytic enzymes such as hexokinase II [23]. Despite the presence of oxygen, cancer cells preferentially convert pyruvate to lactate via lactate dehydrogenase A (LDHA) [51], rather than oxidizing it in the mitochondria. This phenomenon, known as the Warburg effect, is a hallmark of cancer metabolism.

Various factors regulate the switch to glycolysis in cancer cells. Oncogenes such as HIF-1α, c-Myc, and Akt are known to promote glycolysis [51], whereas tumor suppressors like p53 act to suppress it. The loss of p53 in cancer cells often promotes a glycolytic phenotype [51]. For instance, HIF-1α is a key regulator of cellular response to hypoxia and promotes glycolysis through several mechanisms: it increases the expression of glucose transporters GLUT1 and GLUT3, enhancing glucose uptake; upregulates nearly all glycolytic enzymes, including hexokinases (HK1 and HK2), phosphofructokinases (PFKL and PFKP), and pyruvate kinase M (PKM); and enhances the expression of lactate dehydrogenase A (LDHA) and monocarboxylate transporter 4 (MCT4), facilitating lactate production and export. Additionally, HIF-1α reduces oxidative phosphorylation by promoting mitophagy and decreasing mitochondrial biogenesis [54]. While c-Myc directly activates the transcription of many glycolytic enzyme genes and cooperates with HIF-1α to enhance the transcription of key glycolytic enzymes such as hexokinase 2 (HK2) and pyruvate dehydrogenase kinase 1 (PDK1). This collaboration between c-Myc and HIF-1α leads to additive increases in glucose uptake and lactate production [55]. Furthermore, activation of signaling pathways like PI3K/Akt/mTOR enhances glycolysis, contributing to the metabolic reprogramming observed in cancer cells. For example, Akt activation increases glucose uptake by inhibiting thioredoxin-interacting protein (TXNIP), leading to higher expression of glucose transporters GLUT1 and GLUT4 on the cell surface [56]. It enhances glycolytic enzyme activity by phosphorylating and activating key enzymes such as hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB2), promoting glycolysis [56]. The PI3K/Akt pathway shifts metabolism towards aerobic glycolysis, making cancer cells dependent on glucose [56]. Akt also regulates metabolism through transcription factors by activating mTORC1 and inhibiting FOXO, and it may influence mitochondrial function to sustain TCA cycle flux [57]. Additionally, the pathway causes long-term metabolic reprogramming and interacts with

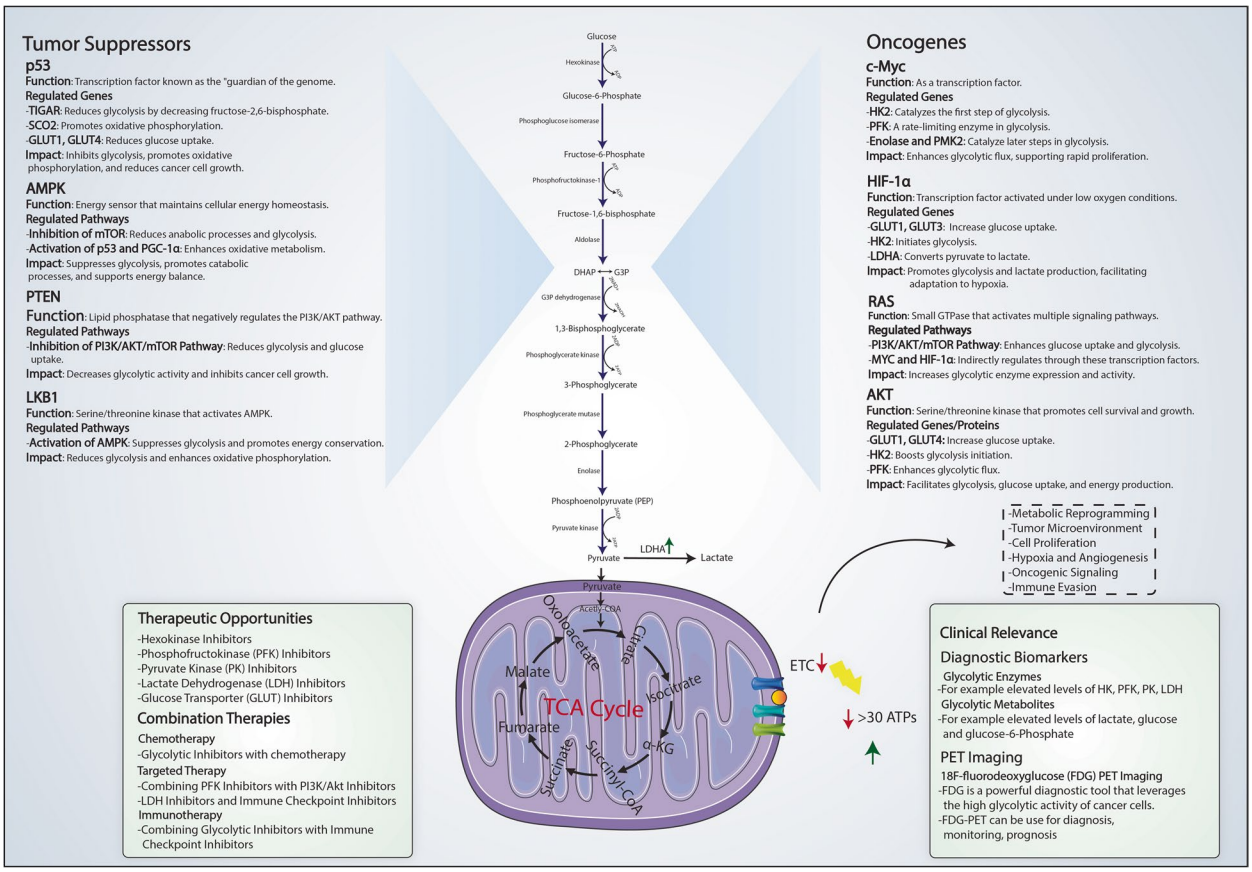


Fig. 1 This figure illustrates glycolysis as a key energy pathway in cancer cells, highlighting the pathway's steps from glucose to pyruvate, including all intermediate metabolites and enzymes (e.g., hexokinase, phosphofructokinase, pyruvate kinase). The roles of oncogenes and tumor suppressors in regulating glycolysis are indicated. The Warburg effect is highlighted by showing increased glycolytic flux and lactate production despite the presence of oxygen, with pyruvate diverted to lactate dehydrogenase instead of mitochondria. The contrast between glycolysis and oxidative phosphorylation in mitochondria is depicted, indicating the reduced reliance on mitochondrial metabolism in cancer cells. Potential therapeutic targets within the glycolytic pathway are showed, and suggestions for combining glycolytic inhibitors with other treatments are included. The clinical relevance is emphasized by showing how glycolytic metabolites or enzyme levels can serve as biomarkers for cancer diagnosis, with reference to 18F-fluorodeoxyglucose (FDG) PET imaging used for detecting high glycolytic activity in tumors

other signaling pathways like HIF-1α to modulate glucose metabolism, contributing to the complex metabolic changes in cancer cells [58].

Targeting glycolysis offers a promising avenue for cancer therapy, aiming to exploit the metabolic vulnerabilities of cancer cells. Several strategies are being explored, including inhibition of glycolytic enzymes, targeting glucose transporters, and exploiting lactate production. Hexokinase inhibitors like 2-deoxyglucose (2-DG) disrupt glycolysis and induce cell death in cancer cells [52, 59]. Small molecules that promote the tetrameric, active form of PKM2 can shift metabolism away from glycolysis towards oxidative phosphorylation, inhibiting cancer cell proliferation [59, 60]. Inhibitors of GLUT1 can restrict glucose uptake, starving cancer cells of their primary energy source [52, 59]. Moreover, inhibiting LDHA blocks the conversion of pyruvate to lactate, accumulating toxic levels of pyruvate and disrupting redox balance [59, 61]. Agents that neutralize the acidic tumor microenvironment can impair cancer cell invasion and enhance immune cell activity [59, 62]. Combining glycolysis inhibitors with conventional therapies such as chemotherapy, radiation, or immunotherapy may enhance overall efficacy by concurrently targeting multiple cancer cell survival mechanisms. Figure 1 illustrates the glycolytic pathway in cancer cells, highlighting key steps, regulatory roles of oncogenes and tumor suppressors, the Warburg effect, reduced reliance on mitochondrial metabolism, potential therapeutic targets, and the clinical relevance of glycolytic metabolites as biomarkers and in 18 F-FDG PET imaging (Fig. 1).

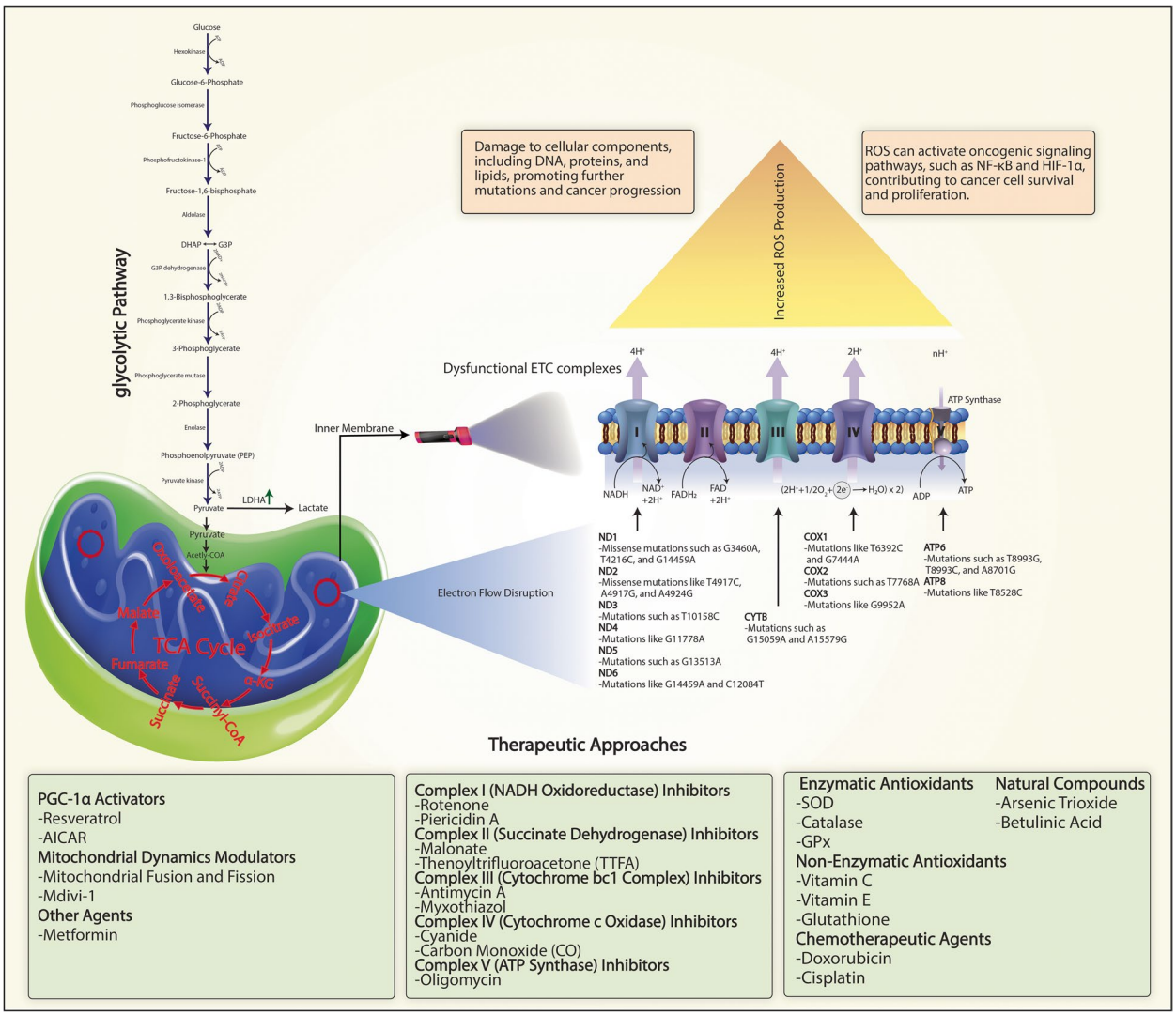


Fig. 2 This figure illustrates the role of Oxidative Phosphorylation (OXPHOS) in cancer metabolism, detailing key components, alterations, and therapeutic targets. The figure depicts the mitochondrial structure, including the electron transport chain (ETC) complexes I-IV and ATP synthase (Complex V), highlighting the flow of electrons from NADH and FADH2 to oxygen, producing water and ATP via chemiosmosis and the proton gradient. The figure also shows common cancer-associated alterations, such as the Warburg effect, mitochondrial dysfunction, and increased reactive oxygen species (ROS) production. Mutations in mtDNA genes can disrupt electron flow, leading to increased ROS production, which damages cellular components like DNA, proteins, and lipids, promoting further mutations and cancer progression. These mutations can also activate oncogenic signaling pathways such as NF-κB and HIF-1α. The bottom panel emphasizes therapeutic strategies, including ETC complex inhibitors, agents affecting mitochondrial biogenesis, and ROS modulation

Oxidative phosphorylation

Oxidative phosphorylation (OXPHOS) is a fundamental metabolic pathway for ATP production through the mitochondria's electron transport chain (ETC). Despite the prominence of the Warburg effect, which describes cancer cells' preference for glycolysis even under aerobic conditions, OXPHOS remains crucial in many cancers and plays an important role in the progression of cancer and could be a potential therapeutic target (Fig. 2). While many cancer cells exhibit increased glycolysis, they often maintain functional OXPHOS. For example, leukemias and lymphomas can maintain functional OXPHOS despite their glycolytic activity, and similar observations are seen in pancreatic ductal adenocarcinoma, where OXPHOS remains active in this aggressive cancer type. Some melanomas, particularly the high OXPHOS subtype, exhibit increased OXPHOS alongside glycolysis, and endometrial carcinoma cells can also persist with active OXPHOS [63]. This dual capability allows cancer cells to adapt to

varying environmental conditions, such as oxygen and nutrient availability fluctuations. OXPHOS serves as an additional ATP source when insufficient glycolysis occurs, ensuring a continuous energy supply essential for rapid cell division and growth [64, 65]. For example, acute myeloid leukemia (AML) cells demonstrate this dual metabolic capability [66, 67]. While many cancer cells primarily rely on glycolysis (the Warburg effect), AML cells, particularly leukemic stem cells (LSCs), strongly prefer OXPHOS [66, 68]. This metabolic flexibility allows AML cells to adapt to different microenvironments and resist chemotherapy. For instance, studies have shown that chemotherapy-resistant AML cells have enhanced mitochondrial respiration capacity. These cells, characterized by a low SoNar ratio, primarily reside in the vascular niche and are enriched with functional leukemia-initiating cells. The SoNar-low AML cells demonstrate higher levels of oxidative phosphorylation, contributing to their resistance to cytosine arabinoside (Ara-C), a common chemotherapy drug [66]. Furthermore, research has found that treatment-resistant AML LSCs can maintain OXPHOS even under challenging conditions [67]. This metabolic adaptation allows them to survive and potentially lead to disease relapse. The ability to switch between glycolysis and OXPHOS enables these cells to thrive in various oxygen and nutrient conditions within the bone marrow microenvironment [67, 69]. This dual metabolic capability in AML cells highlights the importance of targeting glycolysis and OXPHOS in developing more effective treatments. Cancer cells' ability to switch between glycolysis and OXPHOS, known as metabolic flexibility, is vital for survival [70]. This adaptability supports cancer cells in hostile microenvironments, including hypoxia and nutrient scarcity [71]. For instance, cancer cells may rely more on OXPHOS during metastasis to meet their energy demands. This metabolic flexibility is a key factor in the resilience and aggressiveness of cancer cells [72].

Furthermore, mitochondrial dynamics and function are often altered in cancer cells. Proteins like Drp1 (dynamin-related protein 1) and Mfn1/2 (mitofusins) regulate mitochondrial fission and fusion processes, affecting OXPHOS efficiency [73, 74]. Additionally, cancer cells may enhance mitochondrial biogenesis through factors like PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) to boost their OXPHOS capacity. These adaptations ensure that mitochondria meet proliferating cancer cells' increased energetic and biosynthetic demands [74, 75].

Moreover, key oncogenes and tumor suppressors modulate OXPHOS in cancer. For example, c-Myc enhances mitochondrial biogenesis and respiration, supporting rapid cell growth [74, 75]. Conversely, mutations in tumor suppressors like p53 can disrupt mitochondrial function and OXPHOS, contributing to tumor metabolic reprogramming. These genetic alterations highlight the complex regulation of OXPHOS in cancer and its contribution to tumorigenesis.

Hypoxia-inducible factors (HIFs) are transcription factors activated under low oxygen conditions, playing a critical role in reprogramming cellular metabolism [76, 77]. HIF-1α typically promotes glycolysis and suppresses OXPHOS by inducing pyruvate dehydrogenase kinase (PDK), which inhibits the entry of pyruvate into the tricarboxylic acid (TCA) cycle [78, 79]. However, HIF-2α has been shown to maintain OXPHOS in certain cancer contexts, illustrating the complexity of metabolic regulation under hypoxic conditions [12]. For example, one study demonstrated that HIF-1α primarily regulates VEGF expression in response to hypoxia and IGF-I in MCF-7 cells, while HIF-2α plays a dominant role in driving VEGF and other target gene expression in renal carcinoma cells with VHL loss. The findings also revealed a reciprocal relationship between HIF-1α and HIF-2α, where silencing HIF-2α enhances HIF-1α–mediated VEGF expression under hypoxic conditions. Additionally, the small-molecule inhibitor NSC-134,754 was shown to effectively reduce both HIF-1α and HIF-2α protein levels and VEGF expression, presenting a promising therapeutic strategy for targeting the HIF pathway in cancers [80]. In contrast, another study focusing on gastric cancer found that HIF-1α, but not HIF-2α, dimerizes with HIF-1β to regulate the expression of angiogenesis and glucose metabolism-related target genes, such as VEGF, in response to hypoxia. This emphasizes the critical role of HIF-1α in early-stage gastric cancer development and highlights important insights into the HIF pathway's role in tumor progression, offering potential targets for therapeutic intervention [81].

OXPHOS is also implicated in cancer cell invasion and metastasis [63, 64]. Mitochondrial ATP production supports the energy-intensive processes of cell migration and invasion. Additionally, reactive oxygen species (ROS) generated by OXPHOS can activate signaling pathways that promote metastatic behaviors. OXPHOS in mitochondria is a major source of ROS in cells, as electron transport can lead to electron leakage and partial oxygen reduction, forming superoxide anions that convert to other ROS like hydrogen peroxide [82]. ROS are crucial signaling molecules at moderate levels, activating pathways in cancer progression and metastasis [83]. They can trigger several pro-metastatic signaling cascades, including the NF-κB pathway [84], which regulates genes related to cell survival, proliferation, and metastasis, and MAPK pathways that influence cell proliferation,

survival, and migration [82]. Additionally, ROS can activate the PI3K-Akt pathway, promoting cell survival and metastasis [84]. ROS enhance cell motility and invasion by increasing the expression and activity of matrix metalloproteinases (MMPs), which degrade the extracellular matrix [82, 84]. They also induce epithelial-mesenchymal transition (EMT), endowing cancer cells with a more invasive phenotype, and stimulate the production of pro-angiogenic factors like VEGF, facilitating new blood vessel formation to support metastasis [83, 84]. Moreover, ROS contributes to anoikis resistance, allowing cancer cells to survive in circulation, establish metastases at distant sites, and aid in forming pre-metastatic niches in distant organs, creating environments conducive to secondary tumor establishment [85]. This highlights the role of OXPHOS in energy production and in facilitating cancer progression and metastasis [86, 87].

Similarly, cancer stem cells (CSCs) rely on OXPHOS for their metabolic flexibility and survival in diverse tumor microenvironments. CSCs are a subpopulation of cancer cells within a tumor that can self-renew, differentiate into various cell types, and drive tumor growth and recurrence. This metabolic flexibility allows CSCs to switch between glycolysis and OXPHOS, aiding survival in various tumor microenvironments and supporting therapy resistance. Furthermore, enhanced mitochondrial biogenesis and effective ROS management, regulated by key signaling pathways such as PI3K/AKT/mTOR and AMPK, further support the reliance of CSCs on OXPHOS for their mitochondrial function and energy metabolism [88, 89]. The reliance on OXPHOS makes CSCs resistant to conventional therapies targeting glycolysis-dependent cells, while their ability to enter quiescence and undergo EMT enhances their resilience and metastatic potential [90, 91]. Targeting OXPHOS in CSCs is an emerging strategy to eradicate these resilient cell populations and improve therapeutic outcomes.

Several agents targeting OXPHOS are under investigation, including metformin [92], phenformin [93], and IACS-010759 [94]. These inhibitors reduce ATP production, induce energetic stress, and selectively kill cancer cells with high OXPHOS dependence. Combining OXPHOS inhibitors with other treatments, such as glycolysis inhibitors or conventional chemotherapies, can enhance anti-tumor efficacy. This dual inhibition approach exploits the metabolic flexibility of cancer cells, pushing them beyond their energetic limits. Moreover, mitochondrial uncouplers, such as 2,4-dinitrophenol (DNP), dissipate the proton gradient across the mitochondrial membrane, reducing ATP synthesis and increasing metabolic stress [95, 96]. These agents show potential in preclinical models, though their use requires careful dosing due to potential toxicity [97, 98]. The development of safer and more effective mitochondrial uncouplers could provide another avenue for targeting OXPHOS in cancer.

Glutaminolysis

Glutaminolysis is a metabolic process that converts glutamine to glutamate and subsequently to α-ketoglutarate, which can enter the tricarboxylic acid (TCA) cycle to produce energy and support biosynthetic processes. This pathway is particularly important in cancer metabolism (Fig. 3), as many cancer cells exhibit an increased dependence on glutamine, making it a critical fuel source for their growth and survival [99].

Glutaminolysis begins with the uptake of glutamine, an abundant amino acid in the body, into the cell [100]. Once inside, glutamine is converted to glutamate by the enzyme glutaminase (GLS). Glutamate can then be further converted to α-ketoglutarate by either glutamate dehydrogenase (GDH) or transaminases. α-Ketoglutarate enters the TCA cycle, contributing to the production of ATP and providing intermediates for synthesizing nucleotides, amino acids, and lipids [101, 102]. This metabolic pathway is particularly active in rapidly proliferating cells, including cancer cells, which require a constant supply of these biosynthetic precursors.

Cancer cells often exhibit altered metabolism to support their rapid growth and proliferation. One of these alterations is an increased reliance on glutamine, making glutaminolysis a critical pathway in cancer metabolism. Glutamine provides a carbon source for the TCA cycle and nitrogen for synthesizing nucleotides and amino acids, essential for DNA replication and protein synthesis [100]. This contribution to the TCA cycle supports energy production and the synthesis of other metabolic intermediates [103]. Simultaneously, the nitrogen atoms in glutamine are utilized in the biosynthesis of nucleotides, the building blocks of DNA and RNA, and other amino acids [104]. For example, in rapidly dividing cells like cancer cells or immune cells responding to infection, glutamine is often consumed at high rates to support the increased demand for nucleotide synthesis during DNA replication and amino acid production for protein synthesis [105]. This makes glutamine a critical nutrient for cell growth, proliferation, and survival, particularly when rapid cell division or protein production is required.

Glutaminolysis supports cancer cell survival under various stress conditions, such as nutrient deprivation and hypoxia. By providing intermediates for the TCA cycle, glutaminolysis helps maintain cancer cells' energy balance and redox status. For example, in renal cell carcinoma and glioblastoma cells, which exhibit a high dependency on glutamine. Under conditions of nutrient deprivation, these cancer cells increase the expression

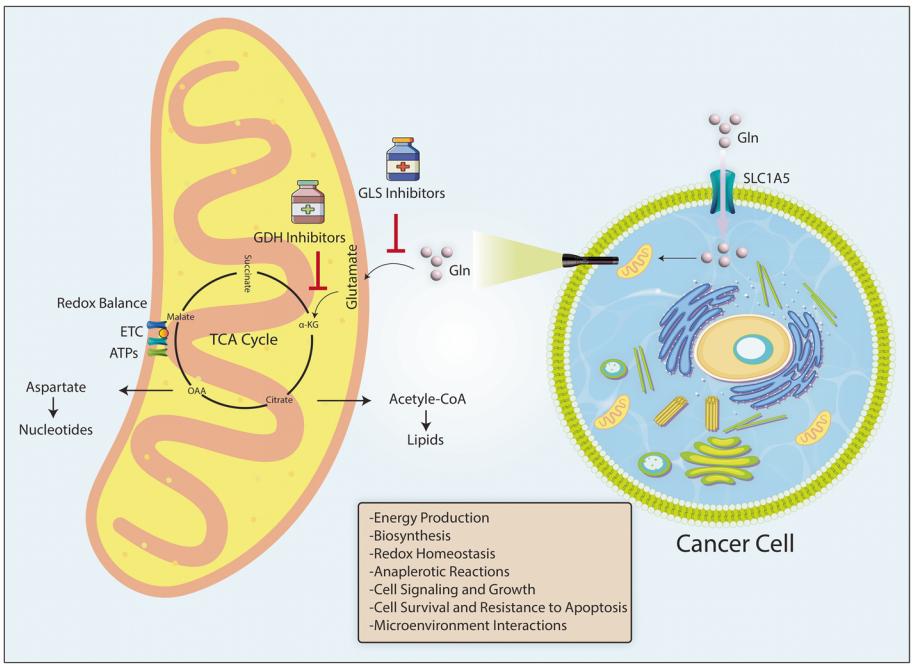


Fig. 3 This figure illustrates glutaminolysis as a Key Energy Pathway in Cancer. Glutamine is transported into cancer cells and converted to glutamate by glutaminase (GLS). Glutamate is further converted to α-ketoglutarate (α-KG), entering the TCA cycle to support energy production. Glutaminolysis also replenishes TCA cycle intermediates and produces biosynthetic precursors for macromolecule synthesis. Additionally, it generates NADPH to maintain redox balance. Key enzymes in this pathway are potential therapeutic targets for cancer treatment

of glutamine transporters like SLC1A5, facilitating enhanced uptake of glutamine. Once inside the cell, glutamine is converted to glutamate by glutaminase, and subsequently, glutamate can be transformed into α-KG through the action of glutamate dehydrogenase (GLUD). This α-KG then enters the TCA cycle, replenishing its intermediates and sustaining energy production necessary for cell survival and growth during stress conditions [29, 106]. Additionally, cancer cells often rely on glutaminolysis to support their metabolic needs. The conversion of glutamine to α-KG not only fuels the TCA cycle but also contributes to the synthesis of nucleotides and amino acids, which are vital for cellular functions and proliferation. This metabolic adaptation allows cancer cells to thrive even when oxygen levels are low, demonstrating the importance of glutaminolysis in maintaining their viability under adverse conditions [100, 107].

Many cancer cells exhibit what is known as "glutamine addiction," where they become highly dependent on glutamine for their growth and survival [108]. This phenomenon is driven by the activation of oncogenes such as MYC, which upregulate glutamine transporters and enzymes involved in glutaminolysis. For example, MYC increases the expression of glutaminase, enhancing the conversion of glutamine to glutamate and subsequently fueling the TCA cycle and biosynthetic processes [108]. This metabolic reprogramming towards increased glutaminolysis provides cancer cells with a growth advantage but also creates a vulnerability. Targeting glutamine metabolism can selectively impair the growth of glutamine-dependent cancer cells while sparing normal cells that are less reliant on this pathway.

The dependence of many cancers on glutaminolysis presents a potential target for therapeutic intervention. Inhibitors of glutaminase, such as CB-839, have shown promise in preclinical and clinical studies by reducing the proliferation of cancer cells and enhancing the efficacy of other anticancer therapies. These inhibitors block the conversion of glutamine to glutamate, disrupting the supply of α-ketoglutarate to the TCA cycle and reducing the production of ATP and biosynthetic precursors. Furthermore, combining glutaminase inhibitors with other metabolic inhibitors or conventional therapies could provide a more effective approach to cancer treatment. For instance, targeting glutaminolysis and glycolysis can simultaneously disrupt the two major metabolic pathways in cancer cells, leading to metabolic stress and cell death. Additionally, therapies that induce oxidative stress, such as radiation or certain chemotherapeutics, may be more effective when combined with glutaminase inhibitors, as cancer cells become more susceptible to oxidative damage when their antioxidant defenses

are compromised. For example, in pre-clinical studies, CB-839 demonstrated significant antiproliferative effects in the triple-negative breast cancer (TNBC) cell line HCC-1806 by markedly reducing glutamine consumption, glutamate production, and levels of several tricarboxylic acid cycle intermediates, as well as decreasing oxygen consumption and glutathione levels. However, CB-839 showed limited activity in the estrogen receptor-positive cell line T47D. The sensitivity of TNBC cells to CB-839 was associated with their reliance on extracellular glutamine for growth, elevated intracellular levels of glutamate and glutamine, and higher expression of GAC. Additionally, CB-839 exhibited notable antitumor efficacy in xenograft models, including a patient-derived TNBC model and the basal-like HER2(+) cell line JIMT-1, both as a single agent and in combination with paclitaxel [109]. Moreover, another study evaluated the effects of CB-839 on radiation sensitivity using human HNSCC cell lines and xenograft models. The combination of IR and CB-839 significantly reduced cell survival, spheroid size, and tumor growth compared to either treatment alone. Additionally, CB-839 decreased the oxygen consumption rate/extracellular acidification rate ratio in CAL-27 and HN5 cells and increased oxidative stress and DNA damage in irradiated CAL-27 cells. These findings suggest that combining IR with CB-839 enhances the anti-tumor response in HNSCC, supporting further clinical investigation of this combination therapy [110].

Lipid metabolism

Lipid metabolism, a crucial cellular process, involves lipids' synthesis, degradation, and utilization. In cancer, lipid metabolism is often reprogrammed to meet malignant cells' high energy demands and rapid growth rates (Fig. 4). This metabolic reprogramming is a hallmark of cancer, enabling tumor cells to sustain their proliferative capabilities, evade apoptosis, and adapt to the tumor microenvironment [111, 112].

Cancer cells exhibit significant alterations in lipid metabolism compared to normal cells. These changes include increased de novo lipogenesis [113], enhanced fatty acid uptake [112], and altered fatty acid oxidation [114]. De novo lipogenesis, the process by which cells synthesize fatty acids from non-lipid precursors, is upregulated in many cancers. Key enzymes involved in this pathway, such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN), are often overexpressed in tumor cells. This results in an abundant supply of fatty acids essential for membrane biogenesis, energy production, and the synthesis of signaling molecules. For example, in breast cancer, DNL is essential for sustaining the membrane composition and energy needs of rapidly proliferating tumor cells. Luminal subtypes rely heavily on DNL for fatty acid replenishment, while basal-like receptor-negative cancers tend to use exogenous fatty acids more. This metabolic shift is driven by various genomic and proteomic changes that influence lipogenic enzyme expression and activity [115, 116]. Inhibiting enzymes involved in DNL, such as FASN, has been shown to reduce tumor growth and enhance chemotherapy sensitivity, highlighting DNL as a promising target for therapeutic intervention [117, 118].

Furthermore, fatty acid uptake is also elevated in cancer cells, facilitated by overexpression of fatty acid transport proteins (FATPs) and CD36, a scavenger receptor involved in lipid uptake [119, 120]. This allows cancer cells to scavenge extracellular fatty acids, providing an additional energy source and building blocks for membrane synthesis. Furthermore, the process of fatty acid oxidation (FAO), which breaks down fatty acids to generate ATP, is often reprogrammed in cancer cells. While some cancers increase FAO to meet their energy demands, others decrease it to divert fatty acids toward lipid synthesis pathways [121].

Lipids serve not only as energy sources but also as critical signaling molecules in cancer. Lipid signaling pathways, mediated by molecules such as phosphoinositides, sphingolipids, and eicosanoids, play pivotal roles in cell proliferation, survival, migration, and invasion [111, 113]. For instance, the PI3K/Akt pathway, frequently activated in cancer, is heavily influenced by lipid signaling. Activation of PI3K catalyzes the production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), a lipid second messenger that recruits and activates Akt, promoting cell survival and growth [122].

Furthermore, sphingolipid metabolism is also intricately linked to cancer progression [123, 124]. Sphingolipid metabolism refers to the biochemical processes involved in synthesising, breaking down, and regulating sphingolipids, a lipid class that plays crucial roles in cell membrane structure and signaling. This pathway involves various enzymes and intermediates, such as ceramide and sphingosine, and is essential for cell growth, differentiation, apoptosis, and responses to stress. Ceramide, a central molecule in sphingolipid metabolism, can induce apoptosis, while its metabolites, sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P), promote cell proliferation and survival [125, 126]. The balance between these opposing lipid signals is often disrupted in cancer, favoring tumor growth and resistance to cell death [113].

The TME, composed of cancer cells, stromal cells, immune cells, and extracellular matrix, plays a crucial role in cancer progression and metastasis. Lipid metabolism within the TME is highly dynamic and contributes to the metabolic crosstalk between different cell types.

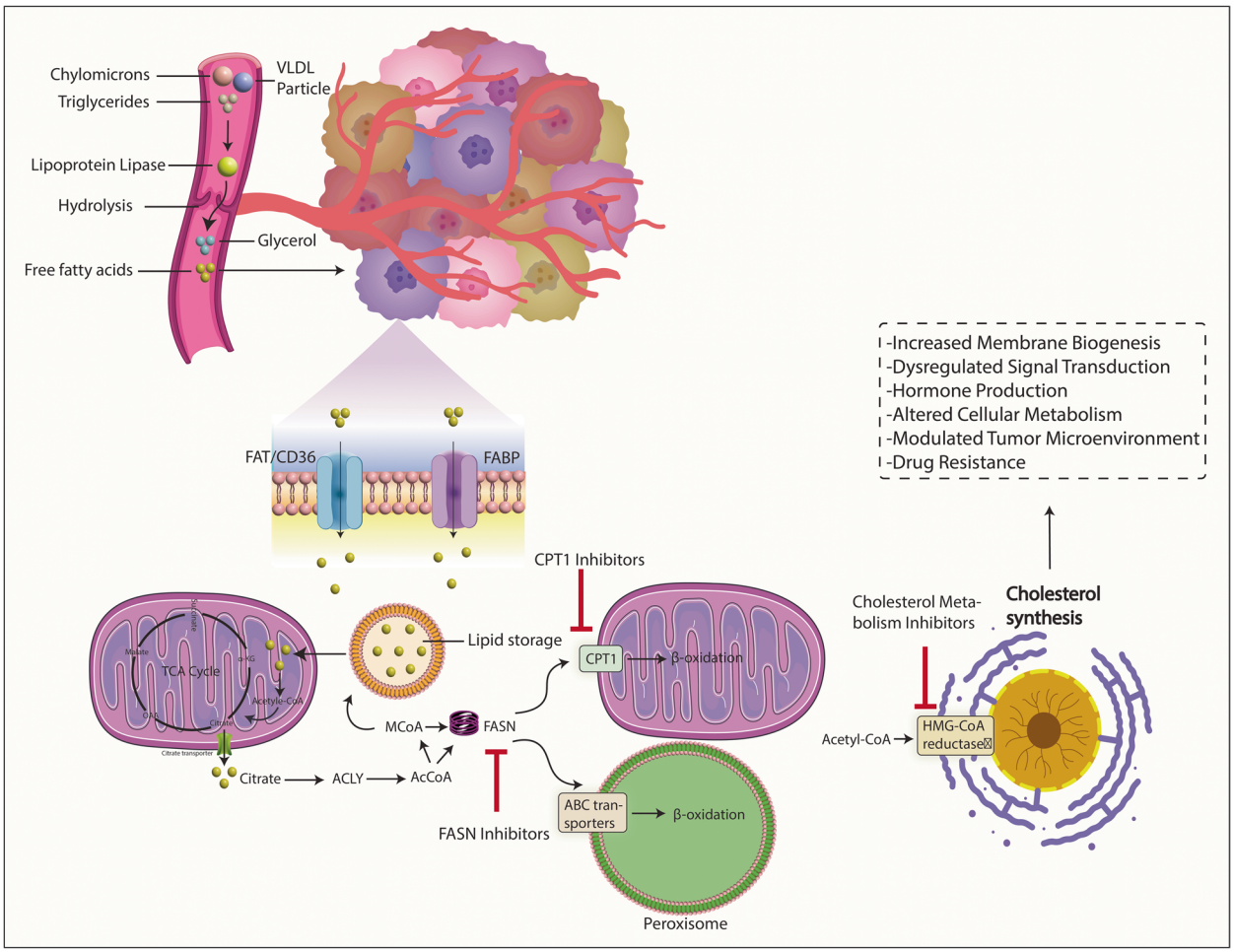


Fig. 4 This figure illustrates the comprehensive pathways of lipid metabolism in cancer cells, highlighting key processes such as lipid uptake, storage, fatty acid synthesis, β-oxidation, and cholesterol metabolism. Lipid uptake involves lipoprotein lipase (LPL), fatty acid transporters (FAT/CD36, FABP), and the formation of lipid droplets. Fatty acid synthesis is detailed from the conversion of citrate to acetyl-CoA, catalyzed by enzymes including ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FASN), with regulation by stearoyl-CoA desaturase (SCD). The figure also depicts fatty acid oxidation (β-oxidation) within mitochondria and peroxisomes, mediated by carnitine palmitoyltransferase I (CPT1) and acyl-CoA dehydrogenases (ACAD). Cholesterol metabolism is shown, which can lead to the progression of cancer. Additionally, potential therapeutic targets and inhibitors, such as FASN and CPT1 inhibitors, are marked, underscoring their relevance in cancer treatment

Cancer-associated fibroblasts (CAFs) and adipocytes within the TME can supply fatty acids to cancer cells, supporting their metabolic needs. Additionally, hypoxic conditions within the TME can induce lipid droplet formation in cancer cells, serving as energy reservoirs that can be mobilized during periods of metabolic stress [114]. As, in a mouse model of gastric cancer, lipid aggregation in tumor-associated macrophages (TAMs) upregulated the expression of phosphoinositide 3-kinase (PI3K-γ) and promoted TAM polarization to the M2 phenotype. This lipid metabolism in TAMs is closely associated with immunosuppression and chemotherapy resistance [127]. Immune cells within the TME, such as TAMs, also exhibit altered lipid metabolism. TAMs can undergo metabolic reprogramming to support tumor growth and suppress anti-tumor immunity. For instance, TAMs often rely on FAO and exhibit increased lipid uptake, which can promote their pro-tumoral functions. Targeting the lipid metabolic pathways in these cells represents a potential therapeutic strategy to modulate the TME and enhance anti-tumor immunity [114].

Given the critical role of lipid metabolism in cancer, targeting lipid metabolic pathways offers promising therapeutic opportunities [128]. Inhibitors of key enzymes involved in de novo lipogenesis, such as FASN inhibitors, have shown potential in preclinical models [129]. Targeting fatty acid uptake and FAO are also being explored as therapeutic strategies. For instance, inhibitors of CD36

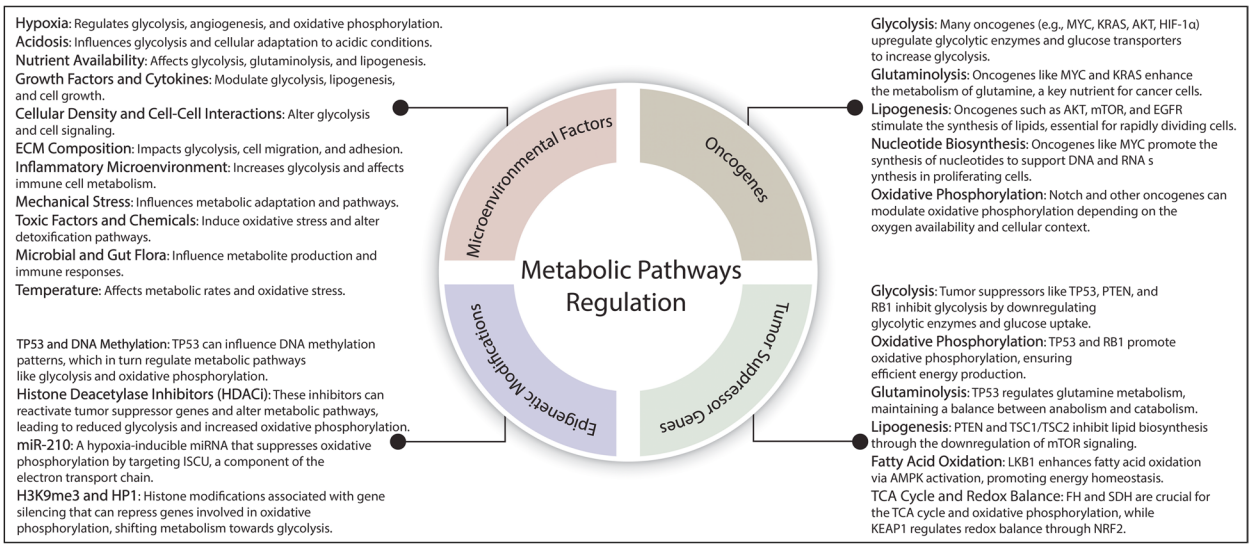


Fig. 5 The figure illustrates the regulatory landscape of metabolic pathways in cancer, highlighting key influences from oncogenes (e.g., MYC, RAS) and tumor suppressor genes (e.g., p53, PTEN). Epigenetic modifications (DNA methylation, histone marks) are shown in the figure with its regulatory role. Microenvironmental factors such as hypoxia, nutrient availability (glucose, glutamine), and immune interactions are illustrated to impact metabolic adaptations in cancer cells. Interactions and feedback loops between these regulatory elements are represented, emphasizing how oncogene activation may enhance glycolysis and alter mitochondrial function, and how epigenetic silencing affects metabolic enzyme expression

and FAO have demonstrated anti-tumor effects in various cancer models [130]. Furthermore, strategies to disrupt lipid signaling pathways, such as PI3K/Akt inhibitors and modulators of sphingolipid metabolism, are under investigation. Combining lipid metabolism-targeting therapies with conventional treatments, such as chemotherapy and immunotherapy, may enhance therapeutic efficacy and overcome resistance.

Regulation of metabolic pathways

Oncogenes and tumor suppressors

In cancer, metabolic pathways can be regulated through various mechanisms, including oncogenes, tumor suppressor genes, epigenetic modifications, and microenvironmental factors (Fig. 5). Cancer involves genetic alterations and significant metabolic changes [131, 132]. The deregulation of metabolic pathways is a hallmark of cancer, heavily influenced by the activities of oncogenes and tumor suppressors [133]. Understanding how these genes regulate metabolism is crucial for developing targeted cancer therapies.

Oncogenes are mutated or overexpressed versions of normal genes, known as proto-oncogenes, that drive uncontrolled cell growth and proliferation [134, 135]. Several oncogenes are known to alter metabolic pathways to support the high energy and biosynthetic demands of rapidly proliferating cancer cells. For example, the MYC oncogene, a transcription factor, upregulates genes involved in glycolysis, glutaminolysis, and nucleotide biosynthesis. MYC enhances the expression of glucose transporters and glycolytic enzymes while stimulating glutamine metabolism, which feeds into the TCA cycle and supports biosynthesis [136, 137]. Similarly, the RAS family of proteins activates pathways like PI3K/AKT and MAPK, which enhance glucose uptake, glycolysis, lipid biosynthesis, and macromolecular synthesis, all crucial for cell growth and proliferation [138]. The PI3K/AKT pathway, a major regulator of cellular metabolism, promotes glucose uptake and glycolysis by upregulating glucose transporters and glycolytic enzymes [139]. Activated AKT enhances protein synthesis and inhibits apoptosis through mTOR signaling [140]. Another key player, HIF-1α, stabilizes under hypoxic conditions typical of tumors and increases the expression of glycolytic enzymes and glucose transporters, promoting anaerobic glycolysis. HIF-1α also upregulates vascular endothelial growth factor (VEGF), enhancing tumor angiogenesis and oxygen supply [141]. These oncogenes collectively shift cellular metabolism towards increased glycolysis, glutaminolysis, and lipid biosynthesis, supporting cancer cells' rapid growth and energy demands.

In contrast, tumor suppressors are genes that inhibit cell growth and proliferation, acting as a defense against cancer [142, 143]. They often counteract the effects of oncogenes and maintain cellular homeostasis. The tumor suppressor p53, for example, is a transcription factor

known as the "guardian of the genome." It responds to cellular stress and DNA damage by inducing cell cycle arrest, apoptosis, and senescence [144]. p53 also regulates metabolism by inhibiting glycolysis and promoting OXPHOS [145]. It activates the expression of TIGAR, which lowers glycolysis and enhances the pentose phosphate pathway, providing antioxidant defense [146].

AMP-activated protein kinase (AMPK) is another critical tumor suppressor, acting as a cellular energy sensor activated by low ATP levels [147, 148]. AMPK inhibits anabolic processes and promotes catabolic processes to restore energy balance [149]. It inhibits mTOR signaling, reduces protein synthesis, and enhances fatty acid oxidation and glucose uptake [150]. LKB1, a tumor suppressor, activates AMPK and several other kinases involved in cellular metabolism, promoting oxidative metabolism and inhibiting mTOR, thereby reducing cell growth and proliferation [151].

The balance between oncogenes and tumor suppressors determines the metabolic phenotype of a cell [152]. In cancer cells, oncogenes are often upregulated or mutated, leading to enhanced glycolysis, glutaminolysis, and biosynthesis [21]. Conversely, tumor suppressors are often inactivated, removing their inhibitory effects on metabolism and allowing uncontrolled cell growth [153]. Targeting metabolic pathways influenced by oncogenes and tumor suppressors presents a promising approach to cancer therapy. For instance, glycolysis inhibitors, such as 2-deoxy-D-glucose, can starve cancer cells of energy, while glutaminase inhibitors can reduce the supply of TCA cycle intermediates [154]. AMPK activators can restore metabolic balance and inhibit cancer cell growth [155]. Therefore, understanding the metabolic regulation by oncogenes and tumor suppressors can lead to the development of personalized cancer therapies aimed at specific metabolic vulnerabilities of cancer cells. This approach holds promise for more effective and targeted treatments, potentially improving outcomes for cancer patients.

Epigenetic modifications

Epigenetic modifications are fundamental in regulating metabolic pathways in cancer, significantly influencing cancer progression, adaptation, and survival [156, 157]. These modifications, including DNA methylation, histone modifications, and non-coding RNAs, modulate gene expression without altering the underlying DNA sequence [157, 158]. The complex relationship between epigenetic changes and metabolic reprogramming is pivotal for the aggressive nature of cancer cells [159].

DNA methylation, the addition of a methyl group to the 5-carbon of cytosine residues within CpG dinucleotides, typically leads to gene silencing. This modification can silence key metabolic genes, affecting pathways such as glycolysis, the tricarboxylic acid (TCA) cycle, and lipid metabolism. For instance, the hypermethylation of genes regulating HIF-1α can enhance its stability and activity, promoting the glycolytic phenotype known as the Warburg effect, which is common in cancer cells [160]. Additionally, DNA methylation can regulate genes involved in glutaminolysis, crucial for providing intermediates for the TCA cycle and biosynthesis in rapidly proliferating cancer cells [161].

Histone modifications also play a significant role in cancer metabolism. Histones, the protein components of chromatin, undergo various post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination, which influence chromatin structure and gene expression. Histone acetylation, mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), generally leads to an open chromatin structure and active transcription [162]. Acetylation of histones at promoters of glycolytic genes enhances their expression, while HDACs can repress genes involved in lipid metabolism, affecting lipid synthesis and oxidation [163]. Similarly, histone methylation can either activate or repress transcription depending on the specific amino acid residues methylated and the number of methyl groups added [164]. This modification can regulate the expression of enzymes involved in the TCA cycle, impacting energy production, biosynthetic precursor availability, and one-carbon metabolism, crucial for nucleotide biosynthesis and methylation reactions [164].

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are also key players in the post-transcriptional regulation of gene expression in cancer metabolism [165]. miRNAs can degrade mRNA or inhibit its translation, affecting various metabolic pathways [166]. For example, miRNAs can target mRNAs of enzymes in glycolysis and gluconeogenesis, altering glucose uptake and utilization [167]. They can also modulate the expression of key enzymes in lipid biosynthesis and breakdown, influencing lipid availability and membrane synthesis. For example, microRNA-195 inhibits breast cancer cell proliferation, invasion, and metastasis by targeting FASN, HMGCR, ACACA, and CYP27B1 [168]. On the other hand, lncRNAs can act as scaffolds, guides, or decoys for chromatin-modifying complexes, impacting gene expression related to amino acid metabolism and redox balance, which are essential for the metabolic needs of cancer cells [169].

The integration of epigenetic modifications and metabolic pathways in cancer is complex and dynamic [170, 171]. Cancer cells often undergo metabolic reprogramming to meet their increased energy and biosynthetic demands, and epigenetic modifications can facilitate this

reprogramming by altering the expression of metabolic enzymes and pathways [152]. For instance, the Warburg effect is supported by the epigenetic silencing of mitochondrial genes and the activation of glycolytic genes, enabling cancer cells to rely on glycolysis for energy production even in the presence of oxygen [172]. Moreover, metabolites themselves can influence epigenetic modifications [173]. For example, α-ketoglutarate, a TCA cycle intermediate, acts as a cofactor for DNA and histone demethylases, linking metabolism directly to epigenetic regulation [174]. S-adenosylmethionine (SAM), a methyl donor for DNA and histone methylation, and NAD+, required for the activity of sirtuins (a class of HDACs), exemplify the direct connection between metabolic intermediates and epigenetic modifications [175].

The therapeutic implications of targeting epigenetic modifications in cancer metabolism are profound. Epigenetic therapies, such as DNA methyltransferase inhibitors (e.g., 5-azacytidine) and HDAC inhibitors (e.g., vorinostat), can reactivate silenced metabolic genes and disrupt the metabolic adaptations of cancer cells [157, 176]. Combining epigenetic drugs with metabolic inhibitors can enhance therapeutic efficacy by targeting the metabolic vulnerabilities of cancer cells [159, 177]. Such as, studies have explored the combination of the histone deacetylase inhibitor vorinostat with different agents in cancer treatment. In one phase I study, vorinostat was safely administered up to 400 mg once daily or 300 mg twice daily with carboplatin and paclitaxel in 28 patients with advanced solid malignancies, demonstrating promising activity [178]. Another phase I study investigated vorinostat combined with pazopanib or ixazomib in patients with metastatic TP53 mutant solid tumors. Results showed that the pazopanib and vorinostat combination yielded significantly higher clinical benefit rates (45% vs. 3.4%; $p<0.001$), longer median progression-free survival (3.5 months vs. 1.7 months; $p=0.002$), and longer median overall survival (12.7 months vs. 7.3 months; $p=0.24$) compared to ixazomib and vorinostat. These findings suggest that antiangiogenesis-based therapy with pazopanib may offer superior clinical outcomes [179]. Additionally, epigenetic modifications can serve as biomarkers for cancer diagnosis, prognosis, and treatment response, providing insights into the metabolic state and potential therapeutic targets in cancer [156, 157]. One example of epigenetic modifications serving as biomarkers in cancer is the role of DNA methylation in CRC. In CRC, specific patterns of DNA methylation, such as hypermethylation of the MLH1 gene promoter, are associated with microsatellite instability (MSI), which is a hallmark of certain CRC subtypes. The presence of MSI can help diagnose and prognosticate CRC, as well as guide treatment decisions [180]. For instance, MSI-high tumors are often more responsive to immune checkpoint inhibitors [181, 182]. Thus, DNA methylation status not only aids in the diagnosis and prognosis of CRC but also provides valuable information for selecting targeted therapies, illustrating how epigenetic modifications can offer insights into cancer's metabolic state and therapeutic strategies.

Microenvironmental factors

The TME is a complex and dynamic network surrounding cancer cells, composed of various cellular and non-cellular components that significantly influence cancer progression and metastasis [183]. This microenvironment includes stromal cells such as fibroblasts, immune cells like macrophages and lymphocytes, endothelial cells forming blood vessels, and the extracellular matrix (ECM) [184]. Each component interacts with cancer cells through biochemical and mechanical signals, creating a niche that supports tumor growth and resistance to therapies [185].

One of the critical elements in the TME is CAFs, which secrete growth factors, cytokines, and ECM components that facilitate tumor cell proliferation, invasion, and angiogenesis [186]. CAFs also contribute to the remodeling of the ECM, providing structural support for tumor expansion and creating barriers to immune cell infiltration [187]. Similarly, immune cells within the TME can adopt pro-tumorigenic roles [188]. For example, TAMs often display an M2-like phenotype that promotes tissue repair and immunosuppression, aiding in tumor immune evasion [189].

Hypoxia, a common feature of solid tumors due to aberrant vasculature, further complicates the TME [190]. Hypoxic conditions stabilize HIFs, which activate a transcriptional program that promotes angiogenesis, metabolic reprogramming, and EMT [191]. This adaptation enables cancer cells to survive in low-oxygen conditions and increases their metastatic potential [192]. Additionally, the acidic and nutrient-depleted environment of the TME results from altered metabolic activity of cancer cells, influencing the behavior of surrounding stromal and immune cells [193].

The interplay between metabolic pathways and the TME further emphasizes the complexity of cancer metabolism. Nutrient availability, such as glucose and amino acids, in the TME influences the metabolic state of cancer and stromal cells. Moreover, metabolic byproducts like lactate can modulate immune cell function, creating an immunosuppressive microenvironment that favors tumor progression [194]. For example, in CRC, tumor cells undergo metabolic changes that alter the availability of nutrients like glucose and amino acids in the TME. This reprogramming leads to an increased reliance on

aerobic glycolysis, commonly referred to as the Warburg effect, where cancer cells preferentially convert glucose to lactate even in the presence of oxygen. This process not only supports rapid tumor growth but also results in the accumulation of lactate in the TME, creating an acidic environment that can suppress immune responses [195, 196]. Targeting these metabolic adaptations presents a promising strategy for cancer therapy, aiming to disrupt the metabolic flexibility of cancer cells and sensitize them to conventional treatments.

Inhibitors for targeting cancer metabolism

Glycolytic inhibitors

Cancer cells often exhibit altered metabolism, characterized by increased glucose uptake and glycolysis, even in the presence of oxygen. This metabolic reprogramming supports rapid cell proliferation and survival. Consequently, targeting glycolysis has emerged as a potential therapeutic strategy in cancer treatment. Various glycolytic inhibitors have been developed to exploit the dependence of cancer cells on this pathway [197]. Table 1 provides an overview of glycolytic inhibitors, their clinical trial phases, status, conditions studied, and respective study periods (Table 1).

Hexokinase inhibitors, such as 2-Deoxy-D-glucose (2-DG) and Lonidamine, play a crucial role in disrupting the initial steps of glycolysis. 2-DG is a glucose analog that competes with glucose for phosphorylation by hexokinase, the enzyme responsible for the first step of glycolysis [198]. This competition impairs ATP production, leading to cancer cell death [199]. Lonidamine specifically inhibits hexokinase II (HKII), which is often overexpressed in cancer cells, thereby reducing glycolytic flux and inducing apoptosis [200]. Combination therapies involving these agents offer hope for improving cancer treatment outcomes. For example, the combination of 2-Deoxy-glucose (2-DG) with different therapeutic approaches has yielded contrasting outcomes in cancer therapy. The pairing of 2-DG with fenofibrate (FF) shows significant potential by synergistically inducing energy and endoplasmic reticulum (ER) stress in tumors, leading to energy depletion, inhibition of mTOR, and cancer cell death, highlighting a promising avenue for clinical development [201]. However, the combination of 2-DG with a ketogenic diet (KD) has resulted in significant dose-dependent toxicity, causing acute thrombocytopenia, interstitial pneumonia, and rapid mortality in treated mice, while being well tolerated on a standard diet [202]. Similarly, lonidamine has shown limited cytotoxicity on its own but significantly enhances the efficacy of various chemotherapeutic agents, such as 5-fluorouracil, methotrexate, etoposide, cisplatin, and mitomycin C, in both mouse and human fibrosarcoma cell lines. Its enhancement of drug effectiveness is time- and concentration-dependent, suggesting its potential role in combination therapies to improve cancer treatment outcomes. By targeting energy metabolism pathways, including monocarboxylate transporter (MCT) and mitochondrial pyruvate carrier (MPC) inhibition, lonidamine selectively targets tumors without causing common side effects like alopecia and myelosuppression [203]. Furthermore, it has shown promising synergistic effects when used alongside physical therapies such as radiotherapy, hyperthermia, and photodynamic therapy [204]. This suggests that combination therapies with hexokinase inhibitors like 2-Deoxy-D-glucose (2-DG) and lonidamine can enhance cancer treatment effectiveness. While 2-DG shows promise when paired with fenofibrate, it can cause severe toxicity with a ketogenic diet. Lonidamine enhances the efficacy of various chemotherapeutic agents and physical therapies, offering potential in multidrug strategies, though outcomes depend on the specific combinations used.

Moreover, inhibitors of phosphofructokinase, such as 3-PO, target a rate-limiting enzyme in glycolysis. 3-PO (3-(3-Pyridinyl)-1-(4-pyridinyl)-2-propen-1-one) was initially thought to inhibit PFKFB3, rather than phosphofructokinase-1 (PFK-1) [205, 206]. However, recent research has revealed that 3-PO does not directly bind to or inhibit PFKFB3 [206]. Instead, it reduces glycolytic activity in cancer cells by a different mechanism. 3-PO accumulates lactic acid inside cells, leading to a decrease in intracellular pH and the subsequent inhibition of glycolytic enzymes [206]. This inhibition of glycolysis can impair cancer cell growth and survival [205], but it is not due to the direct inhibition of PFK-1 or PFKFB3 as previously thought [207]. In contrast, koningic acid is a selective inhibitor of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), disrupting the glycolytic pathway, reducing ATP production, and promoting apoptosis in some cancer cells. While 3-PO and koningic acid affect glycolysis, they do so through different mechanisms and target distinct enzymes within the pathway [207].

Furthermore, targeting pyruvate kinase M2 (PKM2), an isoform expressed in cancer cells that promotes aerobic glycolysis, is another strategy [208]. Shikonin and TEPP-46 are notable PKM2 inhibitors. Shikonin disrupts the final step of glycolysis, reducing ATP production and causing cancer cell death [209]. TEPP-46, on the other hand, activates PKM2, shifting it from its less active dimeric form to the more active tetrameric form, thereby impairing cancer cell proliferation. For example, TEPP-46 was investigated as a potential treatment for triple-negative breast cancer (TNBC). PKM2 phosphorylation at S37 was associated with aggressive breast cancer

Table 1 Overview of inhibitors that target glycolysis directly or indirectly

Glycolytic inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
2-deoxy-D-glucose (2DG)	NCT00096707	Phase 1	Complete	Inhibits hexokinase, reducing glycolysis by competing with glucose.	2004–2008
	NCT00633087	Phase 1/2	Complete		2006–2011
	NCT00247403	Phase 1	Complete		2005–2008
STF31	N/A	N/A	Preclinical studies	Inhibits the glucose transporter GLUT1, reducing glucose uptake and glycolysis.	N/A
Phloretin	N/A	N/A	Preclinical studies	Inhibits glucose transporters GLUT1 and GLUT2, affecting glycolysis indirectly.	N/A
WZB117	N/A	N/A	Preclinical studies	Inhibits the glucose transporter GLUT1, reducing glucose uptake and glycolysis.	N/A
3PO (PFKFB3 inhibitor)	N/A	N/A	Preclinical studies	Inhibits PFKFB3, reducing levels of fructose-2,6-bisphosphate and thereby decreasing glycolytic flux.	N/A
Dichloroacetate (DCA)	NCT05120284	Phase 2	Recruiting	Inhibits pyruvate dehydrogenase kinase (PDK), shifting metabolism from glycolysis to oxidative phosphorylation.	2022–2025
	NCT00703859	Phase 1	Withdrawn		2008–2010
	NCT00540176	Phase 2	Completed		2007–2009
	NCT01163487	Phase 1	Completed		2010–2016
	NCT01386632	Phase 2	Completed		2011–2020
	NCT01111097	Phase 1	Completed		2010–2014
	NCT01029925	Phase 2	Terminated		2009–2011
	NCT00566410	Phase 1	Completed		2007–2013
Oxamic acid	N/A	N/A	Preclinical studies	Inhibits lactate dehydrogenase (LDH), disrupting the conversion of pyruvate to lactate in glycolysis.	N/A
Galloflavin	N/A	N/A	Preclinical studies	Inhibits lactate dehydrogenase (LDH).	N/A
Oxamate	N/A	N/A	Preclinical studies	Inhibits lactate dehydrogenase (LDH).	N/A
FX11	N/A	N/A	Preclinical studies	Inhibits lactate dehydrogenase A (LDHA).	N/A
AZD3965	NCT01791595	Phase 1	Completed	Inhibits MCT1, preventing lactate export, leading to intracellular acidification and inhibition of glycolysis. Effective in cancer cells with high glycolytic rates.	2013–2020
BAY-876	N/A	N/A	Preclinical studies	Inhibits the glucose transporter GLUT1.	N/A
Iodoacetate	N/A	N/A	Preclinical studies	Inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH).	N/A
Koningic acid (KA)	N/A	N/A	Preclinical studies	Inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH).	N/A
3-Bromopyruvate (3-BP)	N/A	N/A	Preclinical studies	Inhibits glycolysis by targeting hexokinase II, disrupting ATP production and causing metabolic stress, particularly in cancer cells.	N/A
Gossypol	NCT01977209	Phase 3	Unknown	Inhibits glycolysis by targeting multiple enzymes, including hexokinase and lactate dehydrogenase, leading to reduced ATP production and metabolic stress, particularly in cancer cells.	2013–2016
	NCT00848016	Phase 2	Completed		2009–2012
	NCT00544596	Phase 1	Completed		2007–2013
	NCT00540722	Phase 2	Completed		2008–2012
	NCT00666666	Phase 2	Completed		2009–2012
	NCT00773955	Phase 2	Completed		2008–2010
	NCT00390403	Phase 1	Completed		2007–2009
	NCT00286793	Phase 1/2	Completed		2006–2009
	NCT00275431	Phase 2	Completed		2005–2008
	NCT00286806	Phase 1/2	Completed		2005–2007
	NCT00561197	Phase 1/2	Terminated		2007–2010
	NCT06133088	Phase 2	Recruiting		2023–2025
	NCT00286780	Phase 2 Phase 1/2	Completed		2006–2007
	NCT00397293	Phase 1	Completed		2006–2008
	NCT00891072	Phase 2	Completed		2009–2011
	NCT01633541	Phase 2	Completed		2012–2021
	NCT01285635	Phase 1	Terminated		2010–2015
	NCT00934076	Phase 2	Withdrawn		2010–2015
	NCT00440388	Phase 1/2	Completed		2006–2008
	NCT01003769	Phase 1/2	Terminated		2015–2018
	NCT05338931	Phase 2	Recruiting		2022–2030
	NCT00988169	Phase 2	Terminated		2009–2010
	NCT00544960	Phase 1	Completed		2007–2009
	NCT02697344	Phase 2	Completed		2016–2023
	NCT00571675		Completed		2007–2010
AZD3965	NCT01791595	Phase 1	Completed	MCT1 inhibitor (indirectly affects glycolysis)	2013–2020

Table 1 (continued)

Glycolytic inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Syrosingopine	N/A	N/A	Preclinical studies	MCT1/MCT4 inhibitor (indirectly affects glycolysis)	N/A
PFK158	NCT02044861	Phase 1	Unknown	Targets the PFKFB3	2014–2015
Shikonin	N/A	N/A	Preclinical studies	Targets the PKM2	N/A

phenotypes. TEPP-46 reduced PKM2 nuclear localization, inhibited tumor growth in a TNBC mouse xenograft model, and synergized with a CDK inhibitor to impair cell invasion and trigger cancer cell death [210].

Lactate dehydrogenase (LDH) inhibitors, such as galloflavin [211] and FX11 [212], prevent the conversion of pyruvate to lactate, a crucial step in glycolysis. By inhibiting LDH, these agents disrupt glycolysis, reducing lactate production and impairing cancer cell growth [212, 213]. These inhibitors are particularly effective in tumors with high glycolytic rates, where they can induce significant metabolic stress.

The mechanisms of action of glycolytic inhibitors encompass various aspects of cancer cell metabolism [52]. These inhibitors cause energy deprivation by reducing ATP production, which is essential for cancer cell survival [214]. They also inhibit biomass production by limiting intermediates for biosynthetic pathways, thus impairing cancer cell growth and proliferation [21]. Disrupting glycolysis can increase reactive oxygen species (ROS) levels, leading to oxidative stress and cell death [154]. Glycolytic inhibitors can also enhance the efficacy of other cancer treatments, such as chemotherapy and radiotherapy, by sensitizing tumors to conventional therapies [215].

Despite their potential, the clinical application of glycolytic inhibitors faces several challenges. Selective targeting of cancer cells without affecting normal cells is crucial to minimize toxicity [59, 60]. This is because normal cells also rely on glycolysis, making it difficult to target cancer cells specifically without harming healthy tissues. Cancer cells can develop resistance to glycolytic inhibitors through various mechanisms, such as upregulation of alternative metabolic pathways, necessitating combination therapies and biomarkers for resistance [59, 216]. For example, cancer cells may adapt by increasing oxidative phosphorylation or glutaminolysis when glycolysis is inhibited. Additionally, the potential toxicity and side effects of glycolytic inhibitors must be carefully managed, particularly in tissues with high glycolytic activity like the brain and muscles. These tissues rely heavily on glucose metabolism for their normal function, and inhibiting glycolysis could lead to serious side effects. Developing effective glycolytic inhibitors with suitable pharmacokinetic properties for clinical use remains a challenge. Many compounds that show promise in preclinical studies may not have the desired properties for use in humans, such as appropriate bioavailability or half-life. Furthermore, the complex interplay between cancer cell metabolism and the immune system needs to be considered when developing glycolytic inhibitors. Inhibiting glycolysis may affect immune cell function, potentially compromising the body's natural defense against cancer.

Based on metabolic profiling of tumors, personalized medicine approaches can enhance therapeutic efficacy of glycolytic inhibitors by identifying patients most likely to benefit from these treatments. Understanding the metabolic heterogeneity of tumors is crucial for developing effective therapies. By addressing these challenges, glycolytic inhibitors can become a valuable addition to the arsenal of cancer treatments, offering new hope for patients with metabolic vulnerabilities in their tumors.

Glutaminase inhibitors

Cancer metabolism has been a focal point of research due to its critical role in the proliferation and survival of cancer cells. One of the central metabolic pathways by cancer cells is glutamine metabolism [106, 217]. Glutamine, a non-essential amino acid, becomes essential for the rapid growth and survival of cancer cells [106]. This is largely because glutamine serves as a carbon and nitrogen source for nucleotide and amino acid synthesis, which are crucial for the growth of proliferating cells [106, 217]. Glutamine serves as a precursor for various biosynthetic processes, including lipid synthesis and energy production through the TCA cycle [106]. The enzyme glutaminase, which converts glutamine to glutamate, is a key player in this metabolic pathway [106, 218]. Consequently, glutaminase inhibitors have emerged as promising therapeutic targets in cancer treatment (Table 2).

Glutaminase exists in two major isoforms in humans: GLS1 (kidney-type glutaminase) and GLS2 (liver-type glutaminase) [100, 219]. GLS1 is predominantly expressed in cancer cells, making it an attractive target for cancer therapy [219]. Inhibition of GLS1 disrupts the conversion of glutamine to glutamate, leading to a reduction in the production of key metabolites required for cell growth and survival [220, 221]. This, in turn, can induce cell death in glutamine-dependent cancer cells [221].

Table 2 Overview of glutaminase inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Telaglenastat (CB-839)	NCT04824937	Phase 2	Unknown	Telaglenastat blocks glutaminase, an enzyme overproduced in some cancers that fuels growth. By inhibiting glutaminase.	2021–2021
	NCT04250545	Phase 1	Active (Not recruiting)		2020–2025
	NCT05521997	Phase 2	Not recruiting		2024–2030
	NCT03875313	Phase 1/2	Terminated		2019–2020
	NCT03057600	Phase 2	Completed		2017–2019
	NCT02771626	Phase 1/2	Terminated		2016–2020
	NCT03798678	Phase 1	Active (Not recruiting)		2019–2025
	NCT03872427	Phase 2	Active (Not recruiting)		2019–2024
	NCT03163667	Phase 2	Completed		2017–2020
	NCT03528642	Phase 1	Active (Not recruiting)		2019–2024
	NCT03965845	Phase 1/2	Completed		2019–2021
	NCT03428217	Phase 2	Completed		2018–2021
	NCT03831932	Phase 1/2	Active (Not recruiting)		2020–2025
	NCT04265534	Phase 2	Terminated		2020–2022
DON	N/A	N/A	Preclinical studies	Inhibits multiple enzymes in glutamine metabolism, including glutaminase.	N/A
BPTES	N/A	N/A	Preclinical studies	BPTES is a selective non-competitive inhibitor of GLS1, binding to an allosteric site to reduce its activity. This decreases glutamate production, impairing the TCA cycle and biosynthetic processes in cancer cells.	N/A
986	N/A	N/A	Preclinical studies	968 is a selective glutaminase inhibitor that blocks the enzyme's active site, preventing the conversion of glutamine to glutamate and limiting glutamate availability for the TCA cycle and other metabolic processes in cancer cells.	N/A
V-9302	N/A	N/A	Preclinical studies	Targets the glutamine transporter ASCT2 (SLC1A5).	N/A

Several studies have demonstrated that glutaminase inhibitors can effectively suppress tumor growth in various cancer models, highlighting their potential as therapeutic agents [100, 220].

One of the most well-known glutaminase inhibitors is CB-839 (Telaglenastat), which selectively inhibits GLS1. Preclinical studies have shown that CB-839 can reduce tumor growth in multiple cancer types [110]. These findings have led to several clinical trials to evaluate the safety and efficacy of CB-839 in cancer patients. Early-phase clinical trials have reported promising results, with CB-839 demonstrating acceptable safety profiles and preliminary evidence of anti-tumor activity. These results have spurred further investigations into the combination of glutaminase inhibitors with other therapeutic agents to enhance their efficacy. For example, in a phase I clinical trial, telaglenastat is being investigated for its safety and efficacy when combined with radiation therapy (RT) and temozolomide (TMZ) in patients with untreated IDH mutant astrocytomas, where it depletes intracellular glutamate and enhances RT efficacy [222]. Similarly, in advanced renal cell carcinoma (mRCC), telaglenastat combined with everolimus demonstrated a favorable safety profile and improved progression-free survival (PFS) in patients previously treated with tyrosine kinase inhibitors (TKIs) and checkpoint inhibitors, suggesting the potential benefit of dual targeting glucose and glutamine metabolism in these cancers [223].

The combination of glutaminase inhibitors with other cancer therapies represents a promising approach to enhance treatment efficacy. Cancer cells often exhibit metabolic flexibility, allowing them to adapt to metabolic stress by switching to alternative pathways. Therefore, combining glutaminase inhibitors with other metabolic inhibitors or standard chemotherapies can create a synthetic lethality scenario, where the simultaneous targeting of multiple pathways overwhelms the cancer cells' adaptive capacity. For example, combining CB-839 with inhibitors of the PI3K/AKT/mTOR pathway, which is often upregulated in cancer, can improve the therapeutic effects [106, 224].

Despite the promising potential of glutaminase inhibitors, several challenges remain. One major challenge is the heterogeneity of tumors and the metabolic plasticity of cancer cells. Not all tumors are equally dependent on glutamine metabolism, and some may develop resistance to glutaminase inhibition by activating alternative metabolic pathways. Therefore, identifying biomarkers that can predict which tumors are most likely to respond to glutaminase inhibitors is crucial for the successful implementation of this therapeutic strategy. Additionally, understanding the mechanisms

Table 3 Overview of the tricarboxylic acid (TCA) cycle inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Fluoroacetate	N/A	N/A	Preclinical studies	Fluoroacetate is metabolized to fluorocitrate, which inhibits aconitase, thereby blocking the conversion of citrate to isocitrate.	N/A
Arsenite	N/A	N/A	Preclinical studies	Arsenite binds to lipoic acid, a cofactor for these enzyme complexes, inhibiting their activity.	N/A
Malonate	N/A	N/A	Preclinical studies	Malonate is a competitive inhibitor of succinate dehydrogenase, blocking the conversion of succinate to fumarate.	N/A
Oxaloacetate	NCT04290897	Phase 2	Recruiting	High levels of oxaloacetate can inhibit citrate synthase through feedback inhibition.	2021–2025
Dimethyl malonate	N/A	N/A	Preclinical studies	Similar to malonate, dimethyl malonate competitively inhibits succinate dehydrogenase.	N/A
Alpha-cyano-4-hydroxycinnamate (CHC)	N/A	N/A	Preclinical studies	CHC inhibits the mitochondrial pyruvate carrier, reducing the entry of pyruvate into the TCA cycle.	N/A
Bromopyruvate	N/A	N/A	Preclinical studies	Inhibits hexokinase and pyruvate dehydrogenase, disrupting glycolysis and the TCA cycle and reducing cellular energy production.	N/A
Oligomycin	N/A	N/A	Preclinical studies	Oligomycin inhibits ATP synthase, leading to a buildup of proton gradient and inhibition of the electron transport chain, which indirectly affects the TCA cycle by reducing NAD + and FAD regeneration.	N/A

underlying resistance to glutaminase inhibition will be essential for developing strategies to overcome resistance and improve patient outcomes.

Inhibitors of the tricarboxylic acid (TCA) cycle

The TCA cycle operates within the mitochondria, where it generates ATP, NADH, and FADH2 through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. These products are essential for the electron transport chain and oxidative phosphorylation. The cycle involves several key enzymes, including citrate synthase, aconitase, isocitrate dehydrogenase (IDH), alpha-ketoglutarate dehydrogenase, succinyl-CoA synthetase, succinate dehydrogenase (SDH), fumarase, and malate dehydrogenase. Dysregulation of these enzymes is often observed in various cancers, making them potential therapeutic targets [225, 226].

Succinate dehydrogenase (SDH), a component of both the TCA cycle and the electron transport chain, is another critical enzyme. Mutations in SDH genes are linked to hereditary paragangliomas, pheochromocytomas, and renal cell carcinoma [227]. Loss of SDH function leads to succinate accumulation, which inhibits alpha-ketoglutarate-dependent dioxygenases and stabilizes HIFs, promoting tumorigenesis [228, 229]. While direct inhibitors of mutant SDH are still under investigation, targeting the metabolic and signaling consequences of SDH loss [230], such as with HIF inhibitors, presents a potential strategy [231]. However, there is a scarcity of clinical trials for the inhibitors of the TCA cycle (Table 3).

Similarly, mutations in fumarase (FH) are associated with hereditary leiomyomatosis and renal cell cancer [232]. Loss of FH activity results in fumarate accumulation, leading to effects similar to those seen with SDH mutations, including HIF stabilization and epigenetic changes. Direct targeting of FH-deficient tumors often involves exploiting the metabolic vulnerabilities and stress responses induced by fumarate accumulation [38].

Strategies for targeting the TCA cycle in cancer therapy include metabolic flux analysis, synthetic lethality, and combination therapies. Metabolic flux analysis, using stable isotope tracing, maps altered metabolic pathways in cancer cells to identify key vulnerabilities. Exploiting synthetic lethality involves targeting secondary pathways cancer cells rely on due to TCA cycle alterations, such as inhibiting glycolysis in tumors with impaired oxidative phosphorylation. Combination therapies pair TCA cycle inhibitors with treatments like chemotherapy, targeted therapies, or immunotherapy to enhance efficacy and overcome resistance. Challenges include ensuring selectivity to minimize toxicity to normal cells, developing cancer-specific delivery systems, identifying biomarkers for patient stratification, and addressing resistance mechanisms through continuous monitoring and combination strategies. More clinical trials are needed to evaluate the safety and efficacy of TCA cycle inhibitors across various cancer types and develop personalized treatments based on each tumor's molecular context.

Fatty acid oxidation inhibitors

Cancer cells undergo significant metabolic reprogramming to support their rapid growth and proliferation. One critical metabolic pathway that these cells exploit is fatty acid oxidation (FAO), the process by which fatty

Table 4 Overview of the fatty acid oxidation inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Etomoxir	N/A	N/A	Preclinical studies	Inhibits carnitine palmitoyltransferase I (CPT-1), preventing the transport of long-chain fatty acids into the mitochondria for β-oxidation.	N/A
Perhexiline	N/A	N/A	Preclinical studies	Inhibits both CPT-1 and CPT-2, reducing mitochondrial fatty acid uptake and oxidation, and shifting myocardial energy metabolism from fatty acids to glucose.	N/A
Trimetazidine	NCT03278444	Phase 3	Unknown	Partially inhibits long-chain 3-ketoacyl-CoA thiolase (LC-3KAT), the last enzyme of the mitochondrial fatty acid β-oxidation pathway, thereby promoting glucose oxidation over fatty acid oxidation.	2017–2021
Ranexa	NCT01992016	N/A	Completed	Inhibits the late sodium current (INaL) in cardiac cells, which indirectly reduces fatty acid oxidation by altering myocardial energy metabolism.	2014–2018
Meldonium	N/A	N/A	Preclinical studies	Inhibits gamma-butyrobetaine dioxygenase, leading to reduced carnitine biosynthesis and transport, which in turn decreases fatty acid oxidation.	N/A
Oxfenicine	N/A	N/A	Preclinical studies	Specifically inhibits CPT-1, similar to etomoxir, reducing the mitochondrial uptake of long-chain fatty acids and their subsequent oxidation.	N/A
Teglicar	N/A	N/A	Preclinical studies	A potent CPT-1 inhibitor that reduces fatty acid transport into mitochondria, thereby decreasing fatty acid oxidation.	N/A
4-Hydroxyphenylglycine (HPG)	N/A	N/A	Preclinical studies	Inhibits CPT-1 activity, reducing the transport and oxidation of long-chain fatty acids in mitochondria.	N/A
HY-65,933	N/A	N/A	Preclinical studies	Inhibiting CPT-1, reducing fatty acid transport into mitochondria.	N/A
Cerulenin	N/A	N/A	Preclinical studies	Primarily inhibits fatty acid synthase (FAS), which indirectly affects fatty acid oxidation by reducing the availability of newly synthesized fatty acids.	N/A
Fasentin	N/A	N/A	Preclinical studies	Targets glucose transport and fatty acid metabolism, impacting fatty acid oxidation pathways, though the exact mechanism is less well-characterized. .	N/A
Bempedoic Acid	N/A	N/A	Preclinical studies	Inhibits ATP-citrate lyase, reducing cholesterol synthesis, which can also impact fatty acid metabolism by decreasing acetyl-CoA availability for fatty acid synthesis and oxidation. .	N/A

acids are broken down in the mitochondria to generate energy. Targeting FAO can disrupt the energy supply and metabolic flexibility of cancer cells, potentially suppressing their growth. As a result, fatty acid oxidation inhibitors (FAO inhibitors) have emerged as promising therapeutic agents in cancer treatment [49, 118] (Table 4). For example, a recent study highlights the metabolic switch from glucose to fatty acid-dependent anabolic and energy metabolism in cisplatin-resistant cancer cells. It demonstrates that inhibition of FAO re-sensitizes these cells to cisplatin treatment, suggesting a combinational therapy of FAO inhibitors and platinum drugs as a potential strategy [233].

FAO plays a pivotal role in cancer metabolism. While the reliance of cancer cells on glycolysis is well-documented, recent studies have highlighted the importance of FAO in cancer. FAO provides ATP, NADPH, and acetyl-CoA, all of which are crucial for maintaining cellular energy homeostasis, redox balance, and biosynthesis [234, 235]. The ATP generated through FAO supports the high energy demands of proliferating cancer cells, while NADPH helps maintain redox balance, protecting cells from oxidative stress [234, 235]. Additionally, acetyl-CoA produced from FAO is essential for fatty acid and cholesterol synthesis, necessary for membrane formation and signaling molecules [118, 236].

FAO inhibitors target various enzymes in the FAO pathway, reducing the availability of energy and essential metabolites for cancer cells. Key enzymes targeted by these inhibitors include Carnitine Palmitoyltransferase 1 (CPT1), Acyl-CoA Dehydrogenase (ACAD), and 3-Ketoacyl-CoA Thiolase (KAT) [234, 237]. CPT1, the rate-limiting enzyme in the transport of long-chain fatty acids into mitochondria, can be inhibited by drugs like etomoxir, blocking fatty acid entry and subsequent oxidation [118, 238]. ACAD inhibitors prevent the initial step of mitochondrial fatty acid β-oxidation, while KAT inhibitors halt the final step, leading to an accumulation of fatty acid intermediates [234, 237].

The therapeutic potential of FAO inhibitors in cancer treatment is significant. Cancer cells that heavily rely on FAO for energy and biosynthesis are particularly vulnerable to these inhibitors. By targeting FAO, these inhibitors can selectively kill cancer cells without affecting normal cells that rely more on glycolysis [239]. Moreover, FAO inhibitors can be used in combination with other cancer therapies to enhance their efficacy. For instance, combining FAO inhibitors with glycolysis inhibitors can target the metabolic flexibility of cancer

cells, making it harder for them to adapt and survive. Furthermore, FAO inhibitors may help overcome drug resistance, which is often a significant challenge in cancer treatment. By targeting the metabolic adaptations that contribute to resistance, FAO inhibitors can improve the effectiveness of conventional therapies.

Examples of FAO inhibitors that have shown potential in cancer therapy include etomoxir, perhexiline, and ranolazine [240, 241]. Etomoxir and perhexiline are CPT1 inhibitors that have demonstrated anticancer activity, particularly against FAO-dependent tumors such as prostate cancer and leukemia [241]. Perhexiline, which inhibits both CPT1 and CPT2, has shown promising results in preclinical cancer studies. It has been found to inhibit proliferation and induce apoptosis in prostate cancer cell lines. Additionally, perhexiline combined with antiandrogen therapies like abiraterone or enzalutamide has demonstrated robust growth inhibition in prostate cancer cell models, including those resistant to enzalutamide [240]. Such as, a previous study highlights the therapeutic potential of co-targeting the androgen receptor (AR) axis and lipid oxidation in metastatic castration-resistant prostate cancer (mCRPC). Inhibition of carnitine palmitoyltransferase 1 A (CPT1A), a key enzyme in lipid oxidation, reduces prostate cancer growth and invasion, with the CPT1A isoform being more abundant in high-grade tumors. Combining CPT1A inhibition with the antiandrogen enzalutamide enhances its efficacy, including in enzalutamide-resistant models, by decreasing AKT activation and increasing AR sensitivity. Fat oxidation inhibitors, such as perhexiline, etomoxir, and ranolazine, in combination with enzalutamide, have shown robust growth inhibition in PCa cell models. Preclinical results further demonstrate significant tumor growth reduction with systemic combination treatment, suggesting that dual targeting of AR and lipid oxidation, including with perhexiline, may offer an effective strategy for mCRPC treatment [242]. It's important to note that while these FAO inhibitors show promise in preclinical studies, their efficacy and safety in clinical cancer treatment still require further investigation.

Despite the promising potential of FAO inhibitors, several challenges remain. Achieving selectivity for cancer cells while sparing normal cells is a significant hurdle. FAO inhibitors need to be developed with a focus on selective targeting to minimize side effects. Additionally, cancer cells may develop resistance to FAO inhibitors through compensatory metabolic pathways. Understanding these resistance mechanisms will be crucial for developing combination therapies that can overcome them. Translating preclinical findings into clinical success also requires rigorous testing and validation in clinical trials.

Lactate dehydrogenase (LDH) inhibitors

Lactate dehydrogenase (LDH) inhibitors have emerged as a promising therapeutic strategy in cancer metabolism, targeting the altered metabolic pathways that are a hallmark of many malignancies. LDH is a key enzyme in the glycolytic pathway, catalyzing the conversion of pyruvate to lactate with concomitant regeneration of NAD+, a crucial step for maintaining glycolysis under anaerobic conditions [243, 244]. Cancer cells often exhibit increased glycolysis rates, even in the presence of oxygen [216, 245]. This metabolic reprogramming facilitates rapid proliferation and survival in the hypoxic TME [216, 245]. LDH inhibitors aim to disrupt this aberrant glycolytic flux, thereby reducing lactate production, acidification of the TME, and overall cancer cell survival [243, 246]. By inhibiting LDH, these agents can also impair the redox balance within cancer cells, leading to increased oxidative stress and apoptosis [246]. Additionally, targeting LDH can hinder the metabolic flexibility of cancer cells, making them more susceptible to other therapeutic interventions [243, 245]. Research and clinical trials are ongoing to optimize the efficacy and specificity of LDH inhibitors (Table 5), with some compounds showing promising preclinical results in reducing tumor growth and metastasis [243, 244]. For example, the pyrazole-based compound series (such as NCI-006) has been rigorously optimized, resulting in nanomolar IC50 values for lead compounds and demonstrated in vivo target engagement and efficacy with oral availability [216]. LDHB, another isoform of LDH, has also been identified as a potential target. LDHB plays a major role in the metabolic adaptability of cancer cells by controlling lysosomal activity and autophagy, enabling an oxidative phenotype [245]. Inhibition of both LDHA and LDHB could be therapeutically useful, as they participate in tumor-stroma metabolic interactions and the exchange of metabolic fuel. Moreover, combining LDH inhibitors like FX-11 with other agents such as DH348 (a CAIX inhibitor) significantly suppressed metastasis in prostate cancer models. Notably, FX-11 also showed synergy with immune checkpoint blockade (anti-PD-1) in pancreatic cancer models. These results suggest that addressing tumor acidity and lactate production could enhance the effectiveness of immunotherapy [247]. Thus, LDH inhibitors represent a novel and exciting avenue in the metabolic targeting of cancer therapy. However, challenges remain, including the need for improved potency, drug-like properties, and in vivo efficacy of natural product-derived LDH inhibitors. Future research should focus on integrating multiple disciplines, including natural product chemistry, medicinal chemistry, and pharmacology, to enhance the development of effective LDH inhibitors for cancer treatment.

Table 5 Overview of the lactate dehydrogenase (LDH) inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
FX11	N/A	N/A	Preclinical studies	FX11 inhibits LDHA, leading to decreased lactate production and an increase in oxidative stress within cancer cells. This inhibition disrupts glycolysis and induces cell death in glycolytic-dependent tumor cells.	N/A
Galloflavin	N/A	N/A	Preclinical studies	Galloflavin is a non-competitive inhibitor of LDH that binds to the enzyme and inhibits its activity, reducing lactate production. This leads to the accumulation of pyruvate and inhibition of glycolytic flux, ultimately resulting in decreased cancer cell proliferation and increased apoptosis.	N/A
Oxamate	N/A	N/A	Preclinical studies	Oxamate acts as a pyruvate analog and competes with pyruvate for binding to LDH. By inhibiting LDH activity, oxamate reduces lactate production and glycolysis, which can decrease tumor growth and induce apoptosis in cancer cells.	N/A
NCI-737	N/A	N/A	Preclinical studies	NCI-737 selectively inhibits LDHA, resulting in reduced lactate production and increased oxidative phosphorylation. This shift in metabolic pathways induces oxidative stress and cell death in cancer cells reliant on glycolysis.	N/A
Stuartin	N/A	N/A	Preclinical studies	Stuartin is a novel LDH inhibitor that specifically targets LDHA. By inhibiting LDHA, stuartin decreases lactate production and disrupts glycolysis, leading to the death of cancer cells with high glycolytic activity.	N/A
3-Bromopyruvate (3-BP)	N/A	N/A	Preclinical studies	3-BP is an alkylating agent that inhibits multiple glycolytic enzymes, including LDH. It decreases lactate production, leading to energy depletion and increased oxidative stress in cancer cells, ultimately causing cell death.	N/A
GNE-140	N/A	N/A	Preclinical studies	GNE-140 inhibits LDHA, reducing the conversion of pyruvate to lactate, leading to pyruvate accumulation and decreased lactate production. This disrupts energy production and metabolic flexibility, making cancer cells less viable, especially in hypoxic tumor conditions.	N/A

Glucose transport inhibitors

Glucose transport inhibitors are emerging as promising agents in the realm of cancer metabolism therapeutics, targeting the unique metabolic dependencies of cancer cells (Table 6). Cancer cells exhibit a heightened glycolytic rate, known as the Warburg effect, where they predominantly rely on glucose for energy production, even in the presence of oxygen. This metabolic reprogramming supports rapid cell proliferation and survival under adverse conditions. By inhibiting glucose transporters, specifically GLUT1, which is often overexpressed in various cancers, these inhibitors effectively starve cancer cells of their primary energy source [60, 216]. This leads to a reduction in ATP production, disruption of cellular homeostasis, and ultimately, cell death [216, 248]. Moreover, glucose transport inhibitors can synergize with other treatments, such as chemotherapy and radiotherapy, by further sensitizing cancer cells to these interventions [249, 250]. For example, recent studies investigated novel anti-cancer treatments through the application of phloretin in two distinct contexts. First, phloretin-based combinations were tested against hepatocellular carcinoma (HCC), where combination 1 involved inhibiting glycolysis with phloretin and gluconeogenesis with sodium metaarsenite, while combination 2 involved inhibiting glycolysis with phloretin and inducing gluconeogenesis with dexamethasone. Both combinations significantly regressed malignant tissue in Swiss albino mice with induced HCC, demonstrating effective modulation of glucose metabolism as indicated by changes in GLUT2 and PEPCK expression. Molecular docking studies confirmed strong binding of the drugs to their targets [251]. In the second context, the synergistic effects of phloretin combined with radiotherapy (RT) were explored using a Lewis lung cancer (LLC) xenograft model. Phloretin enhanced RT efficacy, evidenced by increased survival rates, prolonged tumor growth delay, reduced glucose uptake, and higher apoptosis rates. The combination also reduced the proliferation index. These findings collectively suggest that phloretin-based treatments, whether targeting glucose metabolism or combined with RT, offer promising strategies for cancer therapy through enhanced regulation of glucose metabolism, ATP production, and apoptosis induction [252]. The therapeutic potential of these inhibitors is underlined by their ability to selectively target cancer cells while sparing normal cells, thereby minimizing systemic toxicity. Several glucose transporter inhibitors have shown promising results in preclinical studies, including STF-31, Glutor, BAY-876, and WZB117. These compounds have demonstrated efficacy in inhibiting glucose uptake and suppressing tumor growth in various cancer models [216, 248]. However, challenges remain in translating these findings to clinical applications. Many glucose transport inhibitors have faced limitations such as low selectivity, high toxicity, and side effects. To address these issues, researchers are

Table 6 Overview of the glucose transport inhibitors

Inhibitor	NCT Number	Phase	Status	Mechanism of Action	Year
Phloretin	N/A	N/A	Preclinical studies	Inhibits glucose transporters GLUT1 and GLUT2 by competing with glucose for the binding site.	N/A
Fasentin	N/A	N/A	Preclinical studies	Inhibits GLUT1 by binding to an allosteric site, reducing glucose uptake in cells.	N/A
WZB117	NCT03278444	Phase 3	Unknown	Selectively inhibits GLUT1, disrupting glucose uptake and thereby affecting cellular metabolism and viability.	2017–2021
STF-31	NCT01992016	N/A	Completed	Inhibits GLUT1, leading to decreased glucose uptake and selectively targeting cells dependent on glucose metabolism, such as renal cell carcinoma.	2014–2018
BAY-876	N/A	N/A	Preclinical studies	Selective GLUT1 inhibitor, blocking glucose transport and subsequently reducing glycolytic flux in cancer cells.	N/A
PGG (Penta-O-galloyl-β-D-glucose)	NCT04995094	Phase 2	Withdrawn	Inhibits GLUT1-mediated glucose transport, thereby reducing glucose uptake and glycolysis in cancer cells.	2021–2023
	NCT05159778	Phase 2	Completed		2021–2023
	NCT03003468	Phase 1/2	Active (Not recruiting)		2017–2025
	NCT02981303	Phase 2	Completed		2017–2020
	NCT00912327	N/A	Completed		2009–2012
	NCT02132403	Phase 1	Terminated		2014–2015
	NCT03246685	Phase 2	Terminated		2017–2018
	NCT02086175	Phase 2	Completed		2014–2021
	NCT01309126	Phase 3	Terminated		2011–2017
	NCT00545545	Phase 1/2	Completed		2007–2009
	NCT00874848	Phase 2	Completed		2009–2015
	NCT00874107	Phase 2	Completed		2009–2016
	NCT01269385	Phase 1/2	Completed		2011–2015
	NCT03555149	Phase 1/2	Terminated		2018–2022
CG-5 (Calcein Green 5)	N/A	N/A	Preclinical studies	Inhibits GLUT1 and GLUT3, reducing glucose uptake and affecting cell survival, particularly in cancer cells.	N/A
Ritonavir	NCT05334004	Phase 1	Recruiting	Inhibits GLUT4, primarily used in adipose tissue and muscle, affecting glucose uptake and insulin sensitivity.	2023–2025
	NCT03383692	Phase 1	Completed		2018–2023
	NCT01009437	Phase 1	Completed		2010–2014
	NCT01095094	Phase 2	Terminated		2009–2011
	NCT04455958	Phase 2	Withdrawn		2021–2021
	NCT05679388'	Phase 1	Recruiting		2023–2025
	NCT00637637	Phase 2	Unknown		2007–2009
	NCT05150691	Phase 1/2	Recruiting		2022–2025
	NCT03147378	Phase 1	Completed		2017–2018
	NCT01173913	Phase 1	Completed		2010–2017
	NCT06428045	Phase 1	Not yet recruiting		2024–2029
	NCT01165645	N/A	Withdrawn		2010–2011
	NCT02948283	Phase 1	Completed		2017–2017
	NCT02770378	Phase 1/2	Completed		2016–2020
	NCT00003008	Phase 2	Completed		1997–2006
	NCT00444379	Phase 4	Completed		2007–2012
Apigenin	N/A	N/A	Preclinical studies	Inhibits GLUT1 and reduces glucose uptake by binding directly to the transporter.	N/A
Myricetin	N/A	N/A	Preclinical studies	Inhibits GLUT1 and GLUT4, leading to decreased glucose uptake in cancer cells. .	N/A

Table 6 (continued)

Inhibitor	NCT Number	Phase	Status	Mechanism of Action	Year
Genistein	NCT01985763	Phase 1/2	Completed	Inhibits GLUT1, reducing glucose transport and inducing metabolic stress in cancer cells. .	2013–2018
	NCT02624388	Phase 2	Terminated		2016–2021
	NCT00005827	Phase 1	Withdrawn		1999–2003
	NCT00546039	Phase 2	Unknown		2007–2009
	NCT00882765	Phase 2	Withdrawn		2009–2011
	NCT00001696	Phase 1	Completed		1998–2001
	NCT02766478	Phase 2	Terminated		2017–2021
	NCT00099008	Phase 1	Completed		2004–2006
	NCT02499861	Phase 1/2	Completed		2015–2017
	NCT00769990	Phase 1/2	Withdrawn		2008–2010
	NCT01489813	Phase 2	Active (Not recruiting)		2017–2024
	NCT00058266	Phase 2	Terminated		2002–2009
	NCT00290758	Phase 2	Completed		2006–2009
	NCT01126879	Phase 2	Terminated		2011–2013
	NCT00244933	Phase 2	Completed		2004–2009
	NCT00276835	Phase 1	Completed		2005–2014
	NCT00269555	N/A	Completed		2004–2006
	NCT01538316	N/A	Unknown		2012–2014
	NCT00584532	Phase 2/3	Completed		2003–2007
	NCT01628471	Phase 1/2	Completed		2012–2015
	NCT00376948	Phase 2	Completed		2005–2010
	NCT00118040	Phase 2	Completed		2005–2010
	NCT01325311	Phase 2	Completed		2011–2014
Quercetin	NCT02989129	Phase 1	Withdrawn	Inhibits GLUT1 and GLUT4, decreasing glucose uptake and affecting cellular metabolism.	2018–2020
	NCT05680662	Phase 1	Not yet recruiting		2023–2024
	NCT01732393	Phase 1/2	Completed		2010–2012
	NCT04733534	Phase 2	Recruiting		2022–2025
	NCT03476330	Phase 2	Active (Not recruiting)		2018–2025
	NCT05456022	Phase 2	Unknown		2022–2023
	NCT01538316	N/A	Unknown		2012–2014
	NCT05724329	Phase 2	Recruiting		2023–2027
	NCT00003365	N/A	Terminated		1996–2006
	NCT01912820	Phase 1	Completed		2014–2021
	NCT06355037	Phase 2	Recruiting		2024–2025
	NCT00455416	Phase 2	Unknown		2007–2009
Silibinin	NCT05793489	N/A	Recruiting	Inhibits GLUT1 and GLUT4, resulting in reduced glucose transport and glycolysis in cancer cells.	2023–2026
	NCT05689619	N/A	Recruiting		2023–2027
	NCT01129570	Phase 1	Completed		2010–2013
	NCT00487721	Phase 2	Completed		2006–2011
	NCT02146118	Phase 2	Unknown		2014–2016

exploring combination therapies and developing more advanced and effective glucose metabolism enzyme-targeted anticancer drugs. Ongoing research and clinical trials are crucial to optimize their efficacy, dosing regimens, and to overcome potential resistance mechanisms, making glucose transport inhibitors a pivotal addition to the arsenal against cancer.

Monocarboxylate Transporter (MCT) inhibitors

Monocarboxylate Transporter (MCT) inhibitors are emerging as promising agents in the realm of cancer metabolism therapeutics [253, 254] (Table 7). MCTs, particularly MCT1 [255, 256] and MCT4 [257, 258], play crucial roles in the transport of lactate and other monocarboxylates across cell membranes, which is vital for maintaining the metabolic flexibility and survival of cancer cells in the hypoxic tumor microenvironment. Cancer cells often rely on aerobic glycolysis leading to excessive lactate production, and MCTs facilitate the efflux of this lactate to prevent intracellular acidification and sustain glycolytic flux. Inhibiting MCTs can disrupt this metabolic adaptation, leading to intracellular lactate accumulation, reduced glycolysis, and subsequent metabolic stress in cancer cells. This metabolic disruption can potentiate cell death, reduce tumor growth, and enhance the efficacy of other treatments, such as radiotherapy and chemotherapy [216, 259]. Additionally, MCT inhibitors can target the metabolic symbiosis between glycolytic cancer cells and oxidative tumor cells, further hampering tumor progression. Given their selective action on the altered metabolic pathways in cancer cells, MCT inhibitors offer a targeted therapeutic approach with potentially reduced systemic toxicity. Clinical trials are ongoing to evaluate the efficacy and safety of these inhibitors, making them a significant focus in the development of novel anticancer strategies. Moreover, combination

Table 7 Overview of the Monocarboxylate Transporter (MCT) inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
AZD3965	NCT01791595	Phase 1	Completed	AZD3965 is a selective inhibitor of MCT1. By inhibiting MCT1, AZD3965 prevents the efflux of lactate from glycolytic cancer cells, leading to intracellular acidification, inhibition of glycolysis, and reduced cell proliferation.	2013–2020
ARC155858	N/A	N/A	Preclinical studies	ARC155858 is a potent inhibitor of MCT2. It blocks lactate transport, causing a buildup of lactate inside cancer cells, leading to acidification, metabolic stress, and cell death.	N/A
7ACC2	N/A	N/A	Preclinical studies	7ACC2 is an inhibitor of MCT1. It inhibits lactate transport, resulting in increased intracellular lactate, which disrupts glycolysis and reduces ATP production, leading to cell death.	N/A
SR13800	N/A	N/A	Preclinical studies	SR13800 selectively inhibits MCT1, reducing lactate efflux and causing metabolic stress and growth inhibition in cancer cells.	N/A
BAY-8002	N/A	N/A	Preclinical studies	BAY-8002 is a selective MCT4 inhibitor. Inhibition of MCT4 affects lactate export in glycolytic cancer cells, leading to intracellular lactate accumulation, acidification, and inhibition of cancer cell growth.	N/A
Lonidamine	N/A	N/A	Preclinical studies	Lonidamine inhibits multiple MCTs (including MCT1 and MCT4) and also disrupts mitochondrial function. It impairs lactate export and energy production, leading to apoptosis in cancer cells.	N/A
Syrosingopine	N/A	N/A	Preclinical studies	Syrosingopine inhibits MCT1 and MCT4, preventing lactate export. This leads to intracellular lactate accumulation, metabolic stress, and cell death.	N/A
STF-31	N/A	N/A	Preclinical studies	STF-31 targets MCT1 and inhibits glucose transporter GLUT1, leading to impaired lactate transport and glucose uptake, causing metabolic stress and cancer cell death.	N/A

therapy using MCT inhibitors shows promise. Recent research reveals potential therapeutic strategies for both non-small cell lung cancer (NSCLC) and multiple myeloma (MM) by repurposing syrosingopine in combination with other metabolic inhibitors—UK-5099 for NSCLC and metformin for MM. In NSCLC, the syrosingopine-UK-5099 combination synergistically induces cell cycle arrest, apoptosis, and mitochondrial damage through lactate accumulation and oxidative stress, mediated by the activation of the integrated stress response (ISR) via heme-regulated inhibitor kinase (HRI) [260]. In MM, the syrosingopine-metformin combination targets metabolic vulnerabilities by inhibiting both glycolysis and oxidative phosphorylation, activating p-AMPKα, reducing protein synthesis, and significantly decreasing tumor burden [261].

Amino acid transport inhibitors

Amino acid transport inhibitors represent a promising approach in cancer metabolism therapy by targeting the critical nutrient supply that cancer cells rely on for growth and survival [262, 263] (Table 8). Cancer cells often exhibit increased uptake of amino acids to support their rapid proliferation and metabolic demands. By inhibiting the transporters responsible for amino acid uptake, such as the LAT1 (L-type amino acid transporter 1) and ASCT2 (alanine-serine-cysteine transporter 2), these therapies can effectively starve cancer cells of essential nutrients. This disruption in amino acid supply can lead to impaired protein synthesis, altered cellular metabolism, and the induction of stress responses that may culminate in cell death [262, 263]. Additionally, inhibiting amino acid transport can sensitize cancer cells to other treatments by enhancing metabolic vulnerabilities. As a result, amino acid transport inhibitors are being explored in combination with other therapeutic strategies to achieve more effective cancer control [263, 264]. Such as, a recent study has shown that JPH203 can sensitize cancer cells to radiation therapy by inhibiting radiation-induced amino acid uptake and downregulating mTOR activity, which enhances cellular senescence. This combination of JPH203 and radiation therapy presents a promising approach to cancer treatment, potentially improving the efficacy of radiotherapy while maintaining cellular ATP and GSH levels, indicating minimal toxicity [265]. Ongoing research is focused on identifying specific inhibitors, understanding their mechanisms of action, and optimizing their clinical application to improve patient outcomes in various cancer types. For example, drugs targeting amino acid transporters and related enzymes have transitioned from preclinical research to clinical trials and have demonstrated efficacy in some cases. Clinically, Tamoxifen and Raloxifene block glutamine uptake by inhibiting ASCT2 expression in breast cancer to suppress tumor growth [266]. However, challenges remain in developing selective inhibitors and addressing the metabolic plasticity of cancer cells. Some drugs targeting amino acid metabolism have

Table 8 Overview of the amino acid transport inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
CH3-CHL	N/A	N/A	Preclinical studies	Inhibits the system L amino acid transporter LAT1 (SLC7A5), reducing the uptake of essential amino acids like leucine, thereby impairing mTOR signaling and inhibiting cancer cell growth.	N/A
BCH	N/A	N/A	Preclinical studies	Competitive inhibitor of LAT1, blocking the uptake of large neutral amino acids, leading to reduced protein synthesis and cell proliferation.	N/A
JPH203	UMIN000034080	Phase 2	Completed	Selective LAT1 inhibitor, reduces leucine uptake, impairs mTOR signaling, and induces cell cycle arrest and apoptosis in cancer cells.	2018
GPNA	N/A	N/A	Preclinical studies	Inhibits ASCT2, leading to decreased glutamine uptake, impairing nucleotide synthesis, and reducing cancer cell viability.	N/A
V-9302	N/A	N/A	Preclinical studies	Small molecule inhibitor targeting SLC38A2/SNAT2, reducing glutamine uptake, affecting mTOR signaling, and inducing oxidative stress and apoptosis in cancer cells.	N/A
Telaglenastat	NCT04824937	Phase 2	Unknown	Inhibits glutaminase, an enzyme converting glutamine to glutamate, reducing glutamine utilization in the TCA cycle, and impairing cell growth and survival in glutamine-dependent cancers.	2021–2021
	NCT04250545	Phase 1	Active (Not recruiting)		2020–2025
	NCT05521997	Phase 2	Not yet recruiting		2024–2030
	NCT03875313	Phase 1/2	Terminated		2019–2020
	NCT03057600	Phase 2	Completed		2017–2019
	NCT02771626	Phase 1/2	Terminated		2016–2020
	NCT03798678	Phase 1	Active (Not recruiting)		2019–2025
	NCT03872427	Phase 2	Active (Not recruiting)		2019–2024
	NCT03163667	Phase 2	Completed		2017–2020
	NCT03528642	Phase 1	Active (Not recruiting)		2019–2024
	NCT03965845	Phase 1/2	Completed		2019–2021
	NCT03428217	Phase 2	Completed		2018–2021
	NCT03831932	Phase 1/2	Active (Not recruiting)		2020–2025
	NCT04265534	Phase 2	Terminated		2020–2022

shown promising effects in animal experiments, but realizing their potential clinically is still difficult. Nevertheless, compared to other therapies, amino acid depletion therapy is generally safer for normal cells, making it an attractive avenue for further research and development in cancer treatment.

Isocitrate dehydrogenase (IDH) inhibitors

Isocitrate Dehydrogenase (IDH) inhibitors represent a promising class of targeted therapies in the realm of cancer metabolism (Table 9). IDH enzymes, specifically IDH1 and IDH2, play crucial roles in the citric acid cycle, catalyzing the conversion of isocitrate to alpha-ketoglutarate (α-KG). Mutations in IDH1 and IDH2 genes, often found in various cancers such as gliomas, AML, and cholangiocarcinoma, result in the production of the oncometabolite 2-hydroxyglutarate (2-HG) [43, 267]. This aberrant metabolite disrupts cellular differentiation and promotes tumorigenesis by inhibiting α-KG-dependent dioxygenases, including those involved in DNA and histone demethylation. IDH inhibitors, such as ivosidenib (AG-120) and enasidenib (AG-221), specifically target these mutant enzymes, reducing 2-HG levels and thereby restoring normal cellular differentiation processes [267, 268]. Clinical trials have demonstrated the efficacy of IDH inhibitors, leading to their approval for treating IDH-mutant cancers. The precision of these inhibitors in targeting metabolic pathways unique to cancer cells underscores their potential to offer a more effective and less toxic alternative to traditional chemotherapies, heralding a new era in cancer treatment focused on metabolic vulnerabilities. Moreover, combining IDH inhibitors with other agents can enhance treatment outcomes. For instance, the FDA recently approved ivosidenib in combination with azacitidine for newly diagnosed IDH1-mutated AML in older adults or those with comorbidities. This approval followed a phase 3 study demonstrating improved event-free survival, overall survival, and complete remission rates with the combination therapy [269].

Oxidative phosphorylation (OXPHOS) inhibitors

Oxidative phosphorylation (OXPHOS) inhibitors represent a promising approach in cancer metabolism therapy (Table 10), targeting the unique metabolic dependencies of cancer cells [270, 271]. OXPHOS is a critical process occurring in the mitochondria, where cells produce ATP, the primary energy currency, through the electron transport chain and ATP synthase. Cancer cells often exhibit altered metabolic states, including increased reliance

Table 9 Overview of the Isocitrate dehydrogenase (IDH) inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Ivosidenib (AG-120)	NCT03564821	Phase 1	Completed	Ivosidenib specifically inhibits the mutant IDH1 enzyme, reducing the production of 2-HG. This inhibition allows for the reactivation of normal cellular differentiation processes that are otherwise blocked by the high levels of 2-HG.	2019–2023
	NCT06291987	Phase 1	Not yet recruiting		2024–2026
	NCT04195555	Phase 2	Active (Not recruiting)		2020–2025
	NCT04056910	Phase 2	Completed		2021–2023
	NCT02073994	Phase 1	Completed		2014–2024
	NCT04176393	Phase 1	Completed		2019–2023
	NCT02074839	Phase 1	Recruiting		2014–2025
	NCT04955938	Phase 1	Withdrawn		2021–2023
	NCT03471260	Phase 1/2	Recruiting		2018–2025
	NCT06181734	N/A	Recruiting		2023–2028
	NCT06081829	Phase 2	Active (Not recruiting)		2023–2027
	NCT05209074	Phase 1	Recruiting		2022–2026
	NCT03245424	N/A	Approved		N/A
	NCT02989857	Phase 3	Completed		2017–2021
	NCT06465953	Phase 3	Not yet recruiting		2024–2028
	NCT05876754	Phase 3	Recruiting		2023–2025
	NCT06127407	Phase 3	Recruiting		2024–2030
	NCT04278781	Phase 2	Recruiting		2020–2026
	NCT05756777	Phase 1	Recruiting		2023–2025
	NCT03173248	Phase 3	Active (Not recruiting)		2017–2026
	NCT03839771	Phase 3	Recruiting		2019–2033
	NCT03343197	Phase 1	Active (Not recruiting)		2018–2025
	NCT03503409	Phase 2	Active (Not recruiting		2019–2025
	NCT04493164	Phase 2	Recruiting		2020–2025
	NCT05921760	Phase 1/2	Recruiting		2023–2026
	NCT04088188	Phase 1	Terminated		2021–2023
	NCT04250051	Phase 1	Recruiting		2020–2028
	NCT05615818	Phase 2	Recruiting		2024–2028
	NCT05907057	Phase 3	Recruiting		2023–2026
	NCT06265545	N/A	Not yet recruiting		2024–2026
	NCT04774393	Phase 1/2	Recruiting		2021–2024
	NCT02677922	Phase 1/2	Active (Not recruiting)		2016–2024
	NCT05010772	Phase 1	Recruiting		2021–2026
	NCT03498521	Phase 2	Active (Not recruiting)		2018–2024
	NCT02632708	Phase 1/2	Active (Not recruiting)		2015–2024
	NCT06377579	N/A	Not yet recruiting		2024–2025
	NCT04655391	Phase 1	Withdrawn		2022–2023
	NCT03680677	N/A	Recruiting		2018–2025
	NCT06501625	Phase 1/2	Not yet recruiting		2024–2030
	NCT03013998	Phase 1/2	Recruiting		2016–2026
Enasidenib (AG-221)	NCT01915498	Phase 1/2	Completed	Enasidenib inhibits mutant IDH2, leading to decreased levels of 2-HG, promoting the differentiation of immature myeloid cells, and thereby countering the leukemogenic effects of the IDH2 mutation.	2013–2023
	NCT04522895	Phase 2	Active (Not recruiting)		2020–2024
	NCT03515512	Phase 1	Completed		2018–2023
	NCT02273739	Phase 1/2	Completed		2014–2016
	NCT06176989	Phase 2	Recruiting		2024–2030
	NCT04281498	Phase 2	Completed		2021–2023
	NCT04092179	Phase 1/2	Terminated		2020–2023
	NCT05102370	Phase 1	Active (Not recruiting)		2021–2025
	NCT04955938	Phase 1	Withdrawn		2021–2023
	NCT03728335	Phase 1	Recruiting		2019–2027
	NCT03744390	Phase 2	Active (Not recruiting)		2019–2026
	NCT05441514	Phase 1	Recruiting		2022–2025
	NCT05756777	Phase 1	Recruiting		2023–2025
	NCT03683433	Phase 2	Recruiting		2018–2025
	NCT05282459	Phase 1/2	Recruiting		2022–2024
	NCT03881735	Phase 2	Withdrawn		2019–2022
	NCT04203316	Phase 2	Recruiting		2023–2030
	NCT03839771	Phase 3	Recruiting		2019–2033
	NCT04075747	Phase 1	Completed		2019–2023
	NCT03383575	Phase 2	Recruiting		2018–2025
	NCT02677922	Phase 1/2	Active (Not recruiting)		2016–2024
	NCT03825796	Phase 2	Active (Not recruiting)		2019–2024
	NCT04774393	Phase 1/2	Recruiting		2021–2024
	NCT03720366	Phase 1	Completed		2018–2023
	NCT05010772	Phase 1	Recruiting		2021–2026
	NCT02632708	Phase 1	Active (Not recruiting)		2015–2024
	NCT02577406	Completed	Completed		2015–2024
	NCT02813135	Phase 1/2	Recruiting		2016–2027
	NCT03013998	Phase 1/2	Recruiting		2016–2026
	NCT03732703	Phase 1/2	Uknown		2019–2024
	NCT03878524	Phase 1	Terminated		2020–2020
Vorasidenib (AG-881)	NCT05592743	N/A	Available	Vorasidenib is a dual inhibitor of both IDH1 and IDH2 mutants, reducing 2-HG levels and potentially targeting tumors with either mutation. It is being investigated for its effects in various solid tumors, including gliomas.	N/A
	NCT05609994	Phase 1	Not yet recruiting		2024–2027
	NCT05484622	Phase 1	Recruiting		2023–2027
	NCT06478212	Phase 1/2	Not yet recruiting		2024–2028
	NCT04164901	Phase 3	Active (Not recruiting)		2020–2027
	NCT03684811	Phase 1/2	Completed		2018–2022
Olutasidenib (FT-2102)	NCT06161974	Phase 2	Not yet recruiting	Olutasidenib inhibits the mutant IDH1 enzyme, leading to decreased 2-HG levels and reactivating differentiation in affected cells.	2024–2035
	NCT02719574	Phase 1/2	Completed		2016–2024

Table 9 (continued)

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
BAY1436032	NCT02746081 NCT03127735	Phase 1 Phase 1	Active (Not recruiting) Completed	BAY1436032 inhibits the IDH1 mutant enzyme, reducing 2-HG production and reversing the oncogenic effects associated with the mutation.	2016–2024 2017–2019
IDH305	NCT02826642 NCT02977689 NCT02987010 NCT02381886	Phase 1 Phase 2 Phase 2 Phase 1	Withdrawn Withdrawn Withdrawn Active (Not recruiting)	IDH305 selectively targets the IDH1 R132H mutant, inhibiting 2-HG production and restoring normal metabolic and epigenetic functions.	2016–2016 2018–2020 2019–2019 2015–2025
IDH-C35	N/A	N/A	Preclinical studies	IDH-C35 is an allosteric inhibitor of the IDH1 R132H mutant, inhibiting the production of 2-HG and offering potential therapeutic benefits in cancers harboring this mutation.	N/A

on glycolysis even in the presence of oxygen, but many tumors retain or adapt to a dependence on OXPHOS for survival and proliferation, particularly under nutrient-limited or low-oxygen conditions [50, 272]. Inhibiting OXPHOS disrupts ATP production, generating oxidative stress and triggering cell death in OXPHOS-dependent cancer cells [273]. Various agents, such as metformin, phenformin, and IACS-010759, target different components of the mitochondrial electron transport chain, highlighting the heterogeneity of tumor metabolic dependencies and the need for personalized treatment strategies [63, 274]. Additionally, OXPHOS inhibitors can enhance the efficacy of existing therapies, such as chemotherapy and radiotherapy, by sensitizing cancer cells to these treatments [273, 275]. Despite their potential, challenges remain, including the identification of biomarkers to predict responsiveness and managing off-target effects on normal cells, which also rely on OXPHOS for energy production. Combining oxidative phosphorylation inhibitors with other therapeutic agents can enhance their effectiveness in cancer treatment. Recent research has shown that OXPHOS inhibitors can be particularly effective when used in conjunction with other treatments such as chemotherapy, targeted therapies, or immunotherapies. This combinatorial approach can help overcome resistance mechanisms, and improve tumor response [275]. Therefore, ongoing research is crucial to optimize the therapeutic window and enhance the specificity of OXPHOS inhibitors in cancer treatment.

Fatty acid synthesis inhibitors

Fatty acid synthesis inhibitors represent a promising avenue in cancer metabolism therapy, targeting the metabolic reprogramming characteristic of many cancers [118, 276] (Table 11). Cancer cells often exhibit increased de novo lipogenesis, crucial for rapid cell proliferation and survival [118, 277]. This enhanced fatty acid synthesis is driven by upregulated expression of key enzymes, such as fatty acid synthase (FASN), which catalyzes the formation of palmitate from acetyl-CoA and malonyl-CoA. Inhibiting FASN disrupts the production of fatty acids necessary for membrane biosynthesis, energy storage, and signaling molecule generation, thereby impeding tumor growth and inducing apoptosis [118]. Various FASN inhibitors, including natural products like orlistat and synthetic molecules such as TVB-2640, have demonstrated efficacy in preclinical studies by selectively targeting cancer cells while sparing normal cells, which rely more on dietary fatty acids [118, 278]. By exploiting the metabolic vulnerabilities of cancer cells, fatty acid synthesis inhibitors offer a targeted therapeutic approach that can potentially enhance the efficacy of existing treatments and overcome resistance mechanisms in various malignancies.

Challenges and future directions

There are several challenges associated with cancer metabolism, but various strategies can be implemented to address these issues effectively (Fig. 6). One of the significant challenges in targeting cancer metabolism is overcoming the metabolic plasticity of cancer cells. These cells can dynamically adapt to various microenvironmental stresses such as nutrient deprivation and hypoxia, making it difficult to target a single metabolic pathway effectively [70]. This adaptability is achieved through metabolic flexibility (the ability to use different nutrients) and plasticity (the ability to process metabolic substrates in different ways). Furthermore, metabolic heterogeneity within and between tumors adds another layer of complexity. Different cancer cells within the same tumor may rely on distinct metabolic pathways, complicating the development of universal metabolic inhibitors [70, 279]. This heterogeneity is influenced by factors such as the tissue of origin, driving mutations, and the tumor microenvironment. Redundancy and compensation in metabolic pathways also pose a challenge, as cancer cells can bypass metabolic blockades by upregulating alternative pathways or utilizing neighboring stromal cells to supply essential nutrients, undermining the efficacy of targeted therapies [280, 281]. This ability to switch between different metabolic modes allows cancer cells to maintain growth even during glucose or amino acid deprivation. Additionally, the tumor microenvironment significantly influences cancer metabolism. Interactions

Table 10 Overview of the oxidative phosphorylation (OXPHOS) inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Metformin	Several	Various	Various	Although primarily an antidiabetic drug, metformin indirectly inhibits Complex I by reducing mitochondrial oxidative phosphorylation, leading to a decrease in ATP production and energy stress in cancer cells	N/A
Phenformin	NCT03026517	Phase 1	Active (Not recruiting)	A more potent analog of metformin, phenformin also inhibits Complex I, causing a reduction in ATP production and an increase in reactive oxygen species (ROS).	2017–2025
IACS-010759	NCT02882321 NCT03291938	Phase 1 Phase 1	Terminated Completed	A highly specific Complex I inhibitor, IACS-010759 disrupts mitochondrial respiration, leading to energy depletion and increased oxidative stress in tumor cells.	2016–2022 2017–2020
BAY 87-2243	NCT01297530	Phase 1	Terminated	BAY 87-2243 is an investigational inhibitor of Complex I that induces mitochondrial dysfunction, leading to the inhibition of tumor growth by altering cellular metabolism.	2011–2012
Rotenone	N/A	N/A	Preclinical studies	A naturally occurring pesticide that directly inhibits Complex I, leading to the disruption of electron transport and decreased ATP synthesis.	N/A
Piericidin A	N/A	N/A	N/A	A bacterial metabolite that inhibits Complex I by binding to the quinone binding site, disrupting electron transfer and ATP production.	N/A
Atpenin A5	N/A	N/A	Preclinical studies	A5 specifically inhibits Complex II by binding to the ubiquinone binding site, blocking the electron transfer from succinate to ubiquinone.	N/A
TTFA (Thenoyltrifluoroacetone)	N/A	N/A	Preclinical studies	TTFA is a competitive inhibitor of Complex II that binds to the iron-sulfur clusters within succinate dehydrogenase, preventing electron transfer from succinate to ubiquinone.	N/A
3-Nitropropionic Acid (3-NP)	N/A	N/A	Preclinical studies	3-Nitropropionic acid is an irreversible inhibitor of Complex II that covalently modifies the enzyme, leading to inhibition of electron transfer from succinate to ubiquinone.	N/A
Malonate	NCT00805636 NCT00696943	Phase 2 Phase 2	Unknown Terminated	Malonate is a competitive inhibitor of succinate dehydrogenase that resembles succinate and competes for the active site, thereby inhibiting Complex II activity.	2008–2010 2008–2009
Carboxin	N/A	N/A	Preclinical studies	Carboxin inhibits Complex II by binding to the quinone reduction site, preventing electron transfer from succinate to ubiquinone.	N/A
Dimethylmalonate	N/A	N/A	Preclinical studies	Dimethylmalonate is a prodrug that is metabolized into malonate in cells, which then inhibits Complex II by competing with succinate for the active site.	N/A
Antimycin A	N/A	N/A	Preclinical studies	Antimycin A binds to the Qi site of Complex III, blocking the transfer of electrons from ubiquinol to cytochrome c. This inhibition disrupts the electron transport chain, leading to increased reactive oxygen species (ROS) and apoptosis.	N/A
Myxothiazol	N/A	N/A	Preclinical studies	Myxothiazol inhibits Complex III by binding to the Qo site, preventing the oxidation of ubiquinol and blocking electron transfer to cytochrome c.	N/A
Stigmatellin	N/A	N/A	Preclinical studies	Stigmatellin binds to the Qo site of Complex III, inhibiting the transfer of electrons from ubiquinol to cytochrome c and disrupting the mitochondrial electron transport chain.	N/A
Napthoquinones	N/A	N/A	Preclinical studies	β-Lapachone, a napthoquinone derivative, can inhibit Complex III by inducing the generation of ROS, which disrupts electron transport and leads to mitochondrial dysfunction.	N/A

Table 10 (continued)

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
MOA-1	N/A	N/A	Preclinical studies	MOA-1 inhibits Complex III, leading to the accumulation of ROS and mitochondrial dysfunction, which can induce apoptosis in cancer cells.	N/A
Azide	N/A	N/A	Preclinical studies	Azide inhibits Complex IV by binding to the cytochrome a3 subunit, blocking electron transfer and oxygen reduction, leading to impaired oxidative phosphorylation.	N/A
Oligomycin	N/A	N/A	Preclinical studies	Oligomycin binds to the Fo subunit of ATP synthase, inhibiting proton flow through the enzyme and thereby preventing ATP synthesis.	N/A
Bedaquiline	N/A	N/A	Preclinical studies	Bedaquiline, an antibiotic used to treat multidrug-resistant tuberculosis, inhibits the c subunit of ATP synthase, disrupting proton flow and ATP production.	N/A
Venturicidin	N/A	N/A	Preclinical studies	Venturicidin is a potent inhibitor of ATP synthase that binds to the Fo subunit, blocking proton translocation and ATP synthesis.	N/A
Bongkrekic Acid	N/A	N/A	Preclinical studies	Bongkrekic acid inhibits the adenine nucleotide translocator (ANT) in mitochondria, indirectly affecting ATP synthase by disrupting ATP/ADP exchange across the mitochondrial membrane.	N/A
Dicyclohexylcarbodiimide	N/A	N/A	Preclinical studies	DCCD inhibits ATP synthase by binding to the Fo subunit, blocking proton translocation and thereby preventing ATP production.	N/A
Efrapeptin	N/A	N/A	Preclinical studies	Efrapeptin inhibits ATP synthase by binding to the Fo subunit, preventing proton flow and ATP synthesis.	N/A
Aurovertin B:	N/A	N/A	Preclinical studies	Aurovertin B inhibits the F1 ATPase domain of ATP synthase, blocking ATP synthesis and reducing mitochondrial efficiency.	N/A

Clinical tials for Metformin: https://clinicaltrials.gov/search?cond=Cancer&intr=Metformin

Table 11 Overview of the fatty acid synthesis inhibitors

Inhibitors	NCT Number	Phase	Status	Mechanism of Action	Year
Orlistat	N/A	N/A	N/A	Irreversible inhibitor of FASN, blocking the synthesis of palmitate.	N/A
BCH	N/A	N/A	Preclinical studies	Competitive inhibitor of LAT1, blocking the uptake of large neutral amino acids, leading to reduced protein synthesis and cell proliferation.	N/A
C75	N/A	N/A	N/A	Inhibits FASN activity and induces apoptosis in cancer cells.	N/A
Cerulenin	N/A	N/A	N/A	Covalently binds to the ketoacyl synthase domain of FASN, inhibiting its function.	N/A
Firsocostat (GS-0976)	N/A	N/A	Preclinical studies	Inhibits ACC, reducing fatty acid synthesis.	N/A
TVB-2640	NCT02223247 NCT02980029 NCT03808558 NCT05743621 NCT03032484 NCT03179904	Phase Phase 1 Phase 2 Phase 1 Phase 2 Phase 2	Completed Recruiting Recruiting Recruiting Completed Active (Not recruiting)	Small molecule inhibitor of FASN, blocking lipid biosynthesis in cancer cells.	2013–2017 2017–2024 2019–2026 2023–2027 2017–2021 2017–2024
Triclosan	N/A	N/A	Preclinical studies	Inhibits enoyl-ACP reductase, an enzyme involved in fatty acid synthesis.	N/A
Platensimycin	N/A	N/A	Preclinical studies	Inhibits the condensation step of fatty acid synthesis.	N/A
Soraphen A	N/A	N/A	Preclinical studies	Inhibits ACC, disrupting fatty acid synthesis.	N/A
TOFA (5-(Tetradecyloxy)-2-furoic acid)	N/A	N/A	Preclinical studies	Inhibits ACC and thus fatty acid synthesis.	N/A

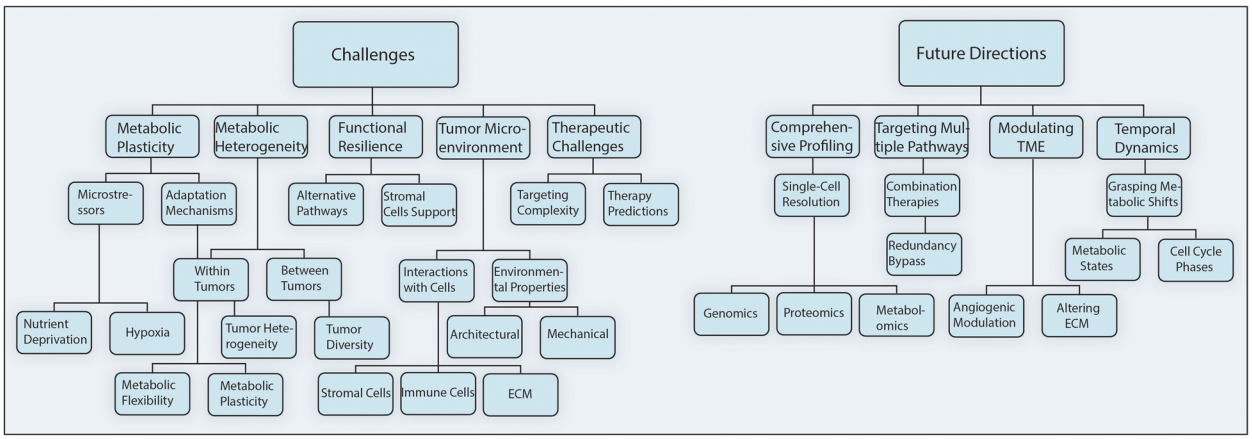


Fig. 6 The flow chart illustrates the multifaceted challenges and future directions in overcoming metabolic plasticity in cancer cells. The left section highlights the primary challenges, including metabolic plasticity, metabolic heterogeneity within and between tumors, redundancy and compensation in metabolic pathways, influence of the tumor microenvironment and the difficulty in effectively targeting single metabolic pathways. The right section outlines future directions, such as comprehensive profiling of cancer metabolism at single-cell resolution using advanced omics technologies, targeting multiple pathways with combination therapies, modulating the tumor microenvironment to reduce metabolic adaptability, and understanding the temporal dynamics of metabolic changes to develop phase-specific therapies

between cancer cells and stromal cells, immune cells, and extracellular matrix components can modify metabolic pathways, making it challenging to predict therapeutic outcomes [279, 281]. The architectural and mechanical properties of the tumor environment play a crucial role in controlling metabolic plasticity.

To address these challenges, future directions include comprehensive profiling of cancer metabolism at single-cell resolution using advanced omics technologies (genomics, proteomics, metabolomics). This approach can help identify key metabolic vulnerabilities. Targeting multiple pathways simultaneously with combination therapies could overcome the redundancy and compensation seen in cancer metabolism. Modulating the tumor microenvironment, such as normalizing blood supply or altering the extracellular matrix, may reduce the metabolic adaptability of cancer cells and enhance the efficacy of metabolic inhibitors. Understanding the temporal dynamics of metabolic changes in cancer cells could lead to therapies that target specific metabolic states or phases of the cell cycle, reducing the likelihood of adaptation.

Combination therapies present another set of challenges in targeting cancer metabolism [154]. One major challenge is the increased risk of toxicity and adverse side effects, which can limit the doses that can be safely administered [282]. Unanticipated interactions between drugs can also affect their efficacy and safety profiles, complicating the design of combination regimens [283]. Optimizing the dosing and scheduling for combination therapies is complex and requires extensive preclinical and clinical testing [284]. Despite these efforts, cancer cells may still develop resistance to combination therapies through various mechanisms, including genetic mutations and epigenetic alterations [285].

To enhance the efficacy of combination therapies, future directions include the rational design of combinations based on mechanistic insights into cancer metabolism and signaling pathways, which can improve efficacy and reduce toxicity. Identifying synergistic drug combinations through high-throughput screening and computational modeling can enhance therapeutic outcomes while minimizing side effects. Adaptive therapy strategies that dynamically adjust treatment based on tumor response and resistance patterns may prolong the efficacy of combination treatments and delay resistance. Personalizing combination therapies to individual patients based on their unique genetic and metabolic profiles can optimize efficacy and reduce adverse effects, leading to more effective and tailored treatment approaches.

Identifying reliable biomarkers for metabolic targeting poses several challenges. One of the primary challenges is the identification and validation of biomarkers that accurately reflect metabolic changes in cancer cells. This requires extensive clinical testing to ensure sensitivity, specificity, and reproducibility [286]. This process is complex and time-consuming, as it involves rigorous evaluation of potential biomarkers across diverse patient populations. Tumor heterogeneity can lead to variability in biomarker expression, complicating their use in predicting therapeutic responses [216]. Additionally, metabolic biomarkers may change dynamically in response to therapy and disease progression, necessitating the development of robust methods for real-time monitoring

[287]. Some metabolic biomarkers may also be difficult to measure non-invasively, limiting their clinical utility.

Future directions in this area include developing liquid biopsy techniques to measure circulating metabolites, exosomes, or other biomarkers, providing minimally invasive methods for monitoring cancer metabolism and treatment response. Integrating multi-omics data (e.g., genomics, proteomics, metabolomics) can help identify comprehensive biomarker signatures that reflect the metabolic state of cancer cells. Advances in imaging technologies and biosensors can enable real-time monitoring of metabolic changes in tumors, aiding in the timely adjustment of therapeutic strategies. Developing predictive biomarkers that can identify patients most likely to benefit from specific metabolic therapies can enhance personalized treatment approaches and improve outcomes. By addressing these challenges and pursuing these future directions, researchers can make significant strides in the effective targeting of cancer metabolism.

Conclusion

The study of altered metabolism in cancer has unveiled crucial energy pathways driving tumor growth and survival, highlighting therapeutic opportunities. Key metabolic mechanisms include the Warburg effect, where cancer cells prefer glycolysis even in oxygen-rich conditions, alongside oxidative phosphorylation, glutaminolysis, and lipid metabolism. These processes, regulated by oncogenes, tumor suppressors, epigenetic changes, and the tumor microenvironment, offer targets for therapy. Potential interventions include glycolysis inhibitors like 2-deoxy-D-glucose, oxidative phosphorylation inhibitors, glutamine metabolism inhibitors such as CB-839, and fatty acid synthase inhibitors. Additionally, modulating key regulators like the mTOR and PI3K/AKT pathways expands therapeutic options. However, cancer cells' metabolic plasticity challenges single-agent therapies, suggesting that combination therapies may enhance efficacy. Identifying biomarkers for metabolic targeting will aid in patient selection and treatment monitoring. Future research should explore the interplay between metabolic pathways and their regulation by the tumor microenvironment to develop effective treatments. Integrating metabolic inhibitors with conventional therapies promises to transform cancer treatment, offering hope for improved patient outcomes. Overall, studying altered cancer metabolism provides critical insights and paves the way for innovative and precise therapeutic strategies.

Abbreviations

TME	Tumor microenvironment
HIFs	Hypoxia-inducible factors
AMPK	AMP-activated protein kinase
LUAD	Lung adenocarcinoma
LDHA	Lactate dehydrogenase A
OXPHOS	Oxidative phosphorylation
ETC	Electron transport chain
AML	Acute myeloid leukemia
LSCs	Leukemic stem cells
ROS	Reactive oxygen species
MMPs	Matrix metalloproteinases
EMT	Epithelial-mesenchymal transition
CSCs	Cancer stem cells
TCA	Tricarboxylic acid
GDH	Glutamate dehydrogenase
FAO	Fatty acid oxidation
PI3K	Phosphatidylinositol 3-kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
CAFs	Cancer-associated fibroblasts
TAMs	Tumor-associated macrophages
VEGF	Vascular endothelial growth factor
HATs	Histone acetyltransferases
HDACs	Histone deacetylases
miRNAs	microRNAs
lncRNAs	Long non-coding RNAs
ECM	Extracellular matrix
PKM2	Pyruvate kinase M2
LDH	Lactate dehydrogenase
IDH	Isocitrate dehydrogenase
CPT1	Carnitine Palmitoyltransferase 1
ACAD	Acyl-CoA Dehydrogenase
MCT	Monocarboxylate Transporter
HK2	Hexokinase 2
PFK	Phosphofructokinase
GLUT	Glucose Transporters
TIGAR	TP53-Induced Glycolysis and Apoptosis Regulator
SCO2	Synthesis of Cytochrome c Oxidase 2
PTEN	Phosphatase and Tensin Homolog
LKB1	Liver Kinase B1

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Declarations

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The authors declare no competing interests.

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