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Exploiting Metabolic Reprogramming and Its Therapeutic Vulnerabilities in Prostate Cancer

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Abstract

Prostate cancer is a metabolically distinct malignancy as it exhibits strong flexibility in how it uses energy and perform physiological processes. In contrast to many solid tumors which mostly depend on aerobic glycolysis, the primary prostate cancer cells still depend mainly on oxidative phosphorylation and tricarboxylic acid (TCA) cycle for energy supply. This unique metabolic pattern is mainly controlled by androgen receptor signaling and also affected by mitochondrial functions and zinc level inside the cells. When the disease goes into advanced stage, especially castration-resistant prostate cancer (CRPC), the tumor cells change their energy system toward glycolytic and lipogenic ways to support hyperactive cell cycle, therapy resistance, and metastasis. This review gives a detailed discussion about metabolic reprogramming in prostate cancer with focus on glycolysis, mitochondrial dysfunction, and dysregulated lipid and cholesterol metabolism. Key enzymes, transporters and transcription factors, such as GLUT1, HK2, PFK1, PKM2, LDHA, PDK, FABP5, ACLY, ACAC, FASN, SREBPs and LXRs are discussed as important players of tumor bioenergetics , and as possible drug targets. Especially lipid metabolism has shown strong relation with CRPC aggressiveness, which is promoted by androgen receptor-controlled increase of lipogenic enzymes and fatty acid transport process. Interaction between metabolic pathways and oncogenic signaling like PI3K/AKT/mTOR makes the situation more complex. The review also covers new therapeutic strategies which make use of these metabolic vulnerabilities, including small molecule inhibitors, natural substances, and combination treatments. Better understanding of metabolic reprogramming of prostate cancer at different disease stages can help in creating more specific therapies to overcome resistance and improve clinical outcomes.

Key words prostate cancer, metabolic reprogramming, mitochondrial dysfunction, glycolysis, oxidative phosphorylation, lipid metabolism, targeted therapy

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Introduction

Prostate cancer is one of the most frequent malignancies among men and still remains a leading cause of cancer related death in many countries. According to the recent global cancer report covering 185 countries, around 1.5 million new cases and about 0.4 million deaths were recorded in 2022, which makes prostate cancer the second most diagnosed and the eighth major cause of death among men [1]. In the United States, it is reported as the most common cancer and second cause of cancer death in male population [2]. The disease shows high variation in clinical behavior, where some tumors grow very slowly but others are aggressive and life threatening. The reasons behind this disease are heterogenous and include both modifiable and non-modifiable risk factors such as age, family history, race, genetic background, and lifestyle pattern [3]. Age is a strong factor because the chance of developing prostate cancer increases from 0.005% in men below 39 years to 13.7% in those between 60-79 years [3]. Early identification through prostate-specific antigen (PSA) screening and digital rectal examination has improved detection and disease management [4]. Local disease is often managed by active surveillance, surgery, or radiotherapy, but metastatic or advanced disease needs systemic therapy, mostly androgen deprivation therapy. Androgen deprivation therapy remains as the main treatment for locally advanced and metastatic prostate cancer [5]. Although it gives good response in the beginning, most patients later develop castration-resistant prostate cancer (CRPC) within one or two years of therapy [6]. The arrival of second generation androgen receptor pathway inhibitors such as enzalutamide and CYP17A1 inhibitor abiraterone, when used with androgen deprivation therapy, has improved survival of many patients [7-9]. However, resistance to these treatments becomes common and is usually due to activation of compensatory signaling and metabolic systems. Therefore, there is urgent need to develop therapies that can attack metabolic weaknesses in CRPC.

Metabolic reprogramming is now considered as a hallmark of cancer and helps tumor cells to adjust under changing nutrients and oxygen levels [10]. In prostate cancer, this metabolic change involves glucose, lipid, and amino acid metabolism. While most cancers rely mainly on aerobic glycolysis (Warburg effect), the early stage prostate cancer keeps oxidative phosphorylation and tricarboxylic acid (TCA) cycle as main energy sources, which is strongly controlled by androgen receptor signaling [11]. When disease advances to CRPC, metabolism shifts more toward glycolysis and lipid biosynthesis, which support tumor survival, growth, and therapy resistance [12]. Among these metabolic processes, lipid metabolism plays a key role. The disturbed de novo lipogenesis, fatty acid uptake, and β-oxidation give cells both structural and signaling components that drive tumor progression [13, 14]. androgen receptor signaling also controls enzymes responsible for steroidogenesis and fatty acid oxidation, thus helping cancer cell survival even in low androgen condition [15]. High lipid accumulation, especially of glycerophospholipids, is linked with therapy resistant CRPC [16]. This combined dependency on oxidative phosphorylation and lipid metabolism makes prostate cancer different from many other solid tumors and provides a group of new therapeutic targets.

This review mainly discusses the metabolic reprogramming in prostate cancer and how glycolysis, mitochondrial function, and lipid metabolism work together. It also describes new metabolic targets and therapeutic strategies which may help in improving the outcome in both hormone-sensitive and castration-resistant stages.

Metabolic reprogramming in prostate cancer

Glucose enters the cell through glucose transporters (GLUTs) and then goes through glycolysis with the help of main enzymes such as hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinase (PK) (**Figure 1**) [17]. Mitochondria are the main organelles responsible for energy production and also control many metabolic signals through TCA cycle and oxidative phosphorylation [18]. Under normal oxygen condition, pyruvate from glycolysis is transported into mitochondria by mitochondrial pyruvate carrier and then converted to acetyl-CoA. This acetyl-CoA enters into TCA cycle and helps to produce ATP efficiently (**Figure 2)** [19]. Mitochondrial dysfunction is a common feature in prostate cancer which can happen due to mutations in mitochondrial DNA, abnormal expression of TCA cycle enzymes, and electron transport chain leakage. These changes cause oxidative stress and disturb the balance between oxidant and antioxidant systems [20]. In contrast to many other solid cancers that mostly depend on aerobic glycolysis (Warburg effect), early stage prostate cancer still uses mitochondrial oxidative phosphorylation as main energy source. As the disease moves into advanced stage, tumor cells develop metabolic plasticity and shift toward glycolytic, lipogenic, and cholesterol based energy process [21]. This is under the control of androgen receptor signaling and mitochondrial pyruvate carrier activity which together modify mitochondrial metabolism to support oxidative energy generation [22, 23]. Normal prostate epithelial cells contain high zinc levels that stop mitochondrial aconitase and block citrate oxidation. But in cancer, zinc uptake decreases due to low expression of zinc transporter proteins, which allows citrate oxidation and helps the TCA cycle to continue [22, 24]. When prostate cancer becomes advanced, especially CRPC, cells become more dependent on glycolysis and lactate production [23, 25]. This metabolic change is also regulated by fibroblast growth factor (FGF)/fibroblast growth factor receptor 1 (FGFR1) pathway that increases lactate dehydrogenase (LDH) level and activity [26]. Hyperactive LDHA promote cancer cells aggressiveness by lowering mitochondrial pyruvate consumption and strengthening glycolysis [27]. HK2 related glycolysis is also linked with CRPC progression, especially in cases with PTEN or TP53 loss [28]. These observations indicate that co-targeting glycolysis and mitochondrial oxidative phosphorylation can be a good strategy for prostate cancer therapy (**Figure 1 and 2**).

Prostate cancer also shows high de novo fatty acid synthesis which is controlled by key enzymes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACAC), and fatty acid synthase (FASN). ACLY converts citrate into acetyl-CoA, then ACAC changes it into malonyl-CoA, and FASN uses malonyl-CoA to make palmitate. Palmitate is further modified by stearoyl-CoA desaturase and ELOVL enzymes to form complex lipids like triacylglycerols (**Figure 3**) [29, 30]. These lipogenic enzymes are often increased in prostate cancer and are also related to androgen receptor and PI3K/AKT/mTOR signaling that promote lipid production and storage [31]. As a result, there is higher amount of phospholipids, sphingolipids, and triglycerides accumulated in lipid droplets, which is known as “lipogenic phenotype.” This type of metabolism is more common in metastatic CRPC and shows aggressive behavior [32]. Besides new lipid formation, prostate cancer cells also increase fatty acid uptake and transport using membrane proteins such as CD36 (fatty acid translocase), fatty acid transport proteins (FATPs), and fatty acid-binding proteins (FABPs) [33]. In PTEN-deficient models, deleting CD36 reduces fatty acid uptake, decreases oncogenic lipid content, and slows tumor progression [34]. CD36 is also related to metastasis because metastatic cells need fatty acid uptake for colonizing new sites [35]. High CD36 expression is connected with poor prognosis [36]. FATPs, especially FATP6, are found in high amount in prostate cancer and linked with lower survival [37]. FABPs like FABP4 and FABP5 help in moving fatty acids inside the cell. FABP4 interacts with peroxisome proliferator-activated receptor gamma (PPARγ),

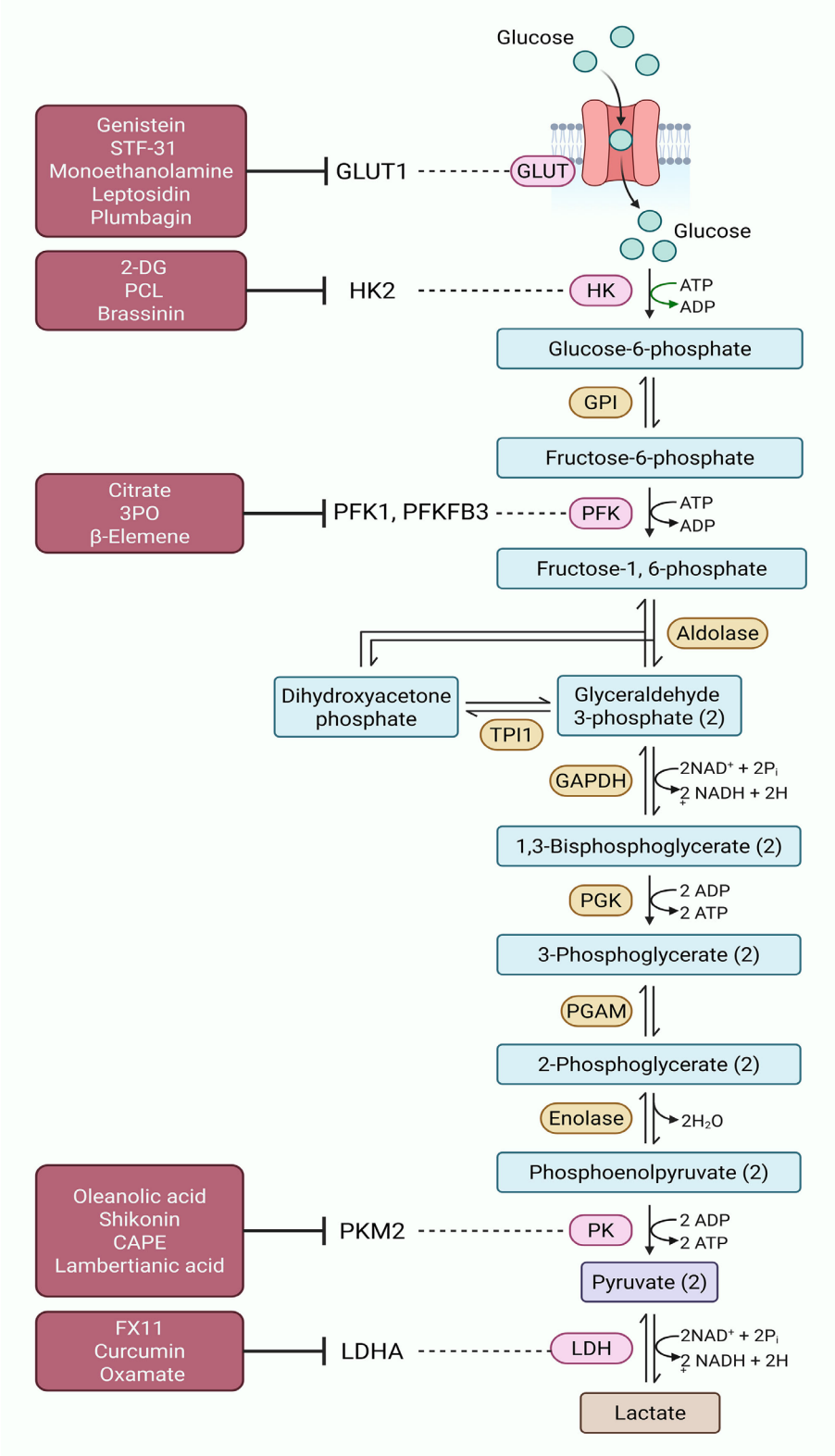

Figure 1. Targeting glycolysis in prostate cancer. Cancer cells often rely on glycolysis for energy production. Various enzymes involved in this process, including GLUT1, HK2, PFK1, PFKFB3, PKM2 and LDHA, are often dysregulated in prostate cancer cells, fueling tumor progression and disease aggressiveness. Different inhibitors, both synthetic and natural (highlighted in maroon boxes), have shown potential to target these metabolic vulnerabilities of glycolysis and alleviate disease aggressiveness in prostate cancer.

thereby helping in proliferation and differentiation [38]. FABP5 is hyperactive in advanced prostate cancer cases, where it supports tumor growth by sending fatty acids to PPARγ, which, in turn, activates genes like vascular endothelial growth factor (VEGF) [39]. FABP5 can also regulate the expression of AR-V7, keeping CRPC growing even under androgen receptor targeted therapy

[40].

Fatty acid β-oxidation (FAO) presents another source of energy in prostate cancer cells (**Figure 2**), especially under nutrient-deprived conditions. Carnitine palmitoyltransferase 1A (CPT-1A) is the main enzyme that controls FAO and is found high in prostate cancer. Inhibition of CPT-1A, together with androgen receptor blockers like enzalutamide, can reduce tumor growth by changing AKT activity and activating the INPP5K pathway [41]. CPT-1B, another isoform controlled by androgen receptor, also helps in castration resistance by maintaining AKT signaling [42]. α-Methylacyl-CoA racemase (AMACR), a peroxisomal enzyme involved in β-oxidation of branched fatty acids, is strongly expressed in prostate cancer and is used as diagnostic and therapeutic marker [43]. Interestingly, in neuroendocrine prostate cancer, which is a very aggressive type, tumor cells depend less on FAO and more on glutamine metabolism. They show low kidney-type glutaminase and high glutaminase 1 (GLS1) xpression to adjust under nutrient stress and therapy [3]. Prostate cancer also increases cholesterol biosynthesis through the mevalonate pathway. Cholesterol works as a membrane part and also as precursor for androgen synthesis [44]. The enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is the main step in cholesterol production and is high in enzalutamide-resistant cells, connecting cholesterol metabolism with drug resistance [45]. Statins, which block HMGCR, can reduce this resistance and slow tumor growth [46]. Prostate cancer cells also improve cholesterol uptake by increasing low-density lipoprotein (LDL) receptors and changing ATP-binding cassette (ABC) transporters [32]. High cholesteryl ester level in lipid droplets, promoted by sterol regulatory element-binding protein 2 (SREBP2) and LDL receptors, supports aggressive behavior [47]. Loss of PTEN, which is common in prostate cancer, activates PI3K/AKT/mTOR pathway that promotes cholesterol storage and helps cell survival [32]. In general, prostate cancer metabolism shows dynamic changes in mitochondrial respiration, glycolysis, lipid production, fatty acid oxidation, and cholesterol metabolism (**Figure 1-3**). These pathways are tightly controlled by oncogenic signals and change under therapy stress. Understanding their interaction can help in designing combination treatments to target these metabolic weaknesses and overcome drug resistance in prostate cancer.

Targeting glycolysis in prostate cancer

Glycolysis is highly active in advanced prostate cancer and supports tumor cells for energy supply, biosynthesis, and stress resistance. Many glycolytic enzymes and glucose transporters are overexpressed, such as glucose transporter 1 (GLUT1), hexokinase 2 (HK2), and pyruvate kinase M2 (PKM2), which make them potential drug targets (**Figure 1**). GLUT1 is a membrane protein responsible for glucose entry and plays an important role in maintaining glycolytic activity in prostate cancer [48]. When GLUT1 is blocked, glucose metabolism reduces and apoptosis becomes higher. Genistein, a natural isoflavone from soy, acts as an ATP competitive inhibitor and lowers GLUT1 level and function, leading to reduced glucose uptake [49]. Genistein also promotes apoptosis by blocking p38 MAPK pathway and activating caspase-3 [50]. Combination of genistein with plumbagin gives stronger effect by increasing ROS and reducing glutathione (GSH), which decreases cell growth [51]. It also increases sensitivity of prostate cancer cells to the IGF1R inhibitor AG1024 during radiation, which leads to more apoptosis [52]. The specific GLUT1 inhibitor STF-31 also blocks glucose transport directly. When used alone it decreases tumor size in C4-2 xenograft models, and when combined with enzalutamide, it increases apoptosis in CRPC [53]. Another agent, monoethanolamine, reduces glucose uptake by suppressing hypoxia-inducible factor 1-alpha (HIF-1α) and activates p53 related apoptosis [54]. Monoethanolamine also prevents movement of GLUT1 to cell membrane, thus reducing energy availability [55]. Leptosidin, a flavonoid compound, has strong antioxidant property and decreases glycolysis by reducing ROS and blocking SIRT1/GLUT1 signaling, leading to androgen receptor independent apoptosis [56].

Hexokinase 2 (HK2) catalyzes the first step of glycolysis and is found high in prostate cancer, mainly in low oxygen conditions. It helps the cells to survive through aerobic glycolysis [57]. 2-Deoxy-D-glucose (2-DG), a glucose analog, inhibits HK activity and lowers glycolytic rate. Early trials showed some benefit but long-term use caused resistance [58]. When 2-DG is combined with metformin, an autophagy inhibitor, apoptosis becomes stronger [59]. Polysaccharide C-type lectin (PCL), a mannose-specific lectin, interacts with epidermal growth factor receptor (EGFR) and lowers HK2 expression-driven glycolysis, ultimately promoting apoptosis [60]. Brassinin, a natural phytoalexin from cruciferous vegetables, blocks MAPK pathway, leading to HK2 inhibition, ROS production and cell death [61]. Phosphofructokinase-1 (PFK1) and its regulator PFKFB (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) control the speed of glycolysis. In prostate cancer, PFK1 and PFKFB3 are usually higher and increase glycolytic rate for tumor survival [62]. Citrate, which naturally inhibits PFK1, can reduce both glycolysis and TCA cycle, resulting in low energy and slow tumor growth [63]. Some small molecules such as 3PO block PFKFB3 by inhibiting fructose-2,6-bisphosphate synthesis, which reduces glucose consumption, increases ROS, and induces autophagy [64]. β-Elemene, a plant compound from traditional Chinese medicine, decreases PFKFB3 expression, reduces lactate formation, slows proliferation, and improves sensitivity to chemotherapy [65]. Thus, PFK and PFKFB3 are considered as important therapeutic targets for metabolic treatment of prostate cancer.

PKM2 controls the final step of glycolysis. Natural compounds like oleanolic acid reduce PKM2 level, induce apoptosis, and cell cycle arrest in prostate cancer cells [66]. Shikonin, a naphthoquinone compound, inhibits PKM2 and increases ROS together with AMPK activation. It is highly effective when used in combination with chemotherapeutic drugs like cabazitaxel [67, 68]. Caffeic acid phenethyl ester (CAPE) also decreases glycolysis and androgen receptor signaling, which causes toxicity in prostate cancer cells [69]. Lambertianic acid, obtained from Pinus species, reduces lactate production and inhibits PKM2 phosphorylation, disturbing PKM2/β-catenin axis that controls tumor growth [70]. LDH, mainly its LDHA isoform, plays a main role in converting pyruvate to lactate and maintaining Warburg effect. LDHA is overexpressed in prostate cancer and linked with tumor growth and drug resistance [71]. Different LDHA inhibitors show promising preclinical activity. FX11, a competitive LDHA inhibitor, reduces lactate generation, decreases glucose uptake, increases oxidative stress, and stops metastasis [72]. Curcumin, a polyphenolic compound from Curcuma longa, induces endoplasmic reticulum stress, increases ROS, and upregulates pro-apoptotic genes. It also reduces LDH expression and affects CD44 positive prostate cancer cell survival [73, 74]. Oxamate, a pyruvate analog, blocks LDH competitively and lowers lactate production. Combination of oxamate (or sodium oxamate) with docetaxel in CRPC models gives better results, reducing tumor growth and improving drug response [75]. These studies suggest that PKM2 and LDHA, are important metabolic targets and their inhibition could be useful, particularly in combination therapy approaches.

Targeting mitochondrial dysfunction in prostate cancer

Mitochondrial dysfunction has an important role in prostate cancer progression and also contributes to changes in energy

balance and therapy resistance. Among the different mitochondrial systems, the pyruvate dehydrogenase complex and mitochondrial respiratory chain are considered as main therapeutic targets (**Figure 2**). Pyruvate dehydrogenase kinase (PDK) acts as a key checkpoint enzyme that inhibits pyruvate dehydrogenase (PDH), which converts pyruvate into acetyl-CoA. This inhibition shifts metabolism toward glycolysis and reduces oxidative phosphorylation, promoting the Warburg effect and tumor growth [76]. Blocking PDK activity can help to restore mitochondrial respiration and bring back oxidative metabolism. Dichloroacetic acid (DCA) is a well-known PDK inhibitor that activates PDH and moves pyruvate into the TCA cycle. In prostate cancer models, DCA was shown to reduce proliferation and increase apoptosis by improving mitochondrial oxidative activity [77]. Phenyl butyrate also helps mitochondrial function by reducing PDH phosphorylation and increasing oxidative phosphorylation [78].

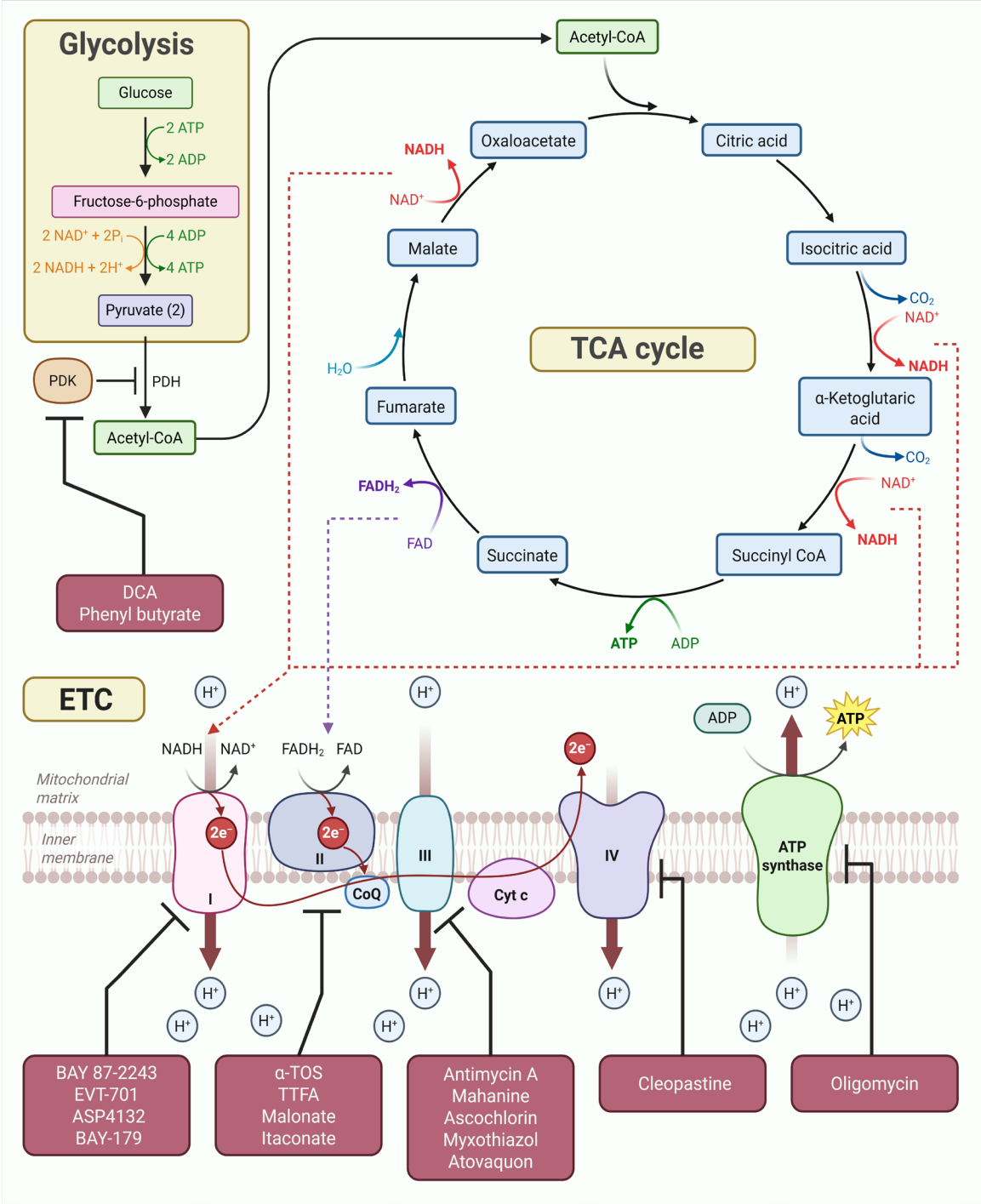

Figure 2. Targeting mitochondrial dysfunction in prostate cancer. As pyruvate exits glycolysis, it is converted into Acetyl-CoA, which serves as fuel for tricarboxylic acid (TCA) cycle. Co-enzymes, NADH and FADH2 produced in TCA cycle then aid electron transport chain complexes in the inter-membrane space of mitochondria to produce energy in the form of ATP. Various enzymes involved in different steps of this process are often dysregulated in prostate cancer cells, leading to mitochondrial dysfunction and tumor progression during early stages of prostate cancer. Different inhibitors, both synthetic and natural (highlighted in maroon boxes), have shown potential to target these metabolic vulnerabilities of mitochondrial dysfunction and alleviate disease aggressiveness in prostate cancer.

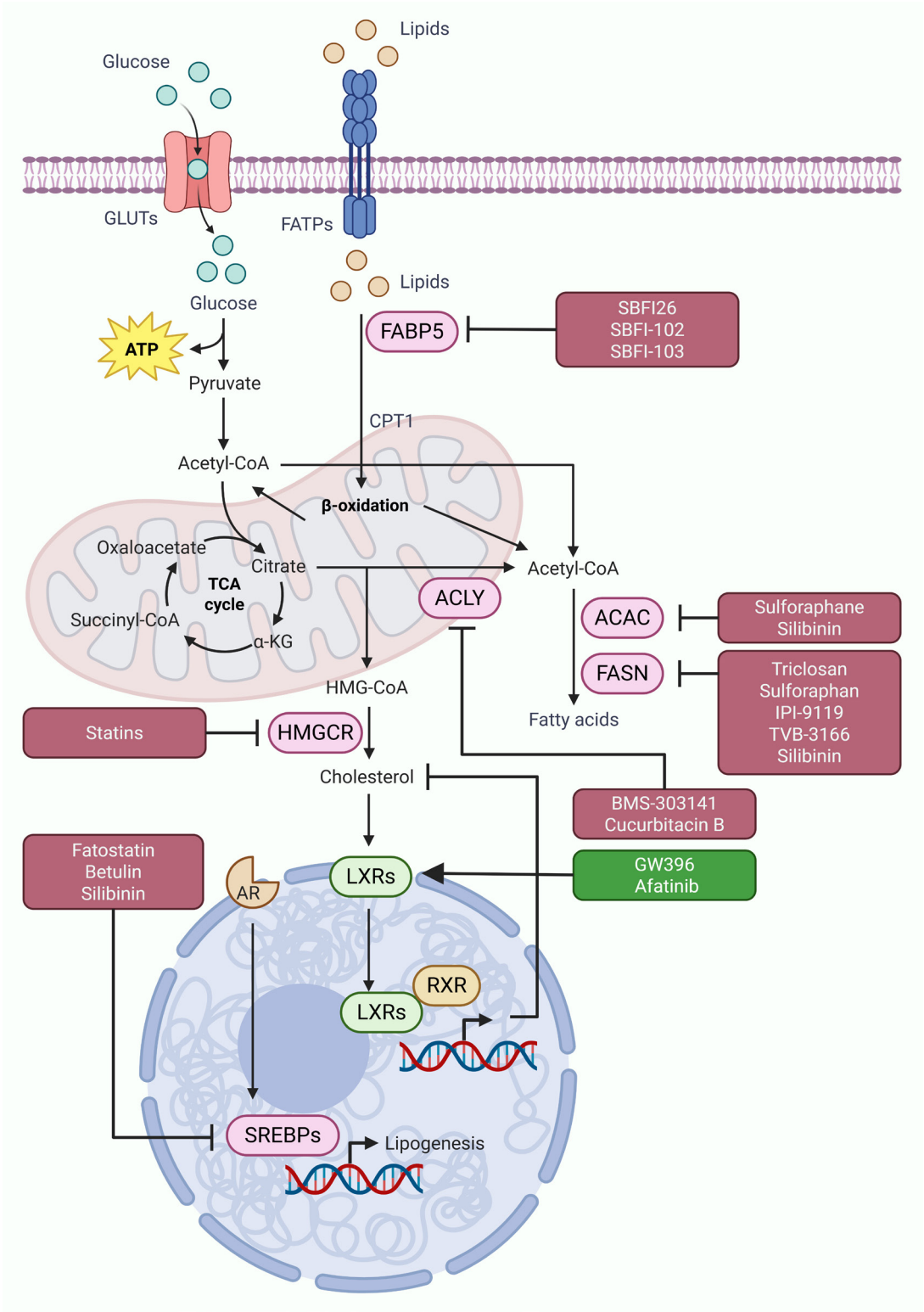

Figure 3. Targeting dysregulated lipid metabolism in prostate cancer. Dsyregulated fatty acid and cholesterol metabolism often contribute to tumor progression and disease aggressiveness in prostate cancer. Various enzymes and transcription factors involved in this process, including FABPs, ACLY, ACAC, FASN, HMGCR, and SREBPs, are often dysregulated in prostate cancer cells, fueling tumor progression and disease aggressiveness. Different inhibitors, both synthetic and natural (highlighted in maroon boxes), have shown potential to target these metabolic vulnerabilities of dysregulated lipid metabolism and alleviate disease aggressiveness in prostate cancer. In addition, restoring LXR signaling through agonists/inducers (highlighted in dark green box) also offer promising approach to suppress dysregulated cholesterol metabolism and limit disease progression in prostate cancer.

The mitochondrial electron transport chain consists of Complexes I to V and is necessary for ATP production and maintaining redox balance. Each of these complexes can be targeted to block tumor metabolism. Complex I (NADH: ubiquinone oxidoreductase)

transfers electrons from NADH to coenzyme Q (ubiquinone) and pumps protons across the inner mitochondrial membrane [79, 80]. Different inhibitors of Complex I have been studied. BAY 87-2243 increases intracellular reactive oxygen species (ROS) and activates AMPK pathway leading to apoptosis [81]. Some newer Complex I inhibitors like EVT-701, ASP4132, and BAY-179 are also showing good results, although their exact mechanisms are still under study [82]. Complex II (succinate dehydrogenase, SDH) is another important part of mitochondrial metabolism. α-Tocopheryl succinate (α-TOS) acts as a competitive inhibitor of SDH by binding to QP and QD sites and causes ROS production and apoptosis [83]. Other inhibitors such as thenoyltrifluoroacetone (TTFA), malonate, and itaconate can also block SDH and increase mitochondrial stress. TTFA has shown better result when used together with cisplatin, improving drug sensitivity [82]. Complex III transfers electrons between cytochrome b and cytochrome c and can be inhibited by compounds like antimycin A, mahanine, ascochlorin, and myxothiazol. These inhibitors disturb electron transport, raise ROS level, and increase oxidative stress [82]. The antimalarial drug atovaquone targets Complex III and blocks growth of prostate cancer stem cells (CSCs) by forcing the metabolism from oxidative phosphorylation toward glycolysis and thus reduces tumor proliferation [84]. Complex IV (cytochrome c oxidase) can also be targeted but its direct inhibitors like hydrogen sulfide, carbon monoxide, cyanide, and azide are very toxic, which limits their clinical use [85]. A compound called Cleopastine shows some antitumor activity by reducing the expression of cytochrome c oxidase subunit 6B1 and decreasing prostate cancer cell growth [86]. Complex V (ATP synthase) performs the final step of ATP formation. Oligomycin, a peptide antibiotic, inhibits ATP synthase and disturbs energy production in mitochondria [87]. Overall, targeting mitochondrial dysfunction either by blocking enzymes such as PDK or by inhibiting different complexes of electron transport chain can be a strong therapeutic approach for prostate cancer. These strategies affect energy balance, increase oxidative stress, and finally lead to apoptosis of tumor cells. However, more detailed studies and improved delivery methods are required before such treatments can be applied safely in clinical practice. cancer cells, leading to mitochondrial dysfunction and tumor progression during early stages of prostate cancer. Different inhibitors, both synthetic and natural (highlighted in maroon boxes), have shown potential to target these metabolic vulnerabilities of mitochondrial dysfunction and alleviate disease aggressiveness in prostate cancer.

Targeting dysregulated lipid metabolism in prostate cancer

Lipid metabolism plays an important role in prostate cancer growth, especially through de novo lipogenesis and cholesterol synthesis (**Figure 3**). FABPs play an important role in prostate cancer. FABP5 in particular has been reported as a good therapeutic target. The small molecule SBFI26, made from α-truxillic acid, decreases fatty acid uptake and PPARγ level in both cells and animal models [88]. Improved versions, SBFI-102 and SBFI-103, show strong anticancer activity across different prostate cancer lines and reduce tumor size in xenograft models [89]. Another form, mutant FABP5 (dmrFABP5), which cannot bind fatty acids, decreases cell proliferation, migration, and metastasis [90]. Other enzymes and regulators of lipid and cholesterol metabolism also provide new drug opportunities. ACLY, which converts citrate into acetyl-CoA for lipid formation, is frequently high in prostate cancer [91]. ACLY interacts with AMPK and androgen receptor, and helps the tumor survive in low androgen situations [92]. Blocking ACLY with BMS-303141 activates AMPK, causes energy stress, and increases sensitivity of CRPC cells to androgen receptor blockers like enzalutamide. This combination decreases androgen receptor expression, inhibits growth, and increases apoptosis [92]. Cucurbitacin B, a compound from cucumber plants, also targets ACLY and decreases cell viability [93]. ACAC, as an important enzyme in lipid metabolism, converts acetyl-CoA to malonyl-CoA. When ACAC is inhibited, lipogenesis is reduced and β-oxidation becomes higher, which suppresses tumor proliferation [94]. On the other hand, FASN is one of the main drug targets because it is highly expressed in prostate cancer. Triclosan, a commonly known antimicrobial compound, disturbs fatty acid synthesis and causes metabolic stress leading to apoptosis [95]. Sulforaphane, a natural compound from cruciferous vegetables, suppresses ACAC and FASN in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model, reducing tumor growth and incidence. SFN treatment also lowers ATP, free fatty acids, phospholipids, and acetyl-CoA levels in plasma and prostate tissues [96]. The selective FASN inhibitor IPI-9119 blocks metastatic CRPC by reprogramming lipid metabolism and downregulating both full-length androgen receptor and its splice variant AR-V7 at mRNA and protein levels [97]. FASN inhibition also decreases palmitate synthesis, which is needed for protein palmitoylation and tumor growth. TVB-3166 reduces tubulin palmitoylation, leading to disorganized microtubules and reduced viability of cancer cells [98]. Silibinin blocks hypoxia-induced lipogenesis by lowering ACAC and FASN, which helps limit tumor survival in low oxygen conditions [99]. These findings highlight the importance of targeting fatty acid transport and signaling in prostate cancer.

SREBP1 and SREBP2 act as main transcription regulators for genes involved in fatty acid and cholesterol production. Blocking SREBP activity has shown promise as a therapeutic approach. Fatostatin, a small-molecule inhibitor which stops SREBP from binding to SREBP cleavage-activating protein (SCAP), shows strong anticancer effect in prostate cancer models [100]. In cell line studies, fatostatin reduces proliferation, migration, and invasion, and in animal models it causes cell cycle arrest and apoptosis [101]. Fatostatin also increases the effect of docetaxel chemotherapy in both androgen receptor-positive and -negative prostate cancer cells. The combination effect is higher in cells with TP53 mutation, suggesting fatostatin may be helpful to overcome therapy resistance [102]. Studies in mouse models further show that fatostatin reduces tumor growth and lymph node metastasis [101]. Several natural products also show activity against lipid metabolism in prostate cancer. Extracts from Withania somnifera inhibit SREBP1, FASN and ACAC, thereby disturbing lipid synthesis and inducing apoptosis in cancer cells [103]. Eriobotrya japonica extract targets both lipid and androgen receptor signaling by blocking the SREBP1, resulting in diminished androgen receptor level and induction of apoptosis [104]. The medicinal fungus Ganoderma tsugae exert its anticancer effects by suppressing SREBP-driven lipogenesis as well [105]. Betulin, a plant-based triterpenoid, suppresses SREBP1 and reduces glutathione peroxidase 4 (GPX4) expression, resulting in ferroptosis induction [106]. Silibinin, a flavonolignan from milk thistle, prevents nuclear transport of SREBP1 through AMPK activation, reducing lipid and cholesterol storage and slowing androgen-independent prostate cancer growth [99]. Cholesterol metabolism is another main area for treatment. Statins, which inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), the key enzyme of the mevalonate pathway, reduce prostate cancer proliferation and migration by inducing apoptosis and cell cycle arrest [107]. Among statins, simvastatin shows strong tumor-suppressive effect in xenograft models [108]. Liver X receptors (LXRs) are also involved in lipid control and prostate cancer. Activation of LXRs can block epithelial-to-mesenchymal transition, which is a key step in metastasis [109]. The LXR-α agonist GW3965 activates tumor-suppressive signaling, while the EGFR inhibitor Afatinib raises LXR-α expression by blocking

AKT and activating FOXO3A. Combination of Afatinib and GW3965 gives a synergistic antitumor effect [110]. In summary, lipid and cholesterol metabolism give many promising therapeutic targets in prostate cancer. Blocking FABPs, ACLY, ACAC, FASN, HMGCR, and SREBPs, and promoting LXRs (**Figure 3**) can disrupt energy homeostasis and results in good clinical outcomes, especially in advanced and resistant prostate cancer cases.

Conclusion and future perspectives

Metabolic reprogramming is now well accepted as one of the important features of prostate cancer and is strongly connected with tumor formation, progression, and therapy resistance. Normal prostate epithelial cells mainly work to produce and release citrate, but in early prostate cancer, the metabolism shifts toward mitochondrial oxidative process. These cells depend more on the TCA cycle and oxidative phosphorylation to meet their energy demand. As the cancer becomes more aggressive and reaches castration-resistant stages, more metabolic changes appear. Tumor cells start to use aerobic glycolysis, glutaminolysis, and high lipid synthesis, which are typical of the Warburg effect. Such metabolic flexibility helps prostate cancer cells to grow faster, avoid apoptosis, and survive under therapy stress. Among different altered pathways, lipid metabolism has been found as one of the most important in driving prostate cancer aggressiveness. Androgen receptor signaling has a key role in controlling important enzymes that regulate de novo lipogenesis, fatty acid oxidation, and cholesterol synthesis. Dysregulated lipid metabolism help tumor cells to grow as well as influence the tumor microenvironment, including the immune cells present in it. From therapeutic point of view, many studies are focusing on metabolic enzymes, transporters and transcription factors like GLUT1, HK2, PFK1, PKM2, LDHA, PDK, FABP5, ACLY, ACAC, FASN, SREBPs and LXRs, using them as direct targets, or targeting in combination with other drugs. Such targeted therapies have potential in both hormone-sensitive prostate cancer and in CRPC. However, clinical success is still limited because of activation of alternate pathways, and possible side effects on normal tissues. In future, more research is needed to design combination treatments that can block multiple metabolic routes together, especially in combination with anti-androgen or chemotherapeutic drugs. This knowledge can help to identify specific metabolic vulnerabilities and create new metabolism-based therapies which can improve treatment response and survival in prostate cancer patients.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Ukasha Ahmed contributed to design of the work, data collection, and drafting the article.

Competing interests

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