

METABOLIC FLEXIBILITY: TARGETING MITOCHONDRIAL DYNAMICS IN CANCER THERAPY

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Abstract

Various types of cancer exhibit distinct sensitivities to anticancer drugs, reflecting their unique developmental pathways. Exploiting mitochondrial dysfunction in cancer cells presents novel therapeutic opportunities. In recent years, advancements have underscored the significance of oxidative phosphorylation, fatty acid oxidation, and glutamine addiction in cancer cells, shifting attention towards mitochondrial metabolism. The foundation of mitochondrial medicine lies in comprehending targeted mitochondrial therapy and the development of specific mitochondrial drugs. Certain alterations within mitochondrial metabolism lead to the accumulation of onco-metabolites, serving as epigenetic regulators, or an increase in reactive oxygen species production, both of which contribute to tumorigenesis. Importantly, the substantial involvement of mitochondrial metabolism in tumorigenesis offers potential avenues for exploiting as strategies for cancer therapy. Integrated pharmacological approaches targeting mitochondrial metabolic pathways are imperative for an effective eradication of tumor masses and a concurrent elimination of small subpopulations of mitochondria. The significance of mitochondria in cancer is undeniable, offering numerous appealing targets for both tailored and personalized cancer therapy.

Key words: cancer, mitochondria, oxidative phosphorylation, tricarboxylic acid cycle

INTRODUCTION

Tumor cells possess the capacity to adapt their bioenergetic profile in response to microenvironmental conditions and nutrient availability. This metabolic plasticity enables the subpopulations of tumor cells to dynamically adapt metabolic processes to the demands of energy generation and biosynthetic requirements. The intratumoral cellular heterogeneity is characterized by notable alterations in metabolic profiles, dependent upon cell type (1). This phenomenon can facilitate tumor cell survival under altered microenvironmental conditions, as well as during and after chemotherapy (2). Each type of cancer exhibits distinct sensitivities to administered anticancer drugs, partially reflecting variations in mitochondrial pathways such as oxidative phosphorylation, fatty acid metabolism, glutamine metabolism, or one-carbon metabolism. These alterations arise from mutations in oncogenes, tumor suppressor genes, and metabolic enzymes (3). Consequently, a metabolic

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reprogramming occurs, facilitating a rapid cell proliferation and the generation of reactive oxygen species, which cancer cells exploit to sustain pro-tumorigenic signaling pathways and evade cell death. Reprogramming of mitochondrial metabolism in cancer presents appealing targets for therapy (1). Despite the challenges inherent in targeting mitochondrial metabolism, several inhibitors of key enzymes are undergoing clinical trials (4–6). Combination strategies and novel drugs targeting metabolic pathways hold a promise for advancing precision medicine in cancer.

Mitochondria and Cancer

The principal mitochondrial metabolic pathways encompass the tricarboxylic acid (TCA) cycle, fatty acid oxidation (FAO), the electron transport chain (ETC), and oxidative phosphorylation (OXPHOS), collectively engaged in the catabolism of biomolecules and energy generation. Furthermore, mitochondria serve as a source of precursors for numerous biomolecules and adjust to varying metabolic conditions through alterations in nuclear transcription (7). The involvement of damaged mitochondria in initiating the Warburg effect across diverse cancer types, characterized by a uniform decrease in OXPHOS, has been firmly established. Notable examples include oncocytic tumors, neuroblastomas, renal cell carcinomas, and astrocytic brain tumors. However, certain cancers exhibiting the Warburg metabolic phenotype preserve intact mitochondrial respiration, including leukemia, lymphoma, pancreatic ductal carcinomas, melanomas of the high OXPHOS subtype, and endometrial carcinoma (8). Furthermore, certain cancer subtypes not only maintain functional mitochondria but also rely on mitochondrial respiration for essential cellular processes. Consequently, these cancers exhibit a sensitivity to the inhibition of OXPHOS (8). In this context, it is firmly established that mitochondrial energy pathways undergo alterations in the regulation of both glycolysis and mitochondrial respiration. Cancer cells are compelled to foster metabolic plasticity to adapt their metabolic processes to the demands of energy generation and biosynthetic requirements (9). The pivotal role of mitochondria in tumorigenesis is unsurprising, given their significant involvement in various aspects of cancer development. They are central to several classical hallmarks of cancer, including metabolic reprogramming, sustained proliferation, promotion of tumor-associated inflammation, evasion of cell death mechanisms, facilitation of invasion, and stimulation of angiogenesis (10).

To counterbalance the 18-fold difference in efficiency, glycolysis is stimulated through the upregulation of glucose transporters, notably GLUT1, to enhance glucose uptake. Additionally, an overexpression of key enzymes in glycolysis, such as hexokinase-2 and lactate dehydrogenase, contributes to this activation. The heightened glycolytic flux leads to the accumulation of glycolytic intermediates, which serve as precursors for various biosynthetic pathways essential for cellular proliferation. These intermediates fuel the pentose phosphate pathway, facilitating ribose production, and cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) generation, crucial for nucleotide and antioxidant synthesis. Moreover, they contribute to one-carbon metabolism, necessary for mitochondrial NADPH production, methylation processes, and nucleotide synthesis (11).

Targets within the TCA cycle

The TCA cycle serves as a source of intermediates required for the synthesis of lipids, proteins, and nucleotides. To maintain the functionality of the TCA cycle, these intermediates must be replenished through a process known as anaplerosis. Two primary anaplerotic pathways have been identified: glutaminolysis (12), which produces α -ketoglutarate from glutamine, and pyruvate carboxylation, which generates oxaloacetate from pyruvate derived from glucose (13).

Various therapeutic strategies targeting the TCA cycle for cancer treatment have been under investigation. The inhibition of the mitochondrial pyruvate transporter with UK5099 attenuates OXPHOS. Perturbations in TCA cycle enzymes lead to the production of oncometabolites such as 2-hydroxyglutarate (2-HG), fumarate, and succinate, implicated in tumorigenesis.

Inhibitors targeting these enzymes include AGI-5198, AG-221, and AG-881 for isocitrate dehydrogenase (IDH), and CPI-613 for α -ketoglutarate dehydrogenase complex (14). Although challenging to target, loss-of-function mutations of the fumarate hydratase (FH) or succinate dehydrogenase (SDH) enzymes have seen success with small compounds inhibiting enzymes with a gain of function. AGI-5198 inhibits mutant IDH, resulting in a reduced 2-HG formation and an induction of glioma cell differentiation (15). Enasidenib (AG-221) and vorasidenib (AG881) are in clinical trials for acute myelogenous leukemia carrying IDH2 or IDH1/2 mutations, respectively (4,6). Additionally, devimistat (CPI-613), targeting α -KG dehydrogenase complex and pyruvate dehydrogenase, is in phase I/II trials for leukemias, lymphomas, and small cell lung cancer (5,16). The elevated levels of glutamate dehydrogenase (GDH) play a contributory role in augmenting fumarate levels, which subsequently bind to and activate the glutathione peroxidase enzyme, thereby enhancing ROS detoxification in myeloma, leukemia, breast, and lung cancer cell lines. Glioblastoma cells demonstrate a significant reliance on GDH (17). Furthermore, GDH plays a crucial role in breast cancer cells by facilitating ammonia recycling, thereby meeting the heightened demand for amino acid synthesis (18). Inhibitors of GDH include epigallocatechin-3-gallate, R162, hexachlorophene, and bithionol have been identified (14).

Numerous pharmaceuticals, encompassing inhibitors of the ETC elicit reactive oxygen species production via diverse mechanisms. Notably, enhanced ROS-induced apoptosis has been observed in cancer cells subsequent to the depletion of ATP resulting from the manipulation of glycolytic enzymes, chemotherapy, or radiation therapy. These findings underscore the potential pivotal role of ROS modulation in the context of anticancer combinatorial therapies. Moreover, recent advancements in ROS-inducing drugs have focused on achieving the fundamental objective of therapeutic selectivity in cancer treatment. Consequently, assessing the baseline ROS levels within a tumor holds a potential utility in evaluating the responsiveness to ROS-inducing agents. This assessment may be complemented by the concurrent administration of inhibitors targeting compensatory mechanisms, such as glycolysis or antioxidant proteins, enhancing the therapeutic strategy's efficacy. Inhibitors targeting the glutamine pathway disrupt glutathione formation, thereby perturbing the antioxidant system. Inhibition of the glutathione system can be accomplished with agents such as NOV-002, L-buthionine-S, R-sulfoximine, canfosfamide, or ezatiostat hydrochloride (19).

Targets within the oxidative phosphorylation

The efficacy of inhibiting OXPHOS as a targeted therapeutic strategy for cancers that depend on OXPHOS has been elucidated in multiple studies. These malignancies comprise diffuse large B-cell lymphoma (20), breast cancer (21), pancreatic ductal adenocarcinoma (22), melanoma (23), and glioma (24). However, the impact of OXPHOS on cancer drug resistance is intricate and influenced by cell types within the tumor microenvironment. Cancer cells universally bolster OXPHOS activity through various signaling pathways, which is essential for conferring the resistance to cancer therapy (25). Nicotinamide adenine dinucleotide and flavin adenine dinucleotide generated in the TCA cycle donate electrons to complexes I and II of the ETC, producing the energy for proton translocation across the inner mitochondrial membrane and ATP synthesis. Mutations in genes encoding enzymes SDH, FH, and IDH cause an abnormal accumulation of oncometabolites, resulting in a deregulation of signaling promoting cancer progression. SDH catalyzes oxidation from succinate to fumarate. It also contributes as part of Complex II of the ETC, reducing ubiquinone to ubiquinol (14). In the absence of oxygen reduction, cells accumulate ubiquinol, leading to the reversal of the SDH complex, facilitating the deposition of electrons onto fumarate. Upon the inhibition of oxygen reduction, the reduction of fumarate supports the activities of dihydroorotate dehydrogenase and complex I. Consequently, under hypoxic conditions, fumarate serves as a terminal electron acceptor in the mammalian electron transport chain to support of crucial mitochondrial functions and that ability is tissue-specific (26).

Previous data indicate a lack of anticancer activity of mitochondrial inhibitors, including metformin or ME-344 (a mitochondrial CI inhibitor), either alone or in combination. While rotenone and methyl-4-phenylpyridinium are known to inhibit Complex I, they exhibit neurotoxic effects. Conversely, deguelin, an analogue of rotenone, shows a promise as a potential chemotherapeutic drug. This scenario underscores the necessity of gaining a deeper insight into the metabolic context in which mitochondrial inhibitors may exert their anticancer effects (27). The inhibition of complex I by tamoxifen increases hydrogen peroxide production. IACS-010759, a promising novel inhibitor targeting Complex I, is undergoing clinical trials (not posted results) for the treatment of acute myeloid leukemia and specific types of solid tumors (28). Several experimental inhibitors targeting Complex II include malonate, nitropropionic acid, thenoyltrifluoroacetone, troglitazone, 3-bromopyruvate, and α -tocopheryl succinate (Fig. 1) (29).

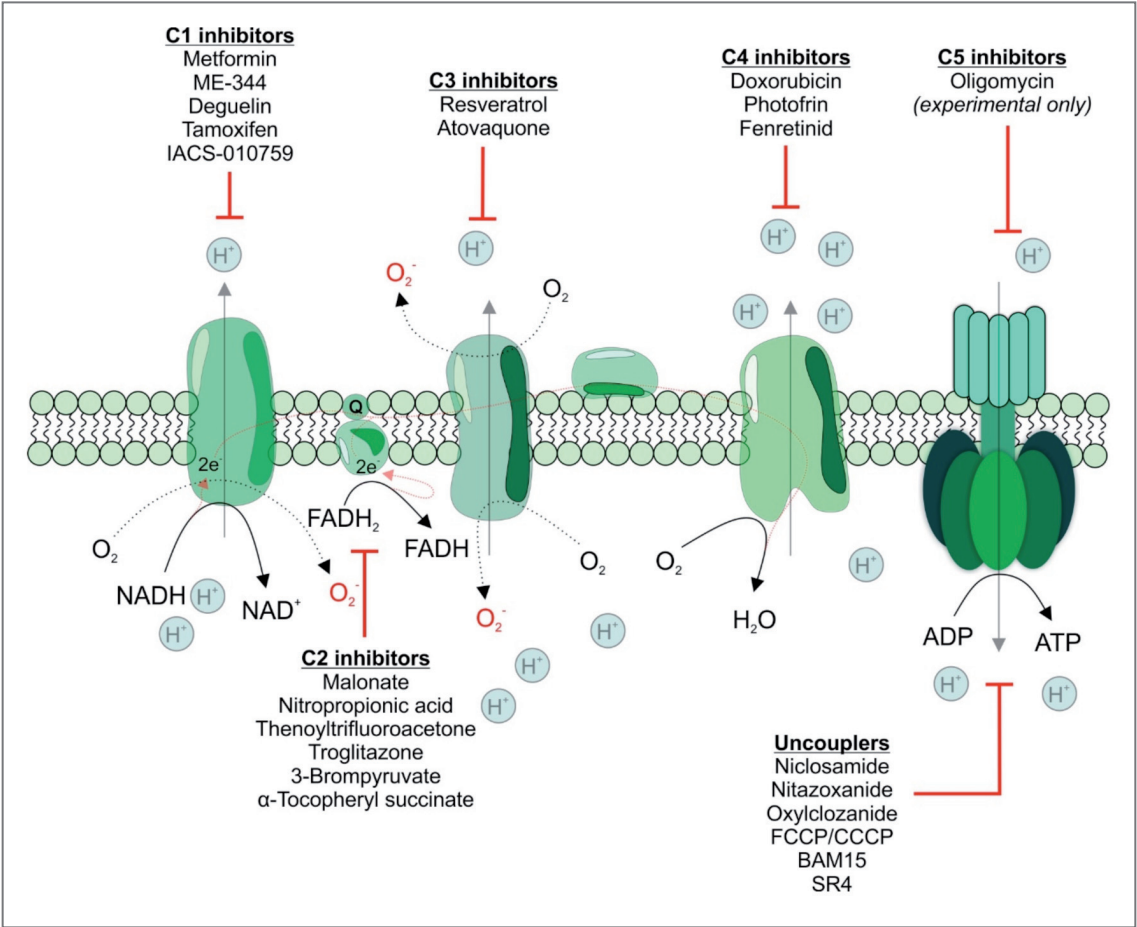


Fig. 1 Inhibiting oxidative phosphorylation as a therapeutic strategy in cancer (complex – C)

Antimycin A is employed in experimental research to inhibit Complex III, whereas resveratrol has been tested for various types of cancer. Atovaquone, on the other hand, is currently being investigated in clinical trials for non-small cell lung cancer (NSCLC), particularly in combination with chemotherapeutic drugs (30). Doxorubicin, a DNA intercalating chemo-

therapeutic agent, and the porphyrin photosensitizer photofrin, sanctioned for esophageal cancer and NSCLC, both possess the capacity to inhibit Complex IV. Meanwhile, fenretinid (N-(4-Hydroxyphenyl) retinamide) is tested for various tumor types, such as ovarian cancer, B-cell non-Hodgkin lymphoma, and breast cancer (31). To date, no promising inhibitors have been reported for Complex V, with oligomycin being the only option available, albeit primarily suitable for experimental purposes (29). Utilizing mitochondrial uncouplers presents an alternative strategy to disrupt ETC function. Compounds such as niclosamide, nitazoxanide, oxyclozanide, FCCP/CCCP, BAM15, or SR4 achieve this by facilitating proton transport across the IMM, thereby short-circuiting ATP synthesis (Fig. 1). Niclosamide finished phase I/II clinical trials for prostate and colon cancer (so far not posted results), while nitazoxanide is in phase II trials for various forms of advanced cancers (32).

CONCLUSION

It is very important to delineate the scenarios in which mitochondrial respiration becomes necessary, making the treatment of oncologic diseases with mitochondrial inhibitors very effective. A remarkable fact about targeted mitochondrial therapy in cancer is its promising potential to address tumor heterogeneity and resistance mechanisms. By specifically targeting the metabolic vulnerability of cancer cells, such therapies aim to disrupt critical pathways involved in tumor growth and survival, thereby offering novel approaches to cancer treatment.

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