Decoding the metabolic-immune crosstalk: The role of glutamine and ammonium reprogramming in prostate cancer immune evasion (Review)

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Received March 12, 2026; Accepted July 29, 2026

DOI: 10.3892/or.2026.9186

Abstract. Prostate cancer progression is typically driven by metabolic reprogramming and immune evasion, yet the interface between these processes remains incompletely understood. Dysregulated glutamine metabolism extends beyond bioenergetic support to actively shape antitumor immunity through nutrient competition and ammonium accumulation within the tumor microenvironment. Ammonium, traditionally viewed as a toxic waste product, is a critical immunosuppressive metabolite that impairs T cell function and promotes macrophage M2 polarization. The present review aimed to summarize the bidirectional crosstalk between tumor metabolism and immune cells, with emphasis on how metabolic alterations drive therapeutic resistance. While the majority of evidence supporting this axis derives from preclinical models, the present review highlights the glutamine-ammonium axis as a promising but largely untapped therapeutic target requiring translation into clinical investigation, including combination strategies with immunotherapy.

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Key words: glutamine metabolism, ammonium, prostate cancer, immune evasion, tumor microenvironment, metabolic reprogramming, immunometabolism, therapeutic target

1. Introduction

Prostate cancer (PCa) is a leading cause of cancer-related morbidity and mortality among male patients worldwide, with recent estimates indicating ~1.4 million new cases and 375,000 deaths annually (1). Despite advances in early detection and treatment, a substantial proportion of patients (10-20% within 5 years) develop castration-resistant PCa (CRPCa), a lethal disease state characterized by therapeutic resistance and poor clinical outcomes (2). Comprehensive genomic analysis has revealed that advanced PCa involves complex molecular alterations that influence disease progression and treatment response (3). Among these, androgen receptor splice variant 7 (AR-V7) has been prospectively validated as a predictive biomarker of resistance to hormone therapy in high-risk patients (4). Furthermore, distinct genomic drivers associated with enzalutamide resistance have been identified in metastatic CRPCa, highlighting the heterogeneous and adaptive nature of treatment failure (5).

The biological evolution from hormone-sensitive to CR disease involves not only genomic alterations but also metabolic reprogramming (6). This metabolic rewiring enables tumor cells to sustain proliferation under therapeutic pressure and nutrient-limited conditions (7). Concurrently, the tumor microenvironment (TME) undergoes notable remodeling that promotes immune evasion, with evidence indicating that metabolic alterations directly influence immune cell function (8). The recognition that metabolic reprogramming and immune evasion are interconnected rather than independent processes has opened novel avenues for therapeutic intervention.

Glutamine metabolism is a central node in PCa pathogenesis, with recent work positioning glutamine and glutamate metabolic reprogramming at the core of tumor progression (9).

Beyond its traditional roles in bioenergetics and biosynthesis, glutamine metabolism actively shapes the immunological landscape of the TME through nutrient competition and the generation of immunosuppressive metabolites (10). While previous reviews have addressed glutamine metabolism in PCa or immune evasion mechanisms in the TME, the present study aimed to promote a unified framework by positioning the glutamine-ammonium axis as an integrated metabolic-immune hub (10,11). The present review aimed to reconceptualize ammonium, traditionally dismissed as a toxic waste product, as an active immunosuppressive signaling molecule that orchestrates T cell dysfunction and macrophage M2 polarization. Ammonium accumulation impairs antitumor immunity and is associated with poor prognosis, whereas its clearance restores T cell function and enhances immunotherapy efficacy (12). The present study aimed to delineate the bidirectional feedback loops whereby immune-derived cytokines reciprocally modulate tumor glutamine and ammonium flux, establishing a self-reinforcing cycle of metabolic adaptation and immune evasion (9,11,13) and summarize the therapeutic implications of targeting this integrated axis (14). The complexity of this metabolic-immune crosstalk is amplified by interactions with stromal elements, including cancer-associated fibroblasts that manipulate glutamine metabolism through paracrine signaling (11), and encompasses bioenergetic support, redox homeostasis, epigenetic regulation and nitrogen recycling (13).

The therapeutic potential of targeting the glutamine-ammonium axis has been demonstrated in preclinical studies (14,15). Metabolic reprogramming of tumor-associated macrophages using glutamine antagonism drives antitumor immunity in myeloid-rich PCa (14). Similarly, targeting of Myc and glutamine-fructose-6-phosphate amidotransferase 1 (GFAT-1), a key enzyme in glutamine metabolism, improves antitumor activity (15). These findings suggest that interventions at the metabolic-immune interface may simultaneously disrupt tumor progression and enhance immune surveillance. The present review aimed to summarize the molecular mechanisms governing glutamine dependency and ammonium accumulation in PCa, with focus on their immunomodulatory consequences. By mapping the bidirectional dialogue between tumor metabolism and antitumor immunity, the present review seeks to identify novel therapeutic strategies to overcome treatment resistance and improve clinical outcomes. The literature for the present narrative review was identified through systematic searches of PubMed databases (pubmed.ncbi.nlm.nih.gov) using combinations of the following keywords: 'PCa', 'glutamine metabolism', 'glutaminase', 'ASCT2', 'ammonium', 'urea cycle', 'tumor microenvironment', 'immune evasion', 'tumor-associated macrophages', 'T cell exhaustion', 'metabolic reprogramming' and 'immunometabolism'. The search was restricted to articles published in English between January 2015 and April 2026, with additional references identified through citation screening of retrieved articles and relevant review papers.

2. Glutamine metabolism in PCa: Mechanisms and regulation

Glutamine is a versatile nutrient that fuels multiple aspects of PCa progression, from bioenergetics and biosynthesis to redox homeostasis and epigenetic regulation. The rewiring of glutamine metabolic pathways represents a hallmark of malignant transformation that distinguishes PCa cells from their normal counterparts. Understanding the molecular mechanisms governing glutamine use is essential for identifying how these tumors establish metabolic autonomy and acquire resistance to therapeutic intervention (6,7,9). Fig. 1 provides a schematic overview of the key transporters, enzymes and metabolic nodes, illustrating the integrated nature of glutamine metabolism in PCa cells.

Glutamine dependency in PCa. PCa cells exhibit dependency on exogenous glutamine, a phenomenon termed glutamine addiction that distinguishes malignant metabolism from normal prostate physiology. This metabolic vulnerability arises from the unique bioenergetic and biosynthetic demands of proliferating tumor cells, which require glutamine not only as a nitrogen donor for nucleotide and amino acid synthesis but also as a carbon source for tricarboxylic acid cycle anaplerosis. PCa cell lines PC-3, DU145 and LNCaP display distinct bioenergetic properties, with mitochondrial adaptations that render them sensitive to glutamine deprivation (16). Targeting alanine-serine-cysteine transporter 2 (ASCT2)-mediated glutamine uptake effectively blocks PCa growth and tumor development, establishing glutamine dependency as a potential therapeutic target (17).

Plasma glutamine levels may serve as prognostic biomarkers in localized PCa, with alterations in circulating glutamine associated with disease outcomes (18). The degree of glutamine dependency varies across disease states: CRPCa cells exhibit heightened reliance on glutamine metabolism compared with hormone-naïve (untreated by androgen deprivation therapy) counterparts, suggesting that therapeutic pressure selects for metabolic adaptations that amplify glutamine addiction (19). This evolutionary trajectory positions glutamine metabolism as a key driver of lethal PCa phenotypes, providing a rationale for developing therapeutic strategies that exploit this dependency across the spectrum of disease progression.

Key transporters and enzymes. The execution of glutamine-dependent metabolic programs requires coordinated action of specialized transporters that mediate glutamine influx and efflux. Among glutamine transporters, ASCT2 (encoded by SLC1A5) is the dominant mediator of glutamine uptake in PCa cells, with elevated expression demonstrated across multiple model systems and clinical specimens (17,20). Mechanistic studies have revealed that ASCT2 expression is directly regulated by multiple oncogenic signaling pathways, positioning this transporter as a nodal point integrating proliferative signals (20,21). The functional importance of ASCT2 is further supported by observations that CRPCa cells exhibit increased ASCT2 expression and glutamine uptake, linking transporter upregulation to therapeutic resistance (21). Beyond ASCT2, the heterodimeric amino acid transporter L-type amino acid transporter 1 (encoded by SLC7A5) participates in glutamine exchange by coupling glutamine efflux with essential amino acid import, which sustains mTOR signaling and protein synthesis (11).

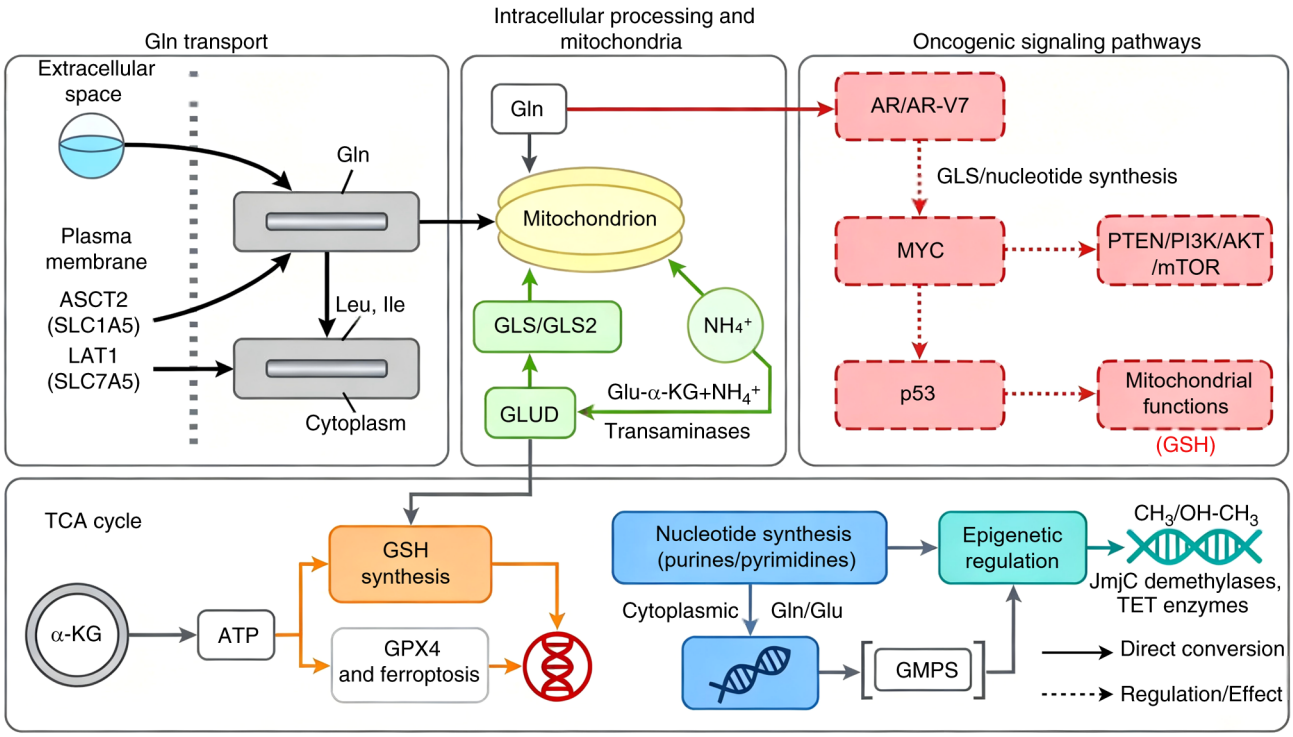

Figure 1. Schematic overview of glutamine metabolism in prostate cancer cells. AR-V7, androgen receptor splice variant 7; ASCT2, alanine-serine-cysteine transporter 2; GLS, glutaminase; GLUD, glutamate dehydrogenase; Gln, glutamine; Glu, glutamate; GSH, glutathione; LAT1, L-type amino acid transporter 1; α-KG, α-ketoglutarate; TCA, tricarboxylic acid.

Once internalized, intracellular enzymes channel glutamine into downstream metabolic pathways. Glutamine enters mitochondria where glutaminase (GLS) catalyzes its deamination to glutamate, representing the first committed step of glutaminolysis (22,23). Elevated GLS expression confers enhanced glucose use capacity in PCa cells, linking glutamine catabolism with broader metabolic reprogramming (22). Pharmacological inhibition of GLS suppresses proliferation and promotes apoptosis in PCa models, validating this enzyme as a druggable vulnerability (23,24). The existence of two GLS isoforms, GLS and GLS2, adds regulatory complexity; an isoform switch from GLS to GLS2 is implicated in therapeutic resistance and disease progression, indicating that isoform-specific targeting strategies may be required for optimal efficacy (25). Glutamate dehydrogenase (GLUD) converts glutamate to α-ketoglutarate, feeding carbon into the tricarboxylic acid cycle while releasing ammonium as a byproduct. The coordinated upregulation of these transporters and enzymes establishes a metabolic axis that sustains PCa cell survival and proliferation (26).

Oncogenic signaling pathways controlling glutamine use. Glutamine metabolism in PCa integrates signals from dominant oncogenic pathways that orchestrate metabolic reprogramming in response to extracellular cues and therapeutic pressures. The androgen receptor (AR) pathway, central to PCa biology throughout disease evolution, exerts control over glutamine metabolism. Differential regulation of metabolic pathways by full-length AR vs. its constitutively active splice variant AR-V7 reveals that androgen signaling directs glutamine use patterns, with AR-V7-expressing cells exhibiting distinct metabolic dependency (27). Glutaminolysis itself is regulated by 5α-dihydrotestosterone, establishing direct hormonal control over this key metabolic route (28). The AR coactivator steroid receptor coactivator-2 coordinates metabolic reprogramming that supports PCa survival and metastasis, linking transcriptional coactivation with glutamine-dependent phenotypes (29).

Myc and the PTEN/PI3K/AKT/mTOR pathway further amplify glutamine use through complementary mechanisms. Myc drives glutamine metabolism through transcriptional activation of GLS and suppression of negative regulators; a long non-coding RNA connects c-Myc to tumor metabolism, illustrating the layered regulatory architecture controlling glutamine use (30). c-Myc-driven glycolysis via thioredoxin-interacting protein suppression depends on the GLS-MLX-interacting protein) axis, revealing crosstalk between glucose and glutamine metabolic programs (31). PTEN loss, typically observed in PCa, induces metabolic reprogramming characterized by enhanced glutamine dependency, linking tumor suppressor inactivation with acquired metabolic vulnerability (32). AKT inhibitors elicit metabolic responses detectable by hyperpolarized magnetic resonance spectroscopy, providing tools to monitor pathway engagement (33). The mTOR pathway, serving as a nutrient sensor, integrates amino acid availability with growth signaling; dual mTOR inhibition alters tumor heterogeneity and metabolic profiles in patient-derived xenografts (34). p53 status modulates glutamine metabolism through transcriptional programs that influence mitochondrial function and redox balance. Knockdown of the cochaperone small glutamine-rich tetratricopeptide repeat-containing protein α suppresses

both androgen and PI3K/Akt signaling while inhibiting proliferation, illustrating the interconnectedness of these pathways (35). The convergence of these oncogenic signals on glutamine metabolism genes establishes a complex regulatory network that adapts to therapeutic intervention and disease progression (36).

Glutamine-derived metabolic fate. Once imported and processed through the glutaminolysis pathway, glutamine-derived carbon is distributed among multiple metabolic fates that support PCa cell survival and proliferation. The most common fate of glutamine carbon is anaplerotic entry into the tricarboxylic acid cycle via conversion to α-ketoglutarate, replenishing intermediates extracted for biosynthetic purposes (37,38). This anaplerotic function is key under conditions of metabolic stress; metformin treatment decreases glucose oxidation and increases the dependency of PCa cells on reductive glutamine metabolism, demonstrating metabolic flexibility that sustains tricarboxylic acid cycle function under pharmacological pressure (37). Pyruvate dehydrogenase E1 subunit α1 knockout in PCa cells results in metabolic reprogramming toward greater glutamine dependence, emphasizing the compensatory association between glucose and glutamine carbon sources (38).

Beyond energy metabolism, glutamine serves as the primary precursor for glutathione synthesis, providing the building blocks required for this notable cellular antioxidant. Glutamine-derived glutathione metabolism is key for survival under chronic cycling hypoxia, where fluctuating oxygen levels generate oxidative stress that must be neutralized to prevent cell death (39). In enzalutamide-resistant PCa, antioxidant programs including glutathione metabolism serve critical roles in sustaining viability under therapeutic pressure (24). The glutamine antagonist JHU083 exerts antitumor effects partly through glutathione depletion, linking pharmacological glutamine interference with redox disruption (40). Glutamine nitrogen supports nucleotide biosynthesis through multiple routes: Amide nitrogen contributes directly to purine and pyrimidine ring synthesis, while amine nitrogen provides nitrogen for non-essential amino acids that feed into nucleotide production. Inhibition of guanosine monophosphate synthetase, which uses glutamine amide nitrogen, blocks glutamine metabolism and PCa growth, validating nucleotide synthesis as a key downstream effector (41).

Glutamine-derived α-ketoglutarate serves as a substrate for epigenetic modifying enzymes including Jumonji C domain-containing histone demethylases and ten-eleven translocation DNA hydroxylases. By modulating the activity of these α-ketoglutarate-dependent dioxygenases, glutamine availability influences histone methylation status and DNA hydroxymethylation patterns, establishing a direct link between nutrient availability and epigenetic regulation (13,42). This metabolic-epigenetic axis allows fluctuations in glutamine supply to translate into heritable changes in gene expression programs that may contribute to phenotypic plasticity and therapy resistance (13,42). The partitioning of glutamine among these competing fates is dynamically regulated in response to microenvironmental conditions and therapeutic interventions, creating metabolic vulnerability that can be exploited for therapeutic benefit (43).

Cross-regulation between oncogenic signaling pathways in controlling glutamine metabolism. The regulation of glutamine metabolism in PCa is not governed by individual oncogenic pathways acting in isolation, but rather through a network of cross-regulatory interactions between AR/AR-V7, Myc and PI3K/AKT/mTOR signaling. These pathways converge on common downstream effectors while simultaneously modulating their activity, creating a highly integrated and adaptive regulatory system. A key distinction exists between full-length AR and its constitutively active splice variant AR-V7 in regulating glutamine metabolism (30,31). While AR activation increases citrate levels, AR-V7 reduces citrate due to enhanced use rather than impaired synthesis, mirroring the metabolic shifts observed in patients with CRPCa (7). Furthermore, flux assays have demonstrated that compared with AR, AR-V7 exhibits increased dependence on glutaminolysis and reductive carboxylation to generate tricarboxylic acid cycle intermediates, establishing AR-V7 as a driver of distinct metabolic vulnerabilities (7). The activity of AR-V7 is regulated by FOXO1 in a PTEN-PI3K-AKT-dependent manner, positioning AR-V7 as both a downstream effector and a proximal node integrating PI3K/AKT signaling with glutamine metabolic reprogramming (11). AR and Myc exhibit reciprocal regulation that amplifies glutamine metabolic reprogramming. AR directly transactivates Myc expression, and Myc enhances AR transcriptional activity through multiple mechanisms, establishing a positive feed-forward loop that drives GLS expression and glutamine uptake (30,31). This AR-Myc axis is further reinforced by long non-coding RNAs that connect c-Myc to tumor metabolism (30). Concurrently, AR signaling intersects with the PI3K/AKT/mTOR pathway at multiple levels. PTEN loss, which activates PI3K/AKT signaling, enhances AR transcriptional activity and promotes glutamine dependency (32). AKT phosphorylation of AR modulates its stability and transcriptional output, while mTOR activation integrates amino acid availability with AR-dependent metabolic programs (34). Regarding the Myc/PI3K/AKT/mTOR interaction, emerging evidence indicates that mTORC1 positively regulates GLS and glutamine flux through ribosomal protein S6 kinase β-1 (S6K1)-dependent control of c-Myc translation, wherein S6K1 enhances Myc translation efficiency by modulating eukaryotic initiation factor 4B phosphorylation (12). The role of Myc in regulating glutamine transporter expression is context-dependent and influenced by PTEN/PI3K status: Myc is unable to upregulate the glutamine transporters SLC1A4 and SLC1A5 in PTEN wild-type cells, whereas this regulation is enabled by PTEN loss (9,16). mTORC1, in contrast, is required for maximal AR-mediated glutamine transporter expression and cell proliferation independent of PTEN status (9). The convergence of these pathways on common transcriptional targets, including GLS and glutamine transporters such as ASCT2, creates a regulatory hub wherein pathway activation at any node sustains glutamine metabolism when other nodes are inhibited (20,36). This network redundancy explains the limited efficacy of single-pathway inhibitors and provides the rationale for combinatorial strategies targeting multiple nodes simultaneously. The adaptive plasticity of this regulatory network enables PCa cells to maintain glutamine addiction under therapeutic pressure, contributing to the evolution of CR phenotypes (19,25).

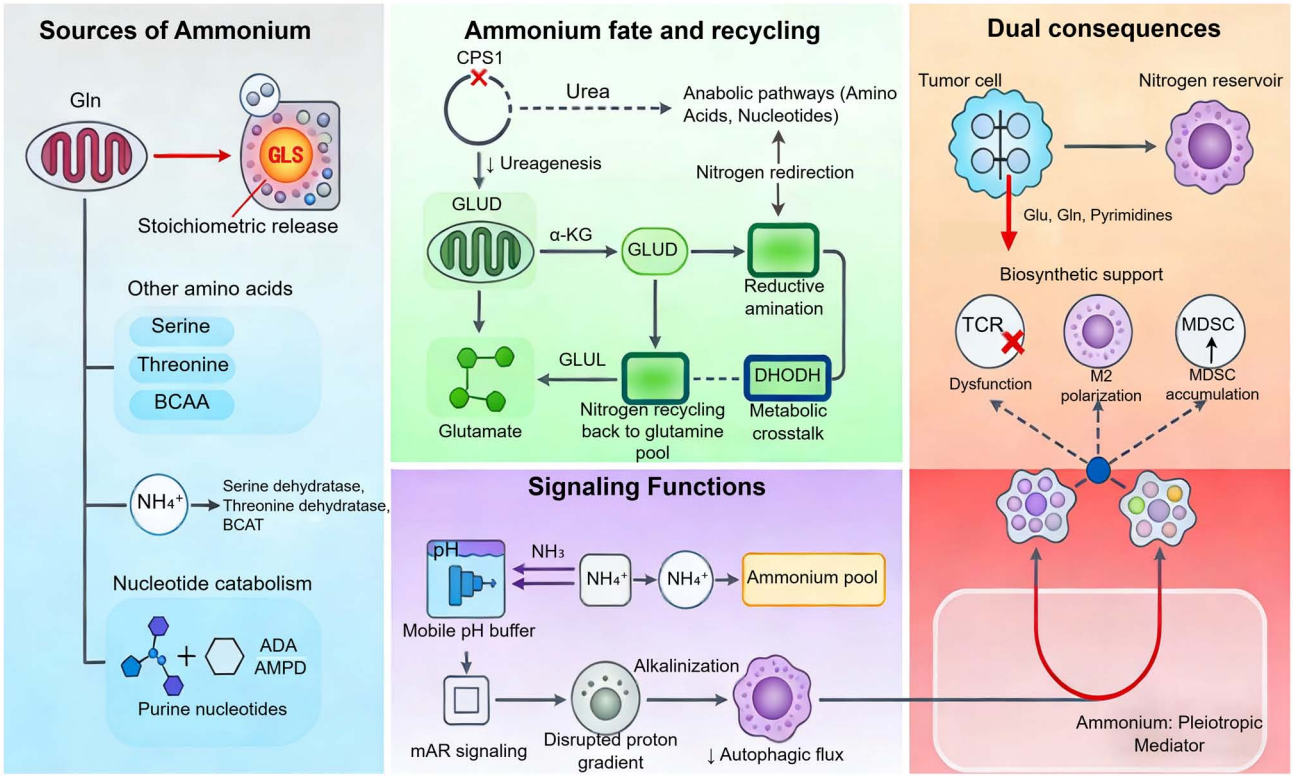

Figure 2. Schematic overview of ammonium metabolism in the prostate tumor microenvironment. ADA, adenosine deaminase; AMPD, adenosine monophosphate deaminase; BCAA, branched-chain amino acid; CPS1, carbamoyl phosphate synthetase I; GLS, glutaminase; GLUD, glutamate dehydrogenase; GLUL, glutamine synthetase; Gln, glutamine; Glu, glutamate; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; α-KG, α-ketoglutarate.

3. Ammonium metabolism

Ammonium has traditionally been viewed as a toxic metabolic byproduct requiring efficient detoxification and elimination. However, evidence positions ammonium as a key signaling molecule and metabolic node within the prostate TME, where its production, partitioning and accumulation profoundly influence both cancer cell behavior and immune cell function (12,13). The rewiring of ammonium metabolism represents an overlooked dimension of PCa pathogenesis that extends beyond nitrogen disposal to encompass pH regulation, stress adaptation and immunosuppressive crosstalk (12,13). Fig. 2 provides a schematic overview of ammonium metabolism in PCa.

Sources of ammonium in the prostate TME. Ammonium within the prostate TME originates from multiple metabolic sources that reflect the heightened catabolic activity of malignant cells. The predominant source is glutaminolysis, wherein GLS catalyzes the deamination of glutamine to glutamate, releasing ammonium as a stoichiometric byproduct. This pathway operates at elevated flux in PCa cells due to glutamine addiction, resulting in constitutive ammonium production that surpasses the rate at which the cells use nitrogen for amino acid and nucleotide biosynthesis, causing ammonium to accumulate and be released into the TME (38).

Beyond glutaminolysis, deamination reactions involving other amino acids contribute to the ammonium pool. Catabolism of serine, threonine and branched-chain amino acids generates ammonium through the action of serine dehydratase, threonine dehydratase and branched-chain amino acid transaminases coupled with GLUD (10,11). Nucleotide catabolism represents an additional source, with adenosine and AMP deaminase releasing ammonium during purine nucleotide degradation (12,13). The relative contribution of each source varies according to metabolic context, nutrient availability and oncogenic driver status. Ye *et al* (12) reviewed ammonium metabolism rewiring in the PCa ME, emphasizing that the convergence of these pathways creates sustained ammonium flux that distinguishes malignant from benign prostate tissue.

Ammonium fate and recycling: Urea cycle dysregulation and nitrogen partitioning. Once generated, ammonium faces several potential fates determined by the expression and activity of nitrogen-handling enzymes within PCa cells. The urea cycle represents the canonical pathway for ammonium detoxification, converting ammonium and bicarbonate to urea through enzymatic reactions distributed between mitochondria and cytoplasm. However, PCa cells exhibit notable urea cycle dysregulation characterized by downregulation of key enzymes including carbamoyl phosphate synthetase I and ornithine transcarbamylase. Bruzzone *et al* (44) demonstrated using nuclear magnetic resonance-based urine metabolomics that patients with PCa display enhanced carbon and nitrogen recycling, with metabolomic signatures indicating redirection of nitrogen away from urea production toward anabolic pathways. This metabolic rewiring favors nitrogen incorporation into amino acids and nucleotides at the expense of ureagenesis, supporting biosynthetic demands of proliferating tumor cells.

GLUD and glutamine synthetase (GLUL) represent alternative fates for ammonium assimilation. GLUD catalyzes the reversible reductive amination of α-ketoglutarate to glutamate, incorporating ammonium into amino acid pools, while GLUL ligates ammonium with glutamate to form glutamine, recycling nitrogen back into the glutamine pool. Luo *et al* (45) revealed that PCa stem cells exhibit aberrant urea cycle activity with selective upregulation of specific urea cycle enzymes that support stemness maintenance, suggesting that nitrogen partitioning is dynamically regulated across tumor subpopulations. Labroy *et al* (46) further demonstrated metabolic crosstalk between the urea cycle and pyrimidine synthesis, identifying dihydroorotate dehydrogenase (DHODH) as a metabolic vulnerability that integrates nitrogen metabolism with nucleotide biosynthesis.

Ammonium as a signaling molecule: Impact on pH homeostasis and autophagy. Beyond its role as a metabolic substrate, ammonium serves as an intracellular signaling molecule that modulates key cell processes including pH homeostasis, autophagy and stress adaptation. Ammonium exists in equilibrium with ammonia, which freely diffuses across membranes and accepts protons to form ammonium, thereby serving as a mobile pH buffer. Chatterjee *et al* (47) demonstrated that membrane AR signaling influences Na^+/H^+ exchanger activity in PCa cells, establishing a link between hormonal signaling and pH regulatory mechanisms that interface with ammonium partitioning.

Accumulation of intracellular ammonium alkalinizes acidic compartments including lysosomes, disrupting the proton gradient required for optimal lysosomal hydrolase activity and autophagic flux. Yang *et al* (48) reported that curcumin induces both apoptosis and protective autophagy in CRPCa cells through mechanisms involving iron chelation, highlighting the interconnectedness of metal homeostasis, oxidative stress and autophagic regulation. Ammonium accumulation influences stress adaptation pathways by modulating mTOR signaling and activating stress-responsive transcription factors. Chen *et al* (49) developed an ammonia-induced calcium phosphate nanostructure that provides insight into how local ammonium concentrations may influence bone metastasis, linking nitrogen metabolism with the establishment of metastatic niches. These signaling functions establish ammonium as a pleiotropic mediator that integrates metabolic state with cell stress responses.

Ammonium accumulation: Metabolic support vs. immunosuppression. Ammonium accumulation within the prostate TME exerts paradoxical effects, simultaneously supporting tumor metabolic adaptation while suppressing antitumor immune responses. For cancer cells, ammonium serves as a nitrogen reservoir that can be assimilated into amino acids and nucleotides via GLUD and GLUL, supporting biosynthetic capacity under nutrient-limited conditions. Metabolomic profiling by Yu *et al* (50) identified distinct metabolic signatures in plasma and urine from patients with PCa, revealing alterations in nitrogenous compounds that reflect systemic metabolic reprogramming.

However, the ammonium accumulation that supports tumor metabolism imposes immunosuppressive consequences on infiltrating immune cells. Ye *et al* (12) reviewed how ammonium metabolic reprogramming drives immunosuppression within the prostate TME through multiple mechanisms including polarization of tumor-associated macrophages (TAMs) toward the M2 phenotype, induction of T cell dysfunction and promotion of myeloid-derived suppressor cell (MDSC) accumulation; direct primary evidence for ammonium-induced T cell dysfunction has been reported in colorectal cancer and effector T cell models (51,52). Ammonium impairs T cell proliferation and effector function by interfering with T cell receptor signaling and inducing metabolic stress, while simultaneously promoting macrophage arginase activity and anti-inflammatory cytokine production. The dual nature of ammonium accumulation creates a therapeutic paradox: Interventions that block ammonium production may deprive tumors of nitrogen for biosynthesis, but interventions that promote ammonium accumulation may reinforce immunosuppression. Understanding this duality is key for developing therapeutic strategies that target nitrogen metabolism without compromising antitumor immunity, positioning ammonium metabolism as a key node connecting tumor biology with immune evasion in PCa (51,52).

4. Metabolic reprogramming of immune cells in the prostate TME

The prostate TME represents a dynamic ecosystem wherein metabolic reprogramming extends beyond cancer cells to encompass diverse immune populations. The competition for limited nutrients, accumulation of metabolic waste products and establishment of hypoxic niches reshape immune cell metabolism, driving functional polarization toward immunosuppressive phenotypes that facilitate tumor progression. Understanding the metabolic adaptations of TAMs, T cells, MDSCs and dendritic cells (DCs) is essential for appreciating how glutamine and ammonium metabolism intersect with antitumor immunity (Table I).

Metabolic landscape of the prostate TME: Nutrient competition, hypoxia and lactate accumulation. The prostate TME is characterized by metabolic alterations that create a hostile landscape for infiltrating immune cells while supporting tumor growth. Hypoxia is a dominant feature, arising from aberrant vascularization and elevated oxygen consumption by proliferating tumor cells. Bharti *et al* (53) demonstrated distinct hypoxia patterns in primary and metastatic PCa environments, revealing that oxygen gradients shape regional metabolic heterogeneity and influence therapeutic responses. Arocena *et al* (54) developed a variant of coverslip hypoxia to visualize tumor cell alterations at increasing distances from an oxygen source, providing mechanistic insight into how oxygen tension gradients drive metabolic adaptation. Bery *et al* (55) demonstrated that hypoxia promotes PCa aggressiveness by upregulating epithelial-mesenchymal transition activator zinc finger E-box binding homeobox 1 and potassium channel expression, linking oxygen deprivation with enhanced metastatic potential.

Lactate accumulation is a defining feature of the PCa TME, resulting from elevated glycolytic flux and the Warburg effect in cancer cells. Bok *et al* (56) used dual-agent hyperpolarized carbon-13 magnetic resonance spectroscopic imaging to reveal

Table I. Metabolic reprogramming of immune cells in the prostate TME.

First author, year	Immune cell type	Model system	Findings	Metabolic features	Immune consequence	(Refs.)
Bharti *et al*, 2019	General TME	Primary and metastatic PCa tissue	Hypoxia shapes regional metabolic heterogeneity and influences therapeutic responses	Hypoxia-driven metabolic adaptation	Immune cell dysfunction	(53)
Arocena *et al*, 2019	General TME	Coverslip hypoxia model	Oxygen gradients drive metabolic adaptation in tumor cells	Hypoxia gradient sensing	Altered immune landscape	(54)
Bery *et al*, 2020	General TME	PCa cell lines (including 22Rv1, PC-3, DU145) and organotypic cultures of human prostate tissue	Hypoxia upregulates Zeb1 and potassium channels, promoting aggressiveness	Hypoxia-induced transcriptional reprogramming	Enhanced metastatic potential	(55)
Bok *et al*, 2019	General TME	Dual-agent hyperpolarized 13C MRSI	Lactate serves as metabolic fuel and signaling molecule in PCa	Lactate metabolism	Metabolic fuel for tumor	(56)
Comito *et al*, 2019	$CD4^+$ T cells	PCa cell line-derived xenograft models in immunodeficient mice	Lactate modulates $CD4^+$ T cell polarization via TLR8/miR21 signaling	Lactate signaling	Immunosuppressive environment	(57)
Chetta *et al*, 2023	General TME	Review	Lactate promotes angiogenesis and suppresses antitumor immunity	Lactate as key metabolite	Multifaceted immunosuppression	(58)
El-Kenawi *et al*, 2019	TAMs	TRAMP transgenic model, subcutaneous grafts, and *in vitro* macrophage cultures	Acidity promotes tumor progression by altering macrophage phenotype	pH sensing	M2 polarization	(59)
Banerjee *et al*, 2019	TAMs	Patient-derived PCa tumor-conditioned medium and co-culture with patient-derived cancer cells	Context-dependent transcriptional programs shape macrophage function	Metabolic plasticity	Altered phagocytic function	(60)
Han *et al*, 2020	TAMs	THP-1 macrophages	IL-6 from prostate epithelial cells induces M2 polarization	Cytokine-driven metabolism	M2 polarization	(61)
Praharaj *et al*, 2024	TAMs	RM-1 prostate cancer subcutaneous graft models	JHU083 reprograms TAMs toward pro-inflammatory phenotype	Glutamine metabolism	Enhanced phagocytosis, decreased angiogenesis	(14)

Table I. Continued.

First author, year	Immune cell type	Model system	Findings	Metabolic features	Immune consequence	(Refs.)
Masetti *et al*, 2022	TAMs	PCa cell line-derived xenograft models (PC-3, DU145) in immuno-deficient mice	Lipid-loaded TAMs sustain tumor growth and invasiveness	Lipid metabolism	Tumor-supportive function	(62)
Li *et al*, 2023	TAMs	Mouse models and PCa cell lines (RM-1, TRAMP-C1)	Dauricine inhibits PI3K/AKT-dependent M2 polarization	PI3K/AKT signaling	Decreased M2 polarization	(63)
Guan *et al*, 2022	T cells	Immunocompetent mouse models	AR activity in T cells limits checkpoint blockade efficacy	Hormonal signaling	T cell dysfunction	(64)
Chang *et al*, 2024	T cells	Prostate tumor tissue-derived microenviron-ment from mouse models and human PCa samples	1-Pyrroline-5-carboxylate inhibits T cell glycolysis via SHP1/PKM2/LDHB	Glycolysis inhibition	T cell dysfunction	(65)
Rastogi and McNeel, 2025	T cells	Post-immunotherapy PCa patient samples	Shared features between antitumor response and immune-associated adverse events	Metabolic adaptation	Altered T cell function	(66)
Zhou *et al*, 2025	$CD8^+$ T cells	PCa cell lines (LNCaP, PC-3, DU145)	EP4 upregulation attenuates $CD8^+$ T cell killing	PI3K/AKT signaling	Decreased cytotoxicity	(67)
Molina *et al*, 2024	T lymphocytes	Prostate tumor tissues from radical prostatec-tomy patients	Regulatory and memory T cell infiltration predicts long-term outcomes	T cell metabolism	Prognostic value	(68)
Hellsten *et al*, 2019	MDSCs	PCa cell lines (LNCaP, PC-3, DU145)	STAT3 inhibitor inhibits MDSC-like monocyte generation	STAT3 signaling	Decreased immunosuppression	(69)
Fu *et al*, 2021	MDSCs	High-dose-irradiated TRAMP-C1 tumors	MDSCs serve as therapeutic target and index for TME status	Radiation-induced metabolism	Immunosuppressive barrier	(70)
Koinis *et al*, 2021	MDSCs	Review	MDSCs are involved in PCa immune evasion	MDSC metabolism	Key role in immunosuppression	(71)
Siemińska and Baran, 2022	MDSCs	Review	MDSCs are key players and promising therapy targets in PCa	MDSC metabolism	Therapeutic targeting potential	(72)

Table I. Continued.

First author, year	Immune cell type	Model system	Findings	Metabolic features	Immune consequence	(Refs.)
Feriz *et al*, 2023	DCs	Human PCa tumor tissues	Heterogeneous transcriptional signatures in tumor-infiltrating DCs	Transcriptional heterogeneity	Differential immunostimulatory capacity	(73)
Hawlina *et al*, 2022	DCs	DC-based vaccine trial in patients with PCa	DC-based vaccines prolong survival independently of vaccine cell number	DC metabolism	Clinical immunotherapeutic efficacy	(74)
Hensler *et al*, 2022	DCs	Patients with PCa (peripheral blood gene signature analysis)	Peripheral gene signatures distinguish patient immunotypes for DC-based vaccines	Metabolic signatures	Biomarker for patient selection	(75)
Li *et al*, 2022	MDSCs	ARID1A knockout genetically engineered mouse models	ARID1A loss induces polymorphonuclear MDSC chemotaxis	Genetic regulation of metabolism	Enhanced MDSC recruitment	(76)

TME, tumor microenvironment; PCa, prostate cancer; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; MRSI, magnetic resonance spectroscopic imaging; TLR8, toll-like receptor 8; EMT, epithelial-mesenchymal transition; AR, androgen receptor; Zeb1, zinc finger E-box-binding homeobox 1; ARID1A, AT-rich interactive domain-containing protein 1A; TRAMP-C1, transgenic adenocarcinoma of the mouse prostate cell line C1; EP4, E-prostanoid receptor 4; SHP1/PKM2/LDHB, Src homology region 2 domain-containing phosphatase 1/pyruvate kinase M2/lactate dehydrogenase B.

the role of lactate metabolism in PCa progression and metastases, demonstrating that lactate serves not only as a waste product but as a critical metabolic fuel and signaling molecule. Comito *et al* (57) demonstrated that lactate modulates $CD4^+$ T cell polarization and induces an immunosuppressive environment through the TLR8/microRNA21 pathway, sustaining prostate carcinoma progression. Chetta *et al* (58) recently reviewed the clinical implications of lactate as a key metabolite in PCa progression, emphasizing its multifaceted roles in promoting angiogenesis, suppressing antitumor immunity and driving therapy resistance. The convergence of hypoxia, nutrient competition and lactate accumulation establishes a metabolic milieu that influences immune cell function and polarization.

TAMs: Glutamine-driven M2 polarization and metabolic plasticity. TAMs represent the most abundant immune population within the prostate TME and exhibit metabolic plasticity that enables adaptation to microenvironmental cues. El-Kenawi *et al* (59) demonstrated that acidity promotes tumor progression by altering macrophage phenotype in PCa, establishing a direct link between extracellular pH and TAM polarization toward immunosuppressive states. Banerjee *et al* (60) examined differential expression of efferocytosis- and phagocytosis-associated genes in TAMs exposed to patient-derived PCa ME, revealing context-dependent transcriptional programs that shape macrophage function. Han *et al* (61) demonstrated that IL-6 produced by prostate epithelial cells stimulated with *Trichomonas vaginalis* promotes proliferation of PCa cells by inducing M2 polarization of human monocytic leukemia cell line THP-1-derived macrophages, highlighting the role of infectious agents in shaping TAM phenotypes.

Glutamine metabolism serves a key role in driving TAM polarization and function. Praharaj *et al* (14) demonstrated that metabolic reprogramming of TAMs using the glutamine antagonist JHU083 drives tumor immunity in myeloid-rich PCa and bladder cancer: JHU083 treatment reprogrammed immunosuppressive TAMs toward a pro-inflammatory phenotype, increasing tumor cell phagocytosis, diminishing pro-angiogenic capacity and promoting inflammatory signaling. Masetti *et al* (62) identified lipid-loaded TAMs as key sustainers of tumor growth and invasiveness in PCa, revealing that metabolic substrate availability shapes macrophage effector functions. Li *et al* (63) demonstrated that dauricine regulates PCa progression by inhibiting PI3K/AKT-dependent M2 polarization of macrophages, providing pharmacological evidence for targeting macrophage metabolism. The metabolic plasticity of TAMs represents both a vulnerability and a therapeutic opportunity in PCa.

T cell metabolism: Glutamine deprivation, effector dysfunction and exhaustion. T cells infiltrating the prostate TME face metabolic challenges that compromise their antitumor effector function and promote exhaustion. Nutrient competition between rapidly proliferating cancer and T cells creates an environment of glutamine deprivation that impairs T cell activation and proliferation. Guan *et al* (64) demonstrated that AR activity in T cells limits checkpoint blockade efficacy, revealing that hormonal signaling directly influences T cell metabolism and function within the prostate TME. Chang *et al* (65) recently demonstrated that 1-pyrroline-5-carboxylate inhibits T cell glycolysis in the PCa microenvironment through the Src homology region 2 domain-containing phosphatase 1/pyruvate kinase M2/lactate dehydrogenase B pathway, identifying a novel metabolite-driven immunosuppressive mechanism.

Memory T cell differentiation and maintenance are influenced by the metabolic landscape. Rastogi and McNeel (66) characterized prostate tumor immune ME changes following immunotherapy, revealing shared features between patients who developed antitumor responses and those experiencing immune-associated adverse events. Zhou *et al* (67) demonstrated that upregulation of E-prostanoid receptor 4 attenuates the killing ability of $CD8^+$ T cells against PCa cells via the PI3K/AKT signaling pathway, identifying a potential target for restoring T cell cytotoxicity. The metabolic competition between tumors and T cells for glutamine and other nutrients shapes the outcome of antitumor immune responses. Molina *et al* (68) demonstrated that regulatory and memory T lymphocytes infiltrating prostate tumors predict long-term clinical outcomes, emphasizing the prognostic value of T cell subset distribution.

MDSCs and DCs: Metabolic adaptation. MDSCs and DCs represent complementary arms of the myeloid compartment that orchestrate immunosuppression within the prostate TME. MDSCs expand in patients with PCa and suppress T cell responses through multiple mechanisms including arginase-1 expression, reactive oxygen species production and nutrient depletion. Hellsten *et al* (69) demonstrated the STAT3 inhibitor galiellalactone inhibits the generation of MDSC-like monocytes by PCa cells and decreases immunosuppressive and tumorigenic factors, validating MDSC targeting as a therapeutic strategy. Fu *et al* (70) examined the role of MDSCs in high-dose-irradiated transgenic adenocarcinoma of the mouse prostate cell line c1 tumors, identifying them as both a therapeutic target and an index for assessing TME status. Koinis *et al* (71) reviewed MDSCs in PCa, emphasizing their key role in immune evasion. Siemińska and Baran (72) further positioned MDSCs as key players and promising therapy targets in PCa, reviewing strategies for MDSC depletion and functional inhibition.

DCs, key for priming antitumor T cell responses, exhibit metabolic and functional alterations within the prostate TME. Feriz *et al* (73) used single-cell RNA sequencing to demonstrate heterogeneous transcriptional signatures in tumor-infiltrating DCs in PCa, revealing distinct DC subsets with differential immunostimulatory capacities. Hawlina *et al* (74) demonstrated that DC-based vaccines prolong survival and time to next therapy independently of vaccine cell number, providing clinical evidence for DC-based immunotherapy. Hensler *et al* (75) identified peripheral gene signatures that distinguish distinct immunotypes of patients with cancer with therapeutic implications for autologous DC-based vaccines, offering biomarkers for patient selection. The metabolic adaptation of MDSCs and DCs to the glutamine-depleted, ammonium-accumulating prostate TME shapes their immunosuppressive vs. immunostimulatory functions. Li *et al* (76) demonstrated that AT-rich interactive domain-containing protein 1A loss induces polymorphonuclear MDSC chemotaxis

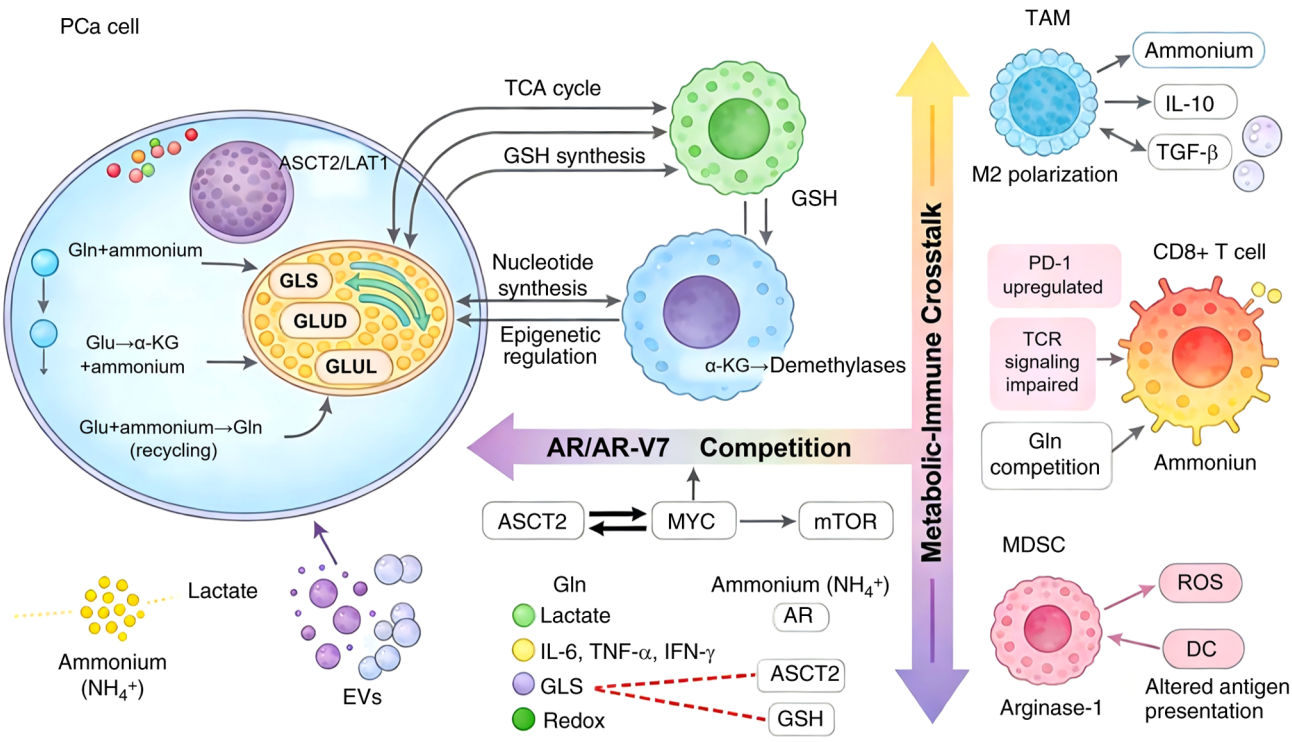

Figure 3. Schematic illustration of the metabolic-immune association mediated by glutamine and ammonium in the prostate tumor microenvironment. ASCT2, alanine-serine-cysteine transporter 2; DC, dendritic cell; EV, extracellular vesicle; GLS, glutaminase; GLUD, glutamate dehydrogenase; GLUL, glutamine synthetase; Gln, glutamine; Glu, glutamate; GSH: Glutathione; LAT1: L-type amino acid transporter 1; MDSC, myeloid-derived suppressor cell; PCa, prostate cancer; ROS, reactive oxygen species; TAM, tumor-associated macrophage; TCR, T cell receptor; α-KG, α-ketoglutarate.

and promotes PCa progression, revealing genetic determinants of myeloid cell recruitment. The immunosuppressive effects of MDSCs and DCs, coupled with their metabolic reprogramming, establishes a-barrier to antitumor immunity that must be overcome for successful immunotherapy.

5. Bidirectional metabolic-immune crosstalk: Glutamine and ammonium as key mediators

The association between tumor metabolism and antitumor immunity is not unidirectional but represents a dynamic, bidirectional association wherein metabolic reprogramming of cancer cells shapes immune cell function, and immune-derived signals feedback to modulate tumor metabolic pathways (9,10). This reciprocal crosstalk establishes a self-reinforcing cycle that drives PCa progression and immune evasion. Glutamine and ammonium metabolism occupy central positions within this association, serving both as substrates for tumor growth and as critical mediators of immunosuppression. Understanding these bidirectional interactions is key for developing therapeutic strategies that simultaneously target tumor metabolism and enhance antitumor immunity (12,13). Fig. 3 provides a schematic overview of the bidirectional metabolic-immune crosstalk, illustrating the tumor-derived signals, nutrient competition, ammonium-mediated immunosuppression, redox interplay and immune-derived feedback loops that shape the prostate TME.

Tumor-derived signals shaping immune cell metabolism: Lactate, kynurenine and extracellular vesicles. PCa cells actively remodel the metabolic landscape of the TME through secretion of metabolites, enzymes and extracellular vesicles that directly modulate immune cell function. Lactate, long considered a metabolic waste product, has emerged as a potent signaling molecule that reprograms immune cell metabolism and polarization (77). Stepka *et al* (77) reviewed metabolic and amino acid alterations in the TME, emphasizing that lactate accumulation suppresses T cell proliferation and promotes regulatory T cell differentiation while driving macrophage polarization toward immunosuppressive M2 phenotypes.

Extracellular vesicles represent an additional mechanism for metabolic communication between tumor cells and immune populations. Mo *et al* (78) demonstrated that long non-coding RNA nuclear-enriched abundant transcript 1 shuttled by PCa cell-secreted exosomes initiates osteoblastic phenotypes in the bone metastatic ME through the microRNA-205-5p/runt-related transcription factor 2/splicing factor proline- and glutamine-rich pathway, revealing that exosomal cargo shapes distant ME niches. Lee *et al* (79) demonstrated that extracellular vesicles derived from PCa cells induce metabolic reprogramming toward a glycolysis phenotype in recipient cells, suggesting vesicle-mediated transfer of metabolic regulators contributes to the establishment of a glycolytic, immunosuppressive ME. Ippolito *et al* (80) showed that extracellular pH modulates neuroendocrine PCa cell metabolism and susceptibility to mitochondrial inhibitors, indicating that the acidic ME resulting from tumor metabolism further influences immune cell function. These tumor-derived signals establish a metabolic landscape that favors immunosuppression while supporting tumor progression.

Glutamine competition between tumor cells and infiltrating lymphocytes. Glutamine is a key nutrient for both proliferating tumor cells and activated lymphocytes, creating a metabolic competition within the prostate TME that shapes antitumor immunity. Alhallaq and Sultan (9) positioned glutamine and glutamate metabolic reprogramming at the center of PCa pathogenesis, describing the dynamic competition between tumor and immune cells for this essential amino acid. This competition deprives infiltrating T cells of the glutamine required for activation, proliferation and effector function, contributing to the exhausted T cell phenotype characteristic of advanced PCa. Matos *et al* (81) examined the role of arginine and arginases in modulating metabolism, TME and PCa progression, demonstrating that competition for amino acid substrates extends beyond glutamine to encompass multiple nitrogenous nutrients.

Bhowmick *et al* (10) reviewed strategies for targeting glutamine metabolism in PCa, emphasizing that therapeutic interventions should consider the differential glutamine requirements of tumor cells vs. antitumor immune populations. This dual benefit arises from differential sensitivity to glutamine antagonism, with tumor-associated macrophages being susceptible to metabolic reprogramming toward pro-inflammatory phenotypes.

Ammonium as an immunosuppressive metabolite: Mechanisms of T cell dysfunction and macrophage polarization toward M2 phenotype. Beyond its role as a nitrogenous waste product, ammonium serves as an active immunosuppressive metabolite that directly impairs T cell function and promotes macrophage polarization toward tumor-supportive phenotypes. Ye *et al* (12) reviewed ammonium metabolism rewiring in the PCa ME, demonstrating that ammonium accumulation drives immunosuppression through multiple mechanisms including polarization of TAMs toward the M2 phenotype, induction of T cell dysfunction and promotion of MDSC accumulation. Primary studies have shown that ammonia directly impairs T cell proliferation and effector function through lysosomal alkalization, mitochondrial swelling and impaired autophagic flux (51,52): Ammonium impairs T cell proliferation and effector function by interfering with T cell receptor signaling and inducing metabolic stress, while simultaneously promoting macrophage arginase activity and anti-inflammatory cytokine production. Elia *et al* (13) demonstrated that nitrogen handling varies between tumor types, with PCa exhibiting unique adaptations that favor ammonium accumulation and recycling. Yang *et al* (82) reviewed TME-driven drug resistance in urological cancers, highlighting that ammonium-mediated immunosuppression contributes to the failure of immunotherapeutic approaches and represents a potential therapeutic target. The immunosuppressive consequences of ammonium accumulation create a therapeutic paradox: Interventions that block ammonium production may deprive tumors of nitrogen for biosynthesis, but interventions that promote ammonium accumulation may reinforce immunosuppression. This duality positions ammonium metabolism as a key node connecting tumor biology with immune evasion in PCa.

Redox interplay: Glutathione metabolism linking tumor antioxidant defense and immune suppression. Glutathione metabolism represents a key intersection where tumor antioxidant defense mechanisms directly influence immune cell function within the prostate microenvironment. Wang *et al* (83) reviewed the integrated regulation of ferroptosis in PCa, demonstrating that glutathione peroxidase 4 and glutathione metabolism protect tumor cells from oxidative stress while simultaneously depleting the antioxidant capacity available to infiltrating immune cells. Linares *et al* (84) demonstrated that activating transcription factor 4-induced metabolic reprogramming represents a synthetic vulnerability of p62-deficient tumor stroma, revealing that oxidative stress responses in the TME are coordinately regulated and influence both cancer cells and supporting stromal elements. Zhang *et al* (15) showed that improved antitumor activity against PCa can be achieved through combined targeting of Myc and GFAT-1, the rate-limiting enzyme in the hexosamine biosynthetic pathway that branches from glutamine metabolism and influences protein glycosylation and redox balance. The glutathione synthesis pathway directly competes with other glutamine-using pathways for substrate, creating metabolic trade-offs that influence both tumor survival and immune function. Tumor cells with elevated glutathione synthesis capacity exhibit enhanced resistance to oxidative stress induced by inflammatory cytokines, while depleting the local cysteine and glutamate pools required for optimal T cell activation and proliferation. This redox interplay establishes a feedback loop wherein tumor antioxidant defense mechanisms actively suppress the oxidative burst required for effective antitumor immunity (15,24).

Feedback loops: Immune-derived cytokines modulating tumor glutamine and ammonium flux. The bidirectional nature of metabolic-immune crosstalk is evident in the feedback loops wherein immune-derived cytokines directly modulate tumor cell glutamine and ammonium metabolism. Hönscheid *et al* (11) demonstrated that PCa-associated fibroblasts manipulate glutamine metabolism in cancer cells through paracrine signaling, revealing that non-immune stromal elements also participate in this metabolic interaction. Lasorsa *et al* (7) demonstrated that inflammatory cytokines including interferon-γ and tumor necrosis factor-α produced by infiltrating lymphocytes feedback to modulate glutamine transporter expression, GLS activity and urea cycle enzyme expression in cancer cells. These immune-derived signals constrain or enhance tumor metabolic capacity depending on the context and duration of exposure. Acute exposure to inflammatory cytokines may suppress glutamine uptake and metabolism, contributing to the anti-proliferative effects of immune activation (7). However, chronic exposure to low-level inflammatory signals, characteristic of the TME, may select for tumor cells with adaptive metabolic programs that maintain glutamine flux despite cytokine-mediated stress. By intervening at the metabolic level, it is possible to simultaneously disrupt tumor metabolic adaptation and enhance the immunostimulatory capacity of TAMs, creating a cycle of antitumor immunity (7). Understanding these complex feedback associations is key for developing combination therapies that maximize therapeutic benefit while minimizing resistance mechanisms.

Integrated regulatory network of glutamine-ammonium mediated metabolic-immune crosstalk. The bidirectional crosstalk between tumor metabolism and antitumor immunity in PCa operates through an integrated regulatory network organized across three interconnected levels. At the transcriptional level, oncogenic drivers including AR, Myc and mutant p53 coordinate glutamine metabolic gene expression through direct transcriptional activation and epigenetic modulation (9,13). AR differentially regulates metabolic pathways via full-length AR vs. AR-V7, while Myc drives GLS expression and glutamine uptake through transcriptional programs (64). PTEN loss enhances glutamine dependency via PI3K/AKT/mTOR pathway activation, and p53 status modulates mitochondrial glutamine use. At the metabolite signaling level, glutamine-derived ammonium directly impairs T cell receptor signaling and promotes macrophage arginase activity, establishing metabolite-driven immunosuppression (12,65). Simultaneously, glutamine-derived glutathione metabolism links tumor antioxidant defense with immune suppression through depletion of local antioxidant capacity (77). At the cell interaction level, feedback loops complete the bidirectional circuit: Immune-derived cytokines including interferon-γ and tumor necrosis factor-α modulate glutamine transporter expression, GLS activity and urea cycle enzyme expression in cancer cells, while tumor-secreted lactate, kynurenine and extracellular vesicles reshape immune cell metabolism and polarization (11,13,77). This multi-level network exhibits redundancy and adaptive plasticity, wherein pathway inhibition at one node typically triggers compensatory activation at alternative nodes, explaining the limited efficacy of monotherapy and providing the rationale for combinatorial strategies targeting multiple network nodes simultaneously.

6. Therapeutic strategies targeting the metabolic-immune interface

The recognition that glutamine and ammonium metabolism orchestrate bidirectional crosstalk between tumor cells and immune populations has opened novel therapeutic avenues targeting the metabolic-immune interface. Rather than pursuing tumor cell-intrinsic metabolic disruption or immune activation as separate strategies, emerging approaches aim to simultaneously inhibit tumor metabolic adaptation while reprogramming the immunosuppressive TME toward antitumor immunity (Table II).

Glutamine metabolism inhibitors: GLS inhibitors and transporter blockade in preclinical and clinical development. Pharmacological targeting of glutamine metabolism has emerged as a promising therapeutic strategy, with multiple agents advancing through preclinical and clinical development for PCa. The GLS inhibitor CB-839 (telaglenastat) is the most clinically advanced agent, having demonstrated the ability to enhance PCa radiosensitivity by regulating redox state, stemness and autophagy (85). Bhowmick *et al* (10) reviewed strategies for targeting glutamine metabolism in PCa, emphasizing that therapeutic interventions should consider the differential glutamine requirements of tumor cells vs. antitumor immune populations. The glutamine antagonist JHU083, a prodrug that selectively activates within the TME, has shown promise in a preclinical study by reprogramming tumor-associated macrophages and enhancing antitumor immunity (14). Moon *et al* (40) demonstrated that targeting glutamine dependence with DRP-104, a novel glutamine antagonist, inhibits proliferation and tumor growth of CRPCa, validating glutamine metabolism as a therapeutic vulnerability in advanced disease. Beyond enzyme inhibition, transporter blockade targeting ASCT2 has shown efficacy in a preclinical model with Ono *et al* (21) demonstrating that fluciclovine uptake is associated with ASCT2 expression in CRPCa cells, providing both a therapeutic target and an imaging biomarker.

GLS inhibitor CB-839, glutamine antagonist prodrug JHU083 and glutamine antagonist DRP-104, exhibit distinct advantages and limitations that inform their therapeutic applicability. CB-839 offers the advantage of selective GLS inhibition with an established safety profile in clinical trials, being well-tolerated with mostly mild adverse effects including nausea, fatigue and photophobia (6,86). However, its clinical efficacy as monotherapy in PCa is limited; single-drug trials do not demonstrate notable clinical benefits, and combination studies with talazoparib were terminated due to challenges in demonstrating efficacy and slow recruitment (6). Furthermore, residual glutamine metabolism via GLS2 or other pathways may circumvent CB-839-mediated blockade (25). By contrast, JHU083 and DRP-104, as prodrugs of the broad glutamine antagonist 6-diazo-5-oxo-L-norleucine, provide broader metabolic inhibition by targeting multiple glutamine-utilizing enzymes beyond GLS, including amidotransferases involved in nucleotide biosynthesis (10). JHU083 offers the advantage of TME-selective activation, which reduces systemic toxicity while achieving potent local glutamine antagonism (14). DRP-104 exhibits broader metabolic inhibition compared with CB-839, further suppressing glycolysis and glutamine-dependent nucleotide biosynthesis (3). However, the broad-spectrum nature of these antagonists raises concerns regarding off-target effects and potential toxicity and their clinical development remains at earlier stages compared with CB-839 (6). The differential mechanisms of these agents and selective GLS inhibition vs. broad glutamine antagonism suggest that patient stratification based on tumor metabolic dependency may be key for optimizing therapeutic benefit.

Targeting ammonium metabolism and nitrogen balance: Urea cycle enzymes, GLUD and ammonia scavengers. The recognition that ammonium metabolism represents a potential therapeutic axis has spurred investigation into strategies targeting nitrogen handling in PCa. Ye *et al* (12) reviewed ammonium metabolism rewiring in the PCa ME, highlighting that urea cycle dysregulation creates tumor-specific vulnerabilities that can be exploited therapeutically. Targeting urea cycle enzymes, GLUD and ammonia scavengers represents an emerging therapeutic frontier with potential to disrupt nitrogen recycling while alleviating ammonium-mediated immunosuppression. Labroy *et al* (46) demonstrated metabolic crosstalk between the urea cycle and pyrimidine synthesis, identifying DHODH as a metabolic vulnerability that integrates nitrogen metabolism with nucleotide biosynthesis in both AR-positive and -negative PCa cells. This finding suggests that targeting nitrogen handling may be effective across PCa subtypes. Luo *et al* (45) revealed that PCa stem cells exhibit aberrant

Table II. Therapeutic strategies targeting the metabolic-immune interface in PCa.

First author, year	Therapeutic agent/strategy	Model system	Target/mechanism	Findings	Combination partner	(Refs.)
Cha *et al*, 2020	CB-839 (telaglenastat)	Preclinical PCa xenograft	Glutaminase inhibition	Enhances radiosensitivity via redox state, stemness and autophagy modulation	Radiotherapy	(85)
Praharaj *et al*, 2024	JHU083 (glutamine antagonist prodrug)	Myeloid-rich PCa and bladder cancer models	Glutamine antagonism	Reprograms TAMs to pro-inflammatory phenotype; increases phagocytosis; decreases angiogenesis	JHU083 (monotherapy)	(14)
Moon *et al*, 2024	DRP-104 (glutamine antagonist)	Human CRPCa cell lines (LNCaP, LAPC4, C4-2/MDVR, PC-3, 22RV1, NCI-H660) and NCI-H660 neuroendocrine PCa xenograft model	Glutamine antagonism	Inhibits proliferation and growth of CRPCa	DRP-104 (monotherapy)	(40)
Ono *et al*, 2015	ASCT2 transporter blockade	CRPCa-like cell lines (LNCaP-SF, LN-REC4) and androgen-dependent LNCaP	ASCT2 inhibition	Fluciclovine uptake is associatedwith ASCT2 expression; ASCT2 is a potential target and imaging biomarker	Imaging (theranostic)	(21)
Ye *et al*, 2025	Urea cycle enzyme targeting; GLUD inhibition; ammonia scavengers	Review	Urea cycle dysregulation; GLUD; nitrogen recycling	Urea cycle dysregulation creates vulnerabilities; targeting nitrogen handling disrupts recycling and alleviates immunosuppression	Not specified	(12)
Labroy *et al*, 2026	DHODH inhibitors	AR-positive and -negative PCa cells	Dihydroorotate dehydrogenase	Metabolic crosstalk between urea cycle and pyrimidine synthesis; DHODH is a metabolic vulnerability	Not specified	(46)
Luo *et al*, 2024	Urea cycle enzyme targeting	Prostate cancer stem cells	Urea cycle enzymes (stemness maintenance)	Aberrant urea cycle activity supports stemness; nitrogen partitioning is dynamically regulated	Combination strategies required	(45)

Table II. Continued.

First author, year	Therapeutic agent/strategy	Model system	Target/mechanism	Findings	Combination partner	(Refs.)
Sharma *et al*, 2020	Nivolumab + ipilimumab	Patients with mCRPCa (CheckMate 650 trial)	PD-1 + CTLA-4 blockade	Clinical activity in mCRPCa; response is associated with tumor mutational burden and immune infiltration	Combination immunotherapy	(87)
Shenderov *et al*, 2021	Nivolumab + ipilimumab ± enzalutamide	Patients with AR-V7-expressing mCRPCa	PD-1 + CTLA-4 blockade	Nivolumab + ipilimumab modestly overcame enzalutamide resistance in a subset of patients with AR-V7-expressing mCRPCa	Enzalutamide	(88)
Powles *et al*, 2022	Atezolizumab + enzalutamide vs. enzalutamide alone	Patients with mCRPCa (randomized phase 3)	PD-L1 blockade	No improvement in unselected patients; biomarker-defined subgroups may benefit	Enzalutamide	(89)
Hegde *et al*, 2021	Evofosfamide + ipilimumab	Advanced solid malignancy (phase 1)	Hypoxia-activated prodrug + CTLA-4 blockade	Proof-of-concept for combining microenvironment-targeted metabolic agents with immune checkpoint blockade	Ipilimumab	(90)
Ono *et al*, 2015	[^{18}F]Fluciclovine PET	CRPCa-like and androgen-dependent PCa cell lines	ASCT2 expression imaging	Fluciclovine uptake is associated with ASCT2 expression; validates amino acid PET for target engagement monitoring	Target engagement monitoring	(21)
Lowentritt and Kipper, 2020	[^{18}F]Fluciclovine PET/CT	Patients with biochemical recurrence of PCa	ASCT2 and LAT1 imaging	Clinical utility for detecting recurrent disease; guides management decisions	Imaging-guided therapy	(91)
Smith *et al*, 2021	Plasma glutamine levels	Patients with localized PCa	Circulating glutamine	Plasma glutamine as prognostic biomarker; alterations are associated with disease outcome	Liquid biopsy	(18)

PCa, prostate cancer; mCRPCa, metastatic castration-resistant prostate cancer; TAM, tumor-associated macrophage; ASCT2, alanine-serine-cysteine transporter 2; LAT1, L-type amino acid transporter 1; GLUD, glutamate dehydrogenase; DHODH, dihydroorotate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; AR-V7, androgen receptor splice variant 7; PET, positron emission tomography; CT, computed tomography; Treg, regulatory T cell.

urea cycle activity with selective upregulation of specific urea cycle enzymes that support stemness maintenance, indicating that nitrogen partitioning is dynamically regulated across tumor subpopulations and may require combination strategies for effective targeting. The therapeutic potential of targeting ammonium metabolism extends beyond direct enzyme inhibition to include ammonia scavengers that may alleviate immunosuppression while depriving tumors of recyclable nitrogen.

Ammonium-targeting strategies are categorized into three principal approaches with distinct translational profiles. Urea cycle enzyme modulation is the most mechanistically direct strategy, aiming to restore ureagenesis and redirect nitrogen away from anabolic pathways, however, the multi-enzyme nature of the urea cycle creates pharmacological complexity, and, to the best of our knowledge, no urea cycle-activating agent has entered PCa clinical development (12,44). GLUD and GLUL inhibition offers a more pharmacologically tractable single-target approach to block nitrogen recycling within tumor cells, but creates a key immunological paradox: Inhibiting these enzymes may local ammonium concentrations, potentially exacerbating T cell dysfunction and macrophage M2 polarization (51,52). Ammonia scavengers, such as sodium phenylbutyrate, are the most translationally attractive strategy due to their US Food and Drug Administration-approved status for urea cycle disorders, yet their efficacy in the PCa TME remains unproven and systemic ammonia scavenging may affect nitrogen homeostasis (12).

To the best of our knowledge, none of the aforementioned ammonium-targeting strategies has been evaluated in combination with immune checkpoint blockade in PCa, representing a translational gap (12). The selection of optimal strategy will likely depend on balancing tumor metabolic disruption against the preservation of antitumor immunity: Urea cycle modulation and ammonia scavengers may alleviate ammonium-mediated immunosuppression but may support tumor nitrogen recycling, whereas GLUD/GLUL inhibition may starve tumors of nitrogen at the cost of worsening the immunosuppressive TME. Future research should prioritize combinatorial regimens that simultaneously target multiple nodes of ammonium metabolism, though such approaches remain hypothetical (12,82).

Combinatorial approaches: Metabolic inhibitors + immune checkpoint blockade. The limited efficacy of immune checkpoint inhibitors as monotherapy in PCa has driven investigation into combination strategies that sensitize tumors to immunotherapy. Sharma *et al* (87) reported preliminary analysis of patients in the CheckMate 650 trial, demonstrating that nivolumab + ipilimumab exhibits clinical activity in metastatic CRPCa, with response rates associated with tumor mutational burden and immune infiltration. Shenderov *et al* (88) conducted a phase 2 non-randomized clinical trial of nivolumab + ipilimumab, with or without enzalutamide, in AR-V7-expressing metastatic CRPCa, revealing that combination immunotherapy overcomes some mechanisms of treatment resistance. Powles *et al* (89) reported results from a randomized phase 3 trial of atezolizumab with enzalutamide vs. enzalutamide alone in metastatic CRPCa, demonstrating that while the addition of immunotherapy did not improve outcomes in unselected patients, biomarker-defined subgroups may derive benefit. Hegde *et al* (90) conducted a phase 1 dose-escalation study evaluating the safety and tolerability of evofosfamide, a hypoxia-activated prodrug, in combination with ipilimumab in advanced solid malignancy, providing proof-of-concept for combining ME-targeted metabolic agents with immune checkpoint blockade. These studies suggest that metabolic inhibitors targeting glutamine and ammonium metabolism may enhance the efficacy of immune checkpoint blockade by alleviating metabolic competition and immunosuppression within the TME.

The combination of metabolic inhibitors with immune checkpoint blockade presents both opportunities and challenges. Preclinical evidence demonstrates that combining glutamine antagonism (via JHU083 or DRP-104) or GLS inhibition (via CB-839) with PD-1/PD-L1 blockade enhances antitumor immunity in mouse models (3,14). However, metabolic inhibition can paradoxically impair $CD8^+$ T cell function by upregulating PD-L1 expression on tumor cells via a reactive oxygen species-dependent EGFR/ERK1/2/c-Jun pathway, necessitating concurrent checkpoint blockade to restore T cell function (9). The differential effects of GLS inhibition vs. broad glutamine antagonism on immune cell populations remain incompletely characterized, representing a key knowledge gap for optimizing combination strategies.

Imaging metabolic vulnerability and biomarker development for patient stratification. The clinical translation of metabolic-immune therapies requires parallel development of imaging biomarkers for patient selection and response monitoring. Ono *et al* (21) demonstrated that fluciclovine uptake is associated with ASCT2 expression in CRPCa cells, validating amino acid positron emission tomography (PET) imaging as a non-invasive approach to assess glutamine transporter expression and target engagement. Lowentritt and Kipper (91) provided a guide for treating patients with biochemical recurrence of PCa using fluciclovine PET/computed tomography, emphasizing the clinical utility of metabolic imaging for detecting recurrent disease. Bhowmick *et al* (10) reviewed strategies for targeting glutamine metabolism in PCa, highlighting the need for predictive biomarkers to identify patients most likely to benefit from metabolic interventions. Smith *et al* (18) demonstrated that plasma glutamine levels may serve as prognostic biomarkers in localized PCa, with alterations in circulating glutamine associated with disease outcome, suggesting that liquid biopsy approaches may complement imaging for patient stratification. The integration of metabolic imaging with circulating biomarkers may enable precision medicine approaches that match patients with specific metabolic vulnerabilities to targeted therapy, ultimately improving outcomes while minimizing unnecessary toxicity.

7. Future perspectives

The present review established the glutamine-ammonium metabolic axis as a key hub integrating tumor progression, immune evasion and therapeutic resistance in PCa. From glutamine addiction driven by oncogenic signaling pathways including AR and Myc, to the role of ammonium as an active immunosuppressive metabolite rather than waste, the bidirectional

crosstalk between tumor metabolism and antitumor immunity affects disease outcomes. Alhallaq and Sultan (9) reviewed the central role of glutamine and glutamate metabolic reprogramming in promoting PCa, emphasizing that this axis represents both a vulnerability and a therapeutic opportunity. The convergence of glutamine-dependent bioenergetics, redox homeostasis and epigenetic regulation with ammonium-mediated immunosuppression creates a self-reinforcing cycle that promotes tumor progression while inhibiting antitumor immune responses. Understanding this integrated network is key for developing next-generation therapeutic strategies that simultaneously target tumor metabolism and enhance immune function.

Despite progress, numerous unanswered questions remain regarding the spatiotemporal dynamics and heterogeneity of metabolic-immune interactions within the prostate TME. Single-cell omics technologies are transforming the understanding of cell heterogeneity, with Yu *et al* (92) demonstrating that single-cell approaches trace the heterogeneity of PCa cells and the TME, revealing distinct metabolic programs across cell subpopulations. Byrne *et al* (93) demonstrated that metabolic reprogramming is spatially heterogeneous, with distinct metabolic profiles across different regions of the tissue that influence therapeutic response. Wang *et al* (94) reviewed integrating multi-omics proteomic approaches in the TME and therapeutic resistance mechanisms, suggesting that comprehensive molecular profiling is key for identifying context-dependent metabolic vulnerabilities. The dynamic nature of metabolic adaptation during disease progression and in response to therapy remains poorly understood, with Mizuno and Beltran emphasizing that future directions for precision oncology in PCa should account for temporal evolution of metabolic phenotypes (95). These technological advances may resolve questions about metabolic heterogeneity and its implications for therapeutic targeting.

The TME represents a complex ecosystem wherein multiple cell types beyond cancer cells contribute to metabolic-immune crosstalk. Cancer-associated fibroblasts are critical regulators of tumor metabolism and immune function, with ChallaSivaKanaka *et al* (96) and Owen *et al* (97) demonstrating that CAFs exhibit marked functional heterogeneity and actively promote tumor progression, metastatic dissemination, and immunosuppression through paracrine signaling and extracellular matrix remodeling. Lupsa *et al* (98) demonstrated PCa-associated fibroblasts, exhibit pronounced functional heterogeneity and actively promote therapeutic resistance through paracrine cytokine signaling and extracellular matrix remodeling, while organ-on-a-chip platforms offer a novel approach for modeling CAF-tumor interactions and screening targeted therapies. Zhou *et al* (99) elucidated that IL-6 and STAT3 signaling in PCa, driven by cancer-associated fibroblasts, promotes immune evasion and represents a therapeutic opportunity. Chen *et al* (100) comprehensively reviewed the PCa ME, emphasizing multidimensional regulation of immune cells, vascular system, stromal cells and microbiota. Li *et al* (101) examined TME-mediated immune evasion and resistance in PCa, synthesizing the key mechanisms by which tumor-stroma crosstalk drives immunosuppression and therapeutic failure, including CAF-derived immunosuppressive cytokines and chemokines, extracellular matrix remodeling that forms a physical barrier to T cell infiltration, and the recruitment of MDSCs and TAMs via metabolic competition and chemokine gradients. The integration of these cell elements creates a highly redundant and adaptive system that complicates therapeutic intervention.

Therapeutic frontiers extend beyond direct targeting of glutamine and ammonium metabolism to encompass epigenetic regulation, ferroptosis and the gut microbiome. Chen *et al* (102) reviewed advances in ferroptosis for CRPCa treatment, identifying drug targets and combination therapy strategies that intersect with glutamine-dependent glutathione metabolism. Rossetto *et al* (103) explored the association between purinergic signaling and oxidative stress in PCa, offering perspectives for therapy that may complement metabolic interventions. Epigenetic regulation of metabolism represents another promising avenue, with Espitia-Pérez *et al* (104) identifying targeting PCa metabolism through transcriptional and epigenetic modulation as a multi-target approach to therapeutic innovation. Naik and Thakur (105) reviewed the association between epigenetic regulation of TGF-β in cancers, highlighting reciprocal associations between signaling pathways and chromatin modifications. The gut microbiome is a modifiable factor influencing PCa progression and treatment response, with Hao *et al* (106) reviewing gut microbiota as a multifaceted modulator of PCa. Qasem and El-Sayed (107) examined the bacterial microbiome and cancer more broadly, summarizing the association between specific bacterial species and cancer development, diagnosis, and treatment, while also discussing mechanisms including genotoxin production, immune modulation, and drug metabolism, alongside future clinical applications such as fecal transplantation, probiotics, prebiotics, and microbiome biomarkers.

The translation of these insights into clinical practice requires parallel development of predictive biomarkers, advanced imaging modalities and personalized treatment strategies. Fidelito *et al* (108) examined whether targeting metabolism is a realistic goal for personalized medicine in PCa, identifying challenges including tumor metabolic heterogeneity, genetic driver variability, and tumor microenvironment complexity, while highlighting opportunities such as the development of more physiologically relevant preclinical models (e.g., patient-derived xenografts) that better recapitulate *in vivo* tumor metabolism to inform patient stratification. Ottini *et al* (109) discussed biomarker-driven immunotherapy for precision medicine in PCa, emphasizing the need for molecular stratification to identify patients most likely to benefit from immune-based approaches. San-Jose Manso *et al* (110) provided a guide for immunome profiling in PCa, outlining how comprehensive immune characterization can inform treatment decisions. Theranostic approaches combining imaging and therapy are evolving, with Sollini *et al* (111) reviewing radiopharmaceuticals and the future of theranostics in genitourinary cancer. Ma *et al* (112) discussed nanoparticle-based drug delivery systems in urological oncology, from targeted therapy to precision theranostics, offering strategies for improving therapeutic index. Pati *et al* (113) reviewed clinical translation for mRNA vaccines in cancer immunotherapy, representing a platform for PCa treatment. As resistance to current therapy remains inevitable due to cell heterogeneity and adaptive metabolic reprogramming, combinatorial strategies targeting

multiple nodes of the glutamine-ammonium immune axis may be required for durable clinical benefit.

At the basic research level, priority should be given to elucidating the spatiotemporal dynamics of ammonium accumulation using single-cell and spatial omics technologies (92,93), defining the molecular sensors and effectors by which ammonium impairs T cell signaling and drives macrophage M2 polarization (12,65) and identifying the causal feedback loops between immune-derived cytokines and tumor ammonium flux using genetically engineered models and organoid systems (11,13). At the clinical translation level, predictive biomarkers, including plasma ammonium, urea cycle enzyme signatures and fluciclovine PET for ASCT2 expression, should be developed to enable patient stratification (18,21). Clinical trials should prioritize biomarker-selected populations for glutamine antagonists (CB-839, JHU083, DRP-104) and combination strategies with immune checkpoint blockade, with attention to sequencing and dosing (10,14,87,114). The development of ammonia scavengers and urea cycle modulators to alleviate ammonium-mediated immunosuppression represents an additional opportunity for preclinical and early-phase clinical evaluation (12). Integration of multi-omics profiling with longitudinal monitoring of metabolic and immune parameters in clinical trials may be key for identifying resistance mechanisms and refining therapeutic strategies.

8. Conclusion

The glutamine-ammonium metabolic axis represents a key hub integrating PCa progression with immune evasion. Glutamine dependency fuels tumor growth while ammonium accumulation, traditionally viewed as waste, actively suppresses antitumor immunity through T cell dysfunction and macrophage M2 polarization. This bidirectional crosstalk creates a self-reinforcing cycle that drives therapeutic resistance. Disrupting this metabolic-immune interface through glutamine antagonism or nitrogen balance modulation offers a promising therapeutic strategy for simultaneously inhibiting tumor progression and enhancing antitumor immunity. However, the majority of evidence supporting this approach is derived from preclinical models, and, to the best of our knowledge, no glutamine-targeted agent has been evaluated in combination with immunotherapy in PCa clinical trials to date.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Gansu Provincial Science and Technology Program (grant no. 23JRRA1628) and Cuiying Science and Technology Innovation (grant no. CY2023-MS-A16).

Availability of data and materials

Not applicable.

Authors' contributions

PW, XL, TM and JM conceived and designed the study. PW, XL and TM performed the literature review. PW and JM wrote and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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