REVIEW

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Fueling Prostate Cancer: The Central Role of Glutamine/ Glutamate Metabolic Reprogramming

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Abstract

Metabolic reprogramming induced by the glutamine/glutamate (Gln/Glu) metabolic pathway is a key mechanism in ATP production, precursor biosynthesis, and redox homeostasis, promoting prostate cancer (PCa) growth and proliferation. This evolutionarily acquired hallmark of cancers enables malignant cells to adapt their bioenergetic and biosynthetic pathways in response to microenvironmental stresses. Therefore, Gln/Glu metabolism orchestrates epigenetic regulation, metastatic capacity, and oxidative homeostasis in PCa, supporting the survival of PCa tumors. Fluctuations in Glu metabolite levels and oxygen tension shape the PCa epigenome by facilitating Glu-derived α-ketoglutarate (α-KG) activation of TET and KDM enzymes, which drive histone and DNA demethylation. Furthermore, tumor progression toward metastatic castration-resistant PCa is characterized by heightened Gln/Glu dependency and increased Gln uptake. Within the tumor microenvironment (TME), a dynamic tug-of-war occurs between tumor and immune cells, competing for Gln metabolites. Gln/Glu converges on critical oncogenic signaling axes, including NF-κB/Nrf2, c-Myc/androgen receptor, MAPK/ERK, and PI3K/AKT/mTOR. Additionally, extracellular Glu release via SLC7A11 and PSMA triggers metabotropic glutamate receptor (mGluR) signaling, further potentiating oncogenic programs. Targeting this Gln/Glu metabolic network thus presents a promising therapeutic approach against PCa. In this review, we summarize the role of Gln/Glu in PCa progression based on the compartmentalization of the Gln/Glu metabolic pathway to elucidate why PCa cells manifest dependence on Gln/Glu. Eventually, we highlight potential therapeutic targets that can be exploited for PCa treatment.

Keywords: Glutamine- glutamate- metastasis- epigenetics- metabolic reprogramming

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Introduction

Metabolic flexibility is a hallmark of prostate cancer (PCa) cells. unsurprisingly, PCa cells can switch between metabolic pathways based on cellular, biochemical, and tumor microenvironment (TME) conditions [1]. Accumulating evidence demonstrates that the glutamine/glutamate (Gln/Glu) metabolic pathway is an inducer of metabolic reprogramming of PCa, a key process that ensures adequate supplies of nucleotides, proteins, and lipids to promote PCa growth and proliferation; thus, it is implicated in the tumorigenesis and progression of PCa into advanced forms such as castration-resistant prostate cancer (CRPCa) [2]. Gln, a non-essential/ conditionally essential amino acid, is the most plentiful amino acid in both human plasma and tissues, and it has pleiotropic functions in cancer since it not only promotes mitochondrial oxidative phosphorylation (OXPHOS) and ATP generation but also provides a carbon source to restore the tricarboxylic acid (TCA) cycle and lipid biosynthesis pathways [3]. The Gln/Glu metabolic pathway is closely linked to other cellular and biochemical pathways via intermediate metabolites, redox homeostasis modulators (glutathione (GSH), NADH, NADPH), Gln/Glu transporters, enzymes (glutaminases (GLSs), aminotransferases, glutamate dehydrogenases (GDH/ GLUDs)), and metabotropic glutamate receptors (mGluRs/ GRMs) signaling, thereby, the Gln/Glu metabolic pathway is essential for PCa survival. Several studies have shown that targeting the Gln/Glu metabolic pathway components (Gln/Glu transporters, glutaminolysis enzymes, mGluRs) has promising results, indicating that it is a scientifically rational approach for the discovery of novel therapeutic targets and the development of anticancer drug candidates [4–6]. This review summarizes each step of the Gln/Glu metabolic pathway in PCa, focusing on its role at the molecular, cellular, and biochemical levels. Furthermore, we highlight potential therapeutic targets for clinical intervention.

The role of the Gln/Glu metabolic pathway in PCa growth and survival

Normal prostate epithelial cells depend primarily on glycolysis to generate most of their ATP and assimilate

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glucose and aspartate to biosynthesize and secrete citrate [7]. The active transport of zinc through SLC39A1 leads to intracellular accumulation of zinc, resulting in aconitase activity downregulation and thus TCA cycle truncation. Therefore, citrate is accumulated and secreted via the prostate gland. In PCa cells, metabolic reprogramming induced by the androgen receptor (AR) leads to a metabolic shift toward OXPHOS coupled with a zinc transporter loss; thus, the concentration of zinc and citrate is much lower in PCa cells compared to normal prostate tissue [8]. On the other hand, in the PCa cells, even with the existence of adequate oxygen and entirely functioning mitochondria, PCa cells show considerably increased glucose consumption and fermentation to lactate (Warburg Effect) [9]. PCa is characterized by multiple genetic aberrations, such as phosphatase and tensin homolog (PTEN) loss, which is observed in 20% of primary PCa and 50% of CRPCa [10]. Moreover, the pentose phosphate pathway is inhibited by TP53; hence, mutation or loss of TP53 promotes the Warburg effect and further anabolic pathways that support tumor growth [11]. Experiments on tumor mouse models with combined reduction of p53 and PTEN show elevation of aerobic glycolysis rate, which induces aggressive PCa development [12].

In 1979, Reitzer's lab experiments using HeLa cells demonstrated that even in the presence of high concentrations of glucose, more than half of the ATP demands are acquired from the Gln/Glu metabolic pathway by fueling the TCA cycle and mitochondrial OXPHOS [13]. Gln is transported into PCa cells through plasma membrane solute carriers (SLCs) such as SLC1A5, SLC1A4, SLC38A2, SLC38A1, and SLC6A14. Gene expression data from PCa patient specimens show a significant increase in SLC1A5 mRNA levels, highlighting the crucial role of the Gln/Glu metabolic pathway in PCa [14–17]. Several transcription factors are involved in the regulation of SLC1A5 in PCa, including Myc, retinoblastoma (RB)/E2F, androgen receptor, and activating transcription factor 4 (ATF4); thus, the protein expression of SLC1A5 is similar in both androgen-independent (PC-3) and androgen-dependent (LNCaP) PCa cell lines [6,17]. This permits an influx of Gln into PCa and facilitates cancer cell growth. Furthermore, the gene expression of SLC1A4 and SLC1A5 in PCa is increased by AR signaling, which in turn promotes the Gln/Glu metabolic pathway [14]. AR variants such as AR-V7 are implicated in anti-androgen resistance, such as enzalutamide and abiraterone, metabolic reprogramming, and progression of PCa by stimulating reliance on the Gln/Glu metabolic pathway [18]. In melanoma cells, SLC1A5 is negatively regulated by oncosuppressor miR-137 [19]. In p53-mutant cancers, the expression of SLC38A2 and SLC6A14 is elevated, thereby increasing Gln influx into cancer cells [16, 20, 21]. The 26S proteasome degradation machine and endoplasmic reticulum are involved in the regulation of SLC38A2 and SLC1A5. Paclitaxel, a microtubule stabilizer, stimulates endoplasmic reticulum stress, resulting in an active ubiquitin ligase ring finger protein 5 (RNF5) with subsequent ubiquitination and degradation of SLC38A2 and SLC1A5; and thus decreased Gln influx [20].

Cytosolic Gln is used for the biosynthesis of nucleotides, hexosamines, and nonessential amino acids such as Glu and asparagine via asparagine synthetase, which are essential precursors for rapidly proliferating cancer cells. Asparagine has several roles, including stimulation of mTORC1, contribution to the biosynthesis of purines and pyrimidines, and interchange of extracellular amino acids such as serine, histidine, and aspartate [22]. Although Gln is a non-essential amino acid, most cancer cells cannot survive in a medium that does not include it. This incompetence is perhaps due to the significant role of the Gln/Glu molecules, which supply both nitrogen and carbon for cellular functions [23]. For mitochondrial glutaminolysis, the SLC1A5 variant, a mitochondrial Gln transporter, transfers cytosolic Gln into the inner mitochondrial membrane. Elevated Gln influx into the mitochondrial matrix via the SLC1A5 variant can promote glutaminolysis and result in metabolic reprogramming toward aerobic glycolysis. Therefore, the high SLC1A5 variant level is correlated with poor prognosis in multiple types of cancers, including PCa [24]. Then, Gln is converted into Glu by three isoforms of GLSs: kidney-type GLS (GLS1), liver-type GLS (GLS2), and GLS C (GAC), a splicing isoform of GLS1. In addition, GLSs are amidohydrolases that catalyze the conversion of Gln into Glu and release ammonia. This step is a rate-limiting step of glutaminolysis, making it an attractive therapeutic target [25]. In addition, glutaminolysis is negatively regulated by tumor suppressor miR-145 in ovarian cancer cells through c-Myc/GLS1 axis repression. Genomic profiling of microRNA reveals that miR-145 is downregulated in PCa and is implicated in the transition from localized to metastatic PCa [26, 27].

At the transcriptional level, the expression of GLS1 and GLS2 is regulated indirectly by c-Myc and mTORC1 [28]. In the PC-3 cell line, c-Myc transcriptionally inhibits targeting GLS 3′untranslated region via miR-23a and miR-23b, resulting in the elevated expression level of GLS, which leads to glutaminolysis upregulation [28]. NF-κB p65 subunit also represses miR-23a expression by binding to its promoter, leading to elevated GLS1 levels [29]. In several types of cancers, including PCa, additional tumor suppressor miRNAs that target GLS expression are inhibited directly, such as miR-1-3p, miR-153, and miR-137 [30, 31]. On the other hand, the GAC isoform is not regulated by miRNAs due to the absence of any miRNA-binding site within its 3′UTR [32]. The c-Jun, an oncogenic transcription factor activated by downstream signaling of Rho GTPases, stimulates the expression of GLS1 by binding to its promoter region. Rho GTPases signaling also increases GLS1 activity via NF-κB by stimulating its phosphorylation [33]. NF-kB regulates GAC through Ser314 phosphorylation mediated by protein kinase Cε [34]. Therefore, cancer cells can utilize a plethora of regulatory mechanisms to stimulate GLSs. Furthermore, experiments on the PC-3 cell line show that GLS1 positively regulates aerobic glycolysis via transcriptional repression of thioredoxin-interacting protein (TXNIP), a robust negative regulator of glucose uptake and aerobic glycolysis. This provides direct evidence that overexpression of GLS1 is correlated

with PCa stage and level of progression in PCa patients [35]. On the other hand, GLS2 is positively regulated by p53, which has a considerably high mutation rate in PCa. Elevated levels of GLS2 increase OXPHOS and, thus, tumorigenesis [36]. In addition, GAC has a crucial role in tumor proliferation in various types of cancers, including PCa. GAC facilitates elevated Gln dependency in aggressive PCa variants such as CRPCa and small-cell neuroendocrine carcinoma. GLS1 inhibitor CB-839 (telaglenastat) exhibited greater antitumor activity in GAC-expressing PCa cell lines [37].

After that, Glu is converted to α-ketoglutarate (α-KG), a TCA cycle intermediate metabolite, via an oxidative deamidation reaction that occurs within the matrix of the mitochondria. α-KG is biosynthesized by two different potential pathways. The first pathway includes the conversion of Glu into α-KG and ammonia by GDH. The second pathway is transaminase reactions, including glutamate-pyruvate transaminase (GPT/ALT) and glutamate-oxaloacetate transaminase (GOT/AST), which contribute to the biosynthesis of other non-essential amino acids such as aspartate and alanine, which are involved in protein production. Cytosolic aspartate is also included in the production of nucleotides. In addition, α-KG replenishes TCA cycle intermediate metabolites, which contribute to ATP production, fatty acid biosynthesis via citrate, oncometabolite production including succinate and fumarate, NADH, FADH2 generation, and NADPH generation via malic enzyme 1 (ME1) to replenish cell reduction capacity. Glu and α-KG participate in the malate aspartate shuttle, leading to the transmission of NADH from the cytosol into mitochondria and thus contributing to ATP production via OXPHOS through the electron transport chain [15, 38]. Figure 1 highlights the major reactions of Gln/Glu metabolism and their interactions with other cellular processes in PCa cells.

In LNCaP, LAPC4, C4-2/MDVR, PC-3, 22RV1, and NCI-H660 cell lines, the prodrug DRP-104 (sirpiglenastat) blocks Gln carbon and nitrogen utilization, resulting in PCa and CRPCa growth suppression and apoptosis upregulation. Furthermore, DRP-104 surprisingly suppressed the growth of neuroendocrine PCa xenograft without measurable toxicity, validating the efficacy of the prodrug [39]. Although Gln's contribution to purine metabolism in PCa is unclear, a recent study showed that decoyinine suppressed guanosine monophosphate synthetase, an enzyme involved in de novo purine synthesis, resulting in Gln metabolism blocking and PCa growth inhibition [40]. Collectively, metabolic reprogramming in PCa cells occurs during cancer progression; hence, the Gln/Glu metabolic pathway has a prominent role in aggressive PCa and CRPCa as it is the most used source of anaplerosis.

The nexus between Gln/Glu metabolism and epigenetic regulation in PCa

Oxygen is essential for biochemical reactions in both normal and cancer cells. However, under hypoxic conditions, normal cells succumb. In cancer cells, the core of the tumor is the most oxygen-limited region, and these cancer cells can undergo transcriptomic changes that permit them to survive in the harsh microenvironment. PCa cells adapt by inducing hypoxia-inducible factors (HIFs) such as the HIF1-α isoform, which stimulates angiogenesis by releasing vascular endothelial growth factor (VEGF). Another significant change that occurred in response to hypoxia is stimulation dependence on Gln, which fuels the TCA cycle and lipid biosynthesis,

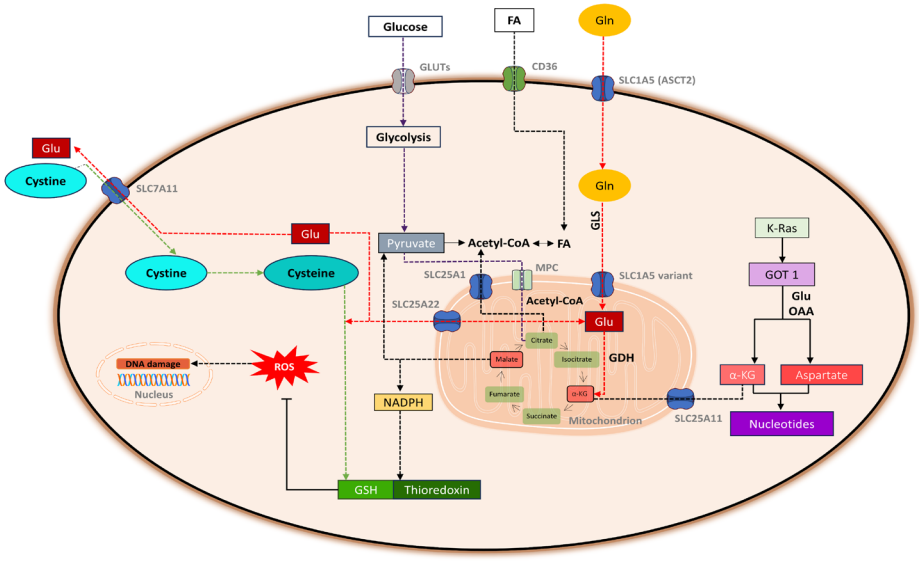

Figure 1. Gln/Glu Metabolites Support PCa Cell Survival and Growth by Reprograming Metabolism toward Gln/Glu Addiction. Gln enters the cell via SLC1A5 and mitochondria via the SLC1A5 variant. Then, Gln is converted to Glu by GLS, leading to the TCA cycle fueling and thus NADPH production that is involved in the generation of thioredoxin and GSH, which contribute to redox homeostasis. SLC7A11 efflux Glu and influx cystine, a component of GSH and thioredoxin biosynthesis. Gln/Glu metabolic reprogramming also contributes to nucleotides and lipid biosynthesis by fueling the TCA cycle and providing an abundance of intermediate metabolites including citrate, aspartate, and asparagine.

indicating the crucial role of hypoxia in PCa metabolic reprogramming [38, 41].

The unmethylated CpG islands, a genomic region containing many CpG dinucleotide repeats, are hypermethylated in several types of cancers, including PCa, upon exposure to harsh conditions such as hypoxia or nutrient deficiency, including Gln/Glu deficiency. Cancer cells distinguished by hypermethylation of DNA have a CpG island methylator phenotype, which is an indicator of poor prognosis due to repression of anti-oncogenes. Glu-derived α-KG is a cofactor for an enzyme family called Fe(II)- and α-KG-dependent dioxygenases [42]. This enzyme family contains two categories of enzymes that are included in the demethylation reactions of DNA as well as histones. DNA demethylation is catalyzed by ten-eleven translocation (TET) hydroxylases 1 and 3. The histone demethylase large family contains the jumonji C domain (KDM 2 to 7)-containing lysine demethylases (KDMs). Furthermore, TET enzymes and KDMs are competitively mitigated by L-2-hyxdroxyglutarate (HG) and R-2-HG. Thus, they are considered considerable regulators of cancer epigenetics [43].

The cytosolic Glu-derived α-KG levels affect the methylation state of DNA and histones. Hence, the activity of DNA and histone demethylases is increased by an elevated ratio of α-KG, which stimulates mTOR signaling and enhances the anabolic process. Nevertheless, in cancer cells that encounter hypoxic conditions, this leads to stimulation of (L)-2-HG accumulation and histone H3 trimethylation at the lysine 9 (H3K9me3) position, resulting in the DNA hypermethylation state in cancer cells by significantly decreasing TET activity [44]. α-KG is considered a signal for the sufficiency of amino acids such as Gln/Glu. Therefore, it might represent an indicator of epigenetic remodeling when Gln/Glu is diminished. The reduction of Gln/Glu is linked to decreased levels of α-KG, which indicates suppression of KDMs in the cancer cells. Consequently, the high level of histone methylation stimulates cancer cell dedifferentiation and thus may lead to a therapy resistance phenotype [45]. Figure 2 shows the relationship between Gln/Glu metabolism and epigenetic regulation in the context of PCa cells.

A recent study has found that the Gln/Glu pathway is substantial for radioresistant PCa cells and a regulator of PCa stem cells. Therefore, Gln/Glu depletion by targeting the Gln/Glu metabolic pathway or their regulators, such as c-Myc by 10058-F4 or GLS1 by CB-839, results in the induction of stress responses, accumulation of DNA double-strand breaks, and radiosensitization of PCa cells. In addition, Gln/Glu starvation leads to a reduced level of α-KG, which results in the accumulation of H3K27me3, a mark of repressive chromatin [46]. PCa cells show various sensitivities towards c-Myc inhibition and Gln starvation. In DU145 cells, the intracellular levels of Glu and α-KG are decreased, resulting in endoplasmic reticulum stress response and apoptosis. On the other hand, in LNCaP cells, which are insensitive to Gln depletion, a pro-survival autophagy adaptive mechanism is activated and restores intracellular Glu and α-KG. Genetic knockdown of the ATG5 gene or chemical inhibition with chloroquine leads to the increased radiosensitizing effect of Gln depletion. Thereby, a combination of Gln/Glu inhibitors as well

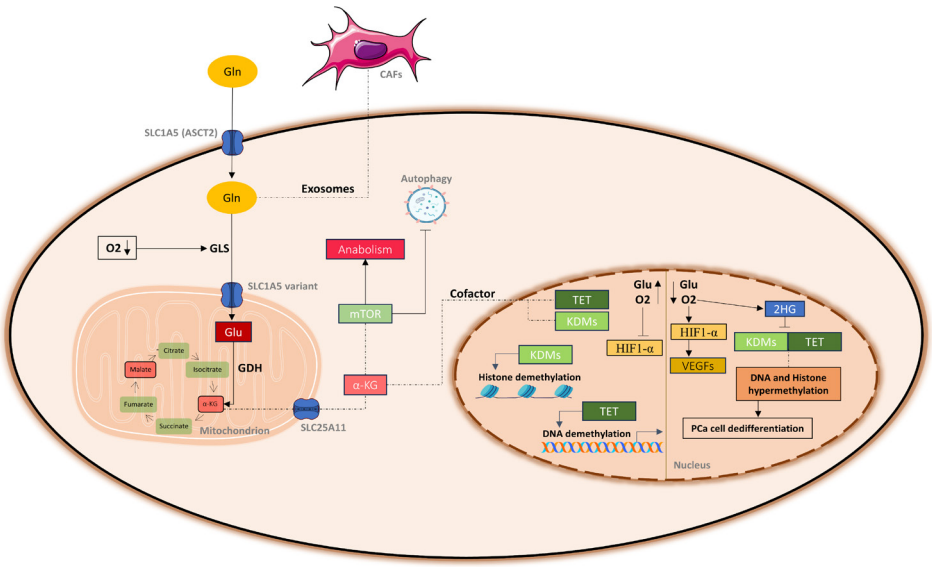

Figure 2. Gln/Glu Metabolism as a Conduit for Epigenetic in PCa Cells. The level of Gln/Glu is related directly to other metabolites implicated in epigenetic regulation, including α-KG, a cofactor for the Fe(II)- and α-KG-dependent dioxygenases enzyme family that includes TET and KDMs. In addition, oxygen abundance in the cell also controls the functions of TET and KDM enzymes. In the presence of Glu and oxygen, Glu-derived α-KG contributes to the activation of TET and KDM enzymes, which stimulate histone and DNA demethylation, leading to upregulation of gene expression and anabolic processes and inhibiting autophagy by mTOR downstream signaling. On the other hand, under hypoxic conditions or in the absence of Glu-derived α-KG, TET, and KDMs are competitively suppressed by L-2-HG and R-2-HG accumulation, resulting in H3K9me3 trimethylation and thus DNA hypermethylation status, which induces PCa cell dedifferentiation, thus PCa could acquire a therapy resistance phenotype. Gln/Glu levels are indicators of epigenetic remodeling in PCa. HIF1-α induces angiogenesis by upregulating VEGF under hypoxic conditions.

as autophagy inhibitors may represent a potentially promising strategy for PCa radiosensitization [46]. Our in vitro experiments using chloroquine on PC-3 prostate cancer cells and MDA-MB-231 breast cancer cells indicated its role in suppressing the migration and survival of these cancer cells, making it promising in combinatorial approaches to tackle a pro-survival autophagy adaptive mechanism in response to Gln/Glu depletion [47, 48]. Metformin also might represent a promising therapy for PCa radiosensitization as it suppresses autophagy and Gln metabolism by suppressing c-Myc and GLS1 activity [49].

Another study has shown that the epigenetic silencing of the rat sarcoma virus (RAS) protein activator-like 3 (RASAL3), an inhibitor of RAS, promotes the synthesis and secretion of Gln by PCa-associated fibroblasts (CAFs) into the TME. Then, PCa uptake of Gln by SLC1A5 and SCL38A2 is elevated through oncogenic RAS activity, and thus, α-KG level is increased. CAF-derived exosomes stimulate PCa metabolic reprogramming and lead to fueling the TCA cycle by Gln metabolites. This process can be prevented by antagonizing Gln uptake by PCa cells [4, 50]. In ovarian cancer, a mutation in the beta subunit of succinate dehydrogenase (SDH) is linked to an alteration in the utilization of glucose and Gln, causing a hypermethylated epigenome [51].

The interplay between Gln/Glu metabolism and oxidative stress in PCa

PCa cells diverge metabolically from their normal counterparts by becoming more dependent on Gln/Glu metabolism. Gln transported via SLC1A5 is converted to Glu and then to α-KG, which fuels the TCA cycle and results in de novo synthesis of NAD+ cofactors and malate. Then, malate generates NADPH when it is metabolized to pyruvate in the cytosol via an oxidation reaction driven by isocitrate dehydrogenase NADP+1 (IDH1) and ME1. NADPH is also synthesized in the mitochondria by IDH2 [52]. NADPH is a cofactor for GSH reductase and thioredoxin reductase; these enzymes have a significant function in redox homeostasis by preserving the reduced state of GSH and thioredoxin, respectively. These enzymes are the main thiol-containing endogenous antioxidant that protects cancer cells against reactive oxygen species (ROS)-induced toxicity. This step is crucial for fast-proliferating PCa cell survival, as the cancer cells generate DNA-damaging byproducts that are involved in oxidative stress [2, 53]. c-Myc upregulation and AR signaling enhance Gln uptake by SLC1A5 and GLS activity. As a result, PCa cells ensure a robust supply of GSH to maintain redox homeostasis and to ensure these signaling molecules remain in their functional reduced states [6, 28].

Oxidative stress is the link between the Gln/Glu metabolic pathway and the Nrf2/NF-κB axis. Oxidative stress activates the IκB kinase (IKK), resulting in the phosphorylation of the inhibitor of NF-κB (IκB), which is eventually degraded by the 26S proteasome. Oxidative stress can be generated by inflammatory cells that produce ROS and connect inflammation to tumorigenesis. At the transcriptional level, NF-κB directly leads to the attenuation of Nrf2 via hypoacetylation of Nrf2 by histone deacetylase 3. The interaction of the p65 subunit with Keap1 inhibits the Nrf2 signaling. On the other hand, Nrf2 is stimulated by elevated oxidative stress levels, leading to Nrf2 translocation into the nucleus and thus increasing the expression of antioxidant and detoxification enzymes, including GSH S-transferase A2, heme oxygenase 1 (HO-1), and γ-glutamylcysteine synthetase [54, 55]. HO-1 is stimulated by the binding of Nrf2 with antioxidant response elements, and its level depends on the Nrf2 level. HO-1 inhibits TNFα-linked stimulation of NF-κB at the transcriptional level by hindering IκB degradation. Thereby, HO-1 activation by Nrf2 is considered a center for communication between Nrf2 and NF-κB. Furthermore, another study suggests that the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway regulates NF-κB/Nrf2 and the pathogenesis of PCa, which is driven by inflammation. Thus, the anti-tumor effect of Nrf2 is obtained by activation of the antioxidant enzymes and decreasing the NF-κB-associated pro-inflammatory signaling. In addition, Nrf2 inhibits AR, whereas NF-κB stimulates AR signaling. Active AR dissociates from heat shock proteins (HSPs) and then translocates to the nucleus, leading to the transcription and translation of AR-regulated proteins such as PSA. Moreover, NF-κB and AR stimulate PSA expression in the androgen-independent pattern of PCa due to the overlap between binding sites of the AR response element and NF-κB [56, 57].

The level of oxidative stress determines the fate of the cell; if the oxidative stress level exceeds the tolerable threshold, the cells are subjected to apoptosis. The crosstalk between oxidative stress and the antioxidant system has a contradictory effect [58]. The upregulation of Nrf2 expression at early stages of cancer development is favorable for cancer eradication. However, the prolonged stimulation of Nrf2 at advanced stages of cancer development leads to cancer progression. Therefore, Nrf2 and the antioxidant system have a double-edged impact on cancer cells. Glu is considered a therapeutic target for several types of cancers, including PCa. Thereby, Glu deprivation therapy leads to decreased GSH synthesis and elevated ROS accumulation, resulting in DNA, lipid, and protein damage [4]. GOT1 is also crucial for redox homeostasis as it rewires the malate–aspartate shuttle to produce NADPH in PCa [59]. Due to the critical role of GLS in the redox homeostasis of cancer cells, targeting GLS by CB-839 is a promising therapeutic approach for ovarian cancer and other cancers, including PCa [60].

Cancer cells efflux Glu into TME and influx cystine via SLC7A11/xCT antiporter protein, which is reduced to cysteine and incorporated into the first and rate-limiting step of GSH synthesis by the enzyme glutamate-cysteine ligase (Figure 1). Nrf2 indirectly stimulates GSH biosynthesis by increasing the expression of SLC7A11/xCT [61]. Riluzole, a Glu release inhibitor, suppresses Glu secretion into the TME and thus restrains Gln/Glu metabolic pathway reactions. A recent study has demonstrated that riluzole blocks the SLC7A11/xCT transporter, leading to Glu-induced oxidative stress status [62]. Riluzole also mediates the interaction between YES-associated protein 1 (YAP1) and p73, resulting in

Table 1. Therapeutic Approaches Targeting the Gln/Glu Metabolic Pathway in PCa.

No.	Agent/Approach	Stage and Model	Mechanism of Action	Effect	Challenges/Notes	References
1	GLS1 inhibitor CB-839 (Telaglenastat)	Preclinical (In vitro + In vivo)	Inhibits GLS1, suppressing Gln → Glu conversion.	Effective against CRPCa tumor xenografts and mitigates metastasis.	Resistance may emerge; combination approaches should be used.	[5,37,126]
2	SLC1A5 (ASCT2) Blocker V-9302	Preclinical (In vitro)	Blocks Gln uptake via SLC1A5.	Reduces cancer cell proliferation and tumor growth and increases cytotoxic T cell infiltration into tumors.	Limited PCa-specific data.	[94,124]
3	DRP-104 (Sirpiglenastat)	Preclinical (In vitro)	DON prodrug; broad Gln antagonist.	Inhibits Gln metabolism, with potential immunomodulation. Results in CRPCa growth suppression and apoptosis upregulation.	Under development, toxicity profiles are under study.	[39]
4	JHU083	Preclinical (In vitro + In vivo)	DON prodrug; Gln metabolic inhibition.	Enhances T cell-mediated tumor clearance and slows growth. Reduces the regulatory T cells.	Toxicity management: further studies are needed.	[80]
5	IACS-6274 (IPN60090)	Preclinical (In vitro)	Potent GLS inhibitor.	Antitumor activity by limiting Gln metabolism.	Limited PCa-specific data.	[127]
6	GLS1 Inhibitor IN-3	Preclinical (In vitro)	GLS1 inhibition.	Decreases Gln catabolism, potential antitumor effect.	Limited PCa-specific data. More studies should be conducted.	[128]
7	Paclitaxel	Preclinical and clinical.	Microtubule stabilizer.	Decreasing Gln influx by degradation of SLC38A2 and SLC1A5.	Resistance and side effects (neuropathy, bone marrow suppression, and hypersensitivity).	[20,129]
8	Decoyinine	Preclinical (In vitro + In vivo)	Inhibits GMP synthesis (Gln-dependent).	Potentially limits growth by reducing nucleotide synthesis. Blocks Gln metabolism and inhibits PCa growth.	Limited prostate-specific data. Further studies are needed.	[40]
9	10058-F4	Preclinical (In vitro + In vivo)	Inhibits c-Myc transcription factor.	Reduces growth and alters Gln metabolism.	Specificity and delivery issues. The compound's pharmacokinetic and pharmacodynamic limitations have restricted it from advancing into clinical testing.	[130]
10	Combination: Gln/Glu Inhibitors + Autophagy Inhibitors (Chloroquine)	Preclinical (In vitro)	It blocks Gln metabolism and prevents autophagy, a pro-survival mechanism under Gln deprivation conditions.	LNCaP radiosensitization.	Future research is needed.	[46,47]
11	Metformin	Preclinical and clinical	AMPK activator affects energy metabolism. Modify Gln metabolism.	Reduces tumor growth. Enhances sensitivity to therapies such as androgen deprivation therapy and docetaxel.	Variable clinical outcomes and metabolic side effects.	[49,131]
12	Riluzole	Preclinical (In vitro + In vivo)	Modulates Glu release via SLC7A11/xCT and inhibits mGluR1 signaling.	Reduces proliferation in mGluR1-expressing PCa cells.	CNS side effects are possible. Investigation of riluzole in PCa remains limited.	[119,121]
13	GLS inhibitor BPTES	Preclinical (In vitro)	Allosteric GLS1 inhibition.	Decreases proliferation by limiting Gln catabolism.	Poor solubility and stability. Lack of clinical data. BPTES and bicalutamide combination had an additive effect on inhibiting LNCaP cell viability.	[70]
14	Sulfasalazine (SLC7A11/xCT Inhibitor)	Preclinical (In vitro + In vivo)	Inhibits cystine/Gln antiporter, SLC7A11/xCT.	Alters redox balance and reduces tumor growth. Suppresses cancer cell metastasis through the caveolin-1/β-catenin pathway. The combination of Sulfasalazine and vitamin C synergistically inhibited GSH.	Gastrointestinal side effects. Limited data in PCa.	[64,132]

Table 1. Continued

No.	Agent/Approach	Stage and Model	Mechanism of Action	Effect	Challenges/Notes	References
15	Combination: Anti-PD-L1 + Gln Deprivation (V-9302/ BPTES/GLS inhibitor 968)	Preclinical (In vitro + In vivo)	Immune checkpoint blockade + metabolic stress in tumor cells by Gln depletion.	Promotes Antitumor Immunity.	Limited data in PCa.	[85,133]
16	Combination: JHU083 + Gefitinib EGFR inhibitor	Preclinical (In vitro + In vivo)	Gln blockade + EGFR pathway inhibition.	Synergistic tumor growth inhibition. Reversed the upregulation of PD-L1 in bladder cancer cells stimulated by prolonged Gln suppression, leading to alleviation of T cell immunosuppression.	Need PCa-specific studies.	[91]
17	Double Targeting of PI3K/ mTOR (DS-7423) and mGluR1 (Riluzole) or HER2 (Lapatinib)	Preclinical (In vitro + In vivo)	Signaling inhibition.	Suggesting a promising therapy for patients with PTEN wild-type PI3K/AKT-mutant PCa. Overcome DS-7423 resistance.	Needs validation in PCa models. Limited clinical data.	[117]
18	Combination: RSL3 + SLC1A5 or GLS1 inhibitors	Preclinical (In vitro)	Ferroptosis inducer and Gln depletion.	Inducing cell death in resistant PCa cells. Repressing SLC1A5 or GLS1 activity could mitigate the antagonistic effect of YAP1 on the ferroptosis of RSL3-stimulated CRPCa cells. Reversing Gln influx by YAP1.	Needs validation in PCa animal models. Limited clinical data.	[66]
19	EGCG (Epigallocatechin-3-gallate)	Preclinical and clinical (NCT00596011).	Polyphenolic catechin and an indirect modulator of Gln uptake/metabolism.	It may reduce growth and proliferation. A modulator of signaling pathways (e.g., AR, MAPK, and PI3K/Akt).	Bioavailability, non-specific effects. In clinical trials, daily intake of a standardized and decaffeinated catechin mixture containing 400 mg EGCG did not reduce the likelihood of PCa in men.	[134]

elevated proapoptotic BAX gene expression [63]. CD44 mediates p62-associated Nrf2 stimulation in cancer cells and attempts to decrease ROS levels, which is a favorable status for cancer stem cells. Riluzole disrupts the interaction between CD44 and SLC7A11/xCT transporter, resulting in Sox2 oxidation and thus Sox2 suppression. Elevated oxidative stress status represses the gene expression of cancer stem cell markers [64, 65]. Another study exhibited that YAP1 suppresses small-molecule RSL3-induced CRPCa cell ferroptosis by enhancing Gln influx via SLC1A5 and increasing the levels of GSH. Thus, repressing SLC1A5 or GLS1 activity could mitigate the antagonistic effect of YAP1 on the ferroptosis of RSL3-stimulated CRPCa cells [66].

Gln/Glu metabolism and metastatic potential of PCa cells

Elevated Gln dependence is linked to the evolution of the metastatic capability of PCa. In 2017, Bhattacharya's lab found that the metastatic castration-resistant subline PC-3M has increased Gln utilization compared to the original PC-3 cells, as the differences in 13C-labeled Gln consumption and succinate labeling suggest Gln addiction phenomena, which is significant to fuel the TCA cycle in PC-3M cells. The researchers also observed that Gln addiction in the metastatic PC-3M subline led directly to high sensitivity to GLS inhibitor CB-839 [5]. This phenomenon, increased dependence on Gln, is also observed in ovarian cancer, and it is related to metastasis progression. Nagrath's lab used isotope tracer and bioenergetic analysis and found that highly invasive ovarian cancer cells are notably Gln-addicted compared to low-invasive ovarian cancer cells, which are Gln-independent. They demonstrated that Gln controls STAT3 activation status, which regulates signaling pathways implicated in ovarian cancer invasion. These findings suggest that blocking both Gln influx into the TCA cycle and targeting Gln generation and STAT3 mediator may represent a promising therapeutic approach against ovarian cancer [67].

In ovarian cancer, SDH suppression results in altered glucose and Gln utilization via reprogramming carbon metabolism, leading to a hypermethylated epigenome that is linked to the metastatic phenotype. The aberrant hypermethylation of H3K27 in mouse ovarian cancer cells is linked to epithelial-to-mesenchymal transition [51]. A previous study illustrated that H3K27 methylation is increased during PCa progression, especially H3K27me1 in patients with advanced pT-stage, lymph node involvement, and higher Gleason score. It also demonstrated that H3K27me1 and H3K27me3 levels were elevated in patients with metastatic PCa and CRPCa compared to localized PCa. On the other hand, H3K27me2 levels were lower in metastatic PCa compared to localized PCa or CRPCa [68]. A previous study used metabolomics, fluxomics, and transcriptomics approaches to characterize metabolic features of metastatic epithelial PCa stem cells that arise independently of epithelial-mesenchymal transition demonstrated that these metastatic epithelial PCa stem cells express metabolic flexibility, including enhanced Warburg effect, utilization of energy from amino acids and fatty acids, and Gln addiction for proton

buffering. The Transcriptomic data harmonized with the metabolic results, generating a metabolic gene signature linked to PCa metastasis [69].

In studies conducted on LNCaP progression models C4, C4-2, and C4-2B, these derivatives exhibited a high propensity to metastasize to the bone. LNCaP-C4-2B cells (androgen-independent) showed reliance on the Gln metabolic pathway compared to other derivatives. Using a similar progression cell model, a group of LNCaP cells evolved to LNCaP-C4-2B cells with increasing expression of GLS enzymes. Moreover, the highly bone metastatic LNCaP-C4-2B cells are characterized by the expression of Gln-dependent osteomimetic biomarkers and the release of GLS-enriched large extracellular vesicles. Fortunately, the evolution of LNCaP-C4-2B from LNCaP cells via GLS-mediated metabolic reprogramming is downregulated by GLS inhibitor BPTES, which has the potency to suppress large extracellular vesicles generation, bone cell-like phenotype differentiation, and PCa metastases to bone [70–72]. PCa cells can shed large extracellular vesicles called large oncosomes (LO) in which their cargo includes a unique set of proteins involved in Gln/Glu metabolism. By transferring enzymes such as GOT1 and GOT2 and other Gln-related proteins to recipient cells, LO can promote Gln/Glu metabolic reprogramming to meet the demands of rapidly growing and spreading prostate tumors. This links LO-mediated Gln/Glu metabolic reprogramming to the potency of PCa cells to invade and metastasize to distant organs [73].

A prior study published by Prasad and colleagues demonstrated mitigated migration and invasion of ovarian cancer cells after Gln depletion, which leads to deactivation of the transcription factor ETS1, an activator of metalloproteases and vimentin expression [74]. On the other hand, in docetaxel-resistant PCa cells, Gln deprivation results in migration suppression; however, the invasion is not affected. These findings show that the Gln pathway controls parts of the metastatic process of docetaxel-resistant metastatic PCa cells, which are dependent on Gln [75]. The Gln metabolic pathway is recognized as an upstream regulator of actin-related protein 2/3 complex subunit 1A (ARPC1A) and thus PCa migration and invasion. Bioinformatics analysis and in vitro experiments on PC-3 and DU-145 displayed that ARPC1A was overexpressed in PCa tissues and cell lines. ARPC1A knockdown suppressed PCa cell migration, invasion, and cytoskeleton formation. Furthermore, in vivo experiments exhibited that ARPC1A overexpression stimulated the lung metastasis of PCa [76]. A prior study conducted on CW22Rv1 cells, LNCaP cells, and the TRAMP PCa mouse model exhibited that nicotine increased Gln consumption and provided evidence that smoking-associated PCa evolution may be Gln-mediated. These findings also demonstrated that nicotine stimulates invasiveness and accelerates PCa metastasis, highlighting a potential mechanism for PCa metastasis in smokers [77].

Attenuating SLC1A5 in PCa showed promising results, as it mitigated metastasis due to the diminished key cell cycle drivers and metabolites produced by Gln/Glu metabolism [17]. Disorganizing SLC7A11/xCT antiporter protein suppresses cancer cell metastasis through the caveolin-1/β-catenin pathway. Sulfasalazine promoted homotypic cell-cell adhesion and attenuated cell-extracellular matrix adhesion, leading to suppression of metastasis in both in vitro and in vivo experimental models [64, 78]. Gln and succinate are considered pro-angiogenesis metabolites that induce intravasation, which is a process stimulated via hypoxic and nutrient-deficient microenvironment. PCa is characterized by enriched immunosuppressive tumor-associated macrophages (TAMs) with pro-angiogenic and metastatic potency. In macrophages, Palmieri et al. exhibited that the Gln metabolic pathway triggers tumor metastasis via the macrophage polarization process. Targeting Gln synthetase (GS), an enzyme that catalyzes Gln biosynthesis using Glu and ammonia, mitigated Gln influx and intracellular Gln and thus reversed the M2 phenotype of TAMs to the M1 phenotype that is mediated by succinate/HIF1-α/glycolysis flux [79]. Coupled with these reactions, succinate generation is activated through the gamma-aminobutyric acid shunt. Inhibiting GS in TAMs enhanced cytotoxic T cell infiltration, mitigated angiogenesis, and reduced the metastatic potency of cancer cells. In contrast to its metastatic inhibitory function in TAMs, succinate stimulates angiogenesis through two pathways. Succinate can suppress HIF prolyl-hydroxylase, an α-KG-dependent dioxygenase, resulting in HIF1-α induction and thus activation of angiogenesis genes, including matrix metalloproteinases, angiopoietin-1/2, VEGFs, VEGFR1/2, and fibroblast growth factors. The second mechanism includes binding succinate to succinate receptor 1 (SUNCR1), leading to VEGF stimulation via the ERK1/2/STAT3 pathway. Thus, succinate may function as a pro- or anti-angiogenic factor [80, 81].

An additional potential target to suppress metastasis in PCa is steroid receptor coactivator 2 (SRC-2/NCOA2), which is an oncogenic transcriptional coregulator that fuels Gln-dependent de novo lipogenesis, promoting PCa survival and metastasis. SRC-2 expression is estimated to be elevated in PCa as it is amplified and overexpressed in 37% of the metastatic prostate tumors investigated. SRC-2 results in citrate biosynthesis via α-KG reductive carboxylation, which drives lipogenesis and Gln/Glu metabolic reprogramming. SRC-2 is activated by Gln-mediated nutrient signaling that stimulates mTORC1-dependent phosphorylation, which upregulates sterol regulatory element binding transcription factor 1 (SREBP-1), resulting in lipogenic enzyme expression. This study highlighted that SRC-2 is a major metabolic coordinator of PCa metastasis. Thus, suppressing SRC-2 in murine models leads to attenuation of PCa metastasis, suggesting SRC-2 targeting as a potential target against PCa metastasis [82].

Gln/Glu metabolism and immune cells in TME

As in many other malignancies, PCa cells reprogrammed their metabolism to depend heavily on Gln, which fuels their growth and survival and remodels the TME to suppress immune cell function. Gln and Glu metabolites are essential components of the TME, regulating several types of immune cells (macrophages, lymphocytes, neutrophils, and other immune cells) and

antitumor immune response. On the other hand, immune cells demand Gln for their stimulation and proliferation during immune reactions. This metabolic rivalry for the Gln nutrients between tumor and immune cells provokes a dynamic tug-of-war in the TME. Little is still known about the crosstalk between Gln/Glu metabolites and prostate immune TME due to several reasons, including depressed immunogenicity, existing immunosuppressive TME with a T cell shortage, abundance of innate immunosuppressive myeloid cells such as TAMs and myeloid-derived suppressor cells (MDSC), and the limited response to immunotherapy [83]. TAMs release immunosuppressive cytokines, including IL-6, IL-10, and TGF-β, that suppress cytotoxic T cell activity in the TME of PCa (Figure 3).

The expression of *PD-1* and *PD-L1* in the TME can be affected by different factors, including the Gln metabolic pathway [84]. In renal cancer, *PD-L1* expression stimulated by Gln depletion is inhibited upon suppression of epidermal growth factor receptor (EGFR), ERK, and c-Jun phosphorylation, indicating that Gln depletion upregulates *PD-L1* in cancer cells through the EGFR/ERK/c-Jun pathway [85]. Nonetheless, in lung and colon cancer cells, Gln deprivation results in elevated *PD-L1* expression by reducing GSH levels, leading to sarcoplasmic reticulum Ca+2-ATPase (SERCA) repression, cytosolic Ca+2 elevation, and calcium/calmodulin-dependent protein kinase II alpha (CaMKIIA) phosphorylation. These modifications activate NF-kB signaling, which promotes *PD-L1* expression (Figure 3). In vitro and in vivo experiments on immunocompetent mice, suppression of the Gln metabolic pathway reduced the antitumor activity of T cells. However, the combination of anti-*PD-L1* and Gln deprivation remarkably provoked antitumor efficacy of T cells due to simultaneous elevation in Fas/CD95 levels [86].

Considering that immune checkpoint inhibitors are now widely utilized against cancers, the role of the Gln metabolic pathway within the TME and its link to immune cells has gained much attention [87]. However, it is noteworthy that experimental characterization is significant in evaluating the cancer model system, as it can affect metabolic phenotypes. For instance, when tumor cells are grown in mice, a higher contribution of glucose and a reduced input of Gln to the TCA cycle is noticed. Otherwise, cancer cells can release metabolites such as lactate to create an antagonistic metabolic TME for immune cells. These factors, along with nutrient interactions, can affect drug sensitivity in cancer therapy [88]. In Gln metabolism, the deamidation and deamination reactions that convert Gln to Glu generate ammonia as a byproduct, forming buffers surrounding tumor cells. Gln/Glu addiction results in significant ammonia production, preventing acid stress caused by lactate excretion and enhancing PCa cell survival. The

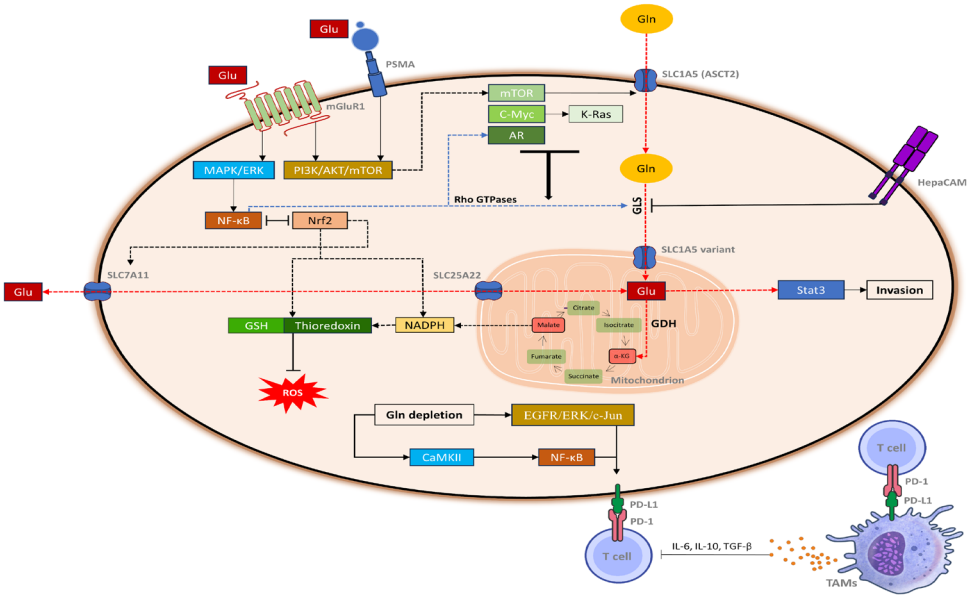

Figure 3. Crosstalk between the Gln/Glu Metabolic Pathway, Cell Signaling, and the Immune System in PCa Cells. Gln enters the cell via SLC1A5 and mitochondria via the SLC1A5 variant. Then, Gln is converted to Glu by GLS, leading to the TCA cycle fueling and thus NADPH production that is involved in the generation of thioredoxin and GSH, which contribute to redox homeostasis. Glu is released outside the mitochondria via SLC25A22 and stimulates Stat3 downstream signaling, which is implicated in cancer invasion. SLC7A11 effluxes Glu and influxes cystine, a component of GSH and thioredoxin biosynthesis, and the secreted Glu provokes mGluR1 signaling, stimulating various signaling pathways including MAPK/ERK and PI3K/AKT/mTOR, promoting NF-κB signaling that stimulates GLS by Rho GTPases. Nrf2 indirectly stimulates NADPH, GSH, and thioredoxin biosynthesis via increasing the expression of SLC7A11/xCT. Moreover, PSMA enzymes, folate hydrolase, and N-acetylated alpha-linked acidic dipeptidase release Glu from the enzyme substrates, leading to upregulation of mGluR1 downstream signaling. AR/c-Myc/mTOR also induces SLC1A5 and GLS, leading to accelerated glutaminolysis. On the contrary, HepaCAM can mitigate GLS activity and negatively regulate glutaminolysis. In addition, mTOR signaling provokes K-Ras, which activates GOT1 that enhances α-KG and aspartate generation, essential components for nucleotide generation. However, Gln depletion leads to PD-L1 elevated expression by EGFR/ERK/c-Jun or CaMKIIA/NF-κB signaling in PCa, resulting in immune cell suppression. TAMs in the TME also express PD-L1 and release immunosuppressive cytokines such as IL-6, IL-10, and TGF-β, inhibiting T cells.

Intratumoral accumulation of ammonia results in T cell activity repression and tumor immune evasion. Thus, the ammonia concentration in urine is considered a biomarker of benign prostatic hyperplasia [89, 90]. In future research, the mechanisms of ammonia metabolism and its accumulation should be investigated and exploited to enhance immunotherapeutic approaches. It is significant to investigate the capacity to tackle ammonia toxicity by improving the clearance capacity in PCa cells.

In a recent study performed on prostate and bladder tumors, researchers exhibited that JHU083-mediated Gln antagonism is induced by TNF, proinflammatory, and mTORC1 signaling in intratumoral TAM clusters. Moreover, JHU083-reprogrammed TAMs and tumor-infiltrating monocytes demonstrated elevated tumor cell phagocytosis and mitigated proangiogenic potency. The in vivo suppression of TAM Gln uptake led to accelerated glycolysis, a broken TCA cycle, and purine metabolism disturbance. The effect of the JHU083 prodrug on tumor-infiltrating T cells was moderate. Nevertheless, the JHU083 prodrug stimulated a stem cell-like phenotype in cytotoxic T cells and reduced the regulatory T cells. In addition, the JHU083 prodrug repressed Gln consumption in prostate and bladder cancer cells, which decreased HIF1-α, c-Myc phosphorylation, and activated cancer cell apoptosis. Ultimately, JHU083 can present a potentially efficient therapeutic approach for tumors enriched in immunosuppressive TAMs [80]. Treatment with JHU083 led to modification in T cell activity by upregulation of *PD-L1* in bladder cancer cells, resulting in modifications of T cell activity from active status to inactive as the administration time extended. A study found that a combination of JHU083 and gefitinib (EGFR tyrosine kinase inhibitor) reversed the upregulation of *PD-L1* in bladder cancer cells stimulated by prolonged Gln suppression, leading to alleviation of T cell immunosuppression [91].

PCa is characterized by T cell shortage, which is compatible with its poor responses to immunotherapy. T cells restricted to the adjacent stroma and benign regions are featured by inactive and immunosuppressive phenotypes. This barrier should be tackled to generate an anti-tumor response by immunotherapies in PCa. Researchers validated that endogenous mesenchymal stem cells (MSCs) are present in PCa sites. These PCa-infiltrating MSCs repress T cell proliferation and upregulate *PD-L1* and PD-L2 expression on their cell surface in the presence of interferon-gamma (IFNγ) and TNFα. These findings suggest that targeting MSCs infiltrating sites could be a promising therapy to restore immunologic recognition and eradicate PCa cells [92]. Of importance, a recent study conducted in melanoma and colon cancer murine syngeneic tumor models illustrated that tumor cells and immune cells, especially type-1 conventional dendritic cells (cDC1), compete for Gln consumption by SLC38A2 transporter to tune antitumor immunity. cDC1 cells are responsible for the priming of the cytotoxic T cells and CD4+ T cells. Gln addition suppresses melanoma and colon cancer growth by augmenting cDC1-mediated cytotoxic T cell immunity and conquering checkpoint blockade resistance and T cell-mediated immunotherapies resistance [93]. For PCa, there is a demand to explore the role of cDC1s in PCa TME. In breast cancer cells, the suppression of the SLC1A5 transporter using V-9302 results in tumor infiltration of cytotoxic T cells and sensitization of breast cancer cells to *PD-1* blockade [94]. V-9302 should be tested on PCa models to validate its immunostimulatory effect on cytotoxic T cell infiltration into PCa cells.

Cuprotosis is a new copper-dependent cell death mode that may be associated with the heterogeneity of PCa TME. Single-cell transcriptome analysis showed that cuprotosis signature genes [pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1), GLS, and dihydrolipoamide branched chain transacylase E2 (DBT)] recruited TAMs to TME by controlling the TCA cycle and Gln and fatty acid metabolism. These signature genes can be utilized as prognostic biomarkers and to evaluate the immunotherapy response in PCa patients, as they can characterize immune cell infiltration in prostate tumors to discriminate patients suitable for immunotherapy [95, 96].

Eventually, despite promising advancements in preclinical models, including PCa cell models, targeting the Gln/Glu metabolic pathway faces obstacles in clinical trials due to the rooted heterogeneity in Gln/Glu metabolism within cancer and immune cells and the TME dynamic ecosystem.

Crosstalk between the Gln/Glu metabolic pathway and cell signaling

The development and progression of PCa are mainly regulated by androgens such as testosterone and 5α-dihydrotestosterone, which directly bind to AR. The AR then liberates from its binding protein, translocates into the nucleus, dimerizes, and attaches to the promoter regions of the androgen response element (ARE), which is involved in cellular growth and proliferation [97]. Dihydrotestosterone remarkably elevates SLC1A5 expression and GLS in the AR-sensitive LNCaP cell line; however, it does not affect the AR-insensitive DU-145 and PC-3 cells. Thus, AR signaling suppression only significantly mitigated the Gln influx in AR-sensitive cells [98, 99]. Androgen is essential to the development of PCa at an early stage; however, in the advanced stage of PCa, when circulating levels of androgen are low, AR signaling works independently through multiple mechanisms, such as AR gene amplification, elevation of AR protein levels, mutations that allow AR to respond to other steroids, and AR activation without ligand binding [100].

AR signaling plays a significant role in Gln metabolism induction by stimulating SLC1A4 and SLC1A5 overexpression, increasing Gln uptake. This occurs in a cell-type-specific manner by multiple mechanisms, including Myc and mTOR signaling [6]. In PCa cells (DU-145, PC-3, LNCaP), the SLC1A5 expression has been demonstrated to be lower in CRPCa cells compared to AR-sensitive PCa cells [98,99]. AR can promote the oncogene Myc, which has a key role in glutaminolysis initiation, via mitochondrial GLS and Gln transporters stimulation. A previous study demonstrated that Myc overexpression promotes prostatic intraepithelial neoplasia, which is converted to invasive adenocarcinoma in a dose-dependent

manner. The activation of glutaminolysis via Myc signaling leads to the reprogramming of mitochondrial metabolism to compensate for the TCA cycle anaplerosis demands to conserve cellular viability and growth. The elevation of Gln uptake by Myc signaling leads to K-Ras enhancement by SLC1A5 upregulation. Further, K-Ras-driven cells are featured by GOT1 and GOT2 overexpression, which catalyze the transamination reaction between oxaloacetate and Glu to produce aspartate and α-KG (Figure 1). Interestingly, the transamination activation and aspartate synthesis in cancer cells by K-Ras are significant in nucleotide biosynthesis upregulation and redox balance maintenance [6, 101].

Additionally, in PCa, AR induces mTOR signaling that increases Gln consumption by the phosphorylation of the S6 position [6]. While mTOR kinase has two signaling complexes, mTORC1 and mTORC2, the mTORC1 complex promotes glutaminolysis, cell proliferation, and anabolic reactions. mTORC1 signaling has a crucial role in cancer metabolic reprogramming by suppressing the transcription of mitochondrial protein Sirtuin 4 (SIRT4), a GDH inhibitor, leading to GDH upregulation. In particular, mTORC1 induces proteasome-mediated destabilization of cAMP response element binding-2 (CREB2) to downregulate SIRT4 transcription. In addition, Gln and α-KG activate the mTORC1 signaling pathway by facilitating leucine influx and regulating mTORC1 assembly and lysosomal localization [101, 102]. The cotreatment of androgens and rapamycin, a mTORC1 complex inhibitor, negatively regulates both basal and androgen-mediated SLC1A5 expression in LNCaP cells and represses the androgen-mediated stimulation of SLC1A4 and SLC1A5 in VCaP cells. Previous evidence suggests that mTOR and Gln influx form a positive feedback loop. In addition, in PCa, both Myc and mTOR signaling can be induced through AR-independent mechanisms such as Gln influx through the SLC1A5 transporter. Correspondingly, SLC1A4 and SLC1A5 function as AR, MYC, and mTOR downstream conduits [6, 103].

In 50% of CRPCa cases, the tumor suppressor gene PTEN loses its function, which leads to activation of the PI3K/Akt pathway that increases Gln influx. Furthermore, PTEN loss and subsequent PI3K/Akt signaling lead to induce mTOR signaling. In PCa models with PTEN and/or PI3K unmodified, Myc is not involved in the upregulation of SLC1A4 and SLC1A5; thus, in PTEN/PI3K wild-type PCa, Gln influx is Myc-independent [103]. Overexpressing PTEN models exhibited modifications in the metabolic profile, including mitochondrial OXPHOS induction coupled with a reduction in glucose and Gln influx through downregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase isoform 3 (PFKFB3) and GLS stability [104]. In addition, Gln is also generated by the macropinocytosis process, an actin-dependent endocytic uptake process, through CAFs, and this process is controlled by RAS, PTEN, and PI3K signaling molecules [6, 50]. In PCa, Gln metabolic reprogramming can be suppressed via hepatocellular cell adhesion molecule (HepaCAM), which downregulates GLS1, SLC1A5 expression induced by PIK3CA signaling, and mitigates Gln influx to the TCA cycle, resulting in its truncation. Thus, the combination of alpelisib, an inhibitor of PIK3CA, with the upregulation of HepaCAM expression may serve as a novel approach for PCa patients. These findings exhibited that HepaCAM reversed PCa stress resistance to Gln depletion [105].

In the context of tumor growth, the stimulation of the PI3K/AKT/mTOR signaling pathway resulted in pyruvate kinase isoenzyme type M-2 (PKM-2) upregulation, which promotes aerobic glycolysis. On the other hand, p53-mediated GLS-2 increases the level of OXPHOS, and TP53 downregulates the pentose phosphate pathway through glucose-6-phosphate dehydrogenase direct interaction. Therefore, TP53 mutation or loss promotes the Warburg effect and additional anabolic pathways [38]. Experiments showed variability in AKT phosphorylation levels at the pS473P position and mTOR in PC-3M versus PC-3 cells. Treatment of PCa cells with rapamycin or CB-839 mitigated ATP generation only in PC-3M cells. Phosphorylated AKT provokes mTOR, which activates Gln influx, which directly modulates the mTOR [5]. GLS can also be positively regulated via the transcription factor NF-κB by miR-23a expression inhibition. Rho GTPases also induce GLS1/2 activity in NF-κB-dependent patterns to increase Gln metabolism by stimulating the phosphorylation of NF-κB (Figure 3). A prior study suggests that NF-κB signaling links lipopolysaccharide-induced inflammation to mitochondrial biogenesis, where Gln is primarily metabolized [29, 106]. SIRT4 leads to a remarkable reduction in NF-κB p65 phosphorylation as well as NF-κB downstream target molecules such as anti-apoptotic Bcl-2, and increases the expression of pro-apoptotic Bax [107]. The IKKβ subunit is significant for NF-κB activation. Through the IKKβ–p53 signaling axis, cancer cells can adapt to metabolic stress. The depletion of Gln leads to phosphorylation of p53 on Ser392 by IKKβ in an independent pattern of the NF-κB pathway, resulting in p53 transcriptional activity. Nonetheless, a mutation in the Ser392 residue attenuated the p53 activity, promoting cancer cell survival and growth despite Gln depletion [108].

Prostate-specific membrane antigen (PSMA), a significant biomarker for PCa and a type II transmembrane glycoprotein, is highly expressed in PCa. There are two types of PSMA enzymatic activities, folate hydrolase and N-acetylated alpha-linked acidic dipeptidase. These enzymes are capable of releasing Glu from the enzyme substrates [109]. Researchers also hypothesized that PSMA is involved in the progression of PCa to CRPCa through its capability to modulate signaling pathways included in the pathogenesis of PCa, particularly PI3K/AKT/mTOR, which are activated in approximately half of advanced PCa. The PI3K/Akt/mTOR axis can be stimulated by Glu metabolite cleaved by PSMA from folates, which provokes GPCRs upstream of the PI3K β-isoform. Targeting mTOR1 by rapamycin elevates PSMA expression, perhaps as a compensatory mechanism [110]. The modulatory capability of PSMA depends on the enzymatic substrate, such as vitamin B9, which can be hindered by the PMSA inhibitor, 2-PMPA. It has been observed that PSMA stimulates the PI3K signaling

pathway by p110β phosphorylation, independent of the PTEN status. PSMA activation through Glu also activates PI3K signaling and establishes a reciprocal negative regulatory loop that links the AR and PI3K signaling pathways. This loop is a major challenge for future targeted therapies against PCa [111]. Suppression of PI3K in a PTEN-deficient model stimulates AR signaling, and vice versa, repressing AR signaling provokes PI3K-dependent AKT phosphorylation. Using a combination of AR inhibitor enzalutamide and PSMA inhibitor showed a more marked effect which is consistent with a combinatorial approach of PI3K and AR inhibitors due to the reciprocal crosstalk between these two primary oncogenic signaling molecules [109].

mGluRs as oncogenic receptors

mGluRs, conventionally associated with synaptic signaling in the nervous system, have also been implicated in PCa tumorigenesis and progression. Certain mGluR subtypes, including mGluR1, are expressed in PCa tissues and PCa cell lines such as LNCaP, as well as PC-3 [112].

mGluR1, a GPCR, belongs to the mGluR Group I family and acts as an oncogene in various types of tumors, including PCa, renal cell cancer, and breast cancer [4]. mGluR1 activates several signaling pathways upon its activation via Glu metabolites released by PSMA enzymatic activity and SLC7A11/xCT antiporter to the TME, then diacylglycerol stimulates protein kinase C, by which several signaling pathways are activated, such as PLC, PI3K/AKT/mTOR, NF-κB, and MAPK (Figure 3). These pathways are implicated in apoptosis inhibition, malignant cellular transformation, and metastasis. The active PI3K/AKT pathway is involved in epithelial-to-mesenchymal transition, cell survival, and angiogenesis upon RAS binding to the p110 catalytic subunit of PI3K. Active RAS phosphorylates MEK, which is responsible for the phosphorylation and activation of MAPK, resulting in the inhibition of apoptosis. Therefore, mGluR1 exerts an oncogenic function when ectopically expressed in epithelial PCa cells through activation of the AKT/MAPK signaling cascade [113]. Active AKT attenuates apoptosis via phosphorylation of Bcl-2 agonist of cell death (BAD), which hinders the interaction of BAD with antiapoptotic proteins, including Bcl-2 and Bcl-xL.[114]. AKT-associated activation of NF-κB takes place through stimulation of IKK, which stimulates proteasomal degradation of IκB. Then, NF-κB translocates to the nucleus to activate survival genes like inhibitors of apoptosis (IAP), which repress apoptosis through deactivation of caspase-9 and -3. AKT inhibits p53 through phosphorylation of mouse double minute 2 homolog (MDM2), which is a p53-binding protein involved in the regulation of p53 activity via targeting p53 for ubiquitination and proteasomal degradation by E3 ubiquitin ligase [115]. PI3K/AKT signaling has a role in tumor angiogenesis, which is mediated partially through HIF1-α and proteins stimulated by NF-κB, such as VEGF. Inhibition of thrombospondin-1, an angiogenesis inhibitor, is also implicated in tumor angiogenesis [116].

A recent study has shown that activation of PI3K and PTEN leads to the transmission of signals that are crucial for cell metabolism, progression, proliferation, and survival. A recent study has demonstrated that PTEN wild-type PCa cell lines, such as CWR22 and 22RV1, can resist dual PI3K/mTOR inhibitor DS-7423 through upregulating the expression of mGluR1, PSMA, and human epidermal growth factor receptor 2 (HER2). Whereas, PTEN mutant LNCaP cells can resist DS-7423 treatment via upregulating the expression of AR and HER3. The experiments on xenograft models have shown that double targeting of PI3K/mTOR with either mGluR1 or HER2 inhibitors leads to reduced tumor growth and thus decreases cell survival [117].

To investigate the specific role of mGluR1, researchers have used short-interfering RNAs for mGluR1 knockdown, which results in MAPK repression via reduced extracellular signal-regulated protein kinase phosphorylated state and suppression of the PI3K/AKT via decreased active AKT state [118]. Several studies show that riluzole, an inhibitor of mGluR1 signaling by decreasing Glu in TME through blocking SLC7A11/xCT, inhibits DNA synthesis in PCa cell lines as well as activates apoptosis through stimulating caspase-3, -8, and -9 [119]. Riluzole also suppresses VEGF-stimulated protein kinase C, proliferation, migration, and progression of PCa cells [120]. Another study has shown that riluzole inhibits androgen-dependent and CRPCa cells through the degradation of mutant ARs, AR-FL, and AR-V7. Riluzole also stimulates protein degradation of AR by activating ER stress [121]. LY367385 or BAY36-7620 are also known as competitive or noncompetitive mGluR1 antagonists, respectively, and they prevent Glu influx and Glu signaling [4].

mGluR1 signaling affects Gln/Glu metabolism as it stimulates the conversion of Gln to Glu via activation of GLS1/2 and induces angiogenic factors such as VEGF-A and IL-8 [122]. Another study demonstrates that Nrf2 stimulates SLC7A11/xCT, which promotes Glu efflux and cystine influx, and then, extracellular Glu activates mGluR1 oncogenic signaling [123]. Another study indicates that PSMA colocalizes with and stimulates mGluR1. However, in the state of mGluR1 absence, PSMA and Glu levels are not sufficient for p110β phosphorylation and AKT activation. Hence, mitigation of mGluR1, PSMA, or p110β equally attenuates AKT signaling [111].

A previous study selected genetic alterations in the mGluR1 gene in PCa cell lines and patient samples. First is a missense mutation (C1744T) that affects protein stability and function, the second is a mutation at an exon-intron junction altering splicing, the third is a missense SNP (T2977C), and multiple non-coding variants in the 3′-UTR. These modifications affect mGluR1 activity, thus contributing to PCa tumorigenesis [124].

Prior study reveals that mGluRs, such as mGluR1, mGluR2, mGluR3, mGluR4, and mGluR5, were expressed in both PC-3 and LNCAP (+dihydrotestosterone and –dihydrotestosterone) cells. mGluR5 has shown activity either in the absence or presence of GPCR ligands. Furthermore, the mRNA expression of mGluR6, mGluR7, and mGluR8 was absent in PC-3; however, in +dihydrotestosterone LNCaP cells, mGluR6 and mGluR7

were expressed, but in -dihydrotestosterone LNCaP, mGluR6 and mGluR8 were expressed. These receptors play a key role in the proliferation of PCa cells mediated by intracellular signaling, which is involved mainly in the phosphorylation of ERKs [4, 112]. Despite the evidence indicating the role of mGluR1 in PCa progression, more studies should be conducted to explore the oncogenic effect of other mGluRs in PCa.

Metabolic targeting of the Gln/Glu axis for the treatment of PCa

The interrelated interactions between the Gln/Glu metabolic reprogramming and other cellular and biochemical functions, including signaling pathways, epigenetic regulation, and redox homeostasis, highlight the significant role of the Gln/Glu metabolic pathway in PCa progression and therapy resistance. Gln/Glu metabolic rewiring is driven by Gln transporters overexpression and elevated GLS activity, which together funnel Gln-derived carbon into α-ketoglutarate and maintain GSH pools via Glu, buffering oxidative stress [3, 25]. Thus, it is rational to target Gln/Glu metabolism and its related components to suppress PCa growth and survival. Therapeutic strategies target Gln metabolism by blocking Gln uptake or its conversion to Glu. Inhibitors of Gln transporters such as SLC1A5 (ASCT2) and GLS1 inhibitors (like CB-839 or BPTES), both deplete TCA cycle intermediates, elevate ROS, and induce apoptosis in preclinical PCa models [66,125,126]. However, their clinical impact as monotherapies has been limited by on-target toxicities, immunometabolism consequences, and a lack of predictive biomarkers, such as high GLS1 expression, to identify responsive patients. Broad-spectrum Gln antagonists (DON prodrugs like DRP-104) disrupt multiple Gln-dependent enzymes but are hindered by metabolic plasticity within the tumor microenvironment, which involves compensatory nutrient scavenging and autophagy-mediated Glu recycling [39]. Therefore, effective translation of Gln/Glu targeting in PCa will depend on combination regimens that pair metabolic inhibitors with other modalities and employ biomarkers to overcome metabolic plasticity and minimize toxicity. Table 1 shows therapeutic strategies targeting the Gln/Glu metabolic pathway that could be utilized.

In conclusion, PCa cells can evolve to reprogram their metabolism and become addicted to Gln/Glu metabolites, which are essential for growth and survival by fueling the TCA cycle, evading the immune system, and providing nutrients. The Gln/Glu metabolic pathway is also interrelated with oncogenic signaling pathways that lead to PCa progression into CRPCa, which resists conventional therapies. Targeting the Gln/Glu metabolic pathway in PCa has emerged as a promising approach to prevent PCa progression, tackle PCa therapy resistance, enhance immunotherapeutic responses, synergize with conventional therapies, and hinder metabolic reprogramming. Preclinical models have exhibited promising findings regarding suppressing key enzymes, transporters, and downstream pathways involved in Gln/Glu utilization. Nevertheless, multiple limitations remain before implementing this approach in the clinic. PCa subtypes are metabolically heterogeneous; thus, not all prostate tumors will respond uniformly to Gln/Glu targeting. In addition, the potential toxicity linked with Gln/Glu metabolic inhibitors and the delicate balance between interfering with cancer metabolism and harming normal cells requires specific targets and careful dose optimization. Our current comprehension of the intricacy of PCa Gln/Glu metabolism and associated cellular and molecular pathways is rapidly evolving, and substantial principles of PCa metabolic reprogramming continue to be redefined.

Author Contribution Statement

Both authors contributed equally to conceptualization, methodology, investigation, data curation, visualization, writing the original draft, and revision.

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Conflict of Interests

The authors declare no potential conflict of interest.

References

1. Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. Cell Metab. 2016;23(1):27–47. https://doi.org/10.1016/j.cmet.2015.12.006.
2. Zhao B, Wang J, Chen L, Wang H, Liang CZ, Huang J, et al. The role of glutamine metabolism in castration-resistant prostate cancer. Asian J Androl. 202325(2):192-7. https://doi.org/10.4103/aja2022105.
3. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: Metabolism and Immune Function, Supplementation and Clinical Translation. Nutrients. 2018;10(11):1564. https://doi.org/10.3390/nu10111564.
4. Koochekpour S, Majumdar S, Azabdaftari G, Attwood K, Scioneaux R, Subramani D, et al. Serum Glutamate Levels Correlate with Gleason Score and Glutamate Blockade Decreases Proliferation, Migration, and Invasion and Induces Apoptosis in Prostate Cancer Cells. Clin Cancer Res. 2012;18(21):5888–901. https://doi.org/10.1158/1078-0432.CCR-12-1308.
5. Zacharias NM, McCullough C, Shanmugavelandy S, Lee J, Lee Y, Dutta P, et al. Metabolic Differences in Glutamine Utilization Lead to Metabolic Vulnerabilities in Prostate Cancer. Sci Rep. 2017;7(1):16159. https://doi.org/10.1038/s41598-017-16327-z.
6. White MA, Lin C, Rajapakshe K, Dong J, Shi Y, Tsouko E, et al. Glutamine Transporters Are Targets of Multiple Oncogenic Signaling Pathways in Prostate Cancer. Mol Cancer Res. 2017;15(8):1017–28. https://doi.org/10.1158/1541-7786.MCR-16-0480.
7. Massie CE, Lynch A, Ramos-Montoya A, Boren J, Stark R, Fazli L, et al. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. EMBO J. 2011;30(13):2719–33. https://doi.org/10.1038/emboj.2011.158.
8. Franklin RB. Zinc and zinc transporters in normal prostate function and the pathogenesis of prostate cancer. Front Biosci. 2005;10:2230. https://doi.org/10.2741/1692.

9. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science. 2009;324(5930):1029–33. https://doi.org/10.1126/science.1160809.
10. Jamaspishvili T, Berman DM, Ross AE, Scher HI, De Marzo AM, Squire JA, et al. Clinical implications of PTEN loss in prostate cancer. Nat Rev Urol. 2018;15(4):222–34. https://doi.org/10.1038/nrurol.2018.9.
11. Jiang P, Du W, Wang X, Mancuso A, Gao X, Wu M, et al. p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. Nat Cell Biol. 2011;13(3):310–6. https://doi.org/10.1038/ncb2172.
12. Wolf A, Agnihotri S, Micallef J, Mukherjee J, Sabha N, Cairns R, et al. Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. J Exp Med. 2011;208(2):313–26. https://doi.org/10.1084/jem.20101470.
13. Reitzer LJ, Wice BM, Kennell D. Evidence that glutamine, not sugar, is the major energy source for cultured HeLa cells. J Biol Chem. 1979;254(8):2669–76.
14. Wang Q, Tiffen J, Bailey CG, Lehman ML, Ritchie W, Fazli L, et al. Targeting Amino Acid Transport in Metastatic Castration-Resistant Prostate Cancer: Effects on Cell Cycle, Cell Growth, and Tumor Development. J Natl Cancer Inst. 2013;105(19):1463–73. https://doi.org/10.1093/jnci/djt241.
15. Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med. 2023;55(4):706–15. https://doi.org/10.1038/s12276-023-00971-9.
16. Bhutia YD, Ganapathy V. Glutamine transporters in mammalian cells and their functions in physiology and cancer. Biochim Biophys Acta. 2016;1863(10):2531–9. https://doi.org/10.1016/j.bbamcr.2015.12.017.
17. Wang Q, Hardie R, Hoy AJ, van Geldermalsen M, Gao D, Fazli L, et al. Targeting ASCT2-mediated glutamine uptake blocks prostate cancer growth and tumour development. J Pathol. 2015;236(3):278–89. https://doi.org/10.1002/path.4518.
18. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, et al. AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer. N Engl J Med. 2014;371(11):1028–38. https://doi.org/10.1056/NEJMoa1315815.
19. Luo M, Wu L, Zhang K, Wang H, Zhang T, Gutierrez L, et al. miR-137 regulates ferroptosis by targeting glutamine transporter SLC1A5 in melanoma. Cell Death Differ. 2018;25(8):1457–72. https://doi.org/10.1038/s41418-017-0053-8.
20. Jeon YJ, Khelifa S, Ratnikov B, Scott DA, Feng Y, Parisi F, et al. Regulation of Glutamine Carrier Proteins by RNF5 Determines Breast Cancer Response to ER Stress-Inducing Chemotherapies. Cancer Cell. 2015;27(3):354–69. https://doi.org/10.1016/j.ccell.2015.02.006.
21. Riley T, Sontag E, Chen P, Levine A. Transcriptional control of human p53-regulated genes. Nat Rev Mol Cell Biol. 2008;9(5):402–12. https://doi.org/10.1038/nrm2395.
22. Krall AS, Xu S, Graeber TG, Braas D, Christofk HR. Asparagine promotes cancer cell proliferation through use as an amino acid exchange factor. Nat Commun. 2016;7:11457. https://doi.org/10.1038/ncomms11457.
23. Zhang J, Pavlova NN, Thompson CB. Cancer cell metabolism: the essential role of the nonessential amino acid, glutamine. EMBO J. 2017;36(10):1302–15. https://doi.org/10.15252/embj.201696151.
24. Yoo HC, Park SJ, Nam M, Kang J, Kim K, Yeo JH, et al. A Variant of SLC1A5 Is a Mitochondrial Glutamine Transporter for Metabolic Reprogramming in Cancer Cells. Cell Metab. 2020;31(2):267-283.e12. https://doi.org/10.1016/j.cmet.2019.11.020.
25. Choi YK, Park KG. Targeting Glutamine Metabolism for Cancer Treatment. Biomol Ther (Seoul). 2018;26(1):19–28. https://doi.org/10.4062/biomolther.2017.178.
26. Li J, Li X, Wu L, Pei M, Li H, Jiang Y. miR-145 inhibits glutamine metabolism through c-myc/GLS1 pathways in ovarian cancer cells. Cell Biol Int. 2019;43(8):921–30. https://doi.org/10.1002/cbin.11182.
27. Ambs S, Prueitt RL, Yi M, Hudson RS, Howe TM, Petrocca F, et al. Genomic Profiling of MicroRNA and Messenger RNA Reveals Deregulated MicroRNA Expression in Prostate Cancer. Cancer Res. 2008;68(15):6162–70. https://doi.org/10.1158/0008-5472.CAN-08-0144.
28. Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, et al. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature. 2009;458(7239):762–5. https://doi.org/10.1038/nature07823.
29. Rathore MG, Saumet A, Rossi JF, de Bettignies C, Tempé D, Lecellier CH, et al. The NF-κB member p65 controls glutamine metabolism through miR-23a. Int J Biochem Cell Biol. 2012;44(9):1448–56. https://doi.org/10.1016/j.biocel.2012.05.011.
30. Zhang J, Wang L, Mao S, Liu M, Zhang W, Zhang Z, et al. miR-1-3p Contributes to Cell Proliferation and Invasion by Targeting Glutaminase in Bladder Cancer Cells. Cell Physiol Biochem. 2018;51(2):513–27. https://doi.org/10.1159/000495273.
31. Bertoli G, Panio A, Cava C, Gallivanone F, Alini M, Strano G, et al. Secreted miR-153 Controls Proliferation and Invasion of Higher Gleason Score Prostate Cancer. Int J Mol Sci. 2022;23(11):6339. https://doi.org/10.3390/ijms23116339.
32. Masamha CP, Xia Z, Peart N, Collum S, Li W, Wagner EJ, et al. CFIm25 regulates glutaminase alternative terminal exon definition to modulate miR-23 function. RNA. 2016;22(6):830–8. https://doi.org/10.1261/rna.055939.116.
33. Lukey MJ, Greene KS, Erickson JW, Wilson KF, Cerione RA. The oncogenic transcription factor c-Jun regulates glutaminase expression and sensitizes cells to glutaminase-targeted therapy. Nat Commun. 2016;7:11321. https://doi.org/10.1038/ncomms11321.
34. Han T, Zhan W, Gan M, Liu F, Yu B, Chin YE, et al. Phosphorylation of glutaminase by PKCε is essential for its enzymatic activity and critically contributes to tumorigenesis. Cell Res. 2018;28(6):655–69. https://doi.org/10.1038/s41422-018-0021-y.
35. Pan T, Gao L, Wu G, Shen G, Xie S, Wen H, et al. Elevated expression of glutaminase confers glucose utilization via glutaminolysis in prostate cancer. Biochem Biophys Res Commun. 2015;456(1):452–8. https://doi.org/10.1016/j.bbrc.2014.11.105.
36. Suzuki S, Tanaka T, Poyurovsky MV, Nagano H, Mayama T, Ohkubo S, et al. Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. Proc Natl Acad Sci U S A. 2010;107(16):7461–6. https://doi.org/10.1073/pnas.1002459107.
37. Xu L, Yin Y, Li Y, Chen X, Chang Y, Zhang H, et al. A glutaminase isoform switch drives therapeutic resistance and disease progression of prostate cancer. Proc Natl Acad Sci U S A. 2021;118(13):e2012748118. https://doi.org/10.1073/pnas.2012748118.
38. Ahmad F, Cherukuri MK, Choyke PL. Metabolic reprogramming in prostate cancer. Br J Cancer. 2021;125(9):1185–96. https://doi.org/10.1038/s41416-021-01435-5.

39. Moon D, Hauck JS, Jiang X, Quang H, Xu L, Zhang F, et al. Targeting glutamine dependence with DRP-104 inhibits proliferation and tumor growth of castration-resistant prostate cancer. Prostate. 2024;84(4):349–57. https://doi.org/10.1002/pros.24654.
40. Wang Q, Guan YF, Hancock SE, Wahi K, van Geldermalsen M, Zhang BK, et al. Inhibition of guanosine monophosphate synthetase (GMPS) blocks glutamine metabolism and prostate cancer growth. J Pathol. 2021;254(2):135–46. https://doi.org/10.1002/path.5665.
41. Krock BL, Skuli N, Simon MC. Hypoxia-Induced Angiogenesis: Good and Evil. Genes Cancer. 2011;2(12):1117–33. https://doi.org/10.1177/1947601911423654.
42. Carey BW, Finley LWS, Cross JR, Allis CD, Thompson CB. Intracellular α-ketoglutarate maintains the pluripotency of embryonic stem cells. Nature. 2015;518(7539):413–6. https://doi.org/10.1038/nature13981.
43. Chowdhury R, Yeoh KK, Tian Y, Hillringhaus L, Bagg EA, Rose NR, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. EMBO Rep. 2011;12(5):463–9. https://doi.org/10.1038/embor.2011.43.
44. Thienpont B, Steinbacher J, Zhao H, D'Anna F, Kuchnio A, Ploumakis A, et al. Tumour hypoxia causes DNA hypermethylation by reducing TET activity. Nature. 2016;537(7618):63–8. https://doi.org/10.1038/nature19081.
45. Pan M, Reid MA, Lowman XH, Kulkarni RP, Tran TQ, Liu X, et al. Regional glutamine deficiency in tumours promotes dedifferentiation through inhibition of histone demethylation. Nat Cell Biol. 2016;18(10):1090–101. https://doi.org/10.1038/ncb3410.
46. Mukha A, Kahya U, Linge A, Chen O, Löck S, Lukiyanchuk V, et al. GLS-driven glutamine catabolism contributes to prostate cancer radiosensitivity by regulating the redox state, stemness and ATG5-mediated autophagy. Theranostics. 2021;11(16):7844–68. https://doi.org/10.7150/thno.58655.
47. Alhallaq A, Elsherbini Y, Abdraboh M. Chloroquine inhibits proliferation, survival, and migration of metastatic androgen-independent PC-3 prostate cancer cells. J Environ Sci Mansoura univ. 2023;52(4). https://doi.org/10.21608/joese.2023.246381.1034.
48. Sultan N, El-Dein M, Elmorsy M, Abdraboh M. Chloroquine suppresses proliferation, survival and migration of metastatic MDA-MB-231 breast cancer cells. J Environ Sci Mansoura univ .2024;53. https://doi.org/10.21608/joese.2023.245062.1033.
49. Zannella VE, Dal Pra A, Muaddi H, McKee TD, Stapleton S, Sykes J, et al. Reprogramming Metabolism with Metformin Improves Tumor Oxygenation and Radiotherapy Response. Clin Cancer Res. 2013;19(24):6741–50. https://doi.org/10.1158/1078-0432.CCR-13-1787.
50. Mishra R, Haldar S, Placencio V, Madhav A, Rohena-Rivera K, Agarwal P, et al. Stromal epigenetic alterations drive metabolic and neuroendocrine prostate cancer reprogramming. J Clin Invest. 2018;128(10):4472–84. https://doi.org/10.1172/JCI99397.
51. Aspuria P-JP, Lunt SY, Väremo L, Vergnes L, Gozo M, Beach JA, et al. Succinate dehydrogenase inhibition leads to epithelial-mesenchymal transition and reprogrammed carbon metabolism. Cancer Metab. 2014;2:21. https://doi.org/10.1186/2049-3002-2-21.
52. Smolková K, Ježek P. The Role of Mitochondrial NADPH-Dependent Isocitrate Dehydrogenase in Cancer Cells. Int J Cell Biol. 2012;2012:1–12. https://doi.org/10.1155/2012/273947.
53. Ren X, Zou L, Zhang X, Branco V, Wang J, Carvalho C, et al. Redox Signaling Mediated by Thioredoxin and Glutathione Systems in the Central Nervous System. Antioxid Redox Signal. 2017;27(13):989–1010. https://doi.org/10.1089/ars.2016.6925.
54. Yu M, Li H, Liu Q, Liu F, Tang L, Li C, et al. Nuclear factor p65 interacts with Keap1 to repress the Nrf2-ARE pathway. Cell Signal. 2011;23(5):883–92. https://doi.org/10.1016/j.cellsig.2011.01.014.
55. Khurana N, Sikka S. Targeting Crosstalk between Nrf-2, NF-κB and Androgen Receptor Signaling in Prostate Cancer. Cancers (Basel). 2018;10(10):352. https://doi.org/10.3390/cancers10100352.
56. Soares MP, Seldon MP, Gregoire IP, Vassilevskaia T, Berberat PO, Yu J, et al. Heme Oxygenase-1 Modulates the Expression of Adhesion Molecules Associated with Endothelial Cell Activation. J Immunol. 2004;172(6):3553–63. https://doi.org/10.4049/jimmunol.172.6.3553.
57. Liu GH, Qu J, Shen X. NF-κB/p65 antagonizes Nrf2-ARE pathway by depriving CBP from Nrf2 and facilitating recruitment of HDAC3 to MafK. Biochim Biophys Acta. 2008;1783(5):713–27. https://doi.org/10.1016/j.bbamcr.2008.01.002.
58. Udensi UK, Tchounwou PB. Oxidative stress in prostate hyperplasia and carcinogenesis. J Exp Clin Cancer Res. 2016;35(1):139. https://doi.org/10.1186/s13046-016-0418-8.
59. Lee B, Mahmud I, Marchica J, Dereziński P, Qi F, Wang F, et al. Integrated RNA and metabolite profiling of urine liquid biopsies for prostate cancer biomarker discovery. Sci Rep. 2020;10(1):3716. https://doi.org/10.1038/s41598-020-60616-z.
60. Shen YA, Hong J, Asaka R, Asaka S, Hsu FC, Suryo Rahmanto Y, et al. Inhibition of the MYC-Regulated Glutaminase Metabolic Axis Is an Effective Synthetic Lethal Approach for Treating Chemoresistant Ovarian Cancers. Cancer Res. 2020;80(20):4514–26. https://doi.org/10.1158/0008-5472.CAN-19-3971.
61. Lin W, Wang C, Liu G, Bi C, Wang X, Zhou Q, et al. SLC7A11/xCT in cancer: biological functions and therapeutic implications. Am J Cancer Res 2020;10:3106–26.
62. Li Z, Qiao X, Liu XM, Shi SH, Qiao X, Xu JY. Blocking xCT and PI3K/Akt pathway synergized with DNA damage of Riluzole-Pt(IV) prodrugs for cancer treatment. Eur J Med Chem. 2023;250:115233. https://doi.org/10.1016/j.ejmech.2023.115233.
63. Raghubir M, Azeem SM, Hasnat R, Rahman CN, Wong L, Yan S, et al. Riluzole-induced apoptosis in osteosarcoma is mediated through Yes-associated protein upon phosphorylation by c-Abl Kinase. Sci Rep. 2021;11(1):20974. https://doi.org/10.1038/s41598-021-00439-8.
64. Ishimoto T, Nagano O, Yae T, Tamada M, Motohara T, Oshima H, et al. CD44 Variant Regulates Redox Status in Cancer Cells by Stabilizing the xCT Subunit of System xc− and Thereby Promotes Tumor Growth. Cancer Cell. 2011;19(3):387–400. https://doi.org/10.1016/j.ccr.2011.01.038.
65. Ding LN, Yu YY, Ma CJ, Lei CJ, Zhang HB. SOX2-associated signaling pathways regulate biological phenotypes of cancers. Biomed Pharmacother. 2023;160:114336. https://doi.org/10.1016/j.biopha.2023.114336.
66. Fu X, Wu H, Li C, Deng G, Chen C. YAP1 inhibits RSL3-induced castration-resistant prostate cancer cell ferroptosis by driving glutamine uptake and metabolism to GSH. Mol Cell Biochem. 2024;479(9):2415–27. https://doi.org/10.1007/s11010-023-04847-4.
67. Yang L, Moss T, Mangala LS, Marini J, Zhao H, Wahlig S, et al. Metabolic shifts toward glutamine regulate tumor growth, invasion and bioenergetics in ovarian cancer. Mol Syst Biol.

2014;10(5):728. https://doi.org/10.1002/msb.20134892.
68. Ellinger J, Kahl P, von der Gathen J, Heukamp LC, Gütgemann I, Walter B, et al. Global Histone H3K27 Methylation Levels are Different in Localized and Metastatic Prostate Cancer. Cancer Invest. 2012;30(2):92–7. https://doi.org/10.3109/07357907.2011.636117.
69. Aguilar E, Marin de Mas I, Zodda E, Marin S, Morrish F, Selivanov V, et al. Metabolic Reprogramming and Dependencies Associated with Epithelial Cancer Stem Cells Independent of the Epithelial-Mesenchymal Transition Program. Stem Cells. 2016;34(5):1163–76. https://doi.org/10.1002/stem.2286.
70. Dorai T, Shah A, Summers F, Mathew R, Huang J, Hsieh T, et al. NRH:quinone oxidoreductase 2 (NQO2) and glutaminase (GLS) both play a role in large extracellular vesicles (LEV) formation in preclinical LNCaP-C4-2B prostate cancer model of progressive metastasis. Prostate. 2018;78(15):1181–95. https://doi.org/10.1002/pros.23693.
71. Dorai T, Dorai B, Pinto JT, Grasso M, Cooper AJL. High Levels of Glutaminase II Pathway Enzymes in Normal and Cancerous Prostate Suggest a Role in 'Glutamine Addiction.' Biomolecules. 2019;10(1):2. https://doi.org/10.3390/biom10010002.
72. Bhowmick N, Posadas E, Ellis L, Freedland SJ, Vizio D Di, Freeman MR, et al. Targeting Glutamine Metabolism in Prostate Cancer. Front Biosci (Elite Ed). 2023;15. https://doi.org/10.31083/j.fbe1501002.
73. Minciacchi VR, You S, Spinelli C, Morley S, Zandian M, Aspuria PJ, et al. Large oncosomes contain distinct protein cargo and represent a separate functional class of tumor-derived extracellular vesicles. Oncotarget. 2015;6(13):11327–41. https://doi.org/10.18632/oncotarget.3598.
74. Prasad P, Roy SS. Glutamine regulates ovarian cancer cell migration and invasion through ETS1. Heliyon. 2021;7(5):e07064. https://doi.org/10.1016/j.heliyon.2021.e07064.
75. Beier A-MK, Ebersbach C, Siciliano T, Scholze J, Hofmann J, Hönscheid P, et al. Targeting the glutamine metabolism to suppress cell proliferation in mesenchymal docetaxel-resistant prostate cancer. Oncogene. 2024;43(26):2038–50. https://doi.org/10.1038/s41388-024-03059-4.
76. Chen YH, Chen H, Lin TT, Zhu JM, Chen JY, Dong RN, et al. ARPC1A correlates with poor prognosis in prostate cancer and is up-regulated by glutamine metabolism to promote tumor cell migration, invasion and cytoskeletal changes. Cell Biosci. 2023;13(1):38. https://doi.org/10.1186/s13578-023-00985-w.
77. Prueitt RL, Wallace TA, Glynn SA, Yi M, Tang W, Luo J, et al. An Immune-Inflammation Gene Expression Signature in Prostate Tumors of Smokers. Cancer Res. 2016;76(5):1055–65. https://doi.org/10.1158/0008-5472.CAN-14-3630.
78. Chen RS, Song YM, Zhou ZY, Tong T, Li Y, Fu M, et al. Disruption of xCT inhibits cancer cell metastasis via the caveolin-1/β-catenin pathway. Oncogene. 2009;28(4):599–609. https://doi.org/10.1038/onc.2008.414.
79. Palmieri EM, Menga A, Martín-Pérez R, Quinto A, Riera-Domingo C, De Tullio G, et al. Pharmacologic or genetic targeting of glutamine synthetase skews macrophages toward an M1-like phenotype and inhibits tumor metastasis. Cell Rep. 2017;20(7):1654–66. https://doi.org/10.1016/j.celrep.2017.07.054.
80. Praharaj M, Shen F, Lee AJ, Zhao L, Nirschl TR, Theodros D, et al. Metabolic Reprogramming of Tumor-Associated Macrophages Using Glutamine Antagonist JHU083 Drives Tumor Immunity in Myeloid-Rich Prostate and Bladder Cancers. Cancer Immunol Res. 2024;12(7):854–75. https://doi.org/10.1158/2326-6066.CIR-23-1105.
81. Wei Q, Qian Y, Yu J, Wong CC. Metabolic rewiring in the promotion of cancer metastasis: mechanisms and therapeutic implications. Oncogene. 2020;39(39):6139–56. https://doi.org/10.1038/s41388-020-01432-7.
82. Dasgupta S, Putluri N, Long W, Zhang B, Wang J, Kaushik AK, et al. Coactivator SRC-2–dependent metabolic reprogramming mediates prostate cancer survival and metastasis. J Clin Invest. 2015;125(3):1174–88. https://doi.org/10.1172/JCI76029.
83. Wang B, Pei J, Xu S, Liu J, Yu J. A glutamine tug-of-war between cancer and immune cells: recent advances in unraveling the ongoing battle. J Exp Clin Cancer Res. 2024;43(1):74. https://doi.org/10.1186/s13046-024-02994-0.
84. Zheng Y, Yao Y, Ge T, Ge S, Jia R, Song X, et al. Amino acid metabolism reprogramming: shedding new light on T cell anti-tumor immunity. J Exp Clin Cancer Res. 2023;42(1):291. https://doi.org/10.1186/s13046-023-02845-4.
85. Ma G, Liang Y, Chen Y, Wang L, Li D, Liang Z, et al. Glutamine Deprivation Induces *PD-L1* Expression via Activation of EGFR/ERK/c-Jun Signaling in Renal Cancer. Mol Cancer Res. 2020;18(2):324–39. https://doi.org/10.1158/1541-7786.MCR-19-0517.
86. Byun JK, Park M, Lee S, Yun JW, Lee J, Kim JS, et al. Inhibition of Glutamine Utilization Synergizes with Immune Checkpoint Inhibitor to Promote Antitumor Immunity. Mol Cell. 2020;80(4):592-606.e8. https://doi.org/10.1016/j.molcel.2020.10.015.
87. Ma G, Zhang Z, Li P, Zhang Z, Zeng M, Liang Z, et al. Reprogramming of glutamine metabolism and its impact on immune response in the tumor microenvironment. Cell Commun Signal. 2022;20(1):114. https://doi.org/10.1186/s12964-022-00909-0.
88. Muir A, Danai LV, Vander Heiden MG. Microenvironmental regulation of cancer cell metabolism: implications for experimental design and translational studies. Dis Model Mech. 2018;11(8):dmm035758. https://doi.org/10.1242/dmm.035758.
89. Bell HN, Huber AK, Singhal R, Korimerla N, Rebernick RJ, Kumar R, et al. Microenvironmental ammonia enhances T cell exhaustion in colorectal cancer. Cell Metab. 2023;35(1):134-49.e6. https://doi.org/10.1016/j.cmet.2022.11.013.
90. Won JH, Parekattil SJ, Davidson SD, Luddy JS, Choudhury MS, Mallouh C, et al. Ammonium-chloride-induced prostatic hypertrophy in vitro: urinary ammonia as a potential risk factor for benign prostatic hyperplasia. Urol Res. 1999;27(5):376–81. https://doi.org/10.1007/s002400050166.
91. Ma G, Jia H, Li Z, Zhang X, Wang L, Zhang Z, et al. Gefitinib Reverses *PD-L1*–Mediated Immunosuppression Induced by Long-term Glutamine Blockade in Bladder Cancer. Cancer Immunol Res. 2024:OF1–18. https://doi.org/10.1158/2326-6066.CIR-24-0039.
92. Krueger TE, Thorek DLJ, Meeker AK, Isaacs JT, Brennen WN. Tumor-infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? Prostate. 2019;79(3):320–30. https://doi.org/10.1002/pros.23738.
93. Guo C, You Z, Shi H, Sun Y, Du X, Palacios G, et al. SLC38A2 and glutamine signalling in cDC1s dictate anti-tumour immunity. Nature. 2023;620(7972):200–8. https://doi.org/10.1038/s41586-023-06299-8.
94. Li Q, Zhong X, Yao W, Yu J, Wang C, Li Z, et al. Inhibitor of glutamine metabolism V9302 promotes ROS-induced autophagic degradation of B7H3 to enhance antitumor

immunity. J Biol Chem. 2022;298:101753. https://doi.org/10.1016/j.jbc.2022.101753.
95. Li C, Xiao Y, Cao H, Chen Y, Li S, Yin F. Cuproptosis Regulates Microenvironment and Affects Prognosis in Prostate Cancer. Biol Trace Elem Res. 2024;202(1):99–110. https://doi.org/10.1007/s12011-023-03668-2.
96. Xu X, Ding C, Zhong H, Qin W, Shu D, Yu M, et al. Integrative analysis revealed that distinct cuprotosis patterns reshaped tumor microenvironment and responses to immunotherapy of colorectal cancer. Front Immunol. 2023;14:1165101. https://doi.org/10.3389/fimmu.2023.1165101.
97. Aurilio G, Cimadamore A, Mazzucchelli R, Lopez-Beltran A, Verri E, Scarpelli M, et al. Androgen Receptor Signaling Pathway in Prostate Cancer: From Genetics to Clinical Applications. Cells. 2020;9(12):2653. https://doi.org/10.3390/cells9122653.
98. Oka S, Okudaira H, Yoshida Y, Schuster DM, Goodman MM, Shirakami Y. Transport mechanisms of trans-1-amino-3-fluoro[1-14C]cyclobutanecarboxylic acid in prostate cancer cells. Nucl Med Biol. 2012;39(1):109–19. https://doi.org/10.1016/j.nucmedbio.2011.06.008.
99. Cardoso HJ, Figueira MI, Vaz CV, Carvalho TMA, Brás LA, Madureira PA, et al. Glutaminolysis is a metabolic route essential for survival and growth of prostate cancer cells and a target of 5α-dihydrotestosterone regulation. Cell Oncol. 2021;44:385–403. https://doi.org/10.1007/s13402-020-00575-9.
100. Kaarbø M, Klokk TI, Saatcioglu F. Androgen signaling and its interactions with other signaling pathways in prostate cancer. BioEssays. 2007;29(12):1227–38. https://doi.org/10.1002/bies.20676.
101. Yoo HC, Yu YC, Sung Y, Han JM. Glutamine reliance in cell metabolism. Exp Mol Med. 2020;52(9):1496–516. https://doi.org/10.1038/s12276-020-00504-8.
102. Csibi A, Fendt SM, Li C, Poulogiannis G, Choo AY, Chapski DJ, et al. The mTORC1 Pathway Stimulates Glutamine Metabolism and Cell Proliferation by Repressing SIRT4. Cell. 2013;153(4):840–54. https://doi.org/10.1016/j.cell.2013.04.023.
103. Tsouko E, Khan AS, White MA, Han JJ, Shi Y, Merchant FA, et al. Regulation of the pentose phosphate pathway by an androgen receptor–mTOR-mediated mechanism and its role in prostate cancer cell growth. Oncogenesis. 2014;3(5):e103. https://doi.org/10.1038/oncsis.2014.18.
104. Singh R, Mills IG. The Interplay Between Prostate Cancer Genomics, Metabolism, and the Epigenome: Perspectives and Future Prospects. Front Oncol. 2021;11:704353. https://doi.org/10.3389/fonc.2021.704353.
105. He Z, Gao Y, Li T, Yu C, Ou L, Luo C. HepaCAM PIK3CA axis regulates the reprogramming of glutamine metabolism to inhibit prostate cancer cell proliferation. Int J Oncol. 2022;60(4):37. https://doi.org/10.3892/ijo.2022.5327.
106. Matés JM, Di Paola FJ, Campos-Sandoval JA, Mazurek S, Márquez J. Therapeutic targeting of glutaminolysis as an essential strategy to combat cancer. Semin Cell Dev Biol. 2020;98:34–43. https://doi.org/10.1016/j.semcdb.2019.05.012.
107. Cai G, Ge Z, Xu Y, Cai L, Sun P, Huang G. SIRT4 functions as a tumor suppressor during prostate cancer by inducing apoptosis and inhibiting glutamine metabolism. Sci Rep. 2022;12(1):12208. https://doi.org/10.1038/s41598-022-16610-8.
108. Ishak Gabra MB, Yang Y, Lowman XH, Reid MA, Tran TQ, Kong M. IKKβ activates p53 to promote cancer cell adaptation to glutamine deprivation. Oncogenesis. 2018;7(11):93. https://doi.org/10.1038/s41389-018-0104-0.
109. Palamiuc L, Emerling BM. PSMA brings new flavors to PI3K signaling: A role for glutamate in prostate cancer. J Exp Med. 2018;215(1):17–9. https://doi.org/10.1084/jem.20172050.
110. Sheehan B, Guo C, Neeb A, Paschalis A, Sandhu S, de Bono JS. Prostate-specific Membrane Antigen Biology in Lethal Prostate Cancer and its Therapeutic Implications. Eur Urol Focus. 2022;8(5):1157–68. https://doi.org/10.1016/j.euf.2021.06.006.
111. Kaittanis C, Andreou C, Hieronymus H, Mao N, Foss CA, Eiber M, et al. Prostate-specific membrane antigen cleavage of vitamin B9 stimulates oncogenic signaling through metabotropic glutamate receptors. J Exp Med. 2018;215:159–75. https://doi.org/10.1084/jem.20171052.
112. Pissimissis N, Papageorgiou E, Lembessis P, Armakolas A, Koutsilieris M. The glutamatergic system expression in human PC-3 and LNCaP prostate cancer cells. Anticancer Res. 2009;29(1):371–7.
113. Teh JLF, Shah R, la Cava S, Dolfi SC, Mehta MS, Kongara S, et al. Metabotropic glutamate receptor 1 disrupts mammary acinar architecture and initiates malignant transformation of mammary epithelial cells. Breast Cancer Res Treat. 2015;151(1):57–73. https://doi.org/10.1007/s10549-015-3365-8.
114. Schwartz PS, Manion MK, Emerson CB, Fry JS, Schulz CM, Sweet IR, et al. 2-Methoxy antimycin reveals a unique mechanism for Bcl-xL inhibition. Mol Cancer Ther. 2007;6(7):2073–80. https://doi.org/10.1158/1535-7163.MCT-06-0767.
115. Zhou BP, Liao Y, Xia W, Zou Y, Spohn B, Hung MC. HER-2/neu induces p53 ubiquitination via Akt-mediated MDM2 phosphorylation. Nat Cell Biol. 2001;3:973–82. https://doi.org/10.1038/ncb1101-973.
116. Okumura N, Yoshida H, Kitagishi Y, Murakami M, Nishimura Y, Matsuda S. PI3K/AKT/PTEN Signaling as a Molecular Target in Leukemia Angiogenesis. Adv Hematol. 2012;2012:1–6. https://doi.org/10.1155/2012/843085.
117. Gómez V, Galazi M, Weitsman G, Monypenny J, Al-Salemee F, Barber PR, et al. HER2 Mediates PSMA/mGluR1-Driven Resistance to the DS-7423 Dual PI3K/mTOR Inhibitor in PTEN Wild-type Prostate Cancer Models. Mol Cancer Ther. 2022;21(4):667–76. https://doi.org/10.1158/1535-7163.MCT-21-0320.
118. Wangari-Talbot J, Wall BA, Goydos JS, Chen S. Functional Effects of GRM1 Suppression in Human Melanoma Cells. Mol Cancer Res. 2012;10(11):1440–50. https://doi.org/10.1158/1541-7786.MCR-12-0158.
119. Blyufer A, Lhamo S, Tam C, Tariq I, Thavornwatanayong T, Mahajan S. Riluzole: A neuroprotective drug with potential as a novel anti cancer agent (Review). Int J Oncol. 2021;59(5):95. https://doi.org/10.3892/ijo.2021.5275.
120. Yoo MH, Hyun HJ, Koh JY, Yoon YH. Riluzole Inhibits VEGF-Induced Endothelial Cell Proliferation In Vitro and Hyperoxia-Induced Abnormal Vessel Formation In Vivo. Invest Ophthalmol Vis Sci. 2005;46:4780. https://doi.org/10.1167/iovs.05-0376.
121. Wadosky KM, Shourideh M, Goodrich DW, Koochekpour S. Riluzole induces AR degradation via endoplasmic reticulum stress pathway in androgen-dependent and castration-resistant prostate cancer cells. Prostate. 2019;79(2):140–50. https://doi.org/10.1002/pros.23719.
122. Eddy K, Chen S. Glutamatergic Signaling a Therapeutic Vulnerability in Melanoma. Cancers (Basel) 2021;13(15):3874. https://doi.org/10.3390/cancers13153874.
123. García-Gaytán AC, Hernández-Abrego A, Díaz-Muñoz M, Méndez I. Glutamatergic system components as potential biomarkers and therapeutic targets in cancer in non-neural

organs. Front Endocrinol (Lausanne). 2022;13:1029210. https://doi.org/10.3389/fendo.2022.1029210.
124. Ali S, Shourideh M, Koochekpour S. Identification of Novel GRM1 Mutations and Single Nucleotide Polymorphisms in Prostate Cancer Cell Lines and Tissues. PLoS One. 2014;9(7):e103204. https://doi.org/10.1371/journal.pone.0103204.
125. Schulte ML, Fu A, Zhao P, Li J, Geng L, Smith ST, et al. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. Nat Med. 2018;24(2):194–202. https://doi.org/10.1038/nm.4464.
126. Lam ET, Su LJ, Salzmann-Sullivan M, Nordeen SK, Flaig TW. Preclinical evaluation of teleglenastat (CB-839) in prostate cancer. J Clin Oncol. 2023;41:378–378. https://doi.org/10.1200/JCO.2023.41.6_suppl.378.
127. Yap TA, Dumbrava EE, Rodon Ahnert J, Hong DS, Pant S, Karp DD, et al. First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumors. J Clin Oncol. 2021;39:3001. https://doi.org/10.1200/JCO.2021.39.15_suppl.3001.
128. Demir U, Celik AB. The Anti-proliferative Effect of a Novel Glutaminase Inhibitor IN-3 on Prostate Cancer Cells. Medeni Med J. 2024;39(3):169-74. https://doi.org/10.4274/MMJ.galenos.2024.87094.
129. Kolevska T, Ryan CJ, Huey V, Weisberg L, Wang S, Baer D, et al. Phase II trial of nab-paclitaxel as first-line therapy of hormone refractory metastatic prostate cancer (HRPC). J Clin Oncol. 2009;27:5152. https://doi.org/10.1200/jco.2009.27.15_suppl.5152.
130. Bai S, Cao S, Jin L, Kobelski M, Schouest B, Wang X, et al. A positive role of c-Myc in regulating androgen receptor and its splice variants in prostate cancer. Oncogene. 2019;38(25):4977–89. https://doi.org/10.1038/s41388-019-0768-8.
131. Fleshner NE, Bernardino RM, Lajkosz K, Saad F, Izawa J, Drachenberg D, et al. A randomized, double-blind, placebo-controlled trial of metformin in reducing progression among men on expectant management for low-risk prostate cancer: The MAST (Metformin Active Surveillance Trial) study. J Clin Oncol. 2024;42:LBA5002. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA5002.
132. Zheng Z, Luo G, Shi X, Long Y, Shen W, Li Z, et al. The Xc− inhibitor sulfasalazine improves the anti-cancer effect of pharmacological vitamin C in prostate cancer cells via a glutathione-dependent mechanism. Cell Oncol. 2020;43(1):95–106. https://doi.org/10.1007/s13402-019-00474-8.
133. Wang JJ, Siu MKY, Jiang YX, Leung THY, Chan DW, Wang HG, et al. A Combination of Glutaminase Inhibitor 968 and *PD-L1* Blockade Boosts the Immune Response against Ovarian Cancer. Biomolecules. 2021;11(12):1749. https://doi.org/10.3390/biom11121749.
134. Kumar NB, Pow-Sang J, Egan KM, Spiess PE, Dickinson S, Salup R, et al. Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate Cancer Prevention. Cancer Prev Res. 2015;8(10):879–87. https://doi.org/10.1158/1940-6207.CAPR-14-0324.

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