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Metabolic Targets for Potential Prostate Cancer Therapeutics

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Abstract

Purpose of Review—Prostate cancer (PCa) demonstrates characteristic changes in metabolism and bioenergetics in the transition from benign to malignant tissue. It is feasible that some of these changes may be targetable for therapeutic purposes. This review will highlight some of the current metabolically targeted therapies being investigated for the treatment of prostate cancer.

Recent Findings—The transition from benign to malignant prostate cells is characterized by decreased intracellular zinc concentration and subsequent release of inhibition of the tricarboxylic acid cycle enzyme m-aconitase which leads to the decrease in citrate concentration within the cancer tissue. Instead of the largely glycolytic phenotype exhibited by most cancers, PCa relies on glutamine and lipids for survival and proliferation. Early studies are beginning to demonstrate that targeting some of the up-regulated pathways with inhibitors of key enzymes such as glutaminase, fatty acid synthase, HMG-CoA reductase, hexokinase, zinc transport, or complex I in the mitochondria may have significant metabolic effects and therapeutic potential.

Summary—The unique metabolic profile of PCa allows for many potential avenues of treatment. Future studies will continue to test if the metabolic characterization and treatment of PCa could be an important approach to provide personalized treatment for the disease.

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I. Introduction

Prostate cancer (PCa) is the most common cancer in men and second leading cause of cancer-related mortality in men worldwide [1]. Cancer cells exhibit altered metabolism, compared to their benign counterparts, partly because their continued growth and division requires a constant supply of energy and structural building blocks. To accommodate the altered energy requirements, cellular metabolism is altered through modifications of the activity and expression of key metabolic enzymes. These metabolic changes often occur downstream of various oncogenes or tumor suppressor genes such as c-Myc, Hif1α, PTEN, and RUNX2 [2–6]. This metabolic switch is not only an adaptive response of cancer cells, but can be a driver of tumorigenicity[3]. A single model cannot account for the sum of metabolic changes in cancer because of the vast heterogeneity that exists within tumors and the complexity of the microenvironments in which they grow. However, as the common metabolic changes involved in tumor progression from indolent to aggressive forms become better understood improved methods of risk-stratification, and ultimately personalized targeted therapy for specific metabolic dysfunctions, may be possible. Here, we will review current advances and future research directions regarding metabolism-focused therapeutic developments in PCa management.

II. Normal Prostate Metabolism

Prostate epithelial cells exhibit specific characteristics that distinguish them from other cells. It is notable that metabolic function in the prostate gland is particularly interesting as even benign prostate tissue demonstrates unique metabolism compared to most other tissues in the body. Perhaps the most significant of these differences is the ability to accumulate and secrete high levels of citrate and zinc into the prostatic fluid which mixes with sperm [7]. Seminal fluid citrate concentrations (40 – 150 mM) are considerably higher than blood plasma levels (0.1 – 0.3 mM) [7]. Citrate is believed to act as a buffering agent, a chelator of calcium and zinc, and a possible scavenger of free radicals [8,9]. In the normal prostate, citrate excretion is maintained by inhibition of m-aconitase, a tricarboxylic acid (TCA) cycle enzyme responsible for the conversion of citrate to isocitrate [10]. Thus the prostatic epithelial cells experience a buildup of mitochondrial citrate which is then transported to the cytoplasm and ultimately excreted into seminal fluid. Costello et al found that the aconitase inhibition is mediated by the unusually high levels of zinc in prostatic cells [10] [figure 1]. This is, in turn, regulated by an abundance of ZIP1 zinc transporters in prostatic epithelial cells [11]. Intriguingly, it has been well established that PCa loses the ability to concentrate zinc and citrate [11]. This results in the hallmark transformation of prostate epithelial cells from benign and citrate-secreting to malignant and citrate-oxidizing cells, which occurs through the TCA cycle.

III. Metabolic Characteristics of Prostate Cancer

Prostate tumorigenesis is a highly complex process. In addition to the aforementioned changes in zinc and citrate metabolism, prostatic carcinoma exhibits aberrations in nearly all major aspects of metabolism. There is a dynamic reliance on glucose, increased glutamine demand, extensive alterations in lipid metabolism and a strong reliance on the pentose phosphate pathway (PPP) [5]. These alterations in metabolomics allows for novel targeted approaches for diagnosis, prognosis, monitoring, and anti-cancer therapy.

Prostate cancer metabolism remains a nascent field. Several challenges remain that impede characterization of changes that occur with prostate tumorigenesis. These include the heterogeneous nature of the disease and a shifting metabolic picture depending on the grade of the disease. The vast majority of solid cancers undergo the Warburg effect, a phenomenon of increased glucose uptake and glycolysis resulting in pyruvate and lactic acid build up despite aerobic conditions [12]. This change in energy metabolism seems almost counterintuitive considering the heightened energy requirements of cancer and the lower ATP-producing efficiency of glycolysis relative to oxidative phosphorylation. One of the leading theories as to why this occurs is that increased glycolysis allows for increased production of intermediates which are required for anaplerosis [13]. Another reason is the more rapid flux of glucose through glycolytic pathways relative to oxidative phosphorylation [14]. However, PCa does not seem to undergo Warburg metabolic changes [5]. While glucose and glutamine metabolism are usually noted as some of the chief energy sources for cellular respiration, PCa is not heavily reliant on glucose. Rather, what seems to occur is an increased reliance on oxidative phosphorylation. This is mediated by the decreased activity of ZIP1 transporters in PCa, with the resultant decrease in zinc concentrations leading to increased activity of m-aconitase and the TCA cycle. Although not fully understood, the metabolic pathways of greatest importance with prostate cancer seem to be more fatty acid metabolism and glutamine metabolism [5]. We will next discuss various metabolically targeted therapies under consideration for treatment of prostate cancer.

IV. Metabolic Therapeutic Targets

There are a variety of modalities for the treatment of PCa. Although optimal treatment is at times difficult to determine, options range from surgical excision and radiation in localized disease to hormone therapy and chemotherapy in advanced disease. The mainstay of advanced PCa is androgen deprivation therapy, usually involving luteinizing hormone-releasing hormone (LHRH) agonists and oral anti-androgens. The majority of cancers respond initially, followed by progression to Castrate Resistant PCa (CRPC), with overexpression of androgen receptors and up regulation of androgen biosynthesis enzymes being among some of the important pathways leading to the CRPC phenotype [15,16]. Newer anti-androgens and androgen biosynthesis inhibitors, such as enzalutamide and abiraterone acetate, have been developed to enhance efficacy in advanced cancers and can improve overall survival. Although chemotherapy can also improve overall survival, the median survival for men with CRPC remains in the 2- to3-year range despite these treatments [16, 17]. Thus, there is a great need for new therapeutic modalities. Because of the significant metabolic changes in PCa, metabolic-targeted therapy and research focused

on the metabolic alterations of prostate cancer is warranted. Below we will discuss the role of zinc metabolism, AMP kinase activators, lipogenesis inhibitors, steroid inhibitors, and glutamine pathway inhibitors as promising therapeutic modalities.

Zinc

Zinc is an essential element of great interest in cancer research due to its anti-oxidant and anti-inflammatory properties and its ability to improve cell-mediated immune functions and inhibit NF-kB [18]. As previously described, normal prostate epithelial cells have the highest concentrations of zinc and changes in zinc metabolism are crucial to PCa pathogenesis. There is much experimental support for the anti-neoplastic effects of zinc. Specifically, many studies show an increase in PCa cell apoptosis with zinc administration [19,20]. Ku et al specifically have reported a dose-dependent apoptotic effect in both androgen-dependent and -independent cell lines [21]. Furthermore, their study was one of the first to show specific changes in apoptotic and anti-apoptotic molecules, which inhibited cell proliferation. Zinc administration was associated with increased expression of BAX mRNA and diminished expression of Bcl-2 and survivin mRNAs [21]. Animal trials have allowed development of various methods of zinc administration, with 5-chloro-7-iodo-8-quinolinol (Clioquinol) being one of the newer forms. Clioquinol is a zinc ionophore that allows intracellular zinc accumulation despite the absence of ZIP zinc transporters in malignant prostate cells [22]. Costello et al demonstrated over 70% suppression of tumor growth in mice treated with Clioquinol, with minimal to no side effects [22]. Epidemiological data on the effect of zinc on PCa has been largely inconsistent [23–25]. There have been over 10 such studies on dietary and supplemental zinc intake, mostly assessing PCa prevention [26,27]. In a more recent study, however, Epstein et al demonstrated that Swedish men with high zinc intake exhibited lower disease-specific mortality, especially in men with localized tumors [27].

Multiple studies are underway to assess the efficacy of combination therapy with zinc and various anti-neoplastic drugs for the treatment of prostate cancer. One such drug is Sorafenib, a multi-kinase inhibitor that is FDA approved for the treatment of renal cell and hepatocellular cancers [28,29] and has displayed anti-neoplastic properties in PCa [30–32]. Chen et al reported increased sensitivity of PCa cells to Sorafenib-induced apoptosis following zinc administration [33]. Thus, it may be possible to maintain the therapeutic efficacy of Sorafenib with reduced dosage. This is of specific interest as Sorafeib therapy is associated with a variety of significant side effects. Another drug similarly potentiated by zinc is paclitaxel. Uzzo et al have shown zinc to sensitize PCa cells to paclitaxel-mediated cell death [34].

AMPK Activators

Adenosine monophosphate-activated protein kinase is a central cellular energy regulator that responds to increased AMP/ATP ratio by enhancing energy producing pathways and down-regulating energy consuming pathways such as lipogenesis and mTORC1 pathways [35]. With its extensive involvement in cellular metabolism, AMPK has enormous potential for anti-cancer therapy. In fact, various AMPK activators have been shown to reduce cancer risk [36,37]. They are divided into two groups, 1) indirect activators, including biguanides such

as metformin and 2) direct activators, including 5-aminoimidazole-4carboxamide-1-β-ribofuranoside (AICAR) and other more recently developed small molecule AMPK activators [5].

Metformin is a guanidine derivative widely used as first-line therapy for type II diabetes mellitus that decreases hepatic gluconeogenesis and enhances peripheral insulin sensitivity. Bowker et al showed that diabetics treated with metformin exhibited lower incidence of cancer and cancer-related mortality compared to patients treated with insulin and sulfonylureas [38]. Another study showed metformin to be associated with a 44% risk reduction in PCa cases [39]. Biguanide's anti-cancer mechanism involves inhibition of Complex 1 of the electron transport chain. This results in reduced ATP synthesis and increased AMP/ATP ratio and subsequent activation of AMPK leading to inhibition of mTORC1 activity and decreased translational efficiency in PCa cells [40]. Although its anti-neoplastic mechanism is yet to be fully illuminated, the existing data may stimulate doctor-patient discussion about starting metformin in hesitant diabetic patients. There are approximately 25 clinical trials currently ongoing to utilize metformin as an adjuvant treatment in a range of PCa patients, either as a stand-alone medication or in combination with other treatments such as surgery, radiation, enzalutamide and docetaxel [clinicaltrials.gov].

The nucleoside AICAR was the first agent reported to activate AMPK in intact cells and in vivo [5]. AICAR is taken up by adenosine transporters and converted to ZMP, a 5'-AMP analog. AICAR has been shown to diminish proliferation of PCa in xenograft models; however, a lack of specificity and poor oral bioavailability has led to a search for more specific and potent direct AMPK activators [5,41,42]. Small molecule AMPK activators are newer, subunit-specific drugs that are under active investigation. Examples include A-769662, PT1 and OSU-53 [5]. These newer agents show potent anti-cancer activity in tumor bearing-mice with OSU-53 resulting in 47–49% growth suppression [43]. Unfortunately, the limitations of poor oral availability and non-specificity remain, and therefore efforts to develop more targeted direct AMPK activators continue.

Inhibitors of lipogenesis

In normal tissues, lipogenesis is inhibited by the presence of dietary fatty acids, with the exception of the liver, adipose tissue and lactating breast tissue [5,44]. In cancer, however, there is an over expression of the major lipogenic enzymes, namely ATP citrate lyase (ACLY), acetyl-Coa carboxylase (ACC), and fatty acid synthase (FASN) [45]. Additionally, expression of many of these enzymes is stimulated by the c-Myc oncogene, which also increases expression of TCA cycle genes responsible for citrate synthesis, a precursor for fatty acids and cholesterol [46]. FASN overexpression is an early event in PCa tumorigenesis and is associated with cancer progression and bone metastasis [47–49]. Additionally, in experiments with prostate epithelial cells, ectopic expression of FASN was associated with development of PIN and progression to invasive tumors [50].

Inhibition of FASN results in suppressed cell adhesion, reduced migration, and attenuation of growth and apoptosis [51]. Several inhibitors of FASN have been described and studied to date, including Orlistat, Cerulenin, C75, and C93. Orlistat, initially marketed as an anti-

obesity drug, has been found to inhibit FASN by forming a covalent bond with the enzyme [52]. Flavin et al showed Orlistat inhibits proliferation and induces apoptosis in PC3 cells [53]. Unfortunately, pharmacological limitations for this drug are multiple and include poor oral availability, poor metabolic stability, low solubility, low cell permeability, and lack of selectivity [53]. Development of C75, Cerulenin, and C93 for cancer treatment has been limited by side effects such as dramatic anorexia and weight loss in animal trials [5,54].

Recently, newer and more potent FASN inhibitors were identified through medicinal chemistry and high-throughput screening: Astra Zeneca developed a series of bisamide derivatives, Merck a series of 3-aryl-4-hydroxyquinolin-2(1H)-one derivatives, and GlaxoSmithKline produced GSK837149, a FASN inhibitor with nanomolar potency [54]. In addition to FASN, other lipogenic enzymes represent promising targets for prostate cancer therapy. ACLY inhibition by RNA interference (RNAi) or with chemical inhibitors SB-204990 and simvastatin inhibited proliferation and survival of tumor cells displaying aerobic glycolysis, which reduced tumor growth *in vivo* [55].

Cholesterol metabolism inhibitors

The tumorigenesis, maintenance, and progression of PCa are largely associated with abnormalities in cholesterol metabolism. There is an epidemiological correlation between hypercholesterolemia and aggressive prostate cancer [56]. Additionally, animal models have linked hypercholesterolemia to increased PCa growth, AKT activation, and progression to metastasis [57,58]. Multiple studies have shown statins to reduce the risk of prostate cancer [56]. Statins inhibit HMG-CoA reductase (HMGCR) which catalyzes the conversion of HMG-CoA to mevalonate, the rate limiting step of steroidogenesis. Treatment of androgen-dependent and - independent PCa cell lines with simvastatin significantly reduced cell migration, invasion and proliferation [59]. Furthermore, treatment of PC3 xenografts with the same drug yielded a reduction in tumor growth [59]. Long term studies have shown reduced risk of advanced PCa with statin therapy; however, data on overall risk for PCa is inconclusive [56]. Multiple studies are underway to elaborate this relationship.

Glutamine inhibitors

Glutamine is an abundant nutrient, essential for cell survival. It functions as a major source of energy, a source of nitrogen for amino acids, and in the synthesis of the antioxidant glutathione. In cancer, glutamine is increasingly converted to glutamate and then alpha keto-glutarate which maintains the TCA cycle to satisfy the elevated energy requirements of cancer cells [5]. Glutaminase (GLS) catalyzes the conversion of glutamine to glutamate, exists in multiple forms (GLS-1, GLS-2), and is under the control of the c-Myc oncogene [46]. GLS-1 is found in the kidney and also present in prostate cancer cells [60]. Pan et al showed that GLS-1 promotes cell proliferation and survival; furthermore, t elevated GLS correlates with higher grade and more advanced tumors [61]. Reduced expression of GLS-1 by siRNA or bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide (BPTES), a direct inhibitor, resulted in reduced glucose uptake, diminished ATP levels, and a resultant inhibition of cell proliferation and progression [61]. These findings indicate GLS-1 may be a viable therapeutic target in PCa treatment.

Inhibitors of other metabolic enzymes

Several metabolic enzymes such as hexokinase (HK), lactate dehydrogenase A(LDHA) and pyruvate dehydrogenase kinase 1(PDK1) are direct targets of oncogenic transcription factors, such as c-Myc and hypoxia-inducible factor-1a (HIF1a) [46]. These enzymes represent opportunities for targeted therapy. Most notably, HK has an important role in both glycolysis and apoptosis, and its inhibitors, such as 2-deoxyglucose (2-DG), 3-bromopyruvate (3-BrPA), and Lonidamine (LND), are in pre-clinical and early phase clinical trials [62].

V. Conclusion

The unique metabolic characteristics of prostate cancer provide opportunities for advanced, more targeted therapy. Perhaps the most distinct characteristic of prostate epithelial cells is their ability to concentrate zinc and its involvement in tumorigenesis. Although data on the therapeutic efficacy of zinc supplementation is inconsistent, new work shows its potential benefit in terms of disease-specific mortality. A variety of lipid metabolism aberrations are present in PCa, specifically the upregulation of FASN and steroidogenesis, which suggests promising avenues for treatment. The most exciting and clearly beneficial AMPK activator is metformin. Although further clarification of its effects on PCa is necessary, there is a clear reduction in PCa incidence in metformin-treated diabetics. Finally glutaminase-1 inhibitors show strong potential as therapeutic metabolic targets as they inhibit prostate cancer progression. Continued research into how metabolic dysfunction is associated with prostate cancer tumorigenesis and progression may lay the foundation for future refined research on potential metabolic targets of interest.

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Key Points

- Unlike most solid tumors, prostate cancer delays the onset of the Warburg effect, resulting in a greater reliance on glutamine and lipids for energy.
- Prostate epithelial cells are unique in terms of zinc metabolism and the relative suppression of the TCA cycle.
- There is much experimental data supporting the antineoplastic effects of zinc on prostate cancer and, more specifically, the safe use of zinc ionophore as treatment.
- Metformin reduces all cancer-related mortality and reduces prostate cancer incidence.
- Statins reduce risk of aggressive prostate cancer and trials are underway to further clarify their effect on the full range of prostate cancer disease states.

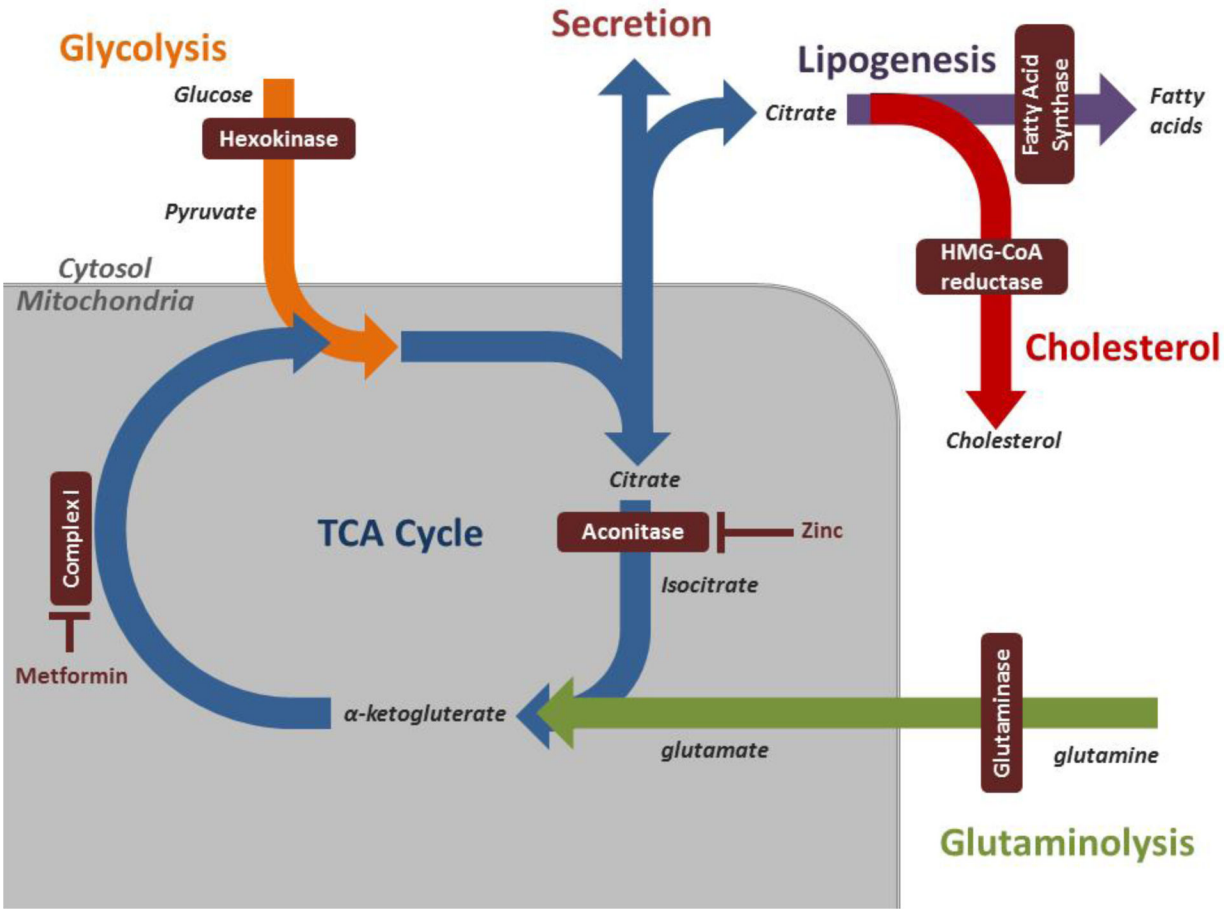

Figure 1: Therapeutic Targets of Prostate Cancer Metabolism

Prostate cancer is characterized by changes in glycolysis, the tricarboxylic acid (TCA) cycle, lipogenesis, cholesterol metabolism, and glutaminolysis which are inter-related as demonstrated here. Benign prostate tissue demonstrates increased zinc accumulation, which leads to inhibition of m-aconitase and citrate secretion. This zinc buildup is lost with tumorigenesis leading to loss of citrate secretion and numerous other metabolic changes within the cell. Targetable enzymes in prostate cancer metabolism are highlighted (maroon boxes).