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Metabolic Reprogramming in Prostate Cancer: A Potential Therapeutic Target

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ABSTRACT

Prostate cancer (PCa) remains one of the leading causes of cancer-related deaths among men worldwide. Despite advancements in detection and treatment, resistance to conventional therapies and disease recurrence remain significant challenges. Emerging evidence highlights the pivotal role of metabolic reprogramming in prostate cancer progression. Cancer cells adapt their metabolism to meet increased energy demands, support rapid proliferation, and survive in hostile environments. These alterations include enhanced glycolysis (Warburg effect), lipid metabolism, and dysregulation of mitochondrial function, all of which contribute to PCa progression and therapy resistance. Understanding the unique metabolic pathways employed by prostate cancer cells provides an opportunity for developing novel therapeutic strategies. Targeting metabolic pathways could disrupt the energy supply and biosynthetic precursors critical for cancer cell survival. This review explores the key aspects of metabolic reprogramming in prostate cancer, including glycolytic shifts, lipid metabolism alterations, and mitochondrial dynamics, and discusses potential therapeutic approaches targeting these metabolic pathways.

Keywords: Prostate cancer, metabolic reprogramming, Warburg effect, lipid metabolism, mitochondrial dysfunction, therapeutic targeting

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer in men globally, with an increasing incidence due to aging populations and improved detection methods. While localized prostate cancer is generally curable through surgery or radiotherapy, advanced stages, particularly castration-resistant prostate cancer (CRPC), pose a therapeutic challenge[1–3]. Conventional treatments targeting androgen receptor (AR) signaling and chemotherapy have limited efficacy in advanced stages, often leading to resistance and disease progression. Recent research has focused on understanding the underlying molecular mechanisms driving PCa, with metabolic reprogramming emerging as a critical feature of cancer biology[4, 5]. This metabolic plasticity not only supports tumor growth but also creates opportunities for novel therapeutic interventions.

Overview of Metabolic Reprogramming in Cancer

Metabolic reprogramming is a hallmark of cancer, allowing tumor cells to meet the demands of rapid growth, division, and survival under stress[6, 7]. Unlike normal cells, cancer cells exhibit altered glucose metabolism, favoring glycolysis over oxidative phosphorylation, even in the presence of oxygen, a phenomenon known as the Warburg effect[8–10]. Additionally, cancer cells rewire lipid metabolism, enhance glutamine utilization, and modulate mitochondrial dynamics to adapt to nutrient limitations and maintain redox balance[11, 12]. In prostate cancer, these metabolic adaptations are intricately linked to the androgen receptor (AR) pathway, contributing to tumor progression and resistance to therapies.

Glycolytic Shifts in Prostate Cancer: Prostate cancer cells exhibit a shift in glucose metabolism characterized by an increased reliance on glycolysis, even under aerobic conditions[13, 14]. This metabolic switch, first described by Otto Warburg, allows cancer cells to rapidly generate ATP and biosynthetic intermediates essential for cell proliferation. AR signaling in PCa further drives this glycolytic shift by upregulating glycolytic enzymes such as hexokinase 2 (HK2)

and lactate dehydrogenase A (LDHA)[14]. Moreover, the tumor microenvironment, including hypoxia, enhances glycolytic activity by activating hypoxia-inducible factors (HIFs). Inhibiting key glycolytic enzymes has been explored as a therapeutic strategy to target the energy metabolism of prostate cancer cells.

The Role of Hexokinase and Lactate Dehydrogenase

Hexokinase 2 (HK2), a key enzyme in the glycolytic pathway, phosphorylates glucose to form glucose-6-phosphate, committing it to glycolysis. In prostate cancer, HK2 is upregulated, promoting increased glucose flux into glycolysis[15]. Similarly, lactate dehydrogenase A (LDHA) facilitates the conversion of pyruvate to lactate, enabling cancer cells to sustain glycolysis under anaerobic conditions.[16] Elevated levels of lactate in the tumor microenvironment contribute to acidosis, which promotes invasion, metastasis, and immune evasion. Targeting HK2 and LDHA represents a promising approach to disrupting glycolytic metabolism in prostate cancer cells.

Lipid Metabolism in Prostate Cancer

Prostate cancer cells exhibit extensive rewiring of lipid metabolism, which is critical for membrane biosynthesis, energy storage, and signaling molecule production[17]. The AR plays a pivotal role in modulating lipid metabolism, particularly by regulating the expression of enzymes involved in de novo lipid synthesis, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). Elevated levels of these enzymes have been associated with poor prognosis in prostate cancer[18]. Additionally, prostate cancer cells preferentially utilize lipids as a fuel source through β-oxidation, providing an alternative energy supply under nutrient-limited conditions[19].

De Novo Lipogenesis: De novo lipogenesis is significantly upregulated in prostate cancer, driven by the overexpression of enzymes like FASN and sterol regulatory element-binding proteins (SREBPs)[20]. This lipid biosynthetic pathway provides the building blocks for rapidly dividing cancer cells to construct new cellular membranes and produce signaling lipids. Inhibiting FASN has been shown to reduce tumor growth and induce apoptosis in prostate cancer models, making it an attractive target for therapeutic intervention[21].

Lipid Storage and β-Oxidation: In addition to increased lipid synthesis, prostate cancer cells rely on lipid storage and fatty acid β-oxidation to generate ATP and sustain growth under metabolic stress. The upregulation of fatty acid-binding proteins (FABPs) and peroxisome proliferator-activated receptor gamma (PPARγ) enhances lipid uptake and utilization. Inhibiting β-oxidation enzymes or targeting FABPs may reduce the energy supply and limit prostate cancer progression.[22, 23]

Mitochondrial Function and Dynamics

Mitochondria play a crucial role in energy production and maintaining redox balance in prostate cancer cells. Unlike other cancers that rely heavily on glycolysis, prostate cancer cells retain functional mitochondria and use oxidative phosphorylation (OXPHOS) as a key energy-generating pathway[24]. However, mitochondrial function in PCa is also altered, with changes in mitochondrial dynamics, including increased mitochondrial biogenesis and fission, promoting tumor growth and survival. Targeting mitochondrial function, either by inhibiting OXPHOS or disrupting mitochondrial dynamics, represents another promising therapeutic avenue[24].

Targeting Mitochondrial Biogenesis Increased mitochondrial biogenesis is a feature of advanced prostate cancer, driven by factors such as PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator)[25]. This enhanced mitochondrial activity allows cancer cells to meet increased bioenergetic and biosynthetic demands. Inhibiting PGC-1α-mediated mitochondrial biogenesis or targeting mitochondrial fission proteins such as dynamin-related protein 1 (DRP1) has been proposed as a therapeutic approach to impair the metabolic flexibility of prostate cancer cells[25, 26].

Therapeutic Targeting of Metabolic Pathways in Prostate Cancer

Given the essential role of metabolic reprogramming in prostate cancer progression, targeting these altered metabolic pathways offers a potential therapeutic strategy. Several metabolic inhibitors targeting glycolysis, lipid metabolism, and mitochondrial function have shown promise in preclinical models. For example, inhibitors of HK2, FASN, and OXPHOS have demonstrated anti-tumor effects in vitro and in vivo. Additionally, combination therapies that target both metabolic and AR signaling pathways may enhance therapeutic efficacy and overcome resistance mechanisms in prostate cancer.[27]

CONCLUSION AND FUTURE DIRECTIONS

Metabolic reprogramming in prostate cancer represents a critical driver of tumor progression and therapy resistance. Understanding the complex interplay between androgen signaling

and metabolic pathways provides new opportunities for therapeutic intervention. Future research should focus on identifying specific metabolic vulnerabilities in prostate cancer and developing targeted therapies that exploit these weaknesses. Combination strategies that integrate metabolic inhibitors with existing therapies may improve outcomes for patients with advanced prostate cancer.

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