Targeting mitochondrial metabolism in cancer: Therapeutic strategies and challenges.

Sui Rant*

Department of Biochemistry, University of Dundee, Dundee, UK.

Introduction

Mitochondria play a central role in cellular energy production, biosynthesis, and redox balance, making them critical regulators of cell survival and proliferation. While the Warburg effect initially suggested that cancer cells rely predominantly on glycolysis even in the presence of oxygen, it is now widely recognized that mitochondrial metabolism remains active and is essential for the growth and survival of many tumors. As such, targeting mitochondrial function has emerged as a promising therapeutic strategy in cancer. However, the complexity of mitochondrial biology and tumor heterogeneity presents significant challenges in translating this approach into effective clinical treatments [1, 2].

Cancer cells exploit mitochondrial metabolism to support their anabolic needs and maintain cellular homeostasis. The tricarboxylic acid (TCA) cycle provides intermediates for amino acid, lipid, and nucleotide biosynthesis, while oxidative phosphorylation (OXPHOS) contributes to ATP production and redox regulation. Many tumors, particularly those in nutrient-limited or hypoxic environments, rely heavily on mitochondrial pathways to sustain their energy and biosynthetic requirements [3, 4].

Therapeutic strategies targeting mitochondrial metabolism aim to disrupt these functions and selectively impair cancer cell viability. One approach involves inhibiting components of the electron transport chain (ETC), thereby suppressing OXPHOS and inducing energetic stress. Agents such as IACS-010759, a complex I inhibitor, have shown promise in preclinical and early clinical trials, particularly in cancers with high mitochondrial dependency, such as acute myeloid leukemia (AML) and certain brain tumors [5, 6].

Another strategy focuses on targeting mitochondrial enzymes involved in the TCA cycle or metabolic anaplerosis. Inhibitors of glutaminase, such as CB-839 (telaglenastat), aim to block glutamine utilization, a major fuel for the TCA cycle in many cancers. By depriving tumor cells of this key nutrient, these agents can reduce growth and sensitize tumors to other therapies. Similarly, targeting enzymes like isocitrate dehydrogenase (IDH1/2), which are frequently mutated in gliomas and leukemias, has led to the development of specific inhibitors that restore normal metabolic flux and reduce the production of oncometabolites like 2-hydroxyglutarate [7].

Mitochondria also play a pivotal role in apoptosis regulation. Agents that modulate mitochondrial membrane potential or target anti-apoptotic proteins of the BCL-2 family can trigger programmed cell death in cancer cells. Venetoclax, a BCL-2 inhibitor, exemplifies this strategy and has demonstrated efficacy in hematological malignancies, especially when combined with agents that disrupt mitochondrial metabolism [8].

Despite these advances, several challenges hinder the widespread application of mitochondrial-targeted therapies. One major obstacle is tumor heterogeneity—both within and between tumors—which can influence mitochondrial dependency and drug sensitivity. Some cancers exhibit metabolic plasticity, switching between glycolysis and OXPHOS depending on environmental cues, thereby evading single-pathway inhibitors. Additionally, mitochondrial functions are essential in many normal tissues, raising concerns about toxicity and off-target effects [9].

Another limitation is the lack of reliable biomarkers to identify patients who would benefit most from mitochondrial-targeted therapies. Predictive markers of mitochondrial dependency or specific metabolic vulnerabilities are needed to tailor treatments and improve outcomes. Advances in metabolomics, single-cell analysis, and imaging technologies are helping to address this gap by enabling better profiling of tumor metabolism in vivo.

Resistance to mitochondrial inhibitors also poses a significant challenge. Cancer cells can adapt by upregulating compensatory pathways, enhancing antioxidant defenses, or altering drug uptake and efflux. Combination therapies that target multiple metabolic axes or pair mitochondrial inhibitors with conventional chemotherapy, immunotherapy, or targeted agents are being explored to overcome resistance and enhance therapeutic efficacy [10].

Conclusion

In conclusion, targeting mitochondrial metabolism represents a compelling and increasingly validated strategy in cancer therapy. Mitochondria serve as metabolic hubs that support tumor growth and survival, and disrupting their function can impair cancer cell fitness and sensitize them to treatment. However, realizing the full potential of mitochondrial-targeted therapies requires overcoming challenges related to tumor heterogeneity, resistance, and toxicity. Future research efforts focused on identifying metabolic biomarkers, understanding adaptive responses, and optimizing combination regimens will be key to advancing this promising area of oncology.

***Correspondence to:** Sui Rant**,** Department of Biochemistry, University of Dundee, Dundee, UK, E-mail: Ran@cellbio.wustl.edu

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