

MINI-REVIEW

From tumor-resistant cardiac fatty acid oxidation to whole-body metabolic reprogramming: Anti-Warburg effect of the high-fat AMRD diet for cancer therapy

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Abstract

Cancer cells primarily rely on anaerobic glycolysis for energy, a phenomenon known as the Warburg effect, which drives rapid growth, immunosuppression, and tumor microenvironment acidification. In stark contrast, the heart, a tissue remarkably resistant to cancer relies predominantly on fatty acid oxidation (FAO) for its energy demands. This distinctive metabolic resilience inspired the development of a comprehensive therapeutic approach: the Akl metabolic reprogramming diet (AMRD). Unlike conventional strategies that target genetic mutations, AMRD exploits metabolic vulnerabilities, aiming to reprogram cancer cell metabolism from glycolysis to FAO. Central to this approach is the “Akl effect,” a concept proposing that excessive glycolipid accumulation impairs glucose transporter function, forcing cancer cells into a compensatory glycolytic state. By redirecting metabolic pathways toward FAO, AMRD induces metabolic stress, disrupts biosynthetic pathways, and selectively triggers apoptosis in cancer cells. Unlike typical ketogenic diets, AMRD incorporates tailored lipid profiles, moderate protein intake, and controlled carbohydrate levels to maximize metabolic flexibility in healthy tissues while restricting cancer cell metabolism. This dietary strategy has demonstrated potential against glycolysis-dependent cancers like breast cancer, glioblastoma, and non-small cell lung cancer. By increasing reactive oxygen species (ROS) production through enhanced FAO, AMRD imposes oxidative stress that overwhelms cancer cells’ impaired antioxidant defenses, while healthy cells with intact redox homeostasis effectively neutralize ROS. As a precision-based, low-toxicity approach, AMRD represents a paradigm shift in cancer therapy, leveraging the heart’s metabolic resistance to develop a restorative, whole-body strategy against aggressive tumors. This innovative approach has the potential to redefine metabolic cancer therapy.

Keywords: Metabolic reprogramming; Fatty acid oxidation; Warburg effect; Cancer therapy; Dietary system; Akl Metabolic Reprogramming Diet

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1. Introduction

In the human body, energy production is a highly specialized process that varies across different organs based on their specific functions and metabolic needs. While glucose metabolism is the predominant energy source for most tissues, certain organs rely on alternative pathways.

The liver, muscles, and heart exhibit a unique preference for fatty acid oxidation (FAO) as their primary source of adenosine triphosphate (ATP) production.¹ Morphologically, the heart muscle (myocardium) is densely packed with mitochondria, reflecting its high demand for constant energy production. These mitochondria enable the efficient oxidation of fatty acids, which yields more ATP per molecule compared to glucose.² This dependency on fatty acid metabolism stems from the heart's continuous contractile function, which requires a steady and abundant energy supply. Fatty acids, with higher caloric content and longer oxidation cycles, meet this demand more efficiently than glucose, which is typically reserved for anaerobic conditions or short bursts of energy.³

The biochemical pathways within cardiac cells further enhance the reliance on fatty acids. Enzymes such as carnitine palmitoyltransferase I regulate the transport of fatty acids into the mitochondria, ensuring a steady supply of substrates for beta-oxidation (β -oxidation).⁴ This results in the production of large amounts of ATP via the electron transport chain and oxidative phosphorylation. Unlike other tissues where glycolysis is more prominent, the heart minimizes glucose metabolism, particularly under aerobic conditions. This creates a metabolically stable environment that is less susceptible to the rapid, disordered energy demands typically seen in cancer cells.⁵

This metabolic uniqueness of the heart may explain its remarkable resistance to cancer. Cardiac tumors are exceedingly rare, a phenomenon that has intrigued researchers for decades. A potential explanation lies in the metabolic flexibility and stability provided by FAO, which contrasts sharply with the glycolytic phenotype of cancer cells.⁶ In most cancers, a dramatic metabolic shift occurs, known as the Warburg effect, where the cells favor glycolysis over oxidative phosphorylation, even when oxygen is abundant. This shift is not merely a byproduct of cancer but a driving force that supports the rapid proliferation, survival, and invasiveness of tumor cells.⁷

The Warburg effect involves a reprogramming of cancer cell metabolism to prioritize glycolysis, despite its inefficiency in terms of ATP production. Biochemically, this process is orchestrated by key regulatory enzymes and transcription factors, such as pyruvate kinase M2 and hypoxia-inducible factor 1- α , which suppress

the entry of pyruvate into the mitochondria. Instead, pyruvate is converted into lactate, contributing to the acidic microenvironment of many tumors. This acidity not only facilitates cancer cell invasion and metastasis but also suppresses immune cell function, creating an immunosuppressive niche that allows tumors to evade detection.⁸

From a morphological perspective, cancer cells often display enlarged nuclei, altered cell shape, and increased mitotic activity, all of which are sustained by the enhanced glycolytic flux. The rapid conversion of glucose to lactate enables cancer cells to channel glycolytic intermediates into anabolic pathways that support nucleic acid, protein, and lipid biosynthesis essential for the rapid cell division of tumors. This metabolic rewiring is critical for maintaining the tumor microenvironment and ensuring the continued growth of tumors under hypoxic or nutrient-deprived conditions.⁹

In stark contrast, the heart's reliance on FAO provides a stable, oxygen-dependent form of energy production that does not favor the anabolic demands of rapidly dividing cells. The mitochondrial density in cardiac cells supports efficient ATP production without the need for rapid glycolytic bursts, as seen in cancer cells. Furthermore, the continuous use of oxidative phosphorylation in the heart generates reactive oxygen species (ROS) as byproducts, which can trigger apoptosis or programmed cell death if not tightly regulated. This is another protective mechanism that may prevent the unchecked cellular proliferation seen in cancer.¹⁰

By understanding these metabolic differences, a potential therapeutic strategy emerges: Metabolic reprogramming of cancer cells. If cancer cells can be forced to shift from glycolysis to FAO, their energy supply could be disrupted. Unlike glycolysis, which supports rapid growth and biosynthesis, FAO is slower and more dependent on oxygen, making it a less favorable pathway for cancer cells. By promoting FAO through pharmacological interventions or dietary changes such as a ketogenic diet, we could theoretically limit the energy available to tumor cells, reducing their growth and enhancing their susceptibility to treatments.

2. Methodology

A hypothesis was developed through a comprehensive literature review focusing on cancer metabolism, biochemical pathways, and nutritional interventions targeting metabolic reprogramming in cancer cells. The methodology employed a structured and systematic approach to ensure a strong scientific foundation. A targeted search was conducted using PubMed, Google Scholar, and

Scopus to identify relevant peer-reviewed studies. The search strategy incorporated keywords such as Warburg effect, cancer metabolism, oxidative phosphorylation, FAO, ketogenic diet, metabolic reprogramming, and tumor microenvironment. The selection criteria prioritized experimental and clinical studies investigating the metabolic shift from oxidative phosphorylation to glycolysis in cancer cells; research on FAO in physiological and pathological conditions, particularly in organs like the heart, which predominantly utilize fatty acids for energy production; and nutritional and metabolic interventions such as ketogenic, low-carbohydrate, and high-fat diets, in oncology settings. The review focused on studies published in high-impact journals, including both *in vitro* and *in vivo* experimental models, and clinical trials. Articles were included if they provided direct evidence of glycolytic metabolism dominance in cancer cells; investigated the role of FAO in cellular metabolism and its potential therapeutic implications; and explored nutritional approaches targeting cancer metabolism. Studies were excluded if they were opinion-based articles with no experimental validation, focused solely on non-metabolic aspects of cancer therapy, or lacked a clear connection to Warburg effect modulation or FAO activation. Relevant findings were extracted and categorized based on metabolic pathways altered in cancer cells; effects of FAO enhancement on tumor microenvironment and survival; and impact of dietary interventions on metabolic flexibility and tumor progression. Based on the reviewed data, the hypothesis proposes that shifting cancer cell metabolism toward FAO while limiting glycolysis may disrupt tumor growth and enhance treatment efficacy. This concept draws from the natural resistance of cardiac cells to cancer due to their FAO dominance, the observed metabolic plasticity in tumors and their dependency on glucose, and preclinical evidence suggesting metabolic interventions can influence tumor progression. This study is a conceptual analysis rather than an experimental validation. Future work should include preclinical and clinical trials testing whether metabolic reprogramming through FAO activation and glycolytic inhibition can be an effective strategy for cancer therapy.

3. Targeting cancer metabolism: The therapeutic potential of inducing FAO in Warburg-dependent tumors

Metabolic reprogramming in cancer cells, from glycolysis to FAO, marks a profound biochemical shift that alters several crucial cellular processes. Cancer cells typically rely on aerobic glycolysis, a phenomenon known as the Warburg effect, where high glycolytic activity persists despite sufficient oxygen availability. This allows cancer cells to

rapidly generate energy and biosynthetic precursors while accumulating lactate, which supports their proliferative and biosynthetic demands. However, by forcing these cells to switch to FAO, fundamental metabolic pathways are altered, presenting a novel therapeutic strategy.¹¹

FAO primarily occurs within the mitochondria and involves the oxidation of fatty acids through β -oxidation, coupled with oxidative phosphorylation (OXPHOS) via the electron transport chain. Unlike glycolysis, which produces only 2 ATP molecules per glucose molecule, FAO generates significantly more ATP, approximately 106 molecules of ATP per molecule of palmitate. This increased reliance on mitochondrial respiration in cancer cells forces them to utilize OXPHOS, which is more efficient in ATP production but also generates higher levels of ROS. Elevated ROS levels can damage cellular components, triggering oxidative stress, disrupting mitochondrial function, and inducing apoptosis, thereby undermining the cancer cells' survival mechanisms.¹²

In addition, shifting cancer cells from glycolysis to FAO reduces lactate production, a key contributor to the acidic tumor microenvironment. Tumor acidity is known to promote immune evasion by inhibiting immune cell infiltration and function. By normalizing the pH of the tumor microenvironment through reduced lactate output, FAO promotes immune system reactivation, potentially enhancing immune-mediated tumor clearance.¹³ Furthermore, reduced glycolytic flux decreases the availability of intermediates for anabolic pathways such as pentose phosphate pathway, which cancer cells heavily depend on for nucleotide and nicotinamide adenine dinucleotide phosphate synthesis. This deprivation further inhibits cancer cell proliferation and survival.¹⁴

Cancers such as triple-negative breast cancer, glioblastoma, and pancreatic ductal adenocarcinoma are highly dependent on glycolysis and are particularly vulnerable to such metabolic reprogramming. These malignancies exhibit strong reliance on the Warburg effect for rapid growth and survival.¹⁵ Depriving these cancer cells of glucose and compelling them to utilize FAO creates a metabolic bottleneck, thus severely impairing their biosynthetic capabilities. Most importantly, normal cells, which exhibit greater metabolic flexibility, can adapt to FAO without suffering significant harm, thus highlighting the selectivity of this approach for targeting cancer metabolism. Inducing FAO in cancer cells holds a significant therapeutic potential by exploiting their metabolic inflexibility, undermining their survival pathways, and enhancing immune system efficacy within the tumor microenvironment.¹⁶

4. The Akl metabolic reprogramming diet (AMRD): Targeting cancer metabolism through nutritional intervention

The AMRD represents an advanced, scientifically grounded approach targeting cancer metabolism by prioritizing FAO over glucose metabolism. Drawing from the biochemical and physiological principles of metabolic flexibility, AMRD is designed to shift cancer cells away from their reliance on glycolysis, which is the Warburg effect, and force them to depend on mitochondrial FAO, which they are less equipped to handle.¹⁷ Unlike the ketogenic diet, AMRD incorporates a tailored combination of omega-3 fatty acids, medium-chain triglycerides, and monounsaturated fats, which are preferentially oxidized by the mitochondria to generate ATP. This strategy maximizes metabolic efficiency while specifically targeting cancer cells' vulnerabilities.¹⁸

Biochemically, AMRD induces a state of nutritional ketosis, where the liver converts fatty acids into ketone bodies such as beta-hydroxybutyrate. These ketones serve as an efficient alternative energy source that bypasses glycolysis, thereby starving cancer cells of glucose and depriving them of key intermediates necessary for anabolic processes such as nucleotide synthesis via the pentose phosphate pathway.¹⁹ Unlike glucose, which fuels the rapid but inefficient ATP production in glycolysis, ketones are metabolized in the mitochondria, promoting OXPHOS and β -oxidation, and resulting in higher ATP yields along with increased production of ROS. Elevated ROS levels are detrimental to cancer cells, potentially triggering apoptosis due to oxidative stress, while normal cells, with their greater metabolic flexibility, can better tolerate and adapt to the shifts in energy metabolism.²⁰

Physiologically, the AMRD goes beyond traditional ketogenic diets by enhancing the tumor microenvironment through the inclusion of anti-inflammatory omega-3 fatty acids from sources like fish oil and flaxseed. These fatty acids are known to modulate inflammatory pathways, reduce pro-inflammatory cytokine levels, and support mitochondrial function, which is particularly relevant in inflammation-driven cancers such as colorectal and breast cancer.²¹ Furthermore, a diet emphasis on medium-chain triglycerides from coconut oil allows for rapid conversion into ketones, even in tissues less accustomed to fatty acid metabolism, enhancing the body's overall ability to sustain FAO.²²

One of the most critical advantages of AMRD is its potential to normalize the tumor microenvironment. By reducing lactate production and shifting the pH towards a more neutral state, AMRD diminishes immune suppression, allowing for improved immune cell infiltration

and function. This immune reactivation, coupled with the disruption of cancer cells' metabolic pathways, could make tumors more susceptible to immune-based therapies such as immunotherapy.²³ In addition, the normalization of the tumor's pH environment also helps in reducing tumor invasion and metastasis.²⁴

From a nutritional standpoint, AMRD offers superior flexibility and specificity compared to the ketogenic diet, making it a more advanced and targeted dietary intervention. While the ketogenic diet focuses on reducing carbohydrate intake, AMRD is designed to optimize fat metabolism through the strategic use of specific fats that enhance mitochondrial function and reduce systemic inflammation. This targeted approach not only improves the metabolic efficiency of cancer cells but also benefits overall health, making it a viable long-term therapeutic strategy for managing cancer.

Given these mechanistic benefits, AMRD is particularly promising for cancers highly dependent on glycolysis, such as triple-negative breast cancer, glioblastoma, and pancreatic ductal adenocarcinoma. These tumors, characterized by aggressive growth and poor responsiveness to traditional treatments, may be especially sensitive to metabolic reprogramming. By forcing a shift from glucose to FAO, AMRD effectively starves cancer cells while supporting immune function and reducing inflammatory signals, creating a hostile environment for tumor progression.²⁵

5. Discussion

The reprogramming of cancer cell metabolism from glucose-based glycolysis to FAO presents a promising and underexplored therapeutic strategy, particularly in targeting the Warburg effect, a hallmark of many malignant cells. This metabolic shift is more than a mere alteration of energy production; it exploits a fundamental vulnerability in cancer cells, which heavily rely on glycolysis for rapid energy and biosynthetic precursor generation. While traditional therapies target proliferation and survival pathways, metabolic reprogramming tackles the core energy metabolism of tumors, offering a novel approach to cancer treatment. Supporting evidence from both preclinical and clinical studies indicates that tumors with a high dependence on glycolysis, such as glioblastoma, breast cancer, and certain lung cancers, are particularly sensitive to metabolic interventions that limit glucose availability.²⁶ For example, ketogenic diets have shown therapeutic benefits in gliomas by restricting glucose intake, indirectly suggesting that forcing a metabolic shift to FAO could enhance the efficacy of metabolic interventions in glycolysis-dependent cancers.²⁷ These

tumors often exhibit metabolic rigidity, meaning that they are less able to switch to alternative fuel sources like fatty acids, unlike healthy cells that display metabolic plasticity and can easily transition between glycolysis and FAO.²⁸

A key physiological insight supporting this hypothesis comes from cardiac metabolism. The heart, which primarily relies on FAO for energy, is notably resistant to oncogenesis.²⁹ This observation suggests that cells reliant on FAO may lack the metabolic adaptability needed for tumor formation and growth. Forcing cancer cells, which are typically glycolysis-dependent, to shift to FAO could deprive them of the necessary metabolic flexibility, leading to metabolic exhaustion and apoptosis.³⁰

Mechanistically, FAO generates ROS at higher levels, particularly in cells not accustomed to this oxidative pathway, such as cancer cells. Elevated ROS levels induce oxidative stress, which can trigger apoptosis in cancer cells lacking robust antioxidant defenses. Given that cancer cells already experience higher oxidative stress due to their rapid proliferation, they may be especially vulnerable to the additional ROS burden imposed by FAO.³¹ However, normal tissues possess sophisticated antioxidant defense mechanisms, including glutathione, catalase, and superoxide dismutase, which allow them to maintain redox homeostasis. Unlike cancer cells, which often exhibit mitochondrial dysfunction and impaired oxidative phosphorylation, normal cells efficiently regulate ROS production and detoxification, thereby preventing damage from FAO-induced oxidative stress.³²

The glucolipotoxicity hypothesis proposes a novel paradigm in which excessive glycolipid accumulation disrupts glucose transporter functionality, compelling cancer cells into a compensatory glycolytic state. This metabolic shift, referred to as the Maher Akl effect, suggests that the Warburg phenotype observed in tumors is not merely a preferential energy pathway but rather a survival mechanism dictated by impaired glucose homeostasis. At the molecular level, excessive glycolipid accumulation, particularly gangliosides (e.g., GM3 and GD3), ceramides, and sphingolipids, has been shown to impair glucose transporter type 1 and glucose transporter type 4 activity, restricting glucose influx and triggering a compensatory activation of AMP-activated protein kinase and hypoxia-inducible factor 1- α , which in turn enhances the anaerobic glycolysis, lactate production, and tumor microenvironment acidification.³³ This metabolic adaptation perpetuates an inflammatory and immune-evasive state, further reinforcing oncogenic signaling through the mammalian target of rapamycin complex 1 activation, which sustains cell proliferation despite nutrient stress.³⁴ In addition, the accumulation of ceramides and

sphingolipids induces endoplasmic reticulum stress and mitochondrial dysfunction, exacerbating oxidative stress and increasing tumor resilience.³⁵ Given that these pathways collectively drive tumor progression and therapeutic resistance, addressing glycolipid-induced metabolic toxicity represents a promising therapeutic avenue.

Building upon this mechanistic framework, the AMRD diet has been developed as a targeted metabolic intervention designed to counteract the oncogenic effects of glucolipotoxicity by shifting cellular energy metabolism from glucose dependency toward FAO. This metabolic correction strategy directly mitigates the consequences of glycolipid overload by promoting mitochondrial β -oxidation, thereby enhancing lipid clearance, reducing intracellular ceramide accumulation, and restoring glucose transporter functionality. By prioritizing FAO as the primary energy source, AMRD disrupts the tumor's reliance on glycolysis, leading to a substantial reduction in lactate production and extracellular acidification, thereby creating a tumor microenvironment that is less conducive to immune evasion and metastasis. Furthermore, AMRD-mediated metabolic reprogramming is accompanied by PI3K/AKT/mTOR pathway downregulation, as reduced insulin and insulin-like growth factor 1 levels contribute to lower oncogenic signaling and decreased proliferative capacity.³⁶ Additionally, the inhibition of monocarboxylate transporter 4 prevents lactate efflux, further exacerbating metabolic stress in glycolysis-dependent cancer cells.³⁷ By alleviating lipid-induced toxicity while simultaneously depriving cancer cells of their glycolytic adaptation mechanisms, AMRD presents a dual-action approach that not only targets the metabolic vulnerabilities of tumors but also restores cellular homeostasis without inducing toxic side effects.

These macronutrient ratios make AMRD superior to the ketogenic diet for several reasons. First, targeted fat composition: while the ketogenic diet focuses broadly on reducing carbohydrates, AMRD incorporates specific fats that not only induce ketosis but also combat cancer-related inflammation. The addition of omega-3s and medium-chain triglycerides accelerates the body's adaptation to ketone production, enabling quicker transitions into fat oxidation and increasing the diet's effectiveness in targeting cancer cell metabolism.³⁸ Second, balanced protein for preservation: AMRD strikes a balance with its moderate protein content, which prevents muscle wasting in cancer patients and supports immune function. The ketogenic diet, on the other hand, may often lead to excessive protein intake, risking gluconeogenesis, which can provide cancer cells with the glucose they need to thrive.³⁹ Third, flexible carbohydrate management: The slight inclusion of carbohydrates ensures

that healthy cells maintain their flexibility, allowing them to switch between glucose and fat metabolism as needed.⁴⁰ In contrast, the ketogenic diet's severe carb restriction may lead to complications in the long term for non-cancerous cells that still require glucose for proper functioning.⁴¹

6. Conclusion

In conclusion, shifting cancer metabolism from glucose-dependent glycolysis to FAO represents a transformative avenue in oncology, offering a mechanistically driven approach targeting the metabolic rigidity of glycolysis-dependent tumors. By strategically leveraging the metabolic plasticity of healthy tissues while disrupting the energy homeostasis of malignant cells, FAO-based interventions introduce a paradigm shift in cancer therapeutics. Emerging preclinical and clinical insights underscore the potential of this metabolic reprogramming strategy, not only in enhancing the efficacy of existing treatments but also in minimizing systemic toxicity. As future research delves deeper into the clinical application of FAO modulation, this innovative approach holds the promise of ushering in a new era of precision oncology that prioritizes metabolic equilibrium, minimizes collateral damage to normal cells, and ultimately improves patient outcomes in the fight against cancer.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

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